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Blood lead and cadmium levels associated with hematological and hepatic functions in patients from an e-waste-polluted area

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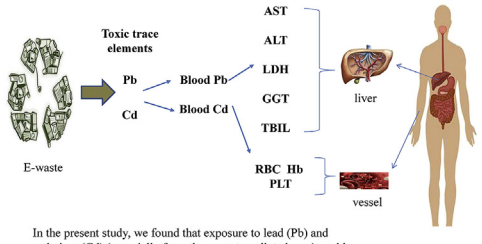
HIGHLIGHTS

- Liver enzymes and red blood cells are affected by blood Pb and Cd.
- Toxic trace metals in blood reflect the burden of liver and red blood cells.
- Risk of abnormal liver function is linked with exposure of Pb and Cd.
- The exposed area is considered as the entry point to explore human liver health.

GRAPHICAL ABSTRACT



In the present study, we found that exposure to lead (Pb) and cadmium (Cd) (especially from the e-waste-polluted area) could affect human hematological and hepatic functions.

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ABSTRACT

Chronic exposures to toxic trace metals have hazardous effects on human health, especially exposure to lead (Pb) and cadmium (Cd). Blood Pb and Cd reflect toxicity on human health. A total of 267 hospitalized patients, of which 158 were from Guiyu (exposed group) in China, and 109 from Jinping (reference group), were recruited in this study. Blood Pb and Cd were measured by graphite furnace atomic absorption spectrometry. Blood Pb and Cd levels from the exposed group were both higher than in the reference group. Blood Pb levels are positively associated with blood Cd levels from the two groups. Blood Pb and Cd levels are associated with elevated hematological and hepatic parameters in patients from the exposed and reference groups. The results suggest toxic trace metals may increase liver metabolic burden, inducing abnormal liver function.

1.1. Introduction

Lead (Pb) and cadmium (Cd) are typical toxic trace metals that are widely found in electronic waste (e-waste) recycling areas. Environmental exposure to these toxic trace metals occurs primarily through smoking and industrial plant emissions, and

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through contaminated food and water (Verougstraete et al., 2003; Satarug and Moore, 2004). Lead has a half-life period of 27–36 days in blood, 30–40 days in tissue and approximately 104 days in bone while Cd has a half-life period of 15–30 years and accumulates in the liver as the main target tissue (Bernard, 2004). A series of animal studies, including mammals and poultry, by Biehusen and Pulaski (1956), show an increase in hepatic cells in response to toxic trace metals. Ten times higher levels of Pb and 40 times higher Cd levels are measured in green turtle livers in South China compared with the reference area (Ng et al., 2018). Two species have high levels of Pb and Cd in livers (Afonso et al., 2018). Exposure to Pb and Cd causes toxic effects in the liver (Tomaszewska et al., 2015).

Blood Pb can bind to iron (Fe), and interferes with cell function which dependent on Fe, such as the formation of hemoglobin, resulting in hypochromic anemia. High levels of blood Pb have been reported to cause impaired cognitive development and anemia (Lubran, 1980). Once Pb gets into the circulation, blood Pb levels reflect the balance between absorption and storage in tissues (Needleman et al., 1979). The level of concern for blood Pb in children is originally set at 10 μg/dL by the U. S. Center for Disease Control and Prevention (CDC) (Centers for Disease and Prevention Advisory Committee on Childhood Lead Poisoning, 2007). This is later amended to 5.0 μg/dL (Betts, 2012). Among various Pb deposit locations, the liver is the largest lead bank in human body (Mudipalli, 2007). Oxidative stress toxicity mainly affects the hematopoietic systems, as well as the liver (Matović et al., 2015). In the dynamics of exogenous toxicology, the liver is the target organ of blood circulation and metabolism (Ergen et al., 2017). Adverse effects of the liver and kidney are found in animals and humans exposed to Pb (Singh et al., 2018). Lead similarly causes serious damage to the liver (Harrington, 2000). Lymphoma protein of B-cell 2 (Bcl-2) and the associated X protein (Bax) are apoptosis related proteins. Apoptosis of hepatic cells is induced by low-dose exposure to Pb, which is associated with levels of Bcl-2, Bax (Yuan et al., 2014). Lead can influence the expression of tumor protein 53 (P53), protein Bcl22, and Bax in the body. The Bcl22 gene family is known to inhibit cell apoptosis during the process of apoptosis regulation. Bax promotes cell apoptosis, increasing the ratio of Bax/Bcl22 (Sharifi et al., 2002; Xin and Deng, 2006).

