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Metal nickel exposure increase the risk of congenital heart defects occurrence in offspring

A case-control study in China

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Abstract

Background: Previous studies have investigated heavy metal exposure could increase the occurrence of congenital heart defects (CHDs). However, there are limited data regarding the relationship between exposure to nickel and CHDs occurrence in offspring. The aim of this study was to analyze the association between nickel exposure in mothers and the risk of CHDs in offspring.

Materials and methods: To explore the association of nickel exposure and occurrence of CHD, a case-control study with 490 controls and 399 cases with CHDs in China were developed. The concentrations of nickel in hair of pregnant woman and fetal placental tissue were measured and used a logistic regression analysis to explore the relationship between nickel exposure and risk of CHD.

Results: The median concentrations of nickel were 0.629 ng/mg, $P < .05$ (adjusted odds ratio [aOR], 1.326; 95% CI, 1.003–1.757) and 0.178 ng/mg, $P < .05$ (aOR, 2.204; 95% CI, 0.783–6.206), in maternal hair and in fetal placental tissue in the CHD group, respectively. Significant differences in the level of nickel in hair were also found in the different CHD subtypes including septal defects ($P < .05$), conotruncal defects ($P < .05$), right ventricular outflow tract obstruction ($P < .01$), and left ventricular outflow tract obstruction ($P < .05$). Dramatically different nickel concentrations in fetal placenta tissue were found in cases with other heart defects ($P < .05$).

Conclusions: The finding suggested that the occurrence of CHDs may be associated with nickel exposure.

Abbreviations: 95% CI = 95% confidence interval, aOR = adjusted odds ratio, BMI = body mass index, CHD = congenital heart disease, cOR = crude odds ratio, ICP-MS = inductively coupled plasma mass spectrometry.

Keywords: congenital heart defects (CHDs), hair biomarker, metal exposure, nickel, placenta tissue

1. Introduction

Congenital heart defects (CHDs), a multifactorial complex disease, are one of the most prevalent birth defects, and have an incidence of 6–8 per 1000 at birth.[1] CHDs may cause perinatal and infant death.[2] Patients with CHDs require invasive procedures, long-term specialty care, and hospitalizations, according to the severity of the defect.[3,4] CHDs are caused by either environmental, genetic factors or both.[5,6] Maternal

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The program was approved by the Ethics Committee of Sichuan University (No. 2010004), and informed consent was obtained from all subjects during the enrollment process.

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diseases such as obesity, diabetes, and systemic lupus erythematosus can contribute to the etiology of most CHDs.[7,8] Environmental factors such as exposure to dilantin, halogenated hydrocarbons, and retinoic acid increase the risk of CHD.[9]

Many studies show that heavy metal pollution is a modifiable risk factor for perinatal outcomes and a number of birth defects including CHDs.[10] These heavy metals include lead, cadmium, arsenic, and copper.[11] Nickel (Ni) is the 24th most abundant element in the earth's crust [12] and can be found in environmental compartments such as water, air, soil, as well as food.[12] High levels of nickel exposure may be seen in certain occupations, such as manufacturing of jewelry, alloys, stainless steel, pigments, food processing industries, and medical devices.[12] Environmental nickel exposure may be low-level and chronic, and the absorption of nickel is in food, soil, or dust.[13,14] Nickel chloride, sulphate, hydroxide, nitrate, carbonate, and oxide are the most commercially important nickel compounds.[15] Human exposure to nickel is by breathing air, consuming food, drinking water, and smoking in general population.[16] Directing contact with jewelry, coins, and stainless are the other sources of exposure to nickel in daily life.[17] Besides, artificial body parts in medical use are another way to exposure to recipients to nickel.[18] Therefore, the sources and pathways of human nickel exposure are diverse.

