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Distribution and predictors of 20 toxic and essential metals in the umbilical cord blood of Chinese newborns

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Abstract

Early-life exposure to heavy metals and/or trace metal imbalances can have negative developmental effects. Here we sought to characterize exposure profiles for 20 heavy metals and trace elements in umbilical cord blood plasma and identify demographic predictors of exposure. Twenty metals were measured in cord plasma from 357 Chinese infants using ICP-MS. Relationships between demographic variables and metals were analyzed using generalized linear models and logistic regression. Ten metals (antimony [Sb], cobalt [Co], cesrium [Cs], copper [Cu], lead [Pb], molybdenum [Mo], rubidium [Rb], selenium [Se], strontium [Sr], titanium [Ti], zinc [Zn]) were detected in all samples. Season of birth was the strongest predictor of metals in cord blood across analyses. Infants born in the spring had 0.1–0.2 μg L-1 higher logAs and logCo in their cord blood (β [95%CI]= 0.22 [0.01,0.42], p=0.04; 0.11 [0.01,0.22], p=0.04), while infants born in the summer had higher Sb, logB, logHg, and logZn (β [95%CI]= 0.74 [0.24,1.24], p=0.004; 0.11 [0.00,0.21], p=0.04; 0.29 [0.08,0.49], p=0.007; 0.18 [0.06,0.31], p=0.005), compared to those born in fall/winter. Prenatal heavy metal exposure and/or trace metal deficiencies are global concerns because of increasing awareness of downstream developmental effects.

Keywords

Metals; Prenatal exposure; Cord blood; China; Neonate

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1. Introduction

Metals have a wide variety of applications in the telecommunications, electronics, agriculture, mining, construction, health care, information technology, and other industries (Mamtani et al., 2011). In the past few decades, China has experienced a technological boom and rapid industrialization, leading to ever-increasing levels of heavy metals in the environment (Chen et al., 2016; Liu et al., 2014). There are reports of heavy metal contamination of soil (Chen et al., 2015; Ye et al., 2015), food (Huang et al., 2013; Pan et al., 2016; Tang et al., 2014; Zhang et al., 2015), air (Zhang et al., 2017), and surface water (Liu et al., 2009; Zhen et al., 2016) in China. The improper handling of "E-waste" is also a growing concern in China, where they produce more than 2 million tons per year (Mamtani et al., 2011). Due to this ubiquitous environmental contamination, humans are exposed to metals via a number of pathways: consumption of food grown in contaminated soil, inhalation of polluted air, drinking or cooking with contaminated water (Mamtani et al., 2011).

This widespread presence of metals in our environment presents important health risks (Mamtani et al., 2011). Heavy metals are persistent in the human body and have been associated with negative health effects on a diverse range of systems, including neurological, cardiovascular, respiratory, reproductive, renal, skeletal, and gastrointestinal systems (Jaishankar et al., 2014; Jarup, 2003; Zeng et al., 2016).

Exposure to heavy metals, in particular, is a concern during gestation and early infancy when rapid development is occurring. Exposure during these sensitive periods could result in permanent structural or functional changes (Caserta et al., 2013). While regarded as a protective barrier for the embryo and fetus, the placenta does not provide protection against heavy metals, such as lead (Pb), cadmium (Cd), and mercury (Hg) (Al-Saleh et al., 2011; Iyengar and Rapp, 2001).

Epidemiological studies have found that prenatal and childhood heavy metal exposures are associated with downstream neurological and cognitive deficits in childhood. For example, prenatal exposure to Pb has been associated with decreases in motor (Parajuli et al., 2013) and sensory (Silver et al., 2016a) function in infants, while childhood Pb exposure has been associated with lower IQ and cognitive abilities, behavioral abnormalities, inattention, and other neurological deficits (Bellinger, 2008; Wigg, 2001). Prenatal exposure to Cd, Hg and other heavy metals have also been found to be associated neurodevelopmental deficits, such as decreased social skills and delayed behavioral development (Gao et al., 2007; Wang et al., 2016).

While heavy metals, such as Pb, arsenic (As), Cd, and Hg can be toxic, even at low levels of exposure, other metals, such as iron (Fe), copper (Cu), zinc (Zn), and selenium (Se), are essential for a host of physiological and metabolic functions (Mamtani et al., 2011). Deficiencies or excesses of these essential trace metals can similarly have negative health effects.

Some trace metals, such as Zn, Cu, manganese (Mn), and Se are essential for proper embryonal and fetal growth and development (Gernand et al., 2016). These elements are

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necessary for a number of important developmental processes, such as embryogenesis and fetal growth, myelin development, skeletal formation, and maintenance of cell membrane integrity (Chan et al., 1998; Hurley, 1981; Linder, 1991; Pieczynska and Grajeta, 2015; Shah and Sachdev, 2001; Srivastava et al., 2002). Other trace metals such as boron (B), rubidium (Rb), and strontium (Sr) may also play a role in fetal growth, though their roles are not well-established (Maynar et al., 2017). Additionally, deficiencies in essential elements such as Cu (Shen et al., 2015), Zn (Jeswani and Vani, 1991; Shen et al., 2015; Tamura et al., 2000; Terrin et al., 2015) and Se (Pieczynska and Grajeta, 2015) during the prenatal and early postnatal periods have been associated with an increased risk of pregnancy complications such as, miscarriage, low birth weight, and intrauterine growth restriction, as well as immune deficiencies.

Deficiencies or excesses in essential metals during pregnancy or childhood can also have negative downstream neurodevelopmental effects. For example, infants with Fe deficiency are more likely to perform worse on cognitive tests and to experience long-term developmental deficiencies, compared to infants with normal Fe (Lozoff et al., 1991). Prenatal Zn deficiency has been found to be associated with defects of the central nervous system (Shah and Sachdev, 2001; Uriu-Adams and Keen, 2010) and increased risk of autism spectrum disorder (ASD) (Arora et al., 2017), while Zn deficiency during infancy has been associated with deficits in memory (Fuglestad et al., 2016). Studies of prenatal Mn have revealed that both deficits and excesses during pregnancy can negatively impact cognitive and motor functions (Chung et al., 2015; Sanders et al., 2015; Zoni and Lucchini, 2013), while pre- and postnatal deficits have been associated with increased risk of ASD (Arora et al., 2017).

