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Baseline blood levels of manganese, lead, cadmium, copper, and zinc in residents of Beijing suburb

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ABSTRACT

Baseline blood concentrations of metals are important references for monitoring metal exposure in environmental and occupational settings. The purpose of this study was to determine the blood levels of manganese (Mn), copper (Cu), zinc (Zn), lead (Pb), and cadmium (Cd) among the residents (aged 12–60 years old) living in the suburb southwest of Beijing in China and to compare the outcomes with reported values in various developed countries. Blood samples were collected from 648 subjects from March 2009 to February 2010. Metal concentrations in the whole blood were determined by ICP-MS. The geometric means of blood levels of Mn, Cu, Zn, Pb and Cd were 11.4, 802.4, 4665, 42.6, and 0.68 μg/L, respectively. Male subjects had higher blood Pb than the females, while the females had higher blood Mn and Cu than the males. There was no gender difference for blood Cd and Zn. Smokers had higher blood Cu, Zn, and Cd than nonsmokers. There were significant age-related differences in blood levels of all metals studied; subjects in the 17–30 age group had higher blood levels of Mn, Pb, Cu, and Zn, while those in the 46–60 age group had higher Cd than the other age groups. A remarkably lower blood level of Cu and Zn in this population as compared with residents of other developed countries was noticed. Based on the current study, the normal reference ranges for the blood Mn were estimated to be 5.80–25.2 μg/L; for blood Cu, 541–1475 μg/L; for blood Zn, 2349–9492 μg/L; for blood Pb, <100 μg/L; and for blood Cd, <5.30 μg/L in the general population living in Beijing suburbs.

1. Introduction

Environmental and occupational exposure to metals is a growing concern, as industrial, agricultural and natural sources have continued to release metals in air, soil and water in developed as well as developing countries (Kristiansen et al., 1997). In China, the geological background levels of heavy metal are generally low; however, recent human activities have rendered soil, water, air, and plants more prone to the pollution by heavy metals; in some cases, these pollutions have caused severe human health problems (Cheng, 2003). Thus, the risk of metal exposure has been and will continue to be a major public health concern. To assess the risk and monitor exposure, there is a need to establish the reference values for metals of concern in the normal, healthy population for comparison purpose.

Reliable reference levels for individual metals are a prerequisite for evaluating metal exposure in both occupational and environmental exposure settings (Kristiansen et al., 1997; Wilhelm et al., 2004). Countries around the world set their own reference values for specific populations. For example, in the United States, the National Report on Human Exposure to Chemicals published by the Centers for Disease Control and Prevention (U.S. CDC) has documented the exposure data in an ongoing basis. The fourth report, which was published in 2009, has already been updated in September 2013, providing new representative biomonitoring data (CDC, 2013). In Germany, the Human Biomonitoring Commission of the German Federal Environmental Agency, which was established in 1992, has developed a set of scientifically based criteria for human biomonitoring; the criteria have recently been updated with newly recommend reference values (Wilhelm et al., 2004).

Abbreviations: Mn, manganese; BMn, Mn concentration in the whole blood; Cu, copper; BCu, Cu concentration in the whole blood; Zn, zinc; BZn, Zn concentration in the whole blood; Pb, lead; BPb, Pb concentration in the whole blood; Cd, cadmium; BCd, Cd concentration in the whole blood

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The Czech Republic has one of the earliest national surveillance systems. The biological monitoring of metal exposure has been in practice under the guideline of the System of Monitoring since 1994 (Cerná et al., 2001). In addition, there has been an ongoing EURO-TERVIHT project (Trace Element Reference Values in Human Tissues), aiming at establishing and comparing the trace metal reference values in inhabitants among different European community countries (Sabbioni et al., 1992).

Among metals of health concern, manganese (Mn), copper (Cu) and zinc (Zn) are nutritionally important, and yet their deficiency or overload is detrimental to human health. Lead (Pb) and cadmium (Cd), on the other hand, are toxic metals commonly present in environment and working places with no beneficial health effects. There are studies in literature to establish the reference values for these metals in various developed countries such as in Canada (Clark et al., 2007), Korea (Lee et al., 2012), Czech Republic (Batáriová et al., 2006; Benes et al., 2005), Spain (Izquierdo-Alvarez et al., 2008; Moreno et al., 1999), Italy (Alimonti et al., 2005; Bocca et al., 2011; Pino et al., 2012), and Sweden (Bárány et al., 2002). However, the reliable reference values among Chinese general population remained uncertain.

