

Relationship of Blood Levels of Pb with Cu, Zn, Ca, Mg, Fe, and Hb in Children Aged 0~6 Years from Wuhan, China

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Abstract The aim of this study was to investigate the relationship of blood lead (Pb) levels with copper (Cu), zinc (Zn), calcium (Ca), magnesium (Mg), iron (Fe), and hemoglobin (Hb) in children aged from 0–6 years in Wuhan, China. A total of 1047 children from six communities, which were randomly selected in Wuhan city and three communities, located in the urban area and others in the suburban area, were recruited for this study between November 2012 and July 2013. The levels of elements in the blood were detected using an atomic absorption spectrometer, and Hb level was tested by an automated hematology analyzer. The results showed that the mean blood lead level (BLL) is $33.72 \pm 19.03 \mu\text{g/L}$. The BLL was significantly higher among boys than girls ($P < 0.05$). Higher BLL was also observed in suburbs compared to that in urban areas ($P < 0.05$). The BLL and Zn level were gradually increased with age. The elevated rate of BLL in children was 20.9 %, while the Zn deficiency rate was 65.0 %. And, the level of Hb in higher BLL group was significantly lower. Negative correlations of the blood levels of Pb with those of Cu ($r = -0.087$, $P = 0.005$), Mg ($r = -0.102$, $P = 0.001$), and Fe ($r = -0.091$, $P = 0.003$) were observed. These data suggested

that the elevated rate of BLL in children from Wuhan is still higher according to the updated reference values in the USA. The deficiency of Cu, Mg, and Fe may indicate the elevation of lead absorption. The dietary supplement of Zn, Ca, and Fe in children requires more attention.

Keyword Blood · Children · Lead · Essential element · Hemoglobin

Introduction

Lead, as a metal element, is found ubiquitously in the environment, and its adverse effect on human health is an important global environmental problem [1, 2]. Floating in the air or attaching to objects, Pb can be absorbed into the human body through the respiratory tract, gastrointestinal tract, or skin. Exposure to high level of lead could harm nearly every system in the body, such as gastrointestinal, hematopoietic, cardiovascular, immune, reproductive, excretory system [3–7], and particularly the nervous system, which is the most sensitive target [8, 9]. Children are more vulnerable than adults to lead exposure because of the growth and development of their neurological and behavioral characteristics [9–11]. Even low levels of lead exposure are associated with impairment of childhood cognitive function and abnormal infant behaviors [12, 13]. Childhood with elevated blood lead levels (BLLs) may result in behavioral disturbances, learning, and concentration difficulties [14].

Essential elements like Cu, Zn, Ca, Mg, and Fe play important roles in the regulation and maintenance of various physiological functions in the human body despite low requirements of them [15]. These elements are key components of metalloenzymes, and they are involved in crucial biological functions, such as oxygen transport, free radical scavenging, and hormonal activity [16]. Their blood levels are often

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considered as an important modifier of the metabolism and toxicity of heavy metals such as lead [17]. Previous study showed that low dietary intakes of Fe, Zn, Cu, and Ca in children have been associated with increased BLLs [18], but the correlation between BLLs and essential elements is not well understood. Besides, lead exposure has an influence on the hematological system. Decreasing trend of the hemoglobin level has been found with increasing BLLs in children [19, 20].

In this study, we evaluated the concentrations of Pb, Cu, Zn, Ca, Mg, Fe, and Hb in the blood of children aged 0–6 years from Wuhan, China. The aim was to analyze the blood level of these elements and hemoglobin in different genders, residential areas, and age groups and to investigate the relationship of BLLs with Cu, Zn, Ca, Mg, Fe, and Hb in those children.

Materials and Methods

Study Population

Six communities (an administrative region delimited by the government of Wuhan city) in this study were randomly selected in Wuhan city. Three communities were located in the urban area, and others were in the suburban area. Children aged 0–6 years in these communities were recruited for this study between November 2012 and July 2013. The study population consisted of 1047 children (602 boys and 445 girls; 654 from the urban area and 393 from the suburban area). Subjects were divided into five age groups: 0-year-old group, $N=455$; 1-year-old group, $N=214$; 2-year-old group, $N=122$; 3-year-old group, $N=104$; and 4–6-year-old group, $N=162$.