Furthermore, deficiencies of essential elements may potentially lead to increased absorption of toxic metals. For example, children with low blood calcium (Ca), Fe, and Zn are at increased risk of high blood Pb levels (Ahamed et al., 2007; Talpur et al., 2017). Similarly, iron deficient children and those with iron deficiency anemia are reported to have elevated blood levels of Cu (Turgut et al., 2007), Cd (Silver et al., 2013; Turgut et al., 2007) and Pb (Ahamed et al., 2007; Bradman et al., 2001; Rondo et al., 2011; Turgut et al., 2007).

Previous studies have investigated cord blood metals in China (Hu et al., 2015; Liang et al., 2017; Tang et al., 2016a; Tang et al., 2016b; Wang et al., 2016; Yang et al., 2013; Yu et al., 2011; Yu et al., 2014; Zheng et al., 2014). With a couple of exceptions (Tang et al., 2016b; Yang et al., 2013), these studies were largely focused solely on toxic metals. Additionally, only one included a robust analysis of predictors of prenatal metal exposure (Yu et al., 2011). Each of these studies focused on a particular geographical region, and their results indicate the presence of regional variation of metals exposure in China. None of the previous studies included Zhejiang province, the site of this study. Reports indicate that agricultural soil in Zhejiang has Pb and Hg levels that exceed the maximum allowable levels set by the Chinese Soil Quality Criterion (Ye et al., 2015) and that rice and other vegetables grown there may contain high levels of Pb, Hg, and Cd (Huang et al., 2013; Pan et al., 2016).

Given the potential for high exposure in Zhejiang and the important developmental implications for prenatal exposure to heavy metals, we sought to determine the

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concentrations of 20 heavy metals and trace elements in umbilical cord blood plasma and to identify demographic predictors of prenatal exposure to those metals. The consideration of both toxic and essential metals allows us to begin to consider the interplay of both environmental toxicants and nutritional exposures. This study will inform future work examining prenatal metals exposure and infant neurodevelopment in this cohort.

2. Methods

2.1 Ethics statement

Institutional review board approval was obtained from ethics committees at the University of Michigan (HUM00010107) and Zhejiang University Children's Hospital. Signed, informed consent was obtained from parents prior to commencing the study.

2.2 Study population

Blood metals analysis was performed for 357 infants. Pregnant women with healthy, uncomplicated, single pregnancies were recruited between 2008 and 2011 from Fuyang Maternal and Children's Hospital in rural Fuyang county, Zhejiang province, China. Women (n = 1187) consented to a cord blood screening at the time of recruitment. Of the infants born at term (37–42 weeks gestation), a subset (n = 359) was then enrolled in a study of infant neurodevelopment. This subset was selected based on cord blood iron status and parental consent for the developmental study. Of those, 229 had a sufficient volume of cord blood available for metals analysis. The remaining metals analysis samples (n = 128) were randomly selected from those with sufficient cord blood volume from the original cord blood screening cohort.

2.3 Determination of metals in umbilical cord blood

Following delivery, 10 mL of cord blood was collected in two royal blue top metals free EDTA tubes. Both tubes were immediately frozen and stored at −20 degrees Celsius (°C). Frozen whole blood samples were transferred twice weekly on dry ice from Fuyang to Hangzhou. Upon arrival at the Zhejiang University Children's Hospital, one tube of whole blood was placed at −20 °C to await whole blood Pb analyses. The other tube was separated and the fractions were stored at −80 °C. Plasma samples were later transferred on dry ice to the Institute of Toxicology at Nanjing Medical University for further analysis.

Lead in whole blood was analyzed using graphite furnace atomic absorption (GFAAS) (PE700 method; Perkin-Elmer Corp., AAnalyst 700, Bodenseewerk, D-88647 Uberlingen and Analytikjeana Corp., ZEEnit 700P) at the Central Lab of the Children's Hospital at Zhejiang University. Internal quality control included running blanks (bovine whole cord blood [Zhejiang Tianhang Biotechnology Co., Ltd.]) and certified Pb reference materials (Chinese Center for Disease Control, Occupational Health, and Poison Control) in parallel with samples. Quality control analyses yielded coefficients of variation between 4% and 5%.

Nineteen metals in cord plasma were analyzed using an iCAP Qc inductively coupled plasma mass spectrometry (ICP-MS) instrument (Thermo Scientific, Bremen, Germany) at the Institute of Toxicology at Nanjing Medical University. The target metals included aluminum (Al), antimony (Sb), As, B, barium (Ba), Cd, cobalt (Co), chromium (Cr), cesium (Cs), Cu, Hg, Mn, molybdenum (Mo), nickel (Ni), Rb, Se, Sr, titanium (Ti), and Zn. The metals analysis protocol was adapted from a previous report (Balcaen et al., 2014). Limits of detection (LODs) were calculated as 3 times the standard deviation of 10 consecutive measurements of the blank diluent (0.05% [v/v] Triton X-100, 0.1% [v/v] nitric acid plus 10 ug/L internal standards including Sc, Y, In, Tb, Bi). Quality control samples (Seronorm Trace Elements Serum L-2 (ref. 203105, Sero, Billingstad, Norway) and blanks were analyzed in parallel with study samples (every 20 samples) for each batch. Coefficients of variation were between 10% and 15%.

Values <LOD were replaced with LOD/√2 for individual metals with detection rates of ≥80% for later analysis as continuous variables. Values <LOD were not imputed for metals with detection rates <80% (Al, Cd, Cr, Ni) since they would only be analyzed categorically.

