Environ Geochem Health (2022) 44:1673–1682
https://doi.org/10.1007/s10653-021-01129-0

ORIGINAL PAPER

The association between hemoglobin level and osteoporosis in a Chinese population with environmental lead and cadmium exposure

Miaomiao Wang · Xinru Wang · Wenjing Cui · Guoying Zhu · Yihuai Liang · Xiao Chen · Taiyi Jin

Received: 21 July 2020 / Accepted: 9 October 2021 / Published online: 26 October 2021

Abstract Low hemoglobin (Hb) level or anemia is associated with osteoporosis and bone fracture. Cadmium (Cd) and lead (Pb) exposure are also risk factors of osteoporosis and anemia. However, the role of anemia in Cd/Pb related bone loss remains unclear. The aim of present study was to investigate the association between Hb level and bone loss in a population with environmental lead and cadmium exposure. One hundred and ninety-four women and 108 men with different levels of Cd/Pb exposure were included in our study. The Cd/Pb exposure was determined using graphite-furnace atomic absorption spectrometry. Forearm bone mineral density (BMD) was determined by peripheral dual-energy X-ray absortiometry. Hb concentration was determined using an automatic blood cellcounter. A logistic model was established to predict the risk of osteoporosis. The BMDs of women that had the highest quartile BCd and BPb were markedly lower than that with the lowest quartile ($p < 0.05$). The BMD and the prevalence of osteoporosis in men with anemia were lower and higher than that with normal Hb ($p < 0.05$), respectively. In men, age, BPb and anemia were independent risk factors for osteoporosis. The odds ratio (OR) of men with anemia was 11.28 (95%confidence interval (CI):1.94-65.54) and 19.56 (95%CI: 2.98-128.78) compared to those with normal Hb after adjusting for potential cofounders. No such association was found in women. The area under the curve was 0.88 (95%CI: 0.82-0.96) in predicting osteoporosis using the logistic model in men. Linear discriminant analysis also showed that 90.7% of osteoporosis was correctly classified. Our data show that anemia is associated with incident of osteoporosis in men but not in women that environmentally exposed to Pb and Cd.

Keywords Cadmium · Lead · Bone · Osteoporosis · Hemoglobin · Anemia

M. Wang · X. Wang · W. Cui · X. Chen (✉)
Department of Radiology, Affiliated Hospital of Nanjing University of Chinese Medicine, Nanjing 210029, China
e-mail: chxwin@163.com

G. Zhu
Institute of Radiation Medicine, Fudan University, 2094 Xietu road, Shanghai 200032, China

Y. Liang · T. Jin (✉)
Department of Occupational Medicine, School of Public Health, Shanghai Medical College of Fudan University, 150 Dongan road, Shanghai 200032, China
e-mail: tyjin@shmu.edu.cn

Introduction

Cadmium (Cd) and lead (Pb) are both distributed in the environment and used in industrial field. Both Cd and Pb can enter the human body via digestive tract. Bone is an important target organ for Cd and Pb toxicity. Cd and Pb exposure are associated with low bone mass or

osteoporosis (Åkesson et al., 2014; Jalili et al., 2020; Li et al., 2016). Moreover, both animal and population studies indicated that Cd and Pb exposure can affect hemoglobin (Hb) level, in particular to Pb exposure. Chronic Pb exposure is a risk factor of hematologic impairments that can decrease the Hb content (Dobrakowski et al. 2015; Li et al., 2018; Nakhaee et al. 2018) and hematocrit (Chwalba et al. 2019; Nakhaee et al. 2018). However, the association and interplay between those outcomes has not been completely clarified (Zhang et al., 2020).

Anemia is a common health problem, especially in old people. The prevalence of anemia in US old men and women (> 65 years old) was 11.0% and 10.2% (Guralnik et al., 2004), respectively. Hb level or anemia is also a risk factor of bone health (Cesari et al., 2005; Fujimoto et al., 1999; Jørgensen et al., 2010; Lee et al., 2019). Low Hb level demonstrated a higher bone loss in old people (Cesari et al., 2005; Oh et al., 2017). In addition, anemia was related to high risk of bone fractures (Jørgensen et al., 2010; Valderrabano et al. 2017). Recently, a nation-wide study in Korea showed that the risk of any bone fracture in men with anemia increased by 29% than those without anemia (Lee et al., 2019). Those studies mainly focused on general populations. Rutten et al. (2013) found that anemia was an independent risk factor of bone loss in patients with chronic obstructive pulmonary disease. However, few study has considered the influence of anemia on bone mineral density (BMD) or osteoporosis in subjects with Cd or Pb exposure. A recent review also points out that it is important to consider the exposure to heavy metal when we investigate the association between bone diseases and anemia (Zhang et al., 2020).

Because Cd and Pb can both affect the bone health and Hb level, it would be important to show the effects of anemia on Cd/Pb induced bone loss or osteoporosis. In this study, we showed an association between Hb and bone loss in a Chinese population that was environmentally exposed to Cd and Pb.