This study was a sub-project of the “Establishing Biological Monitoring Index of Reference Values for Important Chemicals in Population”, carried out by the Institute for Occupational Health and Poison Control in China Center for Disease Prevention and Control (Chinese CDC) from March 2009 to February 2010. The parent project includes studies in seven provinces and municipalities in China. The current study had a unique focus on Beijing suburban population living in southwest of metropolitan Beijing city. The purpose of this study was to establish background blood levels of metals (Mn, Pb, Cd, Cu and Zn) in the healthy people living in Beijing area as a snap shot and to compare the values with literature data obtained from other developed countries. The outcomes shall be of importance for nutritional, environmental and/or occupational monitoring of these metals in human populations.

2. Materials and methods

2.1. Subject selection

This study was performed in the Fengtai District, the southwest of Beijing metropolitan area, which has a total surface area of 305.87 km^2. The distances from the east to the west and from the north to the south are 35 km and 14 km, respectively. There are 2.14 million people, among which 1.69 million are permanent residents with 0.447 million having lived in this area for more than 0.5 year. By using a cluster sampling method, we selected study participants in the following order. Initially, we divided the Fengtai District according to its geographical location into three regions, i.e., eastern (Fangzhuang and Nanyuan), central (Fengtai) and western (Yungang) regions (Fig. 1). We then randomly selected neighborhood communities and schools within each region, i.e., two communities and 2 schools (elementary and middle schools) from the eastern region, one each community from the central and western regions, one each elementary and high school from the central region, and one middle school from the western region. Finally, we randomly selected subjects in each community for this study. Thus, participants were selected from 4 communities, 2 elementary schools, 2 middle schools and 1 high school. A total of 648 subjects participated in this study.

The study subjects met the following requirements: (1) living in the Fengtai District for 5 years; (2) living in areas without any industries; (3) having no history of liver and kidney diseases, diabetes, hyperthyroidism, cancer, or chronic diseases; (4) having not taken calcium, iron, Zn, and other trace elements in dietary supplements within the past 3 months; (5) age in the range of 12–60 years old. Out of 682 people enrolled in the study, 648 subjects accepted to participate, with a participation rate of 95.01%. The study subjects were recruited from the following areas (Fig. 2): 232 from the Yungang area, 157 from the Fengtai area, 88 from the Fangzhuang area, and 151 from the Nanyuan area. A total of 648 blood samples were collected from March 2009 to February 2010.

Participants were required to complete a questionnaire consisting of personal information, employment status, lifestyle, eating habits, and disease history. All participants were required to sign the consent forms, which was approved by the Ethical Censorship Committee of the Institute for Occupational Health and Poison Control at the China Center for Disease Prevention and Control (CDC). Participants agreed to use their blood samples for this biological monitoring research.

2.2. Sample preparation and analysis

Sample collection and processing were carried out in local clinics. A total of 6 mL of blood was collected in a tube containing lithium heparin monometers (BD, USA), and immediately transferred to 2 mL frozen pipe (Axygen, USA) after thorough mixing. All samples were stored at −80 °C freezer until analysis.

At the time of sample analysis, blood samples were brought to room temperature. An aliquot of 500-μL blood samples was diluted with a solution containing 0.01% (V/V) Triton-X-100 (Sigma-Aldrich, USA) and 0.5% ultrapure concentrated nitric acid (Merck, Darmstadt, Germany) to a 5 mL total volume. The samples were vortexed in a table-top vortexer (Heidolph Malti Reax (XWT-204) for 1 min. The diluted samples were then quantified by ICP-MS. The detection limits for Mn, Cu, Zn, Pb and Cd were 0.11, 0.55, 4.3, 0.28 and 0.08 μg/L, respectively.

2.3. Quality control

A previous report by Minoia et al. (1992) suggests that the contamination in the pre-analytical phase during sample collection may lead to the false outcomes, which has become the basis for rejection of scientific manuscripts in various cases. To minimize the contamination, we have pre-tested the heparin monovettes and frozen vials used in our blood collection. By soaking 20 monovettes and 20 vials with 1% (V/V) ultrapure nitric acid for 1 h, we determined the metal concentrations in the soaking solution by LCP-MS. The results showed that the concentrations of Mn, Pb and Cd in these monovettes and vials were lower than their respective detection limits.

All blood samples were analyzed in an authorized laboratory in the Occupational Health and Poison Control at Chinese CDC in Beijing. For internal quality assurance, The SeronormTM Trace Elements Whole Blood Control Level 1 (Sero AS, Billingstad, Norway) and the Blood Control Level 1–2 of China for Pb and Cd (GBW09139, GBW09140) were used. Control standards and reference materials were run together with collected blood samples on a daily basis. If the results of the reference materials were within the expected range, the results of that batch were accepted. The quality of laboratory instruments and procedures was also periodically checked to ensure the reproducibility and accuracy of the assays.