High dose exposure to nickel or nickel compounds can induce variety of pathological effects, including allergy, contact dermatitis, and toxicity of organ systems. It has been reported that nickel is a potential immunomodulatory and immunotoxic agent.[19] Nickel chloride ($NiCl_2$) can increase secretion of the inflammatory cytokine IL-1β and endoplasmic reticulum stress.[20] Nickel oxide nanoparticles (NiONPs) and nickel sulfate ($NiSO_4$) can cause lung inflammation by increasing IL-6 and IL-8 expression.[21] Occupational exposure to nickel increased the incidence of cancers such as lung cancer, breast cancer, head, neck and nasal cancer, stomach cancer, kidney cancer, and so on.[22] Furthermore, nickel exposure can induce reproductive toxicity and development toxicity, including influence on subfertility or fertility, abortions, and birth defects.[23,24] The neuroendocrine and gonadal levels in hypothalamic-pituitary-gonadal axis may be affected by nickel during reproduction.[25] Exposure of nickel at a high concentration could also affect embryonic development, reduction proliferation of inner cell mass, and trophoblast cells.[26] These evidences suggest that nickel exposure have been a serious threatens in the environmental safety and public health.

However, few studies have explored the association between heart development and nickel exposure during pregnancy. We conducted a case-control study on interaction between environmental nickel exposures on CHDs occurrence in offspring. In this study, we collected clinical data, analyzed nickel concentration in pregnant mother's hair, and fetus' placenta tissues to investigate the association between maternal nickel exposure and the risk of occurrence of CHDs in offspring.

2. Materials and methods

2.1. Study population

The case-control study was performed from August 2010 to July 2013 at five maternal and child hospitals cities of Zhengzhou, Shenzhen, Fuzhou, Xi'an, and Wuhan in China. Fetuses diagnosed with cardiac defects prenatally were recruited as the cases. Pregnant mother without any malformations fetuses and within 2 weeks differ from the case fetus and within 2 years different with the cases pregnant mother were selected as control. All live cases and controls were examined by pediatric cardiologists within the first week after delivery through heart auscultation and neonatal echocardiography. Stillbirths or terminated pregnancies were established according to autopsy reports. All clinical data and samples were collected immediately after recruitment. More details regarding the recruitment procedure had been provided in our previous study.[11] The study was approved by the Ethics Committee of Sichuan University (No. 2010004), and each participant was informed during the enrollment process.

All subjects in the study were with gestational ages from 14 to 40 weeks, exclusion criteria for cases and controls as follows: first, mothers unwilling to participate in the study or with mental disease or hair dyed; second, the fetus diagnosed unclear or with chromosomal abnormality or hereditary syndrome; third, CHD family history; fourth, multi-fetal pregnancy. All of the cases with CHDs were divided into six major categories according to the anatomic lesion as described in a previous study[11] are septal, conotruncal, right-sided obstructive, left-sided obstructive, anomalous venous return, and other cardiac structural abnormalities.

2.2. Questionnaire interview and samples collection

Each subject recruited in the study had received a face-to-face interview during the antenatal examination. The questionnaires included information as follows: pregnancy history, working and living environment, life styles, maternal diet and nutrition, drug use history, family history, maternal illness, and folic acid supplementation. Information regarding potential confounders as follows: maternal age, gestational age, body mass index (BMI), education, parental smoking habits, folic acid supplement, and other metal concentration were obtained for covariate analysis.[27]

Maternal hair with 3 to 5 cm long and weighed 0.1 g were collected from the occipital area immediately after the interview during prenatal diagnosis. Just after delivery, placental tissues of approximately 1 cm^3 were sheared from the fetal surface of the placenta. All of the samples were kept in individual labeled sterile microtubes and frozen at −80°C until use. More details of samples collection were provided in previous studies.[28]

2.3. Concentration analysis of nickel in human tissues

The nickel and cadmium concentration of the samples were analyzed as described previously by using an Agilent 7500cx ICP-MS system (Agilent Technologies; Wilmington, DE) equipped with a G3160b I-AS integrated autosampler.[29] The limit of detection for nickel in hair was 0.1 ng/mg and that for nickel in placenta tissue was 0.001 ng/mg. Human hair standard reference materials were obtained from the Shanghai Institute of Nuclear Research (GBW09101).