2.4 Predictors

Demographic and household variables were available for infants in the developmental study (n=229), and were determined by maternal interview at the infant's six-week visit. Household variables included: number of family members living in home, amount of living space (m^2), place of residence (rural/ urban), and annual income (<30,000/ 30,000–49,999/ 50,000–99,999/ ≥100,000 Yuan). Parental characteristics included maternal and paternal age in years, education (middle school or less/ high school or secondary school/ college), and occupation (maternal: other/ housewife; paternal: managerial position [mid- to high- level manager in industry]/ factory or industrial worker/ professional or administrator [educational, technical, professional, or administrative personnel])/ other [commercial or industrial entrepreneur, service staff, or unemployed]. Paternal smoking habits (regular [>10 cigarettes/day]/ occasional [≤10 cigarettes/day]/ never and smokes inside home: ever/ never) and occupational exposure to metals (ever/ never) were also explored as potential predictors. Date of birth was used to create a season of birth variable (Spring [March-May]/ Summer [June– September]/ Fall-Winter [October–February]). Fall and winter were combined due to small numbers of enrollees in those months. All of the variables described here were analyzed as possible predictors of pesticide exposure. The categorical variables were analyzed so that the last category listed was treated as the reference group.

2.5 Statistical Analysis

Statistical analyses were conducted using SAS 9.4 (SAS Institute Inc., Cary, NC, USA). We examined descriptive statistics and frequencies for all variables of interest. Percentile tables were created to determine the distribution of metals within the study sample. Metals with a right-skewed distribution were log-transformed prior to regression analysis. Correlations between the metals were examined using Spearman correlation coefficients.

Relation between predictors and metals were assessed in several ways. First, metals with detection rates of at least ≥80% (Sb, As, B, Ba, Co, Cs, Cu, Pb, Mn, Hg, Mo, Rb, Se, Sr, Ti, Zn) were analyzed using generalized linear models (GLM). Second, logistic regression models were used to assess associations between predictors and all metals, regardless of detection rate. Dichotomous variables for logistic regression were created in several ways.

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First, an “outside of reference range/ within reference range” variable was created using reference ranges for metals in plasma obtained from the Mayo Medical and NMS Laboratories (Mayo, 2017; NMS, 2017). For some metals, the reference range cut-offs did not yield a comparison group of ≥10%, so an “upper quartile/ lower quartiles” variable was created. For metals believed to have a physiological role in the body, a “lower quartile/ upper quartiles” variable was also created. For Zn, a similar “lower/upper” variable was created, though the reference range values were used instead of the quartile cut-offs. This yielded Zn variables that were “above upper reference range cut-off/ below” or “below lower reference range cut-off/above”. Finally, a composite exposure variable was created for each subject to examine the effect of the predictors on a measurement of overall metal exposure. Metal concentrations within the reference range were assigned a score of 0, while concentrations outside of the reference range (either above or below) were assigned a score of 1. These values were then summed to create a composite score. Figure 1 provides a graphic of the analyses completed for each metal; reference range and quartile cut-offs can be found in Supplemental Table 1.

3. Results

All of the 20 metals analyzed were detected and 10 (Sb, Co, Cs, Cu, Pb, Mo, Rb, Se, Sr, Ti, and Zn) were detected in all 357 cord blood samples. Their distributions are shown in Table 1.

Many of the metals were significantly correlated; Spearman correlation coefficients are shown in Figure 2. Ba and Cd were the most strongly correlated metals (ρ=0.70, $p<0.001$). Cs and Rb (ρ=0.68, $p<0.001$), Ba and Cr (ρ=0.64, $p<0.001$), and Se and Zn (ρ=0.63, $p<0.001$) were also strongly correlated. On average, infant cord blood samples had nearly 8 metals (mean [SD] = 7.83 [1.60]; range= 4–14) that did not fall within the reference range.

Demographic characteristics of the study population are given in Table 2. Demographic data was collected for 229 infants. Nearly one-third of the study population self-identified as living in an urban area, while the other two-thirds lived in a rural area. Approximately 40% of parents had only a middle school education or less. Over half of the mothers were employed outside of the home. The most common paternal occupation (38%) was professional or administrative work. More than half of fathers surveyed reported regular or occasional smoking, though the majority (65%) did not smoke inside the home

Statistically significant predictors of metals in cord blood are shown in Table 3. If a metal was significant for either the GLM or logistic models, the results of both models are shown for comparison. The results are largely consistent in direction and trend across model types, even in cases where statistical significance was not reached across model types (Table 3).

The number of family members living in the home was associated with higher exposure to Ba and overall composite exposure. Infants with larger families had more logBa in their cord blood (β [95% CI] = 0.17 [0.04, 0.30]) and increased odds of cord Ba above the reference range (OR [95% CI] = 1.26 [1.01, 1.57]), compared to infants with fewer family members

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living in the home. Composite exposure to metals also increased with family size (β [95% CI] = 0.16 [0.00, 0.33]).

Lower income was associated with lower exposures to B and overall composite exposure. Infants born into low income families had less logB in their cord blood (β [95% CI] = −0.25 [−0.40, −0.09], decreased odds of cord B in the upper quartile (OR [95% CI] = 0.31 [0.11, 0.90]), and increased odds of cord B in the lower quartile (OR [95% CI] = 2.92 [1.26, 6.79]), compared to infants whose families were high income. Composite exposure to metals was also less in low-income families (β [95% CI] = −0.82 [−1.42, −0.22]).

Maternal occupation was significantly associated with Hg in cord blood across models (Table 3). Infants with mothers who worked outside the home had higher logHg in their cord blood (β [95% CI] = 0.30 [0.06, 0.55]) and increased odds of cord Hg in the upper quartile (OR [95% CI] = 1.89 [1.02, 3.51]), compared to infants whose mothers were housewives.