2.4. Statistical analysis

Results from the whole blood sample usually have the skewed distribution. Therefore, the metal concentrations were described in terms of percentiles (P25, P50 and P75), geometric mean (GM) and the 95% confidence interval (95% CI) for the geometric mean. A

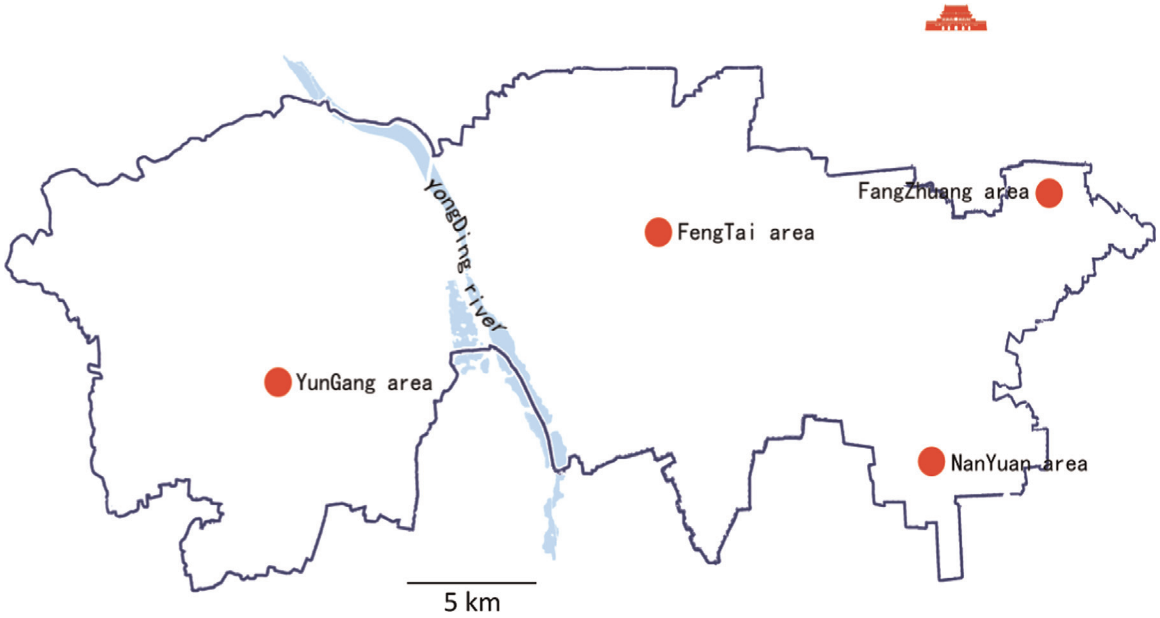

Fig. 1. Location of the Study Population. Fengtai is located in the southwest Beijing metropolitan area. From the center of Fengtai, it expends from the east to the west about 35 km and from the north to the south about 14 km. The district has 2.14 million people.

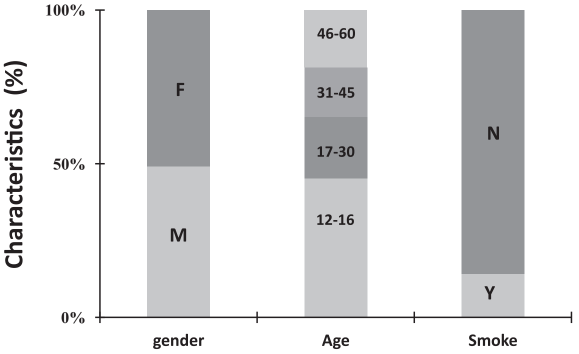

Fig. 2. Characteristics of the Study Population. A total of 648 subjects from 5 communities, 2 elementary schools, 2 middle schools and 1 high school were recruited in this study. F: females; M: males; Y: smokers; and N: nonsmokers.

univariate statistical analysis of the influence was performed using the Rank sum test; univariate statistical analysis of gender and smoking effects was performed using the Wilcoxon test; and a univariate statistical analysis of age effect was performed using the Kruskal–Wallis test. A probability value (*p*) less than or equal to 0.05 was regarded as statistically significant. The reference limits were calculated according to the International Federation of Clinical Chemistry-recommended nonparametric statistical method (IFCC, 1987). The reference values of the data distribution were 95% for Pb and Cd (toxic elements) of unilateral P95; for Mn, Cu and Zn (nontoxic elements), the bilateral P2.5–P97.5 numerical values were used. The SPSS version 13.0 statistical package (SPSS, Chicago, USA) was used in data analysis.

3. Results

Table 1
Age and gender distribution of the study cohort.