The procedures of the study were explained to all the participants and their parents before informed consent were signed. The experimental protocol was reviewed and approved by the Medical Ethics Committee of School of Medicine, Wuhan University.

Sample Collection and Analysis

Blood samples were collected in the Community Health Center and then analyzed in the lab of Renmin Hospital at Wuhan University. One venous blood sample was collected in a vacuum tube (BD, USA) containing EDTA-K2 for hemoglobin detection. Hemoglobin concentrations were determined immediately using an automated hematology analyzer (ADVIA™ 120, Bayer, USA) according to the reference method for hemoglobinometry in human blood by the National

Health and Family Planning Commission of the People's Republic of China in 2011.

Another fasting venous blood sample was collected into a lead-free vacuum tube (BD, USA) containing heparin sodium for element detection. Then, 80 μL of whole blood sample was added to the special tube with 5 % HNO_3 and immediately vortexed before storage at 0–4 °C until further analysis. The analysis of all samples was conducted in the same laboratory. Precaution was taken to avoid contamination. Tubes and glassware were soaked in 10 % nitric acid solution for 24 h and rinsed five to six times with ultra-pure double-distilled deionized water. As part of contamination control, all reagents, glassware, and sample collection devices were checked for contamination with selected elements. The whole blood levels of Pb were detected using graphite furnace atomic absorption spectrometer (283.3 nm) equipped with tungsten atomizer (BH2100, Bohui, China). The concentrations of Cu, Zn, Ca, Mg, and Fe were measured by flame atomic absorption spectrometer (BH5100, Bohui, China) using hollow cathode lamps (324.7, 213.9, 422.7, 285.2, and 248.3 nm for Cu, Zn, Ca, Mg, and Fe, respectively). Each sample was analyzed in duplicate, and the mean of both measurements was used as the final value.

Quality controls were ensured by analyzing reference materials provided by General Administration of Quality, Inspection and Quarantine of the People's Republic of China (GBW(E) 090033, 090034, 090035, and 090036 for lead and GBW(E) 080915, 080916, and 080917 for Cu, Zn, Ca, Mg, and Fe). Reference samples were analyzed before and after ten routine sample measurements. The values of these reference samples were in agreement with the provided ranges.

Elevated BLL was defined as higher than 50 $\mu\text{g/L}$ according to the recommendation of the US CDC Advisory Committee on Childhood Lead Poisoning Prevention [21]. Other reference values of whole blood used in this lab were as follows: Cu 0.75–2.50 mg/L; Ca 62–84 mg/L; Mg 27.2–50.1 mg/L; Fe 420–660 mg/L; Zn 3.79–6.54 mg/L (0–1 year), 4.05–7.19 mg/L (1–2 years), 4.32–7.85 mg/L (2–3 years), 4.71–8.50 mg/L (3–4 years), and 5.00–11.12 mg/L (4–13 years); and Hb 11–16 g/dL.

Statistical Analysis

Data are expressed as mean \pm SD (standard deviation). As to the normally distributed data, such as the concentrations of Cu, Zn, Ca, Mg, Fe, and Hb, Student's *t* test was used to compare the difference of the two groups. And, differences of means in multiple groups were compared using one-way ANOVA, followed by LSD test for multiple pairwise comparisons. While as non-

Table 1 The blood levels of Pb, Cu, Zn, Ca, Mg, Fe, and Hb in children ($N=1047$)

	Mean±SD	Min	Max	GM	Median	P25	P75
Pb ($\mu\text{g/L}$)	33.72±19.03	4.72	96.49	26.81	33.98	19.82	45.96
Cu (mg/L)	1.15±0.30	0.11	2.30	1.12	1.05	0.92	1.37
Zn (mg/L)	3.91±1.09	1.14	7.74	3.76	3.96	3.27	4.47
Ca (mg/L)	66.53±7.21	44.89	84.97	66.13	66.53	62.12	71.34
Mg (mg/L)	37.67±4.37	27.46	50.79	37.42	37.67	34.26	40.82
Fe (mg/L)	454.62±64.79	93.83	816.53	450.15	447.36	412.17	494.83
Hb (g/L)	12.78±1.56	8.4	22.2	12.7	12.6	12.0	13.3