2.4. Statistical analysis

Data analysis was performed using SPSS 16.0 software (Chicago, IL). A case-control analysis was performed to assess the potential effects of nickel using data from identified cases and controls. Differences in demographic information and maternal characteristics between the control and case groups were compared by Chi-square tests (two-tailed values of $P < .05$). The distributions of nickel levels were tested by one-sample Kolmogorov–Smirnov

tests. The distributions of nickel levels are presented as medians, arithmetic means, and 5% to 95% ranges. Differences in nickel levels between the case and control groups were assessed by Wilcoxon–Mann–Whitney tests.

The risk of CHDs associated with nickel exposure was assessed by crude odds ratios (cORs), adjusted odds ratios (aORs), and 95% confidence intervals (95% CIs) using logistic regression. The potential confounding effects were maternal age, gestational age, BMI, education, parental smoking habits, folic acid supplement, and cadmium, lead, and arsenic concentration. The previous study reported that cadmium, arsenic, and lead exposure increased the risk of CHDs in the offspring.[11,28] Therefore cadmium, lead, and arsenic level was just as a covariate in logistic regression analysis in this study.

The nickel levels were normalized using Napierian logarithm and divided into tertiles (low, medium, and high) and the first tertiles of nickel (hair nickel: $\leq$0.4111 ng/mg; fetal placental nickel: $\leq$0.0751 ng/mg) were considered as reference. Two-tailed P values $<$ .05 and 95% CIs excluding 1.00 were considered statistically significant.

3. Results

3.1. Characteristics of participants

Four hundred ninety controls and three hundred ninety nine cases were recruited in the study. The total number of hair samples and placental tissues samples was 587 and 395, respectively. The number of cases in hair samples and placental tissues samples was 263 and 173, respectively. And the number of controls in hair samples and placental tissues samples was 324 and 222, respectively. The maternal characteristics of the samples were listed in Table 1. Gestational age, folic acid supplementation, parental smoking, and education level of the mother were significantly different between the two groups ($P < .05$), while there were no significant differences in maternal age ($P = .099$) and BMI ($P = .192$).

3.2. Nickel concentration in hair samples

Heavy metal nickel in hair was compared between control and case groups. As shown in Table 2, the median concentrations (5%–95% range) of hair nickel in the control and case groups were 0.443 ng/mg (0.182–1.710 ng/mg) and 0.629 ng/mg (0.276–2.250 ng/mg), respectively. The hair nickel levels in cases were higher than controls ($P < .001$). The levels of hair nickel in subtypes of CHDs are presented in Table 2. There were significant differences ($P < .01$) between each CHD subtype for cases and controls. After the value Napierian logarithm transformed, the concentrations of hair nickel in the CHD group were significantly higher than in the control group ($P < .001$) (Fig. 1A and B).

3.3. Nickel levels in fetal placental tissues

Nickel contents were analyzed using an Agilent 7500cx ICP-MS system. The median (5%–95% range) concentrations of fetal placental nickel were 0.1479 ng/mg (0.008–0.954 ng/mg) and

Table 1

Descriptive characteristics of the study sample.

Variable	Control N = 490 (%)	Cases N = 399 (%)	Chi square	*P*-value
Maternal age (years, n)*			7.803	.099
n < 20	12 (2.4)	12 (3.0)		
20 ≤ n < 25	111 (22.7)	113 (28.3)		
25 ≤ n < 30	216 (44.1)	179 (44.9)		
30 ≤ n < 35	108 (22.0)	73 (18.3)		
n ≥ 35	43 (8.8)	22 (5.5)		
Gestational age (week, n) a			37.628	<.001***
n < 15	6 (1.2)	2 (0.5)		
15 ≤ n < 20	69 (14.1)	15 (3.8)		
20 ≤ n < 25	233 (47.6)	182 (45.6)		
26 ≤ n < 31	109 (22.2)	136 (34.1)		
n ≥ 31	73 (14.9)	64 (16.0)		
Folic acid supplement			11.350	.001**
Yes	436 (89.0)	323 (81.0)		
No	54 (11.0)	76 (19.0)		
Parental smoking			15.615	<.001***
Yes	181 (36.9)	200 (50.1)		
No	309 (63.1)	199 (49.9)		
ppBMI (kg/m^2)			5.078	.192
BMI < 18.5	112 (22.9)	107 (26.8)		
18.5-24.5	354 (72.2)	281 (70.4)		
BMI > 24.5	24 (4.9)	11 (2.8)		
mEDU			38.113	<.001***
Primary school and below	3 (0.6)	16 (4.0)		
Junior middle school	77 (15.7)	114 (28.6)		
Senior high school	124 (25.3)	89 (22.3)		
College degree and above	284 (58.0)	173 (43.4)		
Missing	2 (0.4%)	7 (1.7%)		