Materials and methods

Subjects

The detailed information of subjects had been reported in our previous studies (Chen et al., 2015, 2019). The survey was performed on December 2012. Two towns (Yantou and Magu) located in Guizhou province were included in the study. Indigenous zinc smelting had lasted in Hezhang for hundreds of years. The waste water, air and mineral waste residue were directly discharged into environment. Bi et al. (2006) showed that the concentration of heavy metals in local water and soil exceeded the national standard. Cd and Pb were the most seriously contaminant in this area (Bi et al., 2006). The Cd and Pb concentrations in soil were 5.8–58 mg/kg and 60–14,000 mg/kg, respectively, which was obviously higher than national standard (< 0.5 mg/kg for Cd and < 250 mg/kg for Pb) (Bi et al., 2006). Cd and Pb concentrations in cereal also exceed the safety limit, 0.51–1.09 mg/kg for Cd (national standard < 0.2 mg/kg for rice) and 1.46 mg/kg for Pb (national standard < 0.5 mg/kg for cereal) (Chen et al., 2019). The Cd and Pb in groundwater were 0.006 mg/L and 0.05 mg/L which also higher than national standard(Cd and Pb in drinking water should be less than 0.005 mg/ L and 0.01 mg/L, respectively). One hundred and seventy-four subjects were enrolled from this area, including 102 women and 72 men. Another area, 40 km away from Yantou that had low pollution was selected as a control area. One hundred and forty-seven subjects (98 women and 49 men) were recruited from control area. Those subjects with occupational exposure to cadmium, lead or other metals were not included. The subjects living in the two areas had similar life style, diet habits, social conditions and economic status. A questionnaire was obtained from each participant to collect the demographic information, medical history, smoking and drinking habits. Nineteen subjects were excluded from the final analysis because of data missing. We obtained the approval from the Institutional Review Board of Fudan University and the informed consent was obtained from each participant. Declaration of Helsinki was followed.

Pb/Cd and renal tubular biomarker determination

Blood and urine samples were obtained for exposure assay. The containers were soaked in HNO_3 solution to remove the potential metal pollution. The Cd and Pb in blood (BCd, BPb) and urine (UCd and UPb) were measured by graphite-furnace atomic absorption spectrometry (GF-AAS) (Chen et al., 2014). Strict quality control was followed during the measurements (Chen

et al., 2014, 2019). Urinary creatinine was also determined to adjust the UCd and UPb. Urinary n-acetyl-β-D-glucosaminidase (UNAG) was determined as described in our previous study (Chen et al., 2019).

Hb determination and anemia definition

The red blood cell count, hematocrit, mean corpuscular volume (MCV), mean corpuscular hemoglobin concentration (MCHC), Hb were determined using an automatic blood cellcounter(XE5000, Sysmex, Japan). The following criteria were used to define anemia: Hb < 130 g/L in men or Hb < 120 g/L in women (WHO 1968).

Bone mineral density (BMD) determination

BMD was measured on proximal forearm of non-dominant upper limb using peripheral dual-energy X-ray absortiometry (pDEXA, Norland, USA). The repeatability of the results in same person was more than 99%. Quality assurance and phantoms scanning were performed every day. The BMD was measured by a same physician. Osteoporosis was defined by computing the T-score [T-score = (Xμ − Xm) / SD, where Xμ is the measured BMD, Xm is the average BMD of the same sex and young adults (30–40 years old) in the control area, and SD is the standard deviation of Xm] according to WHO criteria. T-score ≤ -2.5 was regarded as osteoporosis.

Statistical analysis

All statistical analysis was done in SPSS 16.0 (SPSS Inc., Chicago, IL, USA). The continuous data were shown as mean ± SD (SE) or median (IQR), and were analyzed by Independent-sample T test, Mann–Whitney *U*-test or one-way ANOVA followed by Bonferroni post hoc test. General linear model was also applied to compare the BMD between normal Hb group and anemia group (age and BPb were considered as covariates). Qualitative data were shown as number (percentage), and were compared by χ^2 test or Fisher' exact test. Linear regression was adopted to show association between Hb level and BMD after adjusting age. The association between prevalence of osteoporosis and anemia was evaluated by logistic regression analysis. Age, BMI, Pb and Cd level, smoking and drinking habits, and chronic kidney disease (CKD) or renal tubular dysfunction were regarded as covariates in three models. We further performed receiver operating characteristic (ROC) curve analysis and linear discriminant analysis (LDA) to show the performance of logistic model in predicting osteoporosis. Statistical significance was reached if $p < 0.05$.

Results

The characteristics of study population

The characteristics of study population are shown in Table 1. Significant differences were found in age, BCd, UCd, BPb, UPb, UANG, MCV, MCHC, prevalence of osteoporosis, CKD and anemia between subjects living in control area and polluted area ($p < 0.01$or 0.05). Women had lower Hb content than men (135.6 g/L vs 149.86 g/L, $p < 0.01$). BMD of women was significantly lower than that of men ($p < 0.01$). The prevalence of osteoporosis in women was higher than that in men (41.8% vs 15.7%, $p < 0.05$). There were no statistical differences in Cd and Pb levels, BMI, UNAG and prevalence of anemia between women and men. The BPb level in men with anemia was obviously higher than that with normal Hb ($p < 0.05$) (Table 2).

The association between BCd/ BPb and BMD

BMD was decreased with the increase in BCd and BPb both in men and women (Fig. 1). The BMDs of women that had the highest quartile BCd and BPb were markedly lower than that with the lowest quartile ($p < 0.05$). Such trends were observed in men, but there was no statistical significance.