Gaussian distributed data, the difference in BLLs was assessed by nonparametric tests. Chi-square tests were used to examine the discrepancy and the trend of different group rates. Partial correlation tests were used to demonstrate the relationships of BLLs with Cu, Zn, Ca, Mg, Fe, and Hb in children. A $P<0.05$ was considered statistically significant. The statistical analyses were conducted using SPSS version 13.0 (SPSS Inc., Chicago, IL, USA).

Results

Concentration of Metal Elements and Hemoglobin in the Blood

The descriptive data including arithmetic mean, standard deviation, range, geometric mean, median, percentiles 25 and 75 of all elements, and hemoglobin in whole blood of all the participants are summarized in Table 1. BLLs of the children ranged from 4.72 to 96.49 $\mu\text{g/L}$, the mean value was 33.72±19.03 $\mu\text{g/L}$, and the median of BLLs was 33.98 $\mu\text{g/L}$. No child had $\text{BLL} \geq 100 \mu\text{g/L}$.

Table 2 presents the comparisons of the whole blood levels of Pb, Cu, Zn, Ca, Mg, Fe, and Hb in different age groups. The BLLs of children in 0- and 1-year-old groups were lower than those of the other three groups ($P<0.05$). The blood concentrations of Pb and Zn both had a tendency to increase with the

age groups. In addition, the blood concentrations of Cu, Ca, Mg, Fe, and Hb in different age groups were also significantly different.

The rates of elevated BLL and deficiencies of Cu, Zn, Ca, Mg, Fe, and Hb in different age groups are shown in Table 3. The elevated BLL rate of all the children is 20.9 %, and the highest rate was 38.3 % of the 4~6-year-old children. Few children were found to have Cu and Mg deficiency. On the other hand, the deficiencies of Zn, Ca, Fe, and Hb were common. In general, 65.0 % of the children were Zn-deficient. The deficiency rates of Ca, Fe, and Hb were 23.4, 28.9, and 7.2 %, respectively. Chi-square test results revealed that the elevated BLL rates increased with age for children aged 0–6 years old in Wuhan, and the deficiency rates of Zn, Ca, Fe, and Hb were also significantly different ($P<0.001$).

Effect of Gender and Residential Area on the Blood Level of Elements and Hemoglobin

Tables 4 and 5 show the blood levels of Pb, Cu, Zn, Ca, Mg, Fe, and Hb by gender and residential area. The BLLs of boys were significantly higher than those of girls (34.12±18.20 vs. 31.18±20.10 $\mu\text{g/L}$, $P<0.05$). Similar results were found in Fe (457.97±68.70 vs. 450.15±59.20 mg/L) and Hb (12.90±1.52 vs. 12.63±1.60 g/dL) ($P<0.05$, $P<0.01$, respectively). However, the blood levels of Cu and Zn in boys were slightly lower than those in girls (Cu, 1.14±0.27 vs. 1.18±0.33 mg/L ;

Table 2 The blood levels of Pb, Cu, Zn, Ca, Mg, Fe, and Hb in different age groups

Age group	<i>N</i>	Pb ($\mu\text{g/L}$)	Cu (mg/L)	Zn (mg/L)	Ca (mg/L)	Mg (mg/L)	Fe (mg/L)	Hb (g/dL)
0	455	30.57±17.68 a	1.11±0.27 a	3.30±0.95 a	65.73±8.42 a	37.18±4.62 a	464.11±78.19 a	13.17±2.15 a
1	214	33.75±18.45 a	1.23±0.30 b	3.96±0.70 b	69.34±4.81 b	37.67±3.89 a	439.54±45.24 b	12.46±0.79 b
2	122	36.55±19.46 b	1.12±0.32 a	4.36±0.67 c	70.14±6.41 b	39.37±4.62 b	456.29±50.82 a	12.31±0.71 b
3	104	37.28±18.04 b	1.13±0.36 a	4.23±1.11 c	65.33±7.21 a	37.91±3.65 a	435.07±60.88 b	12.48±0.74 b
4~6	162	37.92±22.10 b	1.21±0.28 b	4.98±1.04 d	64.53±5.61 a	37.91±3.89 a	460.76±50.27 a	12.73±0.83 b
Total	1047	33.72±19.03	1.15±0.30	3.91±1.09	66.53±7.21	37.67±4.37	454.62±64.79	12.78±1.56