Paternal education, occupation, and self-reported metals exposure at work were also consistently, significantly associated with metals in cord blood across models (Table 3). Infants with less educated fathers (middle school or less) had lower logHg in their cord blood (β [95% CI] = −0.39 [−0.68, −0.09]) and lower odds of cord Hg in the upper quartile (OR [95% CI] = 0.49 [0.24, 0.98]), compared to infants with more educated fathers (college). Infants whose fathers were industrial managers had higher logBa in their cord blood (β [95% CI] = 0.63 [0.09, 1.16]) and higher odds of cord Ba above the reference range (OR [95% CI] = 2.61 [1.12, 6.06]), compared to infants whosefathers were professional or administrative personnel. Infants whose fathers self-reported exposure to metals at work also had higher logBa in their cord blood (β [95% CI] = 0.71 [0.01, 1.41]) and higher odds of Ba above the reference range (OR [95% CI] = 4.04 [1.29, 12.64]), compared to infants with fathers did not report metal exposure.

Season was also highly predictive of metals in umbilical cord blood (Table 3). As and Co were significantly elevated in infants born in the spring, which was consistent across analyses. Infants born in the spring had about 0.1–0.2 μg/L higher logAs and logCo in their cord blood (β [95% CI] = 0.22 [0.01, 0.42] and 0.11 [0.01, 0.22], for As and Co, respectively) and over twice the odds of cord As and Co in the upper quartile (OR [95% CI] = 2.10 [1.12, 3.92] and 2.19 [1.17, 4.09], for As and Co, respectively), compared to infants born in the fall/winter.

Similarly, Sb, B, Hg, and Zn were significantly higher in infants born in the summer, which was consistent across analyses. Infants born in the summer had higher Sb, logB, logHg, and logZn in their cord blood (β [95% CI] = 0.74 [0.24, 1.24], 0.11 [0.00, 0.21], 0.29 [0.08, 0.49], 0.18 [0.06, 0.31], for Sb, B, Hg, and Zn respectively), over twice the odds of cord Sb, B, and Hg in the upper quartile (OR [95% CI] = 2.16 [1.19, 3.92], 2.14 [1.17, 3.92], and 2.15 [1.23, 3.76], for Sb, B, and Hg, respectively), and lower odds of cord Zn below the lower reference range cut-off (OR [95% CI] = 0.43 [0.20, 0.90]), compared to infants born in the fall/winter.

Al, Cr, Se, and Sr were not associated with any of the predictors for any of the models explored here.

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4. Discussion

Here we report exposure profiles for 20 toxic and essential metals in the umbilical cord plasma of Chinese infants from Zhejiang province. In our analysis of predictors of prenatal metal exposure, season was perhaps the most significant predictor of metals in umbilical cord blood. As and Co were significantly elevated in infants born in the spring, while, Sb, B, Hg, and Zn were significantly higher in infants born in the summer, compared to infants born in the Fall/Winter. We also found that infants with mothers who worked outside the home were more likely to have elevated cord blood Hg levels, while infants with less educated fathers had lower cord Hg. Paternal occupation was similarly associated with heavy metals detected in infant cord blood. Barium was elevated in infants whose fathers were mid- to high-level industrial managers, and infants whose fathers reported work-related metals exposure had higher Ba and Cd in their cord blood. The composite analysis revealed that low-income families seemed to have lower overall exposure to metals. Results of the demographic predictors analyses were largely consistent in direction and trend across models.

Of the 20 metals measured in this study, 16 have been previously measured in cord blood in China (Hu et al., 2015; Liang et al., 2017; Tang et al., 2016a; Tang et al., 2016b; Wang et al., 2016; Yang et al., 2013; Yu et al., 2011; Yu et al., 2014; Zheng et al., 2014) and five have been measured in U.S. cohorts (Claus Henn et al., 2017; Claus Henn et al., 2012; Greene and Ernhart, 1991; King et al., 2013; Korpela et al., 1986; Lederman et al., 2008; Zota et al., 2009). For the Chinese studies, we were able to find at least one value in cord serum or plasma for 14 of the 20 metals measured here. We could not find values for any of the metals in cord blood serum or plasma in the U.S. for comparison. In general, the values found in the current study are comparable to those previously reported from varying locations around China. Table 4 compares the 75th percentiles of exposure for the current study with the other available Chinese studies.

The Tang studies reported 75th percentile Cd, Hg, and Se levels that were 14–70 times higher than were observed in the current study (Tang et al., 2016a; Tang et al., 2016b). This may be a result of geographical and/or environmental variation between the two cohorts.

To compare to the U.S., we can roughly use the reference ranges for U.S. adult plasma/ serum levels. Nearly all of our infants had Cu (n=356) and Se (n=353) concentrations below the U.S. adult reference range (Supplemental Table 1). While the levels of these essential nutrients in U.S. adult peripheral blood may not be directly comparable to the cord blood of Chinese infants, this finding is still telling. These trace elements are essential for proper fetal growth and development (Chan et al., 1998; Hurley, 1981; Kantola et al., 2004; Linder, 1991; Pieczynska and Grajeta, 2015), and deficiencies in these important nutrients may affect the health of our cohort. In contrast, nearly all of our infants had Sb (n=356), B (n=357), Rb (n=339), and Ti (n=357) that were above the U.S. adult reference ranges (Supplemental Table 1). While B and Rb may play a small, yet still unknown, role in fetal growth (Maynar et al., 2017), Sb, and Ti are believed to have no physiological purpose in the body and high levels of exposure could be potentially toxic.

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Of the prior Chinese studies, the one by Yu and colleagues included the most robust analysis of demographic predictors of prenatal metals exposure (Yu et al., 2011). They found that living in the suburbs was protective for cord Cd and As and that maternal occupation and maternal passive smoking were associated with cord As. Here, we did not see any associations between place of residence (rural/urban) and any of the metals examined. We also did not see any associations between As and maternal occupation or paternal smoking. Instead, we found elevated cord blood Hg levels in infants whose mothers worked outside the home. While we did not have any information on all sources of maternal passive smoking, we did examine father's smoking habits and found that infants with fathers who were regular smokers had lower Cs levels in their cord blood, compared to infants whose fathers did not smoke. Yu and colleagues did not find any significant associations with maternal age, income or maternal/paternal education in their Shanghai cohort (Yu et al., 2011). It is likely that these differences in findings are due to differences in environment, diet, and lifestyle between Shangai and Fuyang County, where our subjects reside.