Hb level/anemia and BMD/osteoporosis

Figure 2 shows that the BMD of subjects with anemia was lower than that with normal Hb. Significant decreases were observed in men ($p < 0.05$). Such trend was also found in men if considered the covariates of age and BPb ($p = 0.09$). Our data further showed that the prevalence of osteoporosis in men that had anemia was significantly higher than these that had normal Hb ($p < 0.01$) (Table 2). Correlation

Table 1 The characteristics of study population

	Control area (n = 158)	Polluted area (n = 144)	p	Women (n = 194)	Men (n = 108)	p
Age (y)[a]	55.85 ± 14.17	60.81 ± 14.4	< 0.01	56.8 ± 14.4	60.4 ± 14.5	< 0.01
BMI (kg/m^2)[a]	23.06 ± 3.13	23.91 ± 4.13	> 0.05	24.15 ± 3.87	23.13 ± 3.28	> 0.05
Alcohol drinking(yes)	54 (34.18%)	60(41.66%)	> 0.05	21(10.82%)	88(81.48%)	< 0.01
Smoking (yes)	43(27.21%)	34(23.61%)	> 0.05	6(3.09%)	72(66.67%)	< 0.01
Hb (g/L)[a]	141.86 ± 28.38	139.25 ± 27.41	> 0.05	135.6 ± 27.02	149.86 ± 28.24	< 0.01
BMD (g/cm^2)[a]	0.73 ± 0.14	0.69 ± 0.15	> 0.05	0.64 ± 0.13	0.83 ± 0.10	< 0.05
BPb (μg/L)[b]	74 (55.00–112.20)	133.2 (89.40–206.40)	< 0.01	100.80 (62.40–154.00)	103.20 (64.00–163.80)	> 0.05
UPb (μg/g cr)[b]	7.47 (4.27–12.35)	20.73 (13.87–35.78)	< 0.01	14.07 (7.97–26.02)	13.1 (6.20–24.04)	> 0.05
BCd (μg/L)[b]	1.54 (1.16–2.20)	4.04 (2.62–5.84)	< 0.01	2.32 (1.58–3.38)	2.48 (1.48–4.55)	> 0.05
UCd (μg/g cr)[b]	2.35 (1.28–4.82)	3.7	< 0.01	3.12	3.28	> 0.05
UNAG (U/g cr)[b]	12.20 (5.578–20.79)	(2.30–6.41) 22.42 (13.94–42.85)	< 0.01	(1.75–6.02) 16.67 (8.54–28.55)	(1.70–5.39) 18.62 (10.46–34.66)	> 0.05
OP (n/%)	33 (20.88%)	65 (45.13%)	< 0.05	81 (41.8%)	17 (15.7%)	< 0.05
Anemia (n/%)	28 (17.72)	43 (29.86%)	< 0.05	47 (24.2%)	24 (22.2%)	> 0.05
Red blood cell (× 10^{12}/L)	4. 54 ± 0.46	4.46 ± 0.39	> 0.05	4.24 ± 0.34	4.89 ± 0.56	< 0.05
Hematocrit(%)	42.87 ± 3.64	41.40 ± 3.32	> 0.05	40.45 ± 3.74	43.57 ± 4.43	< 0.05
MCV (fL)	92.38 ± 8.76	87.47 ± 7.96	< 0.05	89.12 ± 6.87	91.72 ± 6.43	> 0.05
MCHC(g/L)	342.38 ± 16.89	329.65 ± 18.74	< 0.05	334.54 ± 14.56	338.68 ± 16.84	> 0.05
CKD(n,%)	3 (1.90%)	12(8.33%)	< 0.01	11(5.67%)	4(3.70%)	> 0.05
Menopause (n,%)	59/93(63.44%)	74/101(73.26%)	< 0.01	133(68.56%)	–	

BMI body mass index; *Hb* hemoglobin; *BMD* bone mineral density; *BCd* cadmium in blood; *UCd* urinary cadmium; *BPb* lead in blood; *UPb* urinary lead; *OP* osteoporosis; *MCV* mean corpuscular Volume *MCHC* mean corpuscular hemoglobin concentration; *CKD* chronic kidney disease

[a]Data was shown as mean ± standard deviation

[b]Data was shown as median (IQR)

analysis also demonstrated that BMD was increased with the increasing of Hb levels in men (r = 0.24, $p < 0.01$) (Fig. 3), but not in women. Linear regression analysis further showed similar trend in men (β = 0.005, 95% confidence interval (CI): 0.001–0.012) after adjusting for age.

Risk of osteoporosis associated with anemia

Subsequently, we analyzed the association between osteoporosis and anemia in men and women using logistic regression analysis (Table 3). In men, significant associations were found between osteoporosis and age, anemia and BPb. The odds ratio (OR) of populations with anemia was 4.87 (95% confidence interval (CI):1.22–19.40) compared to that with normal Hb. After adjusted with the confounders, including age, BMI, gender, smoking and alcohol habits, Cd/Pb levels and CKD, the odds ratio was 11.28 (95%CI:1.94-65.54). Similar association was also observed when adjusting renal tubular function. For women, we only found the association between the risk of osteoporosis and age, OR = 1.18 (95%CI: 1.10-