Mean values marked with different letters at the same column were significantly different based on multiple pairwise comparisons ($p<0.05$)

Table 3 The rates of elevated BLL and deficiency of Cu, Zn, Ca, Mg, Fe, and Hb in different age groups (%)

Age group	<i>N</i>	Pb ≥ 50 $\mu\text{g/L}$ (%)	Cu < 0.75 mg/L (%)	Zn ^a mg/L	Ca < 62 mg/L (%)	Mg < 27.2 mg/L (%)	Fe < 420 mg/L (%)	Hb < 11 g/dL (%)
0	445	14.6	0	72.1	32.1	0	28.8	10.1
1	214	15.0	0	56.5	4.7	0	40.2	5.6
2	122	25.4	0.8	49.2	13.1	0	19.7	6.6
3	104	27.9	1.9	81.7	27.9	0	28.8	4.8
4~6	162	38.3	0	58.0	29.0	0	21.6	3.1
Total	1047	20.9	0.3	65.0	23.4	0	28.9	7.2

^a Means Zn < 3.79 mg/L (0~1 year), 4.05 mg/L (1~2 years), 4.32 mg/L (2~3 years), 4.71 mg/L (3~4 year), and 5.00 mg/L (4~6 years) in accordance with the reference value in different age groups

Zn, 3.81 ± 1.09 vs. 4.05 ± 1.08 mg/L) ($P < 0.05$, $P < 0.01$, respectively). No gender differences were found in other elements. On the other hand, lower BLLs were found in the children from the urban group than the suburban group (30.73 ± 18.06 vs. 33.38 ± 18.00 $\mu\text{g/L}$, $P < 0.05$). The blood concentrations of Cu in the children from urban area were higher than suburban area (1.19 ± 0.31 vs. 1.10 ± 0.27 mg/L) ($P < 0.01$), whereas the blood levels of Mg, Fe, and Hb (Mg, 37.42 ± 4.37 vs. 38.15 ± 4.37 mg/L; Fe, 451.27 ± 0.32 vs. 460.76 ± 70.93 mg/L; Hb, 12.67 ± 1.30 vs. 12.98 ± 1.90 g/dL) of the urban children were significantly lower ($P < 0.01$, $P < 0.05$, $P < 0.01$, respectively).

Correlation Analysis

In order to analyze the effect of Pb on essential elements, we defined the BLL ≥ 50 $\mu\text{g/L}$ as a cut-off value. All the children were divided into two different groups according the BLLs. Table 6 shows the mean values of other elements and Hb concentration of these two groups. The blood zinc levels of children in the BLLs < 50 $\mu\text{g/L}$ group were significantly lower compared to children from BLLs ≥ 50 $\mu\text{g/L}$ group (3.87 ± 1.10 vs. 4.07 ± 1.05 mg/L, $P < 0.05$). On the other hand, the concentrations of Fe and Hb in BLLs < 50 $\mu\text{g/L}$ group were significantly higher than those values in the BLLs ≥ 50 $\mu\text{g/L}$ group (Fe, 458.53 ± 61.44 vs. 441.22 ± 74.28 mg/L; Hb, 12.87 ± 1.57 vs. 12.47 ± 1.48 g/dL; both $P < 0.01$).

After controlling for age, gender, and residential area, partial correlation analysis showed that BLLs were inversely correlated with the blood levels of Cu ($r = -0.087$, $P = 0.005$) as shown in Table 7. Negative correlations were also found

between the blood concentrations of Pb and Mg ($r = -0.102$, $P = 0.001$) and Pb and Fe ($r = -0.091$, $P = 0.003$).