* Using base data in following multivariate analysis as continuous variables.
** $P < .01$, two-tailed test, there was statistical significant difference between groups.
*** $P < .001$, two-tailed test, there was statistical significant difference between groups.

Table 2

Descriptive statistics for hair nickel level in the case and control groups.

	Hair nickel (ng/mg)					
	N	AM\	5th p	Median	95th p	*P* value
Control	324	0.648	0.182	0.443	1.710	
Case	263	0.857	0.276	0.629	2.250	<.001***
Septal defects	179	0.816	0.272	0.629	2.123	<.001***
Conotruncal defects	132	0.829	0.279	0.632	2.210	<.001***
Right ventricular outflow tract obstruction	120	0.872	0.258	0.621	2.277	<.001***
Left ventricular outflow tract obstruction	40	0.969	0.264	0.570	4.088	.007**
Anomalous pulmonary venous return	41	0.849	0.248	0.599	3.156	.013*
Other heart defects	47	0.836	0.275	0.686	2.093	.002*

5th p, 95th p = lead level in 5%, 95% percentiles respectively, AM = arithmetic means, N = number.

* Significant differences between the mothers of case and control were indicated by $P < .05$, two-tailed test, Wilcoxon–Mann–Whitney on nonparametric test.

** Significant differences between the mothers of case and control were indicated by $P < .01$, two-tailed test, Wilcoxon–Mann–Whitney on nonparametric test.

*** Significant differences between the mothers of case and control were indicated by $P < .001$, two-tailed test, Wilcoxon–Mann–Whitney on nonparametric test.