Table 2 The characteristics of study population based on hemoglobin (Hb) levels

	Women			Men		
	Normal Hb (n = 147)	Anemia (n = 47)	p	Normal Hb (n = 84)	Anemia (n = 24)	p
Age (y)[a]	56.5 ± 14.1	56.6 ± 15.9	> 0.05	59.7 ± 13.9	67.4 ± 10.1	< 0.05
BMI (kg/m^2)[a]	24.26 ± 3.44	23.54 ± 4.96	> 0.05	23.07 ± 3.16	23.23 ± 3.40	> 0.05
Hb (g/L)[a]	145.58 ± 21.65	104.68 ± 16.73	< 0.01	159.87 ± 21.86	115.04 ± 21.10	< 0.01
BPb (μg/L)[b]	99.6 (65.60–167.80)	116.8 (62.40–162.80)	> 0.05	88 (56.00–152.4)	122.4 (77.00–227.20)	< 0.05
UPb (μg/g cr)[b]	12.83 (7.97–26.02)	15.78 (8.55–25.09)	> 0.05	11.79 (7.73–24.16)	15.84 (8.43–32.7)	> 0.05
BCd (μg/L)[b]	2.46 (1.45–4.24)	2.72 (1.42–4.94)	> 0.05	2.2 (1.58–3.88)	2.74 (1.71–3.24)	> 0.05
UCd (μg/g cr)[b]	3.39 (1.75–5.27)	3.07 (1.44–6.41)	> 0.05	2.9 (1.65–5.40)	3.39 (2.56–6.42)	> 0.05
UNAG (U/g cr)[b]	15.95 (17.37–39.04)	17.33 (8.16–33.16)	> 0.05	16.65 (9.32–34.56)	23.09 (16.13–46.86)	< 0.05
OP (n/%)	61(41.5%)	20(42.5%)	> 0.05	9(10.7%)	8(33.3%)	< 0.01

BMI: body mass index; Hb: hemoglobin; BMD: bone mineral density; BCd: cadmium in blood; UCd: urinary cadmium; BPb: lead in blood; UPb: urinary lead; OP: osteoporosis

[a]Data was shown as mean ± standard deviation

[b]Data was shown as median (IQR)

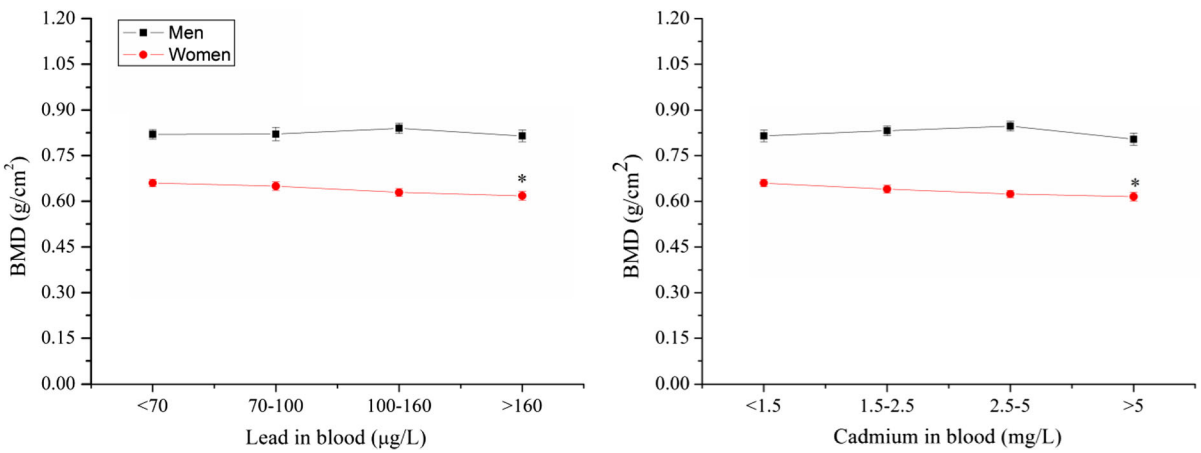

Fig. 1 The association between bone mineral density and cadmium/Lead in blood (BCd, BPb). The BPb and BCd were divided into four group based on interquartile range. The data was analyzed using general linear model (ANCOVA) considering age and was shown as mean with standard error.*$p < 0.05$ compared to the lowest quartile

1.26) for total population and OR = 1.18 (95%CI: 1.10-1.27) for women > 50 years old.

Based on the three risk factors obtained from logistic regression analysis, age, anemia and BPb in men, we established a model to predict the incident of osteoporosis. ROC curve demonstrated that the area under the curve was 0.88 (95%CI: 0.82-0.96) (Fig. 4). LDA showed that 89.7% of osteoporosis was correctly classified.