With the exception of Yu et al., 2011, which examined paternal education, the previous Chinese studies did not include analyses of relations between paternal demographics and cord blood metals. Here we found elevated cord Ba in infants whose fathers held mid- to high-level managerial positions in industry, compared to infants whose fathers were employed in a professional or administrative setting. This finding may be due to differences in workplace environments between the job categories. For example, a manager of an industrial factory may be more likely to be exposed to heavy metals, like Ba (ATSDR, 2007), resulting in higher take-home exposures, compared to someone working in a professional or administrative position. We also found that infants whose fathers reported being exposed to metals at work had higher Ba and Cd in their cord blood, though this result should be interpreted with caution given the small number of men who reported this exposure (n=14). Though the work categories are broad, and sample of fathers who self-reported metals exposure was small, it is still interesting that, in addition to maternal occupation, paternal occupation was also associated with cord metals. Unlike Yu, et al., we also saw an association between paternal education and cord Hg levels. Infants whose fathers had less education had lower exposure to Hg, when compared to infants with more educated fathers. In Fuyang, it may be that lower socioeconomic status families eat less fish and may therefore be exposed to less Hg. Interestingly, we did not see an increase in heavy metals like Cd in the cord blood of infants whose fathers were smokers. This may reflect the fact that the majority of fathers in our cohort (64.6%) did not smoke in the home, resulting in less passive exposure for the mother and fetus.

To our knowledge, this is the first study to examine season of birth as a predictor of umbilical cord metals. We had previously found season to be an important predictor of prenatal pesticide exposure in this cohort (Silver et al., 2016b). Heavy metals in the environment have been shown to vary by season and location in China (Yao et al., 2014; Zhen et al., 2016), and essential nutrients are also likely to fluctuate with season as diets in this region tend to be almost entirely locally sourced. Concentrations of atmospheric metals are known to vary based on local industrial emissions, coal combustion patterns, e-waste incineration, and traffic sources (Qi et al., 2016). Here we found statistically significant seasonal variations in the concentrations of Sb, As, B, Co, Hg and Zn in the umbilical cord

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plasma of newborns. Antimony (Sb), As, and Zn, measured in atmospheric $PM_{2.5}$ samples, have been previously shown to vary by season in Nanjing, China (Qi et al., 2016), though the seasonal variation differed from what we observed in the current study. For example, our Zhejiang infants born in the spring had higher As in their cord blood, while atmospheric As was highest in the winter; infants born in the summer had higher Sb and Zn in their cord blood while atmospheric Sb was highest in the winter, while atmospheric Zn was highest in the autumn (Qi et al., 2016). These discrepancies in the findings are likely due to differences in the point sources in Zhejiang versus Nanjing. Also, the Nanjing $PM_{2.5}$ study used short time periods (five to 15 days) to define "season", which also likely accounts for some of the observed differences.

There were some limitations to this study. While plasma is appropriate for the detection of many of the metals analyzed here, others tend to sequester in red blood cells, making a whole blood a better choice (Schultze et al., 2014). In general, metals detection tends to be lower in serum or plasma than in whole blood (Schultze et al., 2014), which may have contributed to a greater prevalence of non-detects for some of the metals (eg: Ni, Cr, Cd). Additionally, the LOD for Al was quite high (28.3 μg/L) and the resulting large number of non-detects limited our ability to explore predictors of lower, more normal levels of prenatal exposure. Similarlyly, while the use of biologically plausible reference cut-offs for this analysis is potentially useful to provide added context, these cut-offs were assigned based on tests designed for adult peripheral blood and may not be completely appropriate for umbilical cord blood samples. Additionally, the demographic information used in this study is limited in that it was not originally collected as part of an environmental or occupational exposure study. Therefore, some of information collected, such as for paternal occupation, for example, was quite broad and nonspecific, making it difficult to differentiate between the job categories and limiting our ability to draw substantive conclusions. Finally, we performed many statistical analyses and it is possible that some of our findings may be attributable to chance.

Despite its limitations, this work has some important strengths. To our knowledge, this is the most comprehensive exposure assessment of prenatal exposure to metals in China, to date, examining 20 metals, both toxic and essential. In addition, this work also presents some previously unexplored predictors of prenatal metals exposure in China. The prior studies that have included analyses on the determinants of prenatal metals exposure were largely limited to a few basic maternal characteristics. Here we explored a number of household variables, as well as potentially important, previously unexplored, paternal factors, and the effects of season on cord blood metal concentrations.

5. Conclusions

In conclusion, we reported metals exposure profiles for 20 toxic and essential metals in the cord blood plasma of 357 Chinese infants from Zhejiang province. We further examined a variety of demographic predictors of prenatal metal exposure and found that maternal and paternal occupation, paternal education, and season of birth were consistent predictors of metals in umbilical cord blood across analyses. Prenatal exposure to metals is a concern because of the important developmental implications. Prenatal exposure to both toxic heavy

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metals and trace metal deficiencies have been associated with negative neurodevelopmental effects in childhood. While China is believed to be a highly exposed population, prenatal exposure to these metals and the possibility of trace nutrient deficiencies are concerns worldwide.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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- Exposure to heavy metals or trace metal deficiencies/excesses can impact health.
- We measured 20 toxic and essential metals in the cord blood of Chinese infants.
- 10 metals (Sb,Co,Cs,Cu,Pb,Mo,Rb,Se,Sr,Ti,Zn) were detected in all blood samples.
- Birth season and parent occupation were associated with infant cord blood metals.