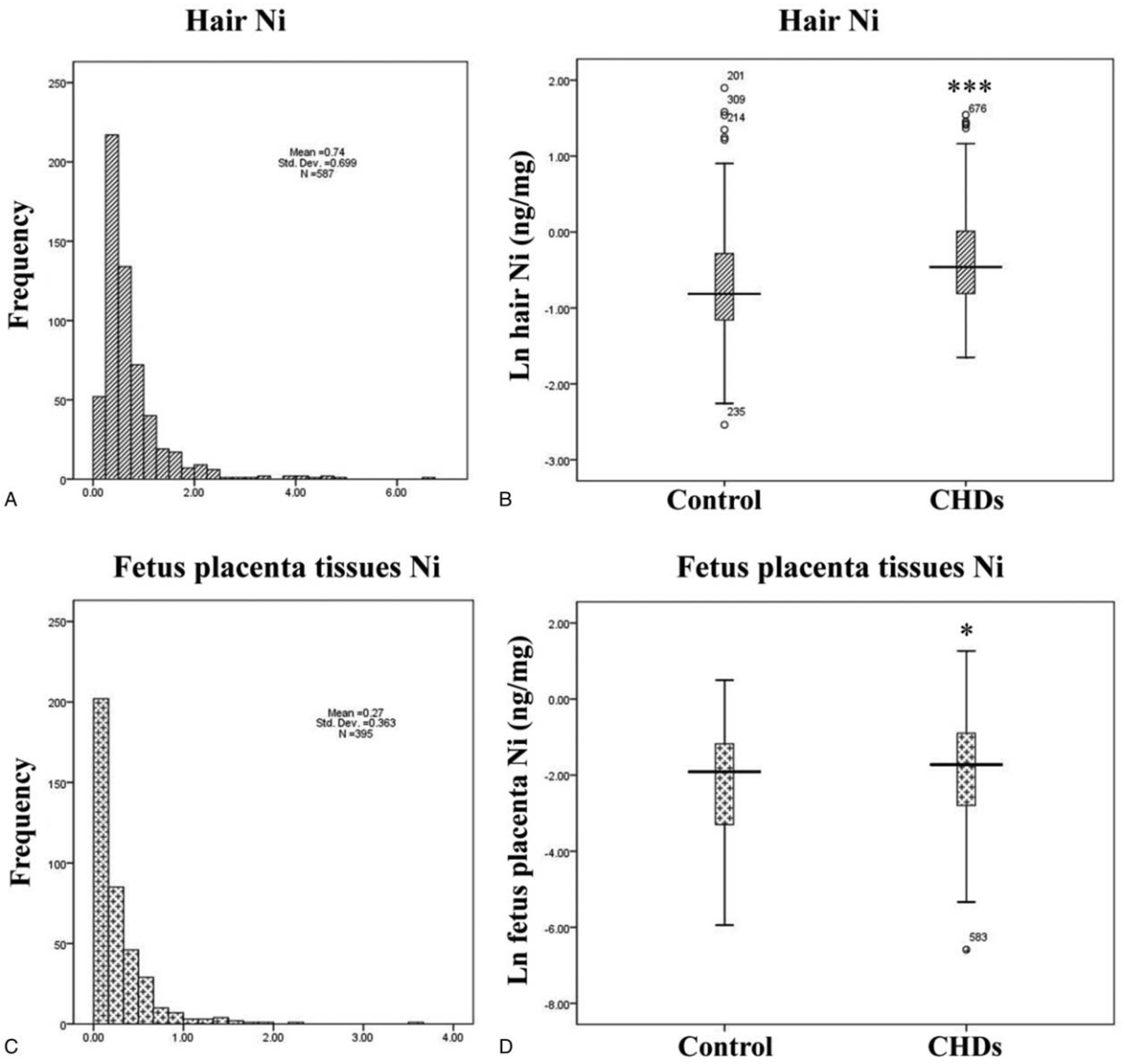

Figure 1. Levels and frequency of nickel in CHDs and control groups. (A) Frequency of nickel in maternal hair, (B) boxplots of nickel levels (Napierian logarithm transformed) of hair samples; (C) frequency of nickel in fetus placental tissues; (D) boxplots of nickel levels (Napierian logarithm transformed) in fetus placental tissues. The line inside the box = medians; the box length = IQR; the upper and lower ends = 95, and 5% value. One-sample Kolmogorov–Smirnov test was used to verify the distributions of nickel. The distributions of nickel did not conform to normal distribution. * $P < .05$ or *** $P < .001$, two-tailed test, Wilcoxon–Mann–Whitney on nonparametric test compared to the control group. CHDs = congenital heart defects, IQR = interquartile range

Table 3

Descriptive statistics for placental tissue nickel level in the case and control groups.

	Tissue nickel (ng/mg)					
	N	AM	5th p	Median	95th p	*P* value
Control	222	0.242	0.008	0.148	0.954	
Case	173	0.308	0.012	0.178	0.851	.039*
Septal defects	118	0.325	0.012	0.176	1.300	.064
Conotruncal defects	91	0.220	0.007	0.148	0.702	.754
Right ventricular outflow tract obstruction	62	0.314	0.014	0.177	0.841	.124
Left ventricular outflow tract obstruction	25	0.265	0.018	0.180	1.091	.333
Anomalous pulmonary venous return	28	0.197	0.015	0.119	0.764	.960
Other heart defects	33	0.471	0.020	0.338	2.319	.002**

5th p, 95th p = lead level in 5%, 95% percentiles respectively, AM = arithmetic means, N = number.

* Significant differences between the placental tissue of case and control were indicated by $P < .05$, two-tailed test, Wilcoxon–Mann–Whitney on nonparametric test.

** Significant differences between the placental tissue of case and control were indicated by $P < .01$, two-tailed test, Wilcoxon–Mann–Whitney on nonparametric test.

0.1784 ng/mg (0.012–0.851 ng/mg,) in the control and case groups, respectively. This result indicated that the concentration of fetal placental nickel in the case group was significantly higher than that in the control group ($P < .05$). In Table 3, fetal placental nickel levels in CHD cases with other noncardiac defects seem significant higher than in controls ($P = .002$). As shown in Figure 1C and D, the distribution of nickel in placental tissues was not normal, and the normalize data indicated that the concentrations of fetus placental tissues nickel in the CHD group were significantly higher than in the control group ($P < .001$).