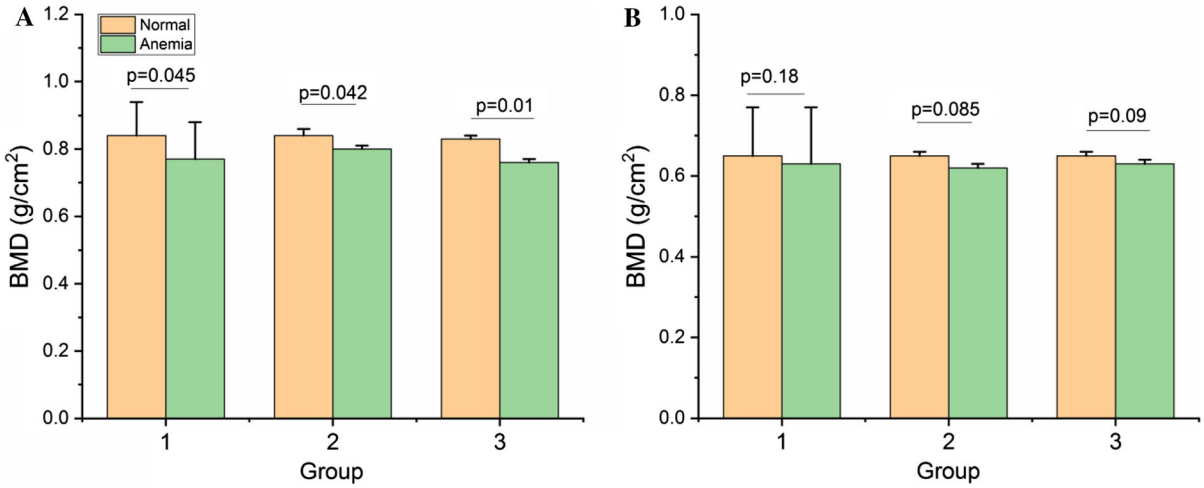

Fig. 2 Bone mineral density of subjects with and without anemia in men (**A**) and women (**B**). Group 1 was analyzed using Independent-sample T test and was shown as mean (standard deviation). Group 2, 3 were analyzed using general linear model (ANCOVA) considering age, and lead in blood as covariates (mean with standard error), respectively

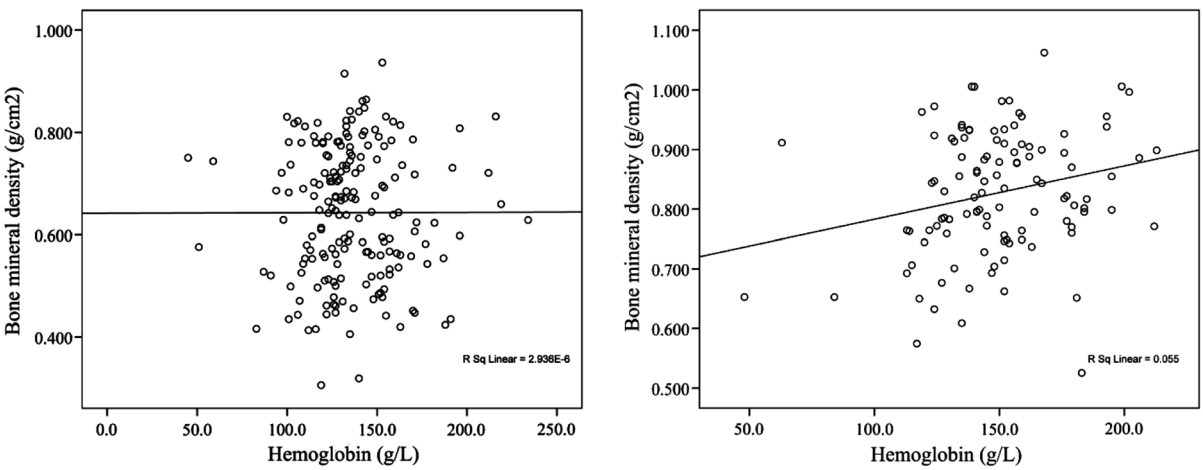

Fig. 3 Correlation analysis between bone mineral density and Hemoglobin levels in women (**left**) and men (**right**)

Discussion

Cd/Pb exposure are risk factors of osteoporosis or anemia (Chen et al., 2015; Jalili et al., 2020). Anemia is also a risk factor of osteoporosis or low bone mass (Lee et al., 2019). However, the association between low Hb level or anemia and osteoporosis in Cd/Pb-exposed population has not been clarified. In this study, we observed that anemia was associated with osteoporosis in men but not in women that environmentally exposed to Cd and Pb. The model based on age, anemia and BPb showed acceptable performance in predicting osteoporosis in men.

Exposure to Cd and the risk of osteoporosis have been widely investigated (Åkesson et al. 2006; Åkesson et al. 2014; Lim et al., 2016; Wallin et al., 2016). Cd exposure may inhibit bone formation and stimulate bone resorption (Bhattacharyya et al. 2009; Chen et al., 2009; Chen et al., 2013; Coonse et al., 2007;Buha et al., 2019). Our data showed that the BMD of women was decreased with the increasing of BCd. Our previous study demonstrated that women who had high BCd (> 2.0 μg/L) was at 1.5-fold higher risk of low bone mass than that had low one (Chen et al., 2014). All those results support that Cd exposure is a risk factor of bone loss.

Table 3 The association between osteoporosis (T score < -2.5) and anemia

	Men				Women			
	Model 1	Model2	Model3	Model 4	Model 1	Model2	Model3	Model 4
Age	1.13 (1.05–1.21)	1.13 (1.05–1.21)	1.13 (1.04–1.23)	1.15 (1.05–1.26)	1.22 (1.15–1.29)	1.23 (1.16–1.30)	1.18 (1.10–1.26)	1.18 (1.10–1.27)
Anemia (yes vs no)	4.87 (1.22–19.40)	4.84 (1.20–19.50)	11.28 (1.94–65.54)	19.56 (2.98–128.78)	1.88 (0.62–5.71)	1.96 (0.63–6.10)	2.05 (0.83–5.08)	2.71 (0.83–8.80)
BPb(≥ 100 vs < 100)	4.34 (1.06–17.71)	4.32 (1.05–17.83)	8.1 (1.28–51.15)	3.8 (0.85–17.22)	1.39 (0.56–3.46)	1.42 (0.56–3.62)	1.24 (0.50–3.14)	1.16 (0.44–3.05)
BMI (kg/m^2)	0.89 (0.71–1.12)	0.89 (0.71–1.12)	0.77 (0.58–1.04)	0.82 (0.64–1.07)	0.98 (0.88–1.10)	0.98 (0.87–1.09)	0.99 (0.89–1.11)	0.98 (0.87–1.10)