	Al																		
Sb	-0.04	Sb																	
As	0.05	0.08	As																
B	0.06	0.27	0.28	B															
Ba	0.52	0.06	0.17	0.07	Ba														
Cd	0.42	0.08	0.06	0.04	0.70	Cd													
Cr	0.52	0.32	0.18	0.13	0.64	0.56	Cr												
Cs	-0.09	0.34	0.13	0.30	-0.02	0.01	0.08	Cs											
Co	0.15	0.24	0.21	0.30	0.24	0.25	0.30	0.27	Co										
Cu	0.04	0.37	0.17	0.38	0.08	0.01	0.11	0.33	0.30	Cu									
Pb[1]	0.02	-0.01	0.03	-0.03	-0.09	-0.07	0.01	-0.08	-0.02	0.02	Pb[1]								
Mn	0.44	0.24	0.26	0.16	0.51	0.30	0.67	0.07	0.21	0.16	-0.05	Mn							
Hg	-0.03	0.20	0.21	0.27	0.04	0.02	0.04	0.12	0.14	0.28	-0.02	0.09	Hg						
Mo	0.01	0.14	0.12	0.33	0.02	-0.07	0.04	0.06	0.18	0.14	0.07	0.02	0.12	Mo					
Ni	0.09	0.28	0.11	0.03	0.19	0.14	0.35	0.05	0.24	0.07	0.13	0.29	-0.01	0.20	Ni				
Rb	-0.07	0.47	0.08	0.20	0.03	0.05	0.12	0.68	0.31	0.38	0.02	0.09	0.23	0.05	0.09	Rb			
Se	0.08	0.46	0.31	0.45	0.16	0.17	0.37	0.25	0.27	0.48	-0.05	0.33	0.37	0.02	0.15	0.33	Se		
Sr	0.29	0.21	0.30	0.32	0.37	0.28	0.38	0.14	0.32	0.33	-0.01	0.37	0.19	0.17	0.14	0.14	0.36	Sr	
Ti	0.30	0.36	0.20	0.45	0.35	0.27	0.39	0.26	0.32	0.52	-0.06	0.35	0.34	0.20	0.07	0.38	0.55	0.57	Ti
Zn	0.07	0.55	0.15	0.38	0.18	0.15	0.30	0.34	0.30	0.41	-0.13	0.35	0.34	0.03	0.22	0.44	0.63	0.31	0.53

$p<0.05$

$p<0.01$

$p<0.001$

Figure 1.

Outline of analyses

1 Log-transformed

2 Used upper and lower reference range cut-offs rather than quartile cut-offs

3 Calculated as the sum of all metals with concentrations outside of the reference range (metals within the reference range were assigned a score of 0, metals outside the reference range [above or below] were assigned a score of 1)

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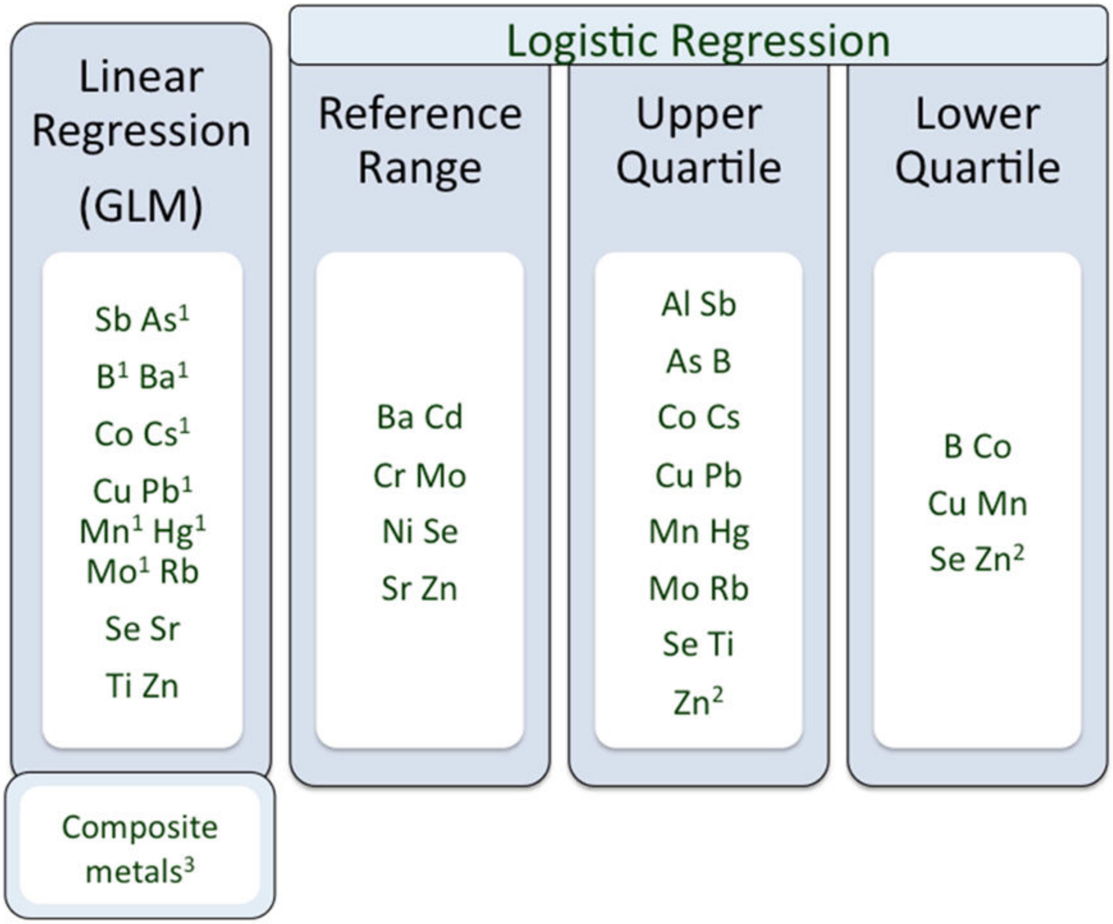

Figure 2.