3.4. Association between maternal hair nickel exposure and CHDs in offspring

The risk of CHDs in association with different levels of nickel in hair samples was further analyzed by tertiles of all samples. Logistic regression analysis showed that the overall risk of CHDs increases with highest tertiles hair nickel concentrations (total CHD aOR, 1.326; 95% CI, 1.003–1.757; $P < .001$) after adjustment for potential risk factors. As shown in Table 4, significant differences were found in the different CHD subtypes including septal defects (aOR, 1.443; 95% CI, 1.082–1.925;

Table 4

Risks for fetal CHD in different maternal hair nickel concentrations.

Group	Total hair Ni	Hair low n = 195 (<0.4111 ng/mg)	Hair medium n = 197 (0.4111–0.7216 ng/mg)	Hair high n = 195 (>0.7216 ng/mg)
Control (N)	324	146	92	86
Cases (N)	263	49	105	109
cOR	1.602***	Reference	3.401***	3.706***
aOR	1.326*	Reference	2.917***	2.672***
95% CI	1.003–1.757		1.829–4.654	1.623–4.399
Septal defects (N)	179	32	74	73
cOR	1.439*	Reference	3.670***	3.873**
aOR	1.242	Reference	3.486***	2.919***
95% CI	0.916–1.685		2.031–5.982	1.647–5.175
Conotruncal defects (N)	132	24	53	53
cOR	1.440*	Reference	3.505***	3.891***
aOR	1.085	Reference	3.051***	2.305***
95% CI	0.770–1.527		1.660–5.607	1.209–4.733
Right ventricular outflow tract obstruction (N)	120	21	50	49
cOR	1.492**	Reference	3.778***	3.961***
aOR	1.278	Reference	3.294***	2.396***
95% CI	0.924–1.768		1.767–6.141	1.213–4.733
Left ventricular outflow tract obstruction (N)	40	7	17	16
cOR	1.490*	Reference	3.854**	3.880**
aOR	1.378	Reference	2.995*	2.554
95% CI	0.933–2.305		1.126–7.967	0.880–7.418
Anomalous pulmonary venous return (N)	41	8	19	14
cOR	1.349	Reference	3.769**	2.971*
aOR	1.231	Reference	3.584*	1.898
95% CI	0.786–1.930		1.413–9.094	0.660–5.469
Other heart defects (N)	47	8	17	22
cOR	1.371	Reference	3.372**	4.669***
aOR	1.091	Reference	2.681*	2.490
95% CI	0.659–1.805		1.040–6.908	0.928–6.681

aOR = adjusted odds ratio, cOR = crude odds ratio, n = number. Logistic regression was used to calculate odds ratios and 95% CIs; the low–medium–high concentration of nickel are referring to the tertiles and lose dose group of nickel was consider as a reference; all models were adjusted for maternal age, gestational age, education, taking folic acid (yes, no), parental smoking (yes, no), maternal pre-pregnancy BMI, hair cadmium concentration, hair arsenic concentration and hair lead concentration.

* Significant differences between the mothers of case and control were indicated by $P < .05$, Chi-square test.

** Significant differences between the mothers of case and control were indicated by $P < .01$, Chi-square test.

*** Significant differences between the mothers of case and control were indicated by $P < .001$, Chi-square test.

Table 5

Risks for fetal CHD subtypes in different fetal placental tissue nickel levels.