BMI: body mass index; BPb: lead in blood

Model 2 was adjusted for BCd, UCd, drinking and smoking habits

Model 3 was additionally adjusted for chronic kidney disease (CKD) and/or menopausal status (women)

For men, Model 4 was adjusted for BCd, UCd, drinking and smoking habits and renal tubular dysfunction; For women, Model 4 was adjusted for BCd, UCd, drinking and smoking habits, menopausal status, CKD and renal tubular dysfunction for women > 50 years old

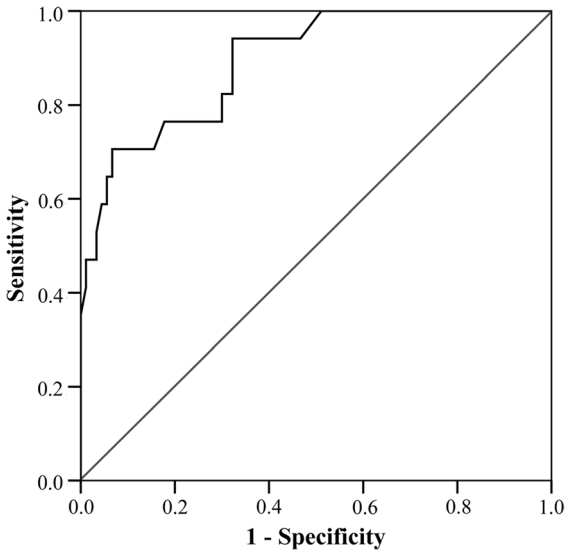

Fig. 4 Receiver operating characteristic (ROC) curve analysis to show the performance of logistic model in predicting osteoporosis in men. The area under the curve was 0.88

Bone is the main organ for Pb accumulation. Some studies demonstrate that Pb exposure is associated with bone loss (Campbell & Auinger, 2007; Jalili et al., 2020). The possible mechanism is that Pb can inhibit the activity and differentiation of osteoblasts (Al-Ghafari et al., 2019; Puzas et al., 1992). Our data show that BPb is a risk factor of osteoporosis in men but not in women. Interestingly, similar result was found in the US adults population (Campbell & Auinger, 2007).

Cd and Pb exposure are also risk factors of low Hb level or anemia (Hu et al. 1994; Horiguchi, 2007; Li et al., 2018). What's more, low Hb level or anemia is a risk factor of osteoporosis and bone fractures (Cesari et al., 2005; Lee et al., 2019; Oh et al., 2017). Did low Hb or anemia play some modified role in Cd/Pb related bone loss? Few data were found in published literatures. Our study found that anemia was associated with incident of osteoporosis in men which indicated that anemia or Hb should be considered in investigating the effects of Cd/Pb on bone. However, no such association was found in women. It is unclear why the risk of osteoporosis differs between sexes, but sex hormones may play important roles (Lee et al., 2019). Age may be another factor. The age of women was younger than men. The association between Hb level or anemia and bone health was mainly observed in older persons (Cesari et al., 2005; Lee et al., 2019). In our study, the age of men was significantly older than women. For those women > 50 years, the association between anemia and osteoporosis became more strong though there was no statistical significance (p = 0.10).

The possible mechanism of Cd and Pb related anemia has been studied. Pb exposure can inhibit pyrimidine 5' nucleotidase activity, decrease the heme amount and cause erythrophagocytosis and

externalization of phosphatidylserine in red blood cells (Zhang et al., 2020). Pb also affects the enzymatic system involved in heme synthesis (Mitra et al., 2017), such as e d-aminolevulinic acid dehydratase (ALAD), aminolevulinic acid synthetase (ALAS). Cd may induce anemia by disturbing iron metabolism and erythropoietin (EPO) production (Zhang et al., 2020). In addition, Cd/Pb exposure increases the production of reactive oxygen species which can cause damage of red blood cell membranes and hemolytic anemia (Mitra et al., 2017).

The possible mechanism of low Hb or anemia-related bone loss is incompletely understood. The critical function of Hb is oxygen-transporting. Chronic hypoxia may be harmful to bone formation by impairing oxygen delivery (Hardy & Cooper, 2009). In addition, hypoxia can stimulate osteoclast differentiation and bone resorption (Arnett et al., 2003; Knowles, 2015; Utting et al., 2010). Hypoxia may induce an acidic microenviroment in bone which can stimulate osteoclast activity (Arnett et al., 2003). Moreover, Hb level is also related with nutritional status, such as iron and B_{12} deficiency. Nutritional status is an important determination factor for bone health (Ettinger, 2003). Iron deficiency may inhibit bone formation (Medeiros et al., 2004; Zhao et al., 2012).

Our study has several limitations. First, we did not have a big sample size of men population. Second, there may be unmeasured confounders, such as iron deficiency and vitamin D level and other metals exposure, although we considered the modified effects of CKD, BMI and drinking habits. Third, previous study indicated that incident of facture was related with anemia. However, this association was not investigated in our study. Fourth, we did not show the interaction of Cd/Pb exposure on bone or anemia because those data have been shown in our previous studies (Chen et al., 2014, 2015). Finally, the BMD was measured at proximal forearm which is the cortical bone, the generalization of our results to vertebral bone or trabecular bone required further exploration.

Conclusion

In conclusion, we observe that anemia is a negative and independent risk of osteoporosis in men but not in women that environmentally exposed to Cd and Pb. Age, BPb and anemia are important factors that are related to osteoporosis in men. A model based on the three factors showed acceptable performance in predicting osteoporosis. Hb level or anemia should be considered when aim to show the association between Pb or Cd exposure and bone loss, in particular to men population.