Discussion

Lead exposure is a child health concern around the world, especially in developing countries [22]. The adverse effects of lead on human health are well known, especially for children under 6 years of age [23]. According to the report in 2005 [24], the mean BLL of children aged 0–6 years in Wuhan was 67.39 $\mu\text{g/L}$, while the study in 2011 [25] showed a value of 54.54 $\mu\text{g/L}$ (sample collected between 2004 and 2008). In our study, the mean BLL for Wuhan children was 33.72 $\mu\text{g/L}$, which revealed the progressive decline of BLLs in children from Wuhan city. This would be most likely due to the change of using unleaded gasoline and reductions of industrial lead pollution.

As shown in Table 2, the BLL trends to increase with the age groups. The trend was consistent with other studies [26, 27]. The elevated BLL rates were also increased by age (Table 3), and the highest BLL rate was 38.3 % in 4–6-year-age group. This can be explained by the following reason: lead exposure of children in China may come primarily from outdoor sources rather than from indoor ones [28], and elder children were more likely to play outdoor, so the chances of lead exposure for them were much higher.

The higher BLLs among boys might be explained by the differences in behavior related to lead exposure. Compared with girls, boys spend more time on outdoor activities and

Table 4 The blood levels of Pb, Cu, Zn, Ca, Mg, Fe, and Hb by gender

Gender	<i>N</i>	Pb ($\mu\text{g/L}$)	Cu (mg/L)	Zn (mg/L)	Ca (mg/L)	Mg (mg/L)	Fe (mg/L)	Hb (g/dL)
Boys	602	$34.12 \pm 18.20^*$	$1.14 \pm 0.27^*$	$3.81 \pm 1.09^{**}$	66.53 ± 7.62	37.91 ± 4.37	$457.97 \pm 68.70^*$	$12.90 \pm 1.52^{**}$
Girls	445	31.18 ± 20.10	1.18 ± 0.33	4.05 ± 1.08	66.53 ± 7.21	37.67 ± 4.37	450.15 ± 59.20	12.63 ± 1.60

* $P < 0.05$, compared with girls; ** $P < 0.01$, compared with girls

Table 5 The blood levels of Pb, Cu, Zn, Ca, Mg, Fe, and Hb by residents

Residents	N	Pb ($\mu\text{g/L}$)	Cu (mg/L)	Zn (mg/L)	Ca (mg/L)	Mg (mg/L)	Fe (mg/L)	Hb (g/dL)
Urban	654	30.73 \pm 18.06*	1.19 \pm 0.31**	3.94 \pm 1.03	66.53 \pm 7.21	37.42 \pm 4.37**	451.27 \pm 0.32*	12.67 \pm 1.30**
Suburban	393	33.38 \pm 18.00	1.10 \pm 0.27	3.87 \pm 1.19	64.53 \pm 7.62	38.15 \pm 4.37	460.76 \pm 70.93	12.98 \pm 1.90

* $P < 0.05$, compared with suburban; ** $P < 0.01$, compared with suburban

Table 6 The blood levels of Cu, Zn, Ca, Mg, Fe, and Hb in different BLL groups

Group	N	Cu (mg/L)	Zn (mg/L)	Ca (mg/L)	Mg (mg/L)	Fe (mg/L)	Hb (g/dL)
BLLs $< 50 \mu\text{g/L}$	828	1.15 \pm 0.30	3.87 \pm 1.10*	66.93 \pm 7.62	37.91 \pm 4.37	458.53 \pm 61.44**	12.87 \pm 1.57**
BLLs $\geq 50 \mu\text{g/L}$	219	1.15 \pm 0.28	4.07 \pm 1.05	66.53 \pm 7.21	37.42 \pm 4.37	441.22 \pm 74.28	12.47 \pm 1.48

* $P < 0.05$, compared with BLLs $\geq 50 \mu\text{g/L}$ group; ** $P < 0.01$, compared with BLLs $\geq 50 \mu\text{g/L}$ group

have more hand-to-mouth and object-to-mouth activities, which have been associated with higher BLLs [29]. It could be proposed that boys may have higher absorption rates by eating more or drinking more. We also noticed that children in suburban areas had higher BLLs than those in urban areas (Table 5), which was consistent with the investigation in Taiyuan City [30]. This may be because of lead-acid battery plant migration to the suburbs to improve urban air quality in recent years.