Group	Total tissue Ni	Tissue low n = 131 (<0.0751ng/mg)	Tissue medium n = 133 (0.0751–0.2658 ng/mg)	Tissue high n = 131 (>0.2658 ng/mg)
Control (N)	222	81	75	66
Cases (N)	173	50	58	65
cOR	1.665	Reference	1.253	1.595
aOR	2.204	Reference	0.771	1.290
95% CI	0.783–6.206		0.36–1.648	0.577–2.884
Septal defects (N)	118	34	41	43
cOR	1.787	Reference	1.302	1.552
aOR	2.371	Reference	0.742	1.266
95% CI	0.803–7.000		0.325–1.694	0.533–3.006
Conotruncal defects (N)	91	30	34	27
cOR	0.747	Reference	1.224	1.105
aOR	0.707	Reference	0.867	0.930
95% CI	0.133–3.749		0.367–2.050	0.368–2.348
Right ventricular outflow tract obstruction (N)	62	15	25	22
cOR	1.643	Reference	1.800	1.800
aOR	2.919	Reference	1.486	2.290
95% CI	0.754–11.305		0.495–4.458	0.723–7.250
Left ventricular outflow tract obstruction (N)	25	7	10	8
cOR	1.262	Reference	1.543	1.403
aOR	1.904	Reference	0.931	1.302
95% CI	0.231–15.689		0.229–3.789	0.311–5.443
Anomalous pulmonary venous return (N)	28	9	14	5
cOR	0.542	Reference	1.680	0.682
aOR	0.210	Reference	1.400	0.323
95% CI	0.009–4.673		0.414–4.730	0.049–2.133
Other heart defects (N)	33	5	8	20
cOR	3.224**	Reference	1.728	4.909**
aOR	11.280**	Reference	0.769	4.538*
95% CI	1.621–78.512		0.174–3.396	1.153–17.853

aOR = adjusted odds ratio, cOR = crude odds ratio, N = number. Logistic regression was used to calculate odds ratios and 95% CIs; the low–medium–high concentration of nickel are referring to the tertiles and lose dose group of nickel was consider as a reference; all models were adjusted for maternal age, gestational age, education, taking folic acid (yes, no), parental smoking (yes, no), maternal prepregnancy BMI, and fetal placental tissue cadmium, arsenic, and lead concentration.

* Significant differences between the mothers of case and control were indicated by $P < .05$, Chi-square test.

** Significant differences between the mothers of case and control were indicated by $P < .01$, Chi-square test.

$P < .05$), conotruncal defects (aOR, 1.376; 95% CI, 1.018–1.859; $P < .05$), right ventricular outflow tract obstruction (aOR, 1.543; 95% CI, 1.140–2.066; $P < .01$), left ventricular outflow tract obstruction (aOR, 1.549, 95% CI, 1.086–2.208; $P < .05$) compared with controls. When the lowest tertiles (<0.4111 ng/mg) was used as the reference, significant differences were observed in the middle (aOR, 2.917, 95% CI, 1.829–4.654; $P < .001$) and highest concentration hair nickel tertiles (aOR, 2.672, 95% CI, 1.623–4.399; $P < .001$). As shown in Table 4, significant differences were found in all subtypes of CHD in the middle concentration groups. Significant differences were found in the high nickel concentration groups including septal defects (aOR, 2.919; 95% CI, 1.647–5.175; $P < .01$), conotruncal defects (aOR, 2.305; 95% CI, 1.209–4.393; $P < .05$) and right ventricular outflow tract obstruction (aOR, 2.396; 95% CI, 1.213–4.733; $P < .05$) compared with controls. All the results indicated that the hair nickel exposure may increase the CHD risk in offspring.

3.5. Association between maternal fetal placental nickel exposure and CHDs in offspring

The risk of CHDs and different levels of nickel in fetal placental tissues was analyzed by trisecting the concentrations of all subjects. Table 5 indicated that the nickel level in fetus placental tissue increased the risk of other defect in offspring, with a 11.280-fold (95% CI 1.621–78.512, $P < .05$) increase. Exposure to the highest fetus placental concentrations (>0.2658 ng/mg) was associated with increased risks of the other heart defects (aOR, 4.538; 95% CI, 1.153–17.853; $P < .05$). It was suggested that the association between nickel level and CHD risk may also display a dose-response relationship for the other heart defects subtype.

4. Discussion

Based on the results of this study, the hair samples of pregnancy mothers with CHDs and placental tissues of fetus with CHDs had higher concentrations of nickel than those of the control group. Epidemiological evidence showed that maternal exposure to nickel had a significant association with the risk of CHDs in offspring and higher concentrations of nickel may be associated with increased risk of CHDs of some major subtypes in offspring.