Acknowledgements This study was funded by National Natural Science foundation of China (No. 81773460, 81102148) and Natural Science Foundation of Jiangsu Province (no. BK20161609).

Data availability Data or materials used in the study are available from the corresponding author by request.

Declarations

Conflicts of interest The authors declare that there are no conflicts of interest.

Consent to participate Informed consent was obtained from each participate.

Consent for publication Consent was obtained from each author.

Ethical approval We obtained the approval from the Institutional Review Board of Fudan University. Declaration of Helsinki was followed during the study.

References

Akesson, A., Bjellerup, P., Lundh, T., Lidfeldt, J., Nerbrand, C., Samsioe, G., et al. (2006). Cadmium-induced effects on bone in a population-based study of women. *Environmental Health Perspectives, 114*, 830–834.

Åkesson, A., Barregard, L., Bergdahl, I. A., Nordberg, G. F., Nordberg, M., & Skerfving, S. (2011). Non-renal effects and the risk assessment of environmental cadmium exposure. *Environmental Health Perspectives, 122*, 431–438.

Al-Ghafari, A., Elmorsy, E., Fikry, E., Alrowaili, M., & Carter, W. G. (2019). The heavy metals lead and cadmium are cytotoxic to human bone osteoblastsvia induction of redox stress. *PLoS One, 14*, e0225341.

Arnett, T. R., Gibbons, D. C., Utting, J. C., Orriss, I. R., Hoebertz, A., Rosendaal, M., et al. (2003). Hypoxia is a major stimulator of osteoclast formation and bone resorption. *Journal of Cellular Physiology, 196*, 2–8.

Bhattacharyya, M. H. (2009). Cadmium osteotoxicity in experimental animals: Mechanisms and relationship to

human exposures. *Toxicology and Applied Pharmacology, 238*, 258–265.

Bi, X., Feng, X., Yang, Y., Qiu, G., Li, G., Li, F., et al. (2006). Environmental contamination of heavy metals from zinc smelting areas in Hezhang County, western Guizhou. *China. Environment International, 32*, 883–890.

Buha, A., Jugdaohsingh, R., Matovic, V., Bulat, Z., Antonijevic, B., Kerns, J. G., et al. (2019). Bone mineral health is sensitively related to environmental cadmium exposure-experimental and human data. *Environmental Research, 176*, 108539.

Campbell, J. R., & Auinger, P. (2007). The association between blood lead levels and osteoporosis among adults–results from the third national health and nutrition examination survey (NHANES III). *Environmental Health Perspectives, 115*, 1018–1022.

Cesari, M., Pahor, M., Lauretani, F., Penninx, B. W. H. J., Bartali, B., Russo, R., et al. (2005). Bone density and hemoglobin levels in older persons: Results from the InCHIANTI study. *Osteoporosis International, 16*, 691–699.

Chen, X., Zhu, G., Gu, S., Jin, T., & Shao, C. (2009). Effects of cadmium on osteoblasts and osteoclasts in vitro. *Environmental Toxicology and Pharmacology, 28*, 232–236.

Chen, X., Wang, G., Li, X., Gan, C., Zhu, G., Jin, T., et al. (2013). Environmental level of cadmium exposure stimulates osteoclast formation in male rats. *Food and Chemical Toxicology, 60*, 530–535.

Chen, X., Wang, K., Wang, Z., Gan, C., He, P., Liang, Y., et al. (2014). Effects of lead and cadmium co-exposure on bone mineral density in a Chinese population. *Bone, 63*, 76–80.

Chen, X., Zhou, H., Li, X., Wang, Z., Zhu, G., & Jin, T. (2015). Effects of lead and cadmium co-exposure on hemoglobin in a Chinese population. *Environmental Toxicology and Pharmacology, 39*, 758–763.

Chen, X., Zhu, G., Wang, Z., Zhou, H., He, P., Liu, Y., et al. (2019). The association between lead and cadmium co-exposure and renal dysfunction. *Ecotoxicology and Environmental Safety, 173*, 429–435.

Chwalba, A., Maksym, B., Dobrakowski, M., Kasperczyk, S., Pawlas, N., Birkner, E., et al. (2018). The effect of occupational chronic lead exposure on the complete blood count and the levels of selected hematopoietic cytokines. *Toxicology and Applied Pharmacology, 355*, 174–179.

Coonse, K. G., Coonts, A. J., Morrison, E. V., & Heggland, S. J. (2007). Cadmium induces apoptosis in the human osteoblast-like cell line Saos-2. *Journal Toxicology Environmental Health. Part A, 70*, 575–581.

Dobrakowski, M., Boroń, M., Czuba, Z. P., Birkner, E., Chwalba, A., Hudziec, E., et al. (2016). Bloodmorphology and the levels of selected cytokines related to hematopoiesis in occupational short-term exposure to lead. *Toxicology and Applied Pharmacology, 305*, 111–117.

Ettinger, M. P. (2003). Aging bone and osteoporosis-strategies for preventing fractures in the elderly. *Archives of Internal Medicine, 163*, 2237–2246.

Fujimoto, H., Fujimoto, K., Ueda, A., & Ohata, M. (1999). Hypoxemia is a risk factor for bone mass loss. *Journal of Bone and Mineral Metabolism, 17*(3), 211–216.

Guralnik, J. M., Eisenstaedt, R. S., Ferrucci, L., Klein, H. G., & Woodman, R. C. (2004). Prevalence of anemia in persons 65 years and older in the United States: Evidence for a high rate of unexplained anemia. *Blood, 104*, 2263–2268.