Studies have shown that Cd damage to cells is caused mainly by the production of reactive oxygen species (ROS) (Stohs and Bagchi, 1995), resulting in single strand damage and destruction of nucleic acid (Mitra, 1984). Stress response systems exposed to Cd demonstrate abnormal levels of heat shock protein, stress response protein, cold shock protein and DNA polymerase (Blom et al., 1992). Metallothionein (MT) was used as the environmental monitoring index to demonstrate oxidative damage to the liver and kidney of rats exposed to Cd. This toxic trace metal can cause liver or renal cell apoptosis in a low dose of exposure (Matović et al., 2015).

Concentrations of toxic trace metals in the liver, kidney and blood showed that Pb and Cd are the most important toxic trace metals for the pollution gradient studied by Vanparys et al. (2008). Increased aspartate aminotransferase (AST) activity and total bilirubin (TBIL) concentrations in serum of animals that are exposed to Pb and Cd which are found to be positively correlated with blood Pb and Cd (Tomaszewska et al., 2015). The activity of alanine aminotransferase (ALT), AST and gamma glutamyl transpeptidase (GGT) also increases significantly in the blood of mice that are exposed to toxic trace metals, such as Pb and Cd (Al-Attar, 2011). The enzyme GGT mainly comes from the liver. It can be used as a sensitive indicator of liver function. The presences of toxic trace metals such as Pb and Cd are the significant risk factor for fatty liver disease in men (Lin et al., 2017). It can be inferred that chronic exposure to toxic trace metals, such as Pb and Cd, has adverse effects on the liver of humans. Thus, we conducted a study of blood Pb and Cd levels and clinical characteristics of patients in the exposed and reference groups to evaluate the environment exposure risk to human liver health.

2. Materials and methods

2.1. Ethics statement

This study was approved by the First Affiliated Hospital of Shantou University Medical Ethics Committee.

2.2. Participants

A total of 267 participants in exposed and reference areas respectively were enrolled from hospitals. Jinping was selected as a reference area because of its relatively low exposure to e-waste-pollution, while it has similar cultural background and social and economic status to Guiyu. The first phase of the study occurred from January 2015 to March 2015, during which 267 subjects were enrolled in the exposed ($n = 158$) and reference groups ($n = 109$). The experimental design excluded subjects with heart or kidney diseases. People with a history of alcohol consumption and smoking were also excluded. We eliminated subjects consuming drugs which have hepatic toxicity, such as glucurolactone and antibiotic and antiviral drugs. Basic information was obtained from medical records. The second phase of the study occurred between May 2015 and June 2015. Liver function was measured at the beginning of hospitalization, before any treatment was administered.

2.3. Blood sample collection and assay

A total of 5 ml of venous blood was collected in the morning from each patient by trained nurses. The patients were required to have 8–10 h of fasting. Approximately 2 ml of the blood was collected in plastic tubes that were filled with EDTA-K2 and stored in a −20 °C refrigerator, and 3 ml of the blood was collected in no added anticoagulant tubes for liver function tests in 2 h. Measurements of blood Pb and Cd were performed by graphite furnace atomic absorption spectrometry (GFAAS, Jena Zeenit 650, Germany) (Xu et al., 2018). All plastic tubes were washed thoroughly, soaked in dilute nitric acid overnight, rinsed with deionized water and dried before use. The main parameters of the blood Pb measurement procedure were a wavelength of 283.3 nm, a lamp current of 4 mA, a slit width of 0.8 nm, drying at 120 °C, ashing at 600 °C, atomizing at 1500 °C and cleaning at 2300 °C. The parameters for blood Cd analysis were a wavelength of 228.8 nm, a lamp current of 2.5 mA, a slit width of 0.8 nm, drying at 120 °C, ashing at 300 °C, atomizing at 900 °C and cleaning at 2100 °C. Rates of the recoveries in the experiments were between 96 and 108%. A Jena Zeenit 650 atomic absorption spectrophotometer was used to measure the concentrations of Pb and Cd in blood, and a biomechanical analyzer AU5800 was used to measure and the level of TBIL and the enzyme activity of AST, ALT, GGT and lactic dahydrogenase (LDH).