Maternal exposure to excessive concentrations of copper, arsenic, lead, and cadmium in hair was shown to significantly increase the risk of CHD in offspring.[11,28] Although hair sample could show long-term exposure to nickel, and may even provide us with information regarding metal exposure of the mother prior to pregnancy,[30,31] we also used fetus placental tissues to analyze the nickel exposure which could be more intuitive displayed fetal

nickel exposure levels in this study. As we know, nickel could be capable of crossing the placenta barrier and exerting the toxicity on the embryonic development.[26,32] Nickel levels in fetus placental tissues could directly display the exposure to nickel during the pregnancy, while part of nickel could not cross the placenta barrier. Other samples such as umbilical cord blood, fetus hair, urine, and serum should be used to analyze metal nickel exposure in the further study.

Nickel and nickel compounds have been recognized to cause neurotoxicity, genotoxicity, reproductive toxicity, nephrotoxicity, and increased the risk of cancers.[20] It has been reported that diets supplemented with nickel 300 mg/kg or over were toxic to male chicks.[33] Dietary $NiCl_2$ in excess of 300 mg/kg could cause immunotoxicity, cytotoxicity, genotoxicity.[33] $NiCl_2$ at the concentration of 1200 mg/kg induced reduction of food intake and weigh loss.[34] Drinking water with nickel sulfate ($NiSO_4$) and $NiCl_2$ could also lead to develop acute gastrointestinal and neurological diseases.[35] Tolerance dietary intake of 2.8 μg/kg body weight was consider as a reference dose for chronic effect in the general population.[14] Low level of nickel release from implanted cardiovascular devices may give rise to allergenic response in some patients.[36] Therefore, long-term, chronic and nonoccupationally exposure to nickel was also adverse threaten to health. However, it has been difficult to measure chronic nickel exposure. Moreover, there was no evidence to show the concentration of nickel in human with CHDs. In this study, average concentration of nickel in hair of CHDs group was 0.857 ng/mg, and the level of nickel in fetus placental tissues was 0.308 ng/mg. In the previous study showed that occupational nickel concentration was 29.9 μg/g in fingernail which was much higher than that of control workers.[37] Concentrations in scalp hair samples of smokers and nonsmokers hypertensive patients were 12.2 ± 1.48 and 15.7 ± 0.96 μg/g, respectively.[38] Concentration of nickel in occupational exposure was much higher than that in nonoccupational exposure. The results provided evidence for cardiac toxicity of chronic nickel exposure in pregnant women.

The possible mechanisms of teratogenesis and embryotoxic effect of nickel were that nickel induced certain mutations in the mitotic apparatus provoking cellular death at critical of fetus heart development,[16] or nickel compounds promoted the generation of ROS (Reactive oxygen species) [39] or nickel lead to epigenetic alterations such as DNA methylation and loss of histone acetylation.[40,41] However, the mechanisms of environmental nickel increased occurrence of fetal cardiac anomalies during gestation need be investigated in the further study.

Moreover, although nickel exposure was related to CHDs occurrence in offspring, there were also some limits in this study. First, the previous study showed that cadmium and nickel present a synergistic effect and with the increase of the concentration proportion of cadmium, the area of synergistic effect had an increasing trend.[42] The cadmium may promote the toxicology of nickel. Lead and nickel have been reported to compete for adsorption.[43] Therefore, the logistic regression analysis was with the concentration of cadmium, lead, and arsenic as a covariate in this study. However, other kinds of metals were not included in this study. Second, there was no normal reference range of hair nickel levels and fetus placental tissues nickel levels available. Therefore, we divided the hair nickel and fetus placental tissues nickel of all subjects into trisector, and the lowest levels of nickel were considered as the reference groups. Third, the sample size was limited, which resulted in small population sizes for the subtypes of CHDs. And the ORs were low, perhaps because of residual confounding and more confounding factors should be investigated in future studies.

5. Conclusion

In summary, maternal and fetal nickel exposure was significantly higher in the CHDs group than that in the control group. Exposure to nickel is possibly associated with the risk for the other heart defect subtypes of CHD in a dose-dependent manner.

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