Our study revealed that although the blood levels of Zn were increased with the age groups, the total deficiency rate of Zn was 65.0 %, which suggests that the Zn deficiency problem of children in Wuhan was quite serious. The essential trace element Zn plays a vital role in some biological functions including cellular division, protein synthesis, and nucleic metabolism [31, 32]. More efforts should be made in order to popularize the adverse outcomes of Zn deficiency in childhood health education. The deficiency of Ca, Fe, and Hb was also common in Wuhan children while few have the Cu and Mg deficiency. These results were consistent with previous reports [33, 34]. So, the dietary supplement of Zn, Ca, and Fe in the children requires more attention.

Table 7 Partial correlations of blood levels of Pb with Cu, Zn, Ca, Mg, Fe, and Hb

	Cu	Zn	Ca	Mg	Fe	Hb
Pb	-0.087**	0.026	-0.005	-0.102**	-0.091**	-0.040
Cu		0.359**	0.330**	0.349**	0.023	-0.150**
Zn			0.320**	0.372**	0.225**	0.020
Ca				0.244**	-0.255**	-0.303**
Mg					0.449**	0.125**
Fe						0.567**

Controlling for age, gender, and residents; ** $P < 0.01$

In the present study, the blood levels of Zn in the BLLs $< 50 \mu\text{g/L}$ group were significantly lower compared to the BLLs $\geq 50 \mu\text{g/L}$ group ($P < 0.05$). While partial correlation analysis results showed that no significant correlation was found between the blood levels of Pb and Zn, which was in consistent with the investigation conducted in Chengdu city [35]. Since the blood levels of Zn were positively correlated with age, a possible explanation for this discrepancy is the different age structures of the two groups.

Our study had revealed the negative correlations between the blood levels of Pb with Cu, Mg, and Fe (Table 7). In the report of Patra [36], a negative correlation between the blood levels of Pb and Cu was found, which were consistent with the present study. However, some studies demonstrated that BLLs were not significantly correlated with blood copper levels [17, 37]. As an essential element in the function of enzymes and manipulating important biological polyphosphate compounds, Mg in blood was significantly decreased in the occupational lead exposure workers [38]. The negative correlation of blood Pb and Mg in our research was also in accordance with the previous study [37].

In addition, iron deficiency was confirmed to be associated with subsequent lead poisoning based on the longitudinal study by Wright and his colleagues [39]. In a cross-sectional study, BLLs were found to be negatively correlated with blood iron levels [40]. Furthermore, recent study revealed that the BLLs of iron-deficient infants decreased significantly compared with pretreatment levels after iron therapy [41]. The results summarized in Tables 6 and 7 were in agreement with the above studies, which indicated that the blood Fe levels decrease as the BLLs rise.

Lead poisoning was a known cause of microcytic anemia [42] by impairment of heme synthesis and increased rate of

red blood cell destruction. Animal research and human investigation both showed that hemoglobin concentration decreased significantly with rising blood lead concentration [43, 44]. Similar result was found in this study; the hemoglobin concentration of children with higher BLLs was significantly lower than that of the children with lower BLLs (Table 6). However, the negative correlation has no significance. This may be that the level of Hb was also affected by other factors, such as the level of Fe, Zn, and so on.

In conclusion, although the BLLs of children have declined, high lead level in children from Wuhan childhood remains a public health issue, with the overall elevated BLL rate according to the new standard [21] of 20.9 %. Meanwhile, the deficiency of and need for the supplementation of Zn, Ca, and Fe had been recognized. We also found that the BLLs were influenced by the status of certain essential trace elements in children. The appropriate volume supplements of Cu, Mg, and Fe in diet were a protective factor contributing to reduce the risk of lead exposure in children.

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Conflict of Interest The authors declare that there are no conflicts of interest.

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