Age groups	Gender		
	Male	Female	Sum
12–16	164	129	293
17–30	48	82	130
31–45	46	58	104
46–60	60	61	121
Total	318	330	648

Subjects (318 men and 330 women) were grouped based on their age: the 12–16 age-group had 293 junior high school students; the 17–30 age-group had 130 subjects who were high school students, college students or young working people; the 31–45 age-group had 104 subjects who were middle-aged workers; and the 46–60 age-group had 121 subjects (Table 1). Other demographic data such as genders and smoking history are presented in Fig. 2.

Data in Table 2 demonstrated that the geometric mean of the blood Mn concentration (BMn) was 11.4 μg/L with a 95% confidence interval (CI) of 11.1–11.8 μg/L. Interestingly, BMn was significantly higher in women (12.9 μg/L) than in men (10.1 μg/L) ($p < 0.01$). The geometric mean and 95% CI of BMn in women and men were 12.9 (12.44–13.43) μg/L and 10.1 (9.68–10.43) μg/L, respectively. There was no statistical significant difference in BMn between smokers and nonsmokers, although smokers BMn level (10.90 μg/L) slightly lower than the nonsmokers (11.51 μg/L). The geometric mean of BMn in the 17–30 age group was significantly higher than other age groups ($p < 0.001$).

The geometric mean of blood Cu concentration (BCu) in this survey was 802.4 μg/L with a 95% CI of 787–820 μg/L (Table 3). Similar to BMn, BCu was significantly higher in women (862.2 μg /L) than in men (744.7 μg/L) ($p < 0.01$). The geometric mean and 95% CI of BCu in women and men were 862.2(837.8–887.2) μg/L and 744.7(727.3–762.8) μg/L, respectively. The mean level of BCu among smokers was 858.7 μg /L, which was significantly higher than that of non-smokers (793.5 μg /L) ($p < 0.05$). In addition, the BCu among the subjects 17–30 years old (1092 μg/L) was statistically significantly higher than all other 3 age groups ($p < 0.001$).

The participants showed the geometric mean of blood Zn concentration (BZn) of 4665 μg/L with a 95% CI of 4544–4780 μg/L. The data did not show any gender difference (Table 4). Similar to BCu, however, the smokers had a mean BZn (5030 μg/L) significantly higher than that of non-smokers (4607 μg/L) ($p < 0.001$). Again, the subjects in the 17–30 age group had the BZn (6399 μg/L) significantly higher than those in other 3 age groups ($p < 0.001$).

Table 2
Blood Mn concentrations (μg/L) in general Chinese population.

Items	Sample size	Geometric mean (95% CI)	P_{25}	P_{50}	P_{75}	*p* Value
BMn (μg/L)	648	11.42 (11.07–11.75)	8.81	11.12	14.72	
Gender						
Male	318	10.05 (9.68–10.43)	8.22	9.59	11.87	< 0.001
Female	330	12.92 (12.44–13.43)	9.98	13.14	16.35	
Smoking status						
Non-smoker	556	11.51 (11.16–11.88)	8.81	11.23	15.01	0.083
Smoker	92	10.90 (10.21–11.67)	8.76	10.09	12.84	
Age (years)						
12–16	293	11.52 (11.03–12.01)	8.80	11.67	15.17	< 0.001
17–30	130	14.39 (13.42–15.42)	10.85	14.30	19.32	
31–45	104	9.740 (9.21–10.31)	8.00	9.37	11.71	
46–60	121	10.01 (9.54–10.53)	8.61	9.61	11.54	

The study cohort had the geometric mean of the blood Pb concentration (BPb) of 42.6 μg/L (95% CI of 40.9–44.4 μg/L), or 4.3 μg/dL. BPb in men (47.3 μg/L, 95% CI of 49.9–49.7 μg/L) was about 23% higher than that in women (38.4 μg/L, 95% CI of 36.1–40.8 μg/L) ($p < 0.01$). There was no statistically significant difference in BPb between smokers and nonsmokers. Differences in BPb among different age groups were also detected ($p < 0.001$), with the age group of 17–30 having a significant higher BPb (51.9 μg/L) than the other 3 age groups ($p < 0.001$) (Table 5).

For blood concentration of Cd (BCd), all participants had BCd geometric mean of 0.68 μg/L with a 95% CI of 0.63–0.73 μg/L. The geometric mean of BCd was essentially same between men (0.68 μg/L) and women (0.69 μg/L) ($p > 0.05$). Smokers apparently had a higher BCd (1.57 μg/L, 95% CI of 1.28–1.94 μg/L) than did the non-smokers (0.59 μg/L, 95% CI of 0.54–0.65 μg/mL) ($p < 0.001$). Differences in BCd among age groups were statistically significant ($p < 0.001$); but the subjects in the age group of 46–60 had the highest BCd (1.23 μg/L) than the other three age groups ($p < 0.001$) (Table 6).