Spearman correlation coefficients

1 Measured in whole blood

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Table 1.

Distribution of metal concentrations in umbilical cord plasma (μg/L) at delivery, Zhejiang Province, China (n=357)

			Percentiles						
Metal	**LOD**	**n > LOD (%)**	**10th**	**25th**	**Median**	**75th**	**90th**	**95th**	**Max**
Aluminium (Al)	28.3	83 (23.2)	<LOD	<LOD	<LOD	<LOD	47.4	97.3	305.9
Antimony (Sb)	0.02	357 (100)	3.3	4.2	5.4	6.7	8.2	9.4	13.5
Arsenic (As)	0.06	356 (99.7)	0.3	0.4	0.7	1.1	2.1	3.0	27.2
Boron (B)	6.9	352 (98.6)	10.9	13.8	18.3	23.5	30.3	34.8	70.6
Barium (Ba)	0.44	335 (93.8)	0.7	2.2	5.6	12.4	32.1	73.8	194.7
Cadmium (Cd)	0.15	142 (39.8)	<LOD	<LOD	<LOD	0.6	3.8	8.0	99.4
Cobalt (Co)	0.03	357 (100)	0.2	0.2	0.3	0.4	0.5	0.6	3.0
Chromium (Cr)	0.26	235 (65.8)	0.2	0.2	0.5	1.3	2.5	4.9	54.0
Cesium (Cs)	0.01	357 (100)	0.8	1.0	1.2	1.6	2.0	2.2	6.3
Copper (Cu)	0.40	357 (100)	169.4	197.8	242.9	289.8	348.2	395.5	1440.3
Lead (Pb)[1]	0.08	357 (100)	17.0	22.5	30.0	37.0	44.0	49.0	97.0
Mercury (Hg)	0.06	298 (81.0)	<LOD	0.1	0.2	0.3	0.4	0.6	1.2
Manganese (Mn)	0.12	355 (99.4)	1.7	2.7	4.2	6.6	11.6	15.2	2845.7
Molybdenum (Mo)	0.08	357 (99.7)	0.5	0.7	0.9	1.3	1.7	2.0	5.1
Nickel (Ni)	0.31	226 (63.3)	<LOD	<LOD	0.7	2.9	9.0	12.4	278.9
Rubidium (Rb)	0.07	357 (100)	688.7	875.6	1037.8	1325.7	1589.6	1687.8	2456.5
Selenium (Se)	0.17	357 (100)	23.6	28.3	35.1	47.9	56.5	60.4	1350.1
Strontium (Sr)	0.32	357 (100)	23.8	27.4	33.5	42.1	52.6	62.0	115.5
Titanium (Ti)	0.07	357 (100)	168.8	186.9	205.6	227.4	250.9	279.8	339.1
Zinc (Zn)	4.7	357 (100)	584.2	742.8	955.2	1254.5	1656.6	1908.8	3009.0

[1]Measured in whole blood

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Table 2.

Family and household characteristics of the study population

Categorical Predictors	N	N (%)	Continuous Predictors	N	Mean (SD)	Range
Household			Household			
Place of residence:	224		# Family in home	228	5.1 (1.3)	1–11
Rural		141 (65.3)	Living space (m^2)	223	210.9 (145.3)	18–720
Urban		75 (34.7)	Maternal			
Annual income (Yuan):	222		Age (years)	224	26.2 (4.0)	18–41
<30,000		46 (20.7)	Paternal			
20,000–49,999		43 (19.4)	Age (years)	213	28.5 (4.6)	19–47
50,000–99,999		66 (29.7)				
≥100,000		67 (30.2)				
Maternal						
Education:	229					
Middle school or less		90 (39.3)				
High school/secondary school		66 (28.8)				
College		73 (31.9)				
Occupation:	229					
Housewife		95 (41.5)				
Other		134 (58.5)				
Paternal						
Education:	217					
Middle school or less		89 (41.0)				
High school/secondary school		61 (28.1)				
College		67 (30.9)				
Occupation:	216					
Industry manager		32 (14.8)				
Factory/industrial worker		32 (14.8)				
Professional/administrator		83 (38.4)				
Other		69 (31.9)				
Smoking habits:	212					
Regular (>10 cigs/day)		58 (27.4)				
Occasional (≤10 cigs/day)		63 (29.7)				
Never		91 (42.9)				
Smokes indoors:	212					
Ever		75 (35.4)				
Never		137 (64.6)				
Occupational metal exposure:	186					
Ever		14 (7.5)				
Never		172 (92.5)				
Seasonal						
Birth season:	356					

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Categorical Predictors	N	N (%)	Continuous Predictors	N	Mean (SD)	Range
March - May		105 (29.5)				
June - September		134 (37.6)				
October - February		117 (32.9)				

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Table 3.