2.4. Data analysis

Descriptive statistics were used to assess patient demographics for each group. Student's *t*-tests and Chi-square tests were used to examine the differences of blood toxic trace metal levels between

the two groups. Spearman rank correlation and multiple stepwise regression analysis were used to explore the relationship between blood Pb and Cd and clinical data of patients from the e-waste-polluted area. A significance level of alpha 0.05 was employed. All statistical analyses were conducted by SPSS version 19.0. GraphPadPrism5 software was used for windows statistical package.

3. Results

3.1. Demographic information, toxic trace metals in blood, and clinical indexes in the exposed and reference groups

The recruitments' mean age (and corresponding SD) was 44 ± 1.6 years in the exposed group and 47 ± 1.9 years in the reference group (range, 4–85 years) (Table A.1). There were more males than females in both groups. A higher median activity of serum GGT was found in the exposed group, 1.6 times greater than the reference group ($p < 0.005$). In the blood routine test, RBC was 7.1% higher in the exposed group than in the reference group. The median level of blood Pb was 71% greater in the exposed group ($p < 0.005$).

3.2. Toxic trace metals in blood and clinical indexes in different sex

Table A.2 shows that the median activity of male GGT in serum was double that in the exposed group ($p < 0.01$). The median activity of female GGT in serum in the exposed group was 1.6 times higher than in the reference group ($p < 0.005$). In the blood routine test, male RBC was 9.5% higher in the exposed group than in the reference group ($p < 0.001$). Female RBC in exposed group was 4.9% greater in the exposed group ($p < 0.05$). The median level of blood Pb was 70.6% higher in the exposed subjects ($p < 0.001$) (Fig A. 1).

3.3. Toxic trace metals in blood and clinical indexes by age group

The results presented in Table A. 3 show patients above 40 years old from the exposed group had a 2.9 times higher activity of GGT in serum in contrast to patients from the reference group ($p < 0.01$). The levels of blood Pb and Cd were elevated with age. Patients above 40 years old from the exposed group had a 72.2% higher blood Pb in serum in contrast to patients above 40 years old from the reference group ($p < 0.01$). Patients below 40 years old from the exposed group had a 59% higher activity of blood Pb ($p < 0.01$). Patients above 40 years old from the exposed group had a 3.7% higher blood Cd in serum in contrast to patients above 40 years old from the reference group ($p < 0.05$).

3.4. Spearman correlation coefficient (r_s) –analysis of association between toxic trace metals in blood and clinical indexes

The results presented in Table B show a significant positive correlation between blood Pb levels and the activity of ALT, RBC and Hb in patients from the two groups. Patients' blood Cd levels were also correlated with AST and ALT. Blood Pb and Cd were both positively associated with ALT. Blood Pb was positively associated with Cd in both groups.

3.5. Multiple stepwise regression analysis

Abnormal liver function was defined to be either more than two kind of transaminases (AST, ALT, and GGT) elevating above normal range or one kind of transaminases at least twice higher than normal range. Multiple stepwise regression analysis was used to explore influencing factors for people with abnormal liver function in the two groups. Exposure to Pb and Cd has a certain toxic effect on liver function, potentially inducing liver disorder in patients with hepatitis. Blood Pb levels were divided into high and low groups by the threshold value of 5 μg/dL (P_{25}), and blood Cd levels were divided in high and low groups by the threshold value of 2.4 μg/dL (P_{50}). The effects on abnormal liver functions were adjusted by logistic regression analysis. Both blood Pb and blood Cd are statistically significant in the regression model ($p < 0.05$). The odd ratio (OR) of blood Pb (≥5 μg/dL) is 1.936 (Table C). We conclude that exposure to Pb is hazardous, inducing abnormal liver function.

4. Discussion

Guiyu is a historical e-waste dismantling center in Guangdong province in China. Previous studies have shown that child blood Pb and Cd levels in Guiyu are significantly higher than those from the proximal areas (Zhang et al., 2011; Yang et al., 2013). Blood Pb and Cd are significantly higher in Guiyu than Haojiang (Zeng et al., 2018). Occupational exposure to Pb and Cd can result in serious harm to various organs and tissues at varying degrees (Gerhardsson et al., 1993). The toxic effect of most elements depends mainly on the absorption, concentration, and persistence of the element (Langman and Kapur, 2006). Concentrations of toxic trace metals in the liver, kidney and peripheral blood show a gradient distribution (Vanparys et al., 2008). Exposure to toxic trace metals can affect hematological and liver function (Korolenko et al., 2007; Mojiminiyi et al., 2008).