By using the percentile method, the normal reference values for the general population in the Beijing area, male/female, and smokers/nonsmokers, were obtained and summarized in Table 7. Based on the current study, the derived reference ranges for the whole blood Mn were 5.80–25.2 μg/L; for the whole blood Cu, 548–1475 μg/L; for the whole blood Zn, 2349–9492 μg/L; for the whole blood Pb, < 100 μg/L; and for the whole blood Cd, < 5.30 μg/L. Because Mn, Cu, and Zn are essential metals, the reference values are set from P2.5 to P97.5. For their toxic properties, the reference values for Pb and Cd are set at P95.

Table 4
Blood Zn concentrations (μg/L) in general Chinese population.

Items	Sample size	Geometric mean (95% CI)	P_{25}	P_{50}	P_{75}	*p* Value
BZn (μg/L)	648	4665 (4544–4780)	3776	4480	5563	
Gender						
Male	318	4564 (4392–4727)	3807	4459	5267	0.273
Female	330	4764 (4577–4965)	3730	4498	6090	
Smoking status						
Non-smoker	556	4607 (4470–4737)	3695	4354	5536	0.001
Smoker	92	5030 (4729–5337)	4264	4852	5582	
Age (years)						
12–16	293	4414 (4236–4592)	3529	4129	5420	< 0.001
17–30	130	6399 (6037–6784)	4774	6900	8571	
31–45	104	3790 (3598–4016)	3176	3889	4623	
46–60	121	4541 (4428–4663)	4088	4643	5016	

4. Discussion

For environmental, occupational, or nutritional monitoring of metals in human subjects, there is a need to establish background concentrations of these metals in the general population. The current study has determined the blood concentrations of Mn, Pb, Cd, Cu, and Zn among 648 healthy Chinese subjects. Our results provide the geometric means and the 95% confidence intervals (95% CI) for each metal examined. Interestingly, our data reveal a gender-associated difference in blood Mn, Pb, and Cu concentrations, and the age-related difference in all 5 metal concentrations in the whole blood. The characteristics of the blood concentrations of each metal among this Chinese population in comparison to literature data are presented in Table 8 and discussed below.

Table 3
Blood Cu concentrations (μg/L) in general Chinese population.

Items	Sample size	Geometric mean (95% CI)	P_{25}	P_{50}	P_{75}	*p* Value
BCu (μg/L)	648	802.4 (786.8–819.6)	685.0	778.0	885.2	
Gender						
Male	318	744.7 (727.3–762.8)	661.9	726.7	822.6	< 0.001
Female	330	862.2 (837.8–887.2)	743.2	825.8	977.1	
Smoking status						
Non-smoker	556	793.5 (776.5–811.7)	674.6	777.0	875.1	0.027
Smoker	92	858.7 (811.6–905.1)	710.6	800.8	943.3	
Age (years)						
12–16	293	705.6 (690.2–722.6)	629.2	708.5	805.1	< 0.001
17–30	130	1092.0 (1042.7–1146.3)	842.6	1192.0	1345.5	
31–45	104	821.8 (798.0–848.3)	748.7	820.3	896.3	
46–60	121	770.7 (754.4–788.6)	706.0	766.9	830.6	

Table 5
Blood Pb concentrations (μg/L) in general Chinese population.

Items	Sample size	Geometric mean (95% CI)	P_{25}	P_{50}	P_{75}	*p* Value
BPb (μg/L)	648	42.55 (40.93–44.39)	31.31	42.27	59.89	
Gender						
Male	318	47.34 (49.90–49.72)	34.75	46.26	62.34	< 0.001
Female	330	38.40 (36.07–40.79)	28.02	39.61	54.20	
Smoking status						
Non-smoker	556	42.32 (40.40–44.17)	31.31	42.06	59.56	0.517
Smoker	92	44.02 (40.07–48.68)	31.44	44.81	61.87	
Age (years)						
12–16	293	47.56 (44.92–50.27)	35.14	45.40	63.20	< 0.001
17–30	130	51.92 (47.67–56.41)	34.45	54.03	75.35	
31–45	104	26.69 (23.86–29.90)	18.36	28.47	42.24	
46–60	121	39.20 (36.61–41.94)	29.39	39.27	50.09	

Table 6
Blood Cd concentrations (μg/L) in general Chinese population.