Statistically significant[1] predictors of prenatal metals exposure

	Linear Reg. (GLM) Results	Logistic Reg. Results[2]
Predictor	**Effect estimate (95% CI)**	**OR (95%)**
Household Characteristics		
Number in family	logB: 0.03 (−0.02, 0.07) logBa: 0.17 (0.04, 0.30) * Cd: N/A Ti: 5.44 (1.43, 9.45) ** Comp. metals: 0.16 (0.00, 0.33) **	LQ B: 0.77 (0.60, 0.99) * RR Ba: 1.26 (1.01, 1.57) * RR Cd: 1.28 (1.01, 1.62) * UQ Ti: 1.16 (0.92, 1.46)
Income: <30,000 Yuan vs. ≥100,000 Yuan	Sb: −1.18 (−1.95, −0.40) ** logB: −0.25 (−0.40, −0.09) ** logBa: −0.38 (−0.87, 0.11) logZn: −0.21 (−0.43, 0.01) Comp. metals: −0.82 (−1.42, −0.22) *	UQ Sb: 0.49 (0.22, 1.11) UQ B: 0.31 (0.11, 0.90) * LQ B: 2.92 (1.26, 6.79) * RR Ba: 0.41 (0.17, 0.99) * UCO Zn: 0.30 (0.14, 0.69) *
Maternal Characteristics		
Age in years	logMn: −0.03 (−0.06, −0.01) * logMo: 0.02 (0.00, 0.04) * Rb: 11.83 (−0.82, 24.47)	UQ Mn: 0.95 (0.89, 1.03) UQ Mo: 1.05 (0.97, 1.13) UQ Rb: 1.10 (1.02, 1.18) *
Occupation: Job outside of home vs. Housewife	logAs: 0.21 (0.02, 0.41) * log Hg: 0.30 (0.06, 0.55) *	UQ As: 1.83 (0.98, 3.30) UQ Hg: 1.89 (1.02, 3.51) *
Paternal Characteristics		
Age in years	Sb: −0.07 (−0.14, −0.01) * logZn: −0.01 (−0.03, 0.01)	UQ Sb: 0.97 (0.91, 1.04) UCO Zn: 0.93 (0.87, 0.99) *
Education: ≤ Middle school vs. College	logHg: −0.39 (−0.68, −0.09) **	UQ Hg: 0.49 (0.24, 0.98) *
Occupation: Industry manager vs. Professional/admini strato r	logBa: 0.63 (0.09, 1.16) *	RR Ba: 2.61 (1.12, 6.06) *
Factory/industrial worker vs. Professional/administrator	logCs: −0.14 (−0.27, −0.01) * logMn: −0.32 (−0.64, 0.01)	UQ Cs: 0.45 (0.17, 1.15) UQ Mn: 0.30 (0.09, 0.93) *
Paternal Metals Exposure: Ever vs. Never	logBa: 0.71 (0.01, 1.41) * Cd: N/A	RR Ba: 4.04 (1.29, 12.64) * RR Cd: 3.41 (1.13, 10.32) *
Paternal smoking: Ever vs. Never	logCs: −0.08 (−0.21, 0.05)	UQ Cs: 0.43 (0.20, 0.95) *
Seasonal Characteristics		
Birth Season: Spring vs. Fall/Winter	logAs: 0.22 (0.01, 0.42) * logCo: 0.11 (0.01, 0.22) *	UQ As: 2.10 (1.12, 3.92) * UQ Co: 2.19 (1.17, 4.09) *
Summer vs. Fall/Winter	Sb: 0.74 (0.24, 1.24) ** logB: 0.11 (0.00, 0.21) * logCu: 0.07 (−0.01, 0.14) logPb: −0.07 (−0.16, 0.02) logHg: 0.29 (0.08, 0.49) ** Ni: N/A Rb: 119.11 (26.35, 211.87) * logZn: 0.18 (0.06, 0.31) **	UQ Sb: 2.16 (1.19, 3.92) * UQ B: 2.14 (1.17, 3.92) * LQ Cu: 0.54 (0.30, 0.97) * UQ Pb: 0.51 (0.28, 0.92) * UQ Hg: 2.15 (1.23, 3.76) *** RR Ni: 0.48 (0.27, 0.83) ** UQ Rb: 1.74 (0.97, 3.13) LCO Zn: 0.42 (0.20, 0.90) **

* $p < 0.05$;

** $p < 0.01$;

*** $p < 0.001$

RR: Reference range; UQ: upper quartile; LQ lower quartile; UCO: Upper RR cut-off; LCO: Lower RR cut-off

[1]- If a metal was statistically significant (p<0.05) for either the GLM or logistic models, the results of both models are shown for comparison

[2] RR shows the odds of a having a metal concentration outside the RR versus within the RR; UQ shows the odds of having a metal concentration in the UQ versus in the lower three quartiles; LQ shows the odds of having a metal concentration in the LQ versus in the upper three quartiles; UCO shows the odds of having a metal concentration above the upper RR cut-off versus below the upper cut-off; LCO shows the odds of having a metal concentration below the lower RR cut-off versus above the lower cut-off

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Table 4.

Comparison of plasma/serum cord blood samples from the current study and previously published studies in China (μg/L)[1]

	Cord plasma/serum concentrations (Mμ/L)[1]	
Metal	**Current study**	**Chinese studies**
Aluminum (Al)	ND	64.9[a]
Arsenic (As)	1.1	3.1[a]; 12.9[3;b]; 375.5[max;h]
Barium (Ba)	12.4	19.4[a]
Cadmium (Cd)	0.6	0.1[a]; 1.0[3;b]; 13.3[c]; 1.7–1.8[e]; 6.5[max;h]
Cobalt (Co)	0.4	0.4[a]; 1.3[3;b]
Chromium (Cr)	1.3	3.2[a]
Copper (Cu)	289.8	368.5[a]; 672.3[d]
Lead (Pb)[2]	37.0	32.0–33.0[I]; 41.7–50.6[j]; 351.0[max;h]
Mercury (Hg)	0.3	0.5[a]; ND[b]; 27.6[c]
Manganese (Mn)	6.6	6.7[a]; 34.6[d]; 9.0[f]
Molybdenum (Mo)	1.3	1.3[a]
Nickel (Ni)	2.9	2.0[a]; 2.5[3;b]
Selenium (Se)	47.9	53.7[a]; 161.8[3;b]; 721.0[d]; 1.9[g]
Zinc (Zn)	1254.5	1011.2[a]; 4180.0[d]; 3.1[g]

[1] 75th percentiles shown unless labeled “max” for maximum

[2] Measured in whole blood

[3] Estimated value: ng/g converted to μg/L using a conversion factor of 1.03 (the weight of plasma/serum)

[a-] (Liang et al., 2017);

[b-] (Hu et al., 2015);

[c-] (Tang et al., 2016a);

[d-] (Tang et al., 2016b);

[e-] (Wang et al., 2016);

[f-] (Yu et al., 2014);

[g-] (Yang et al., 2013);

[h-] (Yu et al., 2011);

[i-] (Silver et al., 2016a);

[j-] (Zheng et al., 2014)