The toxic mechanisms of non-oxidation-reduction trace metals were reviewed by Matović et al. (2015), including Pb and Cd, which cause the damage to liver and kidney by inducing oxidative stress synergistically and cellular lipid, protein, and DNA oxidative damage and inflammatory markers in the liver. In wild boars, Pb and Cd mainly accumulate in the liver (Rudy, 2010). These studies show that low levels of Pb and Cd exposure can promote apoptosis of several parenchyma cells in the liver or kidney, and ultimately affect their function. Toxic trace metals such as Pb and Cd are also known to increase hepatitis viral activity (Gainer, 1974; Checconi et al., 2013). The levels of patient' blood Pb and Cd which were higher in the exposed group.

The liver has a high functional reserve capacity and only shows dysfunction when approximately 50% of the hepatocytes are affected (Pillai et al., 2009). The measurements of AST, ALT, LDH, and GGT were based on the recommendations of the International Federation of Clinical Chemistry (IFCC) (Shaw et al., 1983; Bais and Philcox, 1994; Schumann et al., 2002b, a). Normal reference ranges of key indicators, such as AST: 8–40 U/L, ALT: 5–40 U/L, TBIL: 3.4–17.1 μ mol/L, GGT <40 U/L, and LDH: 230–460 U/L, can reflect human liver health.

Increasing numbers of researchers consider that the presence of liver disease or the rise of ALT leads to the inability of hepatocytes to detoxify pollutants. As a result, the levels of pollutants rise in blood (Cave et al., 2010). When liver cells are damaged, certain liver enzymes are released into the blood, causing the serum transaminase activity to increase. Elevated level of serum enzyme of ALT is considered as a sign of hepatitis hepatic necrosis (Afzali et al., 2010). Therefore ALT can be used as a common biomarker of liver cell injury in clinical diagnosis. Significant increases of ALT and AST are measured in toxic trace metals-treated mice (Green and Flamm, 2002; Al-Attar, 2011). Elevated serum concentrations of ALT and AST above the normal ranges have also been reported in cement workers (Richard et al., 2016). Changes in liver function are closely

related to exposure to excessive toxic trace metals in the environment. In the e-waste area, the serum levels of AST, ALT and TBIL exceeded the limits of normal liver function. In the present study, blood Pb and Cd levels are significant associated with ALT in both groups ($p < 0.05$). These results are consistent with the previous studies discussed above.

The Cd-exposed mice develop morphological disorders in the liver and kidney (Wang et al., 2017). In this study, we found approximately 48.1% patients in Guiyu had various kinds of liver diseases. The present study demonstrates Cd is the influencing factors for people with abnormal liver function (Table C). Vitamin E has been suggested as protecting against Cd-induced liver injury, affecting the expression of GGT (Al-Attar, 2011). Cadmium can lead to mitochondrial oxidative stress and apoptosis in duck livers (Dai et al., 2018). Cadmium has significant toxicity on liver tissue in the freshwater turtle in a dose-dependent manner (Huo et al., 2017). Exposure to Cd alone causes oxidative stress in fish as reflected by reduced thiol redox, increased lipid peroxidation, and induction of anti-oxidative enzymes in the liver (Jamwal et al., 2018). In the research of Milnerowicz et al. (2010), occupational exposure of smelter workers to heavy metals such as Cd lead to GGT activity to be higher than that of the corresponding reference group. Their research suggests that heavy metal structures have toxic effects on the liver. Cd-exposed mice developed morphological disorders in the liver and kidney (Wang et al., 2017). Tomaszewska et al. (2015) added Cd to the diet of rats, and measured jejunum epithelial, liver, hematology and blood biochemical parameters. They find elevated ALT and AST, and structural changes in the liver, such as a small amount of steatosis and increased intercellular space. The enzyme of GGT is found mainly in liver cells and in the bile duct epithelium in the human liver. Serum GGT is linearly associated with important environment pollutants, such as Cd (Lee and Jacobs, 2009). As expected, there is a higher median activity of serum GGT in the exposed group, 1.6 times greater than in the reference group ($p < 0.005$