Items	Sample size	Geometric mean (95% CI)	P_{25}	P_{50}	P_{75}	*p* Value
BCd (μg/L)	648	0.68 (0.63–0.73)	0.42	0.62	1.14	
Gender						
Male	318	0.68 (0.58–0.78)	0.31	0.62	1.47	0.498
Female	330	0.69 (0.64–0.74)	0.46	0.63	0.99	
Smoking status						
Non-smoker	556	0.59 (0.54–0.65)	0.39	0.57	0.99	< 0.001
Smoker	92	1.57 (1.28–1.94)	0.73	1.33	3.27	
Age (years)						
12–16	293	0.44 (0.39–0.50)	0.26	0.48	0.74	< 0.001
17–30	130	1.00 (0.87–1.18)	0.51	0.95	1.57	
31–45	104	0.73 (0.62–0.88)	0.42	0.60	1.07	
46–60	121	1.23 (1.07–1.42)	0.69	0.92	2.08	

Table 7
The normal reference values (recommended) of whole blood concentrations of Mn, Pb, Cd, Cu and Zn for residents in Beijing suburbs (μg/L).

Elements/Groups	P95	P2.5–P97.5	Proposed reference values	Literature data
Mn[a]				
Total population		5.80–25.17	5.80–25.20	4.73–17.0
Male		5.55–20.57	5.50–20.60	4.63–14.2
Female		5.96–27.82	5.90–27.80	5.76–17.8
Non-smoker		5.76–25.20	5.70–25.20	5.31–16.6
Smoker		6.59–25.87	6.60–25.90	5.24–13.5
Cu[a]				
Total population		548.8–1474.7	548–1475	776–1495
Male		550.2–1377.1	550–1378	769–1200
Female		531.2–1563.7	531–1564	805–1574
Non-smoker		530.3–1463.3	530–1463	752–1579
Smoker		595.0–1547.8	595–1548	825–1249
Zn[a]				
Total population		2349–9492	2349–9492	4686–8585
Male		2364–9299	2364–9299	5056–8956
Female		2328–10048	2327–10048	4307–7773
Non-smoker		2318–9393	2318–9392	4699–4699
Smoker		2445–10247	2444–10246	4630–9150
Pb				
Total population	103.06		100.00	75[b], 66[c]
Male	107.50		105.00	80[b], 76[c]
Female	97.83		97.00	65[b], 49[c]
Non-smoker	101.47		100.00	75[b],
Smoker	105.86		105.00	80[b],
Cd				
Total population	5.33		5.30	3[b],
Male	8.59		8.60	3.5[b],
Female	2.00		2.00	3[b],
Non-smoker	3.69		3.70	1.1[b], 0.6[c]
Smoker	9.20		9.20	4.5[b],

More references are included in the main text.

[a] Bocca et al. (2011).
[b] Batáriová et al. (2006).
[c] Kuno et al. (2013).

Mn is an essential element for human health. Nevertheless, excessive exposure or intake may lead to a clinical condition known as manganism, a neurodegenerative disorder resembling, but not identical to, Parkinson'' disease (Crossgrove and Zheng, 2004; Racette et al., 2012). The normal ranges of BMn are between 4–15 μg/L in humans (ATSDR, 2012). Our own data show a geometric mean of BMn about 11.4 μg/L. While this value is within ATSDR's reference range, it is higher than the Chinese national survey value of 8.98 μg/L (Pan et al., 2014b); it is also higher than those reported in some other countries, from 8.9 μg/L in Italians to 10.8 μg/L in Koreans and Canadians (Table 8). Our observation that women have a higher BMn than men (~28.6%) is consistent with the Chinese national survey (female 9.88 μg/L vs. male 8.14 μg/L) (Pan et al., 2014a, 2014b), and also consistent with literature reports, cf. comparable to 25% higher in Korean and Italian women (Lee et al., 2012; Bocca et al., 2011) and about 23% higher in Canadian women (Clark et al., 2007) than respective men's population. Consistent with the literature (Lee et al., 2012; Bocca et al., 2011), the BMn is not affected by the smoking habit in Chinese population. While other reports observe a decrease of BMn with age (Lee et al., 2012) or no changes with age (Clark et al., 2007), our data show a significantly higher BMn in the age of group of 17–30 years old (14.4 μg/L), which, albeit "normal", is in the high end of ATSDR's defined range. Noticeably, however, the subjects in this age group also possess the highest metal concentrations of Cu, Zn, Pb and Cd. The exact reason for this relatively high blood metal level in young adult Chinese remains unknown; it is possible that the active employment and dynamic daily life may render these young adults more prone to exposures in working place as well as in environmental settings. For its nature of intracellular distribution and short blood half-life, BMn may not be an ideal biomarker to distinguish one exposed individual from the rest of the Study Population. Other more advanced methods such as using Mn/Fe ratio, magnetic resonance imaging (MRI) or bone Mn level have been discussed elsewhere (Zheng et al., 2011).

Similar to Mn, Cu is an essential nutrient that is required for numerous metalloenzymes such as tyrosinase, cytochrome c oxidase, superoxide dismutase, ferroxidases, monoamine oxidase, dopamine β-monooxygenase, and ceruloplasmin in diverse biochemical reaction in the body (Zheng and Monnot, 2012).