Hardy, R., & Cooper, M. S. (2009). Bone loss in inflammatory disorders. *Journal of Endocrinology, 201*, 309–320.

Horiguchi, H. (2007). Anemia Induced by Cadmium Intoxication. *Nihon eiseigakuzasshi. Japanese journal of hygiene, 62*, 888–904.

Jalili, C., Kazemi, M., Taheri, E., Mohammadi, H., Boozari, B., Hadi, A., et al. (2020). Exposure to heavy metals and the risk of osteopenia or osteoporosis: a systematic review and meta-analysis. *Osteoporosis International*. https://doi.org/10.1007/s00198-020-05429-6

Jørgensen, L., Skjelbakken, T., Løchen, M.-L., Ahmed, L., Bjørnerem, A., Joakimsen, R., et al. (2010). Anemia and the risk of non-vertebral fractures: The Tromsø Study. *Osteoporosis International, 21*, 1761–1768.

Knowles, H. J. (2015). Hypoxic regulation of osteoclast differentiation and bone resorption activity.*Hypoxia (Auckland, N.Z.)* ,3,73–82.

Lee, E. A., Shin, D. W., Yoo, J. H., Ko, H. Y., & Jeong, S. M. (2019). Anemia and risk of fractures in older Korean adults: A nationwide population-based study. *Journal of Bone and Mineral Research: The Official Journal of the American Society for Bone and Mineral Research, 34*, 1049–1057.

Li, C., Ni, Z. M., Ye, L. X., Chen, J. W., Wang, Q., & Zhou, Y. K. (2018). Dose-response relationship between blood lead levels and hematological parameters in children from central China. *Environmental Research, 164*, 501–506.

Lim, H. S., Lee, H. H., Kim, T. H., & Lee, B. R. (2016). Relationship between heavy metal exposure and bone mineral density in Korean adult. *Journal of Bone Metabolism, 23*, 223–231.

Medeiros, D. M., Stoecker, B., Plattner, A., Jennings, D., & Haub, M. (2004). Iron deficiency negatively affects vertebrae and femurs of rats independently of energy intake and body weight. *Journal of Nutrition, 134*, 3061–3067.

Mitra, P., Sharma, S., Purohit, P., & Sharma, P. (2017). Clinical and molecular aspects of lead toxicity: An update. *Critical Reviews in Clinical Laboratory Sciences., 54*, 506–528.

Nakhaee, S., Amirabadizadeh, A., Brent, J., & Mehrpour, O. (2019). Impact of chronic lead exposure on liver and kidney function and haematologic parameters. *Basic & Clinical Pharmacology & Toxicology, 124*, 621–628.

Oh, Y. H., Moon, J. H., & Cho, B. (2017). Association between hemoglobin level and bone mineral density in Korean adults. *Journal of Bone Metabolism, 24*, 161–173.

Puzas, J. E., Sickel, M. J., & Felter, M. E. (1992). Osteoblasts and chondrocytes are important target cells for the toxic effects of lead. *Neurotoxicology, 13*, 783–788.

Rutten, E. P. A., Franssen, F. M. E., Spruit, M. A., & Wouters, E. F. M. (2013). Anemia is associated with bone mineral density in chronic obstructive pulmonary disease. *COPD, 10*, 286–292.

Utting, J. C., Flanagan, A. M., Brandao-Burch, A., Orriss, I. R., & Arnett, T. R. (2010). Hypoxia stimulates osteoclast formation from human peripheral blood. *Cell Biochemistry Function, 28*, 374–380.

Valderrábano, R. J., Lee, J., Lui, L. Y., Hoffman, A. R., Cummings, S. R., Orwoll, E. S., & Wu, J. Y. (2017). Older men with anemia have increased fracture risk independent of

bone mineral density. *The Journal of Clinical Endocrinology and Metabolism, 102*, 2199–2206.

Wallin, M., Barregard, L., Sallsten, G., Lundh, T., Lorentzon, M., Mellström, D., et al. (2016). Low-level cadmium exposure is associated with decreased bone mineral density and increased risk of incident fractures in elderly men: The MrOS Sweden study. *Journal of Bone and Mineral Research: The Official Journal of the American Society for Bone and Mineral Research, 31*, 732–741.

Watanabe, H., Payton, M., Korrick, S., & Rotnitzky, A. (1994). The relationship between bone lead and hemoglobin. *JAMA, 272*, 1512–1517.

World Health Organization. (1968). Nutritional anaemias. Report of a WHO Scientific Group. Technical Report Series No. 405. World Health Organization, Geneva

Zhang, S., Sun, L., Zhang, J., Liu, S., Han, J., & Liu, Y. (2020). Adverse Impact of Heavy Metals on Bone Cells and Bone Metabolism Dependently and Independently through Anemia. *Advanced Science (weinh), 7*, 2000383.

Zhao, C., Thomson, C. A., Mikel, A., Nicholas, J. S., David, V. W., Lewis, C. E., et al. (2010). The relationship between incidence of fractures and anemia in older multiethnic women. *Journal of the American Geriatrics Society, 58*, 2337–2344.

Zhao, G. Y., Zhao, L. P., He, Y. F., Li, G. F., Gao, C., Li, K., et al. (2012). A comparison of the biological activities of human osteoblast hFOB1.19 between iron excess and iron deficiency. *Biological trace element research, 150*, 487–495.