Table 8
Comparison of mean blood concentrations of Mn, Cu, Zn, Pb, and Cd in Beijing suburban residents with people living in other countries (μg/L).

	BMn	BCu	BZn	BPb	BCd	References
Chinese	11.4	802.4	4665	42.6	0.68	
American	4–15			12.3	0.304	CDC (2009,2013)
Australian				14.5		Kelsall et al. (2013)
Brazilian	9.6	890		65.4	0.4	Nunes et al. (2010)
Canadian	10.8			21.3		Clark et al. (2007)
Czech		800	5800	33;41	0.5;0.7	Batariova et al. (2006); Benes et al. (2000)
Danish	9.1			48.3		Kristiansen et al. (1997)
German	8.6	1020		19;31	0.38;0.44	Heitland and Koster (2006); Becker et al. (2002)
Italian	8.9	1036	6418	33.4	0.53	Bocca et al. (2011); Forte et al. (2011)
Korean	10.8			19.1		Lee et al. (2012)
Spaniard		1070	6950	46.7	0.98	Moreno et al. (1999)

Symptoms associated with Cu deficiency in humans include normocytic, hypochromic anemia, leukopenia, and osteoporosis (ATSDR, 2004). Research suggests that Cu deficiency is one of factors leading to an increased risk of developing coronary heart disease (Liu et al., 2008). The mean BCu from this population (802.4 μg/L), which is similar to Chinese national survey value (795 μg/L) (Pan et al., 2014a), is considerably lower than the values reported in literature. For example, the reported BCu values vary from 890 μg/L in Brazilian to 1070 μg/L in residents of the city Badajoz in Spain (Table 8). The reason for this low BCu in Beijing suburban residents is currently unknown. BCu tends to be about 15–17% higher in women than in men by literature reports (Benes et al., 2005; Bocca et al., 2011). Results of the current research are in line with these literature data, showing about 16% higher in women than men. It has been hypothesized that estrogen-induced ceruloplasmin synthesis in the liver may lead to an increased Cu in blood (Martin-Lagos et al., 1998). In fact, the BCu in girls at age 10 years old is nearly equal to that in boys of the same age (Benes et al., 2000). Another study by Bárány et al. (2002) finds that at age of 15 years old, the BCu in boys and girls has no any significant difference; but the girls at age 17 have a significantly higher BCu than their 15 year-old levels, and are significantly higher than the boys of the same age. Our data show an age-related increase of BCu from 12 to 30 years old, followed by an age-related decline from 31 to 60 years old. Since the sample sizes in groups of age 17–30 and age 31–45 in the current study are higher in women than men, it is possible that the age-related BCu variation may reflect Cu-level changes in women.

Zn plays a pivotal role to human health and its deficiency is a major clinical consideration (Barceloux, 1999; Solomons, 2013). By a conservative estimate, nearly 25% of the world's population is at risk of Zn deficiency, which underlies diseases such as growth retardation, anorexia, delayed sexual maturation, anemia, mental retardation, and impaired visual and immunological function, among others (Maret and Sandstead, 2006). Similar to BCu, our data reveal that the BZn among this Chinese cohort (4665 μg/L), which is higher than the Chinese national survey value (3996 μg/L) (Pan et al., 2014a), is considerably lower than people in other developed countries; it was 24.3% lower than that those living in Czech Republic (Benes et al., 2000), 37.6% lower than Italians (Bocca et al., 2011), and 50% lower than Spaniards (Moreno et al., 1999) (Table 8). The low levels of Cu and Zn in the “normal” Chinese subjects are alarming. For gender-related differences in BZn, some studies in literature including the reports by Chinese national survey suggest a higher level in women than men (Bocca et al., 2011; Pan et al., 2014a), while others report the opposite observation (Benes et al., 2005; Buxaderas and Farré-Rovira, 1985). Our results did not show any significant differences in BZn between men and women. However, the current study did find an age-related change in BZn; this change appeared to be mainly observed in the 17–30 age group compared with other age groups, but no distinct pattern of age-associated increase or decrease in BZn was observed.

Unlike essential metals Mn, Cu and Zn, Pb has no any beneficial health effects but rather detrimental to human health. U.S. Department of Health and Human Services and Environmental Protection Agency (EPA) have listed Pb compounds to be carcinogens, neurotoxicant, and neurodevelopmental toxicant (UNEP, 2006; IARC, 2006). Recent epidemiologic studies have also linked Pb exposure to the declined cognition (Bakulski et al., 2012) and the etiology of Alzheimer's disease (Gu et al., 2011, 2012; Schwartz et al., 2010; Stewart et al., 2006). Main sources of Pb exposure in the general population are food, water and airborne particulate (smoke included) (Forte et al., 2011). Indeed, reduced use of leaded gasoline and tightened control of industrial Pb emissions in industrialized countries over the last several decades have resulted in a general decrease in blood Pb concentrations (Järup, 2003; Forte et al., 2011). The similar reduction of Pb among Chinese children has also been observed; the children's BPb has dropped from 92.9 μg/L in 2004 to 80.7 μg/L in 2009 in China (He et al., 2009), which remains high according to U.S. CDC's recommended level for monitoring BPb in children (< 50 μg/L) (CDC/ACCLPP, 2012). The data from the current study revealed a geometric mean of BPb in this Chinese population to be 42.6 μg/L, which is 100% higher than in Canadians, 42% higher than in Czechs, 123% higher than in Koreans, 194% higher than in Australians, and 246% higher than in Americans (Table 8). Our data on BPb are also higher than the Chinese national average value (34.9 μg/L) (Ding et al., 2014). A higher BPb in men than in women (about 20–48% higher) has been reported in literature (CDC, 2013; Clark et al., 2007; Batáriová et al., 2006; Kelsall et al., 2013). Consistent with these reports, our results showed BPb about 23% higher in men than in women. BPb in adults has also been shown to increase as the function of age (ATSDR, 2007; Bjermo et al., 2013; Kelsall et al., 2013; Zheng et al., 2001); but the current study did not establish this association.

Cd is also a non-essential but toxic metal in humans. A panel in the United Nations' Environment Program ranks Cd as the sixth threats of toxic substances to human health (Liu et al., 2008; UNEP, 2010). Cd intoxication causes kidney dysfunction, damages to skeletal, hemopoietic and cardiovascular systems (FAO/WHO, 2001). BCd has been used as a biomarker for both recent and cumulative exposures (CDC, 2009). In the current Chinese population, we found that BCd was 0.68 μg/L, which is about the same compared with Czechs, but higher than in Germans (0.44 μg/L), Italians (0.53 μg/L) and Americans (0.30 μg/L) (Table 8), and also higher than average Chinese (0.49 μg/L) (Ding et al., 2014). There was no significant gender-associated difference in BCd. Reports by U.S. CDC shows an increase trend of BCd with age (CDC, 2009); our current data appeared to show this trend, since the oldest group (46–60) had BCd about 180% higher than the youngest group (12–16). Forte et al. (2011) confirm the age-related increase in BCd and point out that a plateau level can be reached in subjects above 50 years old, which could be due to an age-related deterioration of kidney function (Satarug and Moore, 2004).

Except for Mn and Pb, tobacco smoking has a great impact on metal concentrations in blood. Our data showed 8%, 9% and 87% of increase in BCu, BZn and BCd, respectively, among smoker in comparison to nonsmokers. The observation on BCu is in a good agreement with literature reports (Bárány et al., 2002; Massadeh et al., 2010). A higher BCu in smokers could be due to an increased release of corticosteroids and catecholamine, which are known to influence the body Cu status (Lapenna et al., 1995). For BZn, we observed only a slight, yet significant increase of BZn among smokers. But, Bocca et al. (2011) report a 13% significant reduction in female smokers. BCd is known to be higher in smokers, because tobacco leaves naturally accumulate Cd and are the known source of Cd exposure (IARC, 2012). In the current study, we showed BCd in smokers about 87% higher than that in non-smokers. Other reports in literature have shown the similar outcomes (Batáriová et al., 2006; Forte et al., 2011; Heitland and Koster, 2006; Järup, 2003).

This study has limitations. First, the sample size involves 648 people, which is sufficient for a snapshot to document local residents, but it does not include children less than 12-year age or adults more than 60 years old. A wider age range with a larger sample size is desirable for a more accurate estimation. Second, this study was conducted in the Beijing area. The metropolitan nature of the study site reflects the metal concentrations in this region, but may not necessarily represent the entire Chinese population, particularly in remote areas. Recent reports published in Chinese literature (Ding et al., 2014; Pan et al., 2014a, 2014b) may offer a broader view of metal concentrations among Chinese. Finally, the subjects in this study are generally identified as the "Han" ethnic group. While this indeed represents more than 90% of Chinese population, there are significant minority groups that are not included in this study. Our future studies will be directed to overcome these limitations.

In conclusion, the results of this study provide the information regarding blood concentrations of metals in residents of Beijing suburbs in China. The data help establish the reference values for blood levels of Mn, Pb, Cd, Cu, and Zn for the Chinese population in that area. These findings shall be useful for future research to monitor occupational and environmental exposure and to compare the exposure levels within China and around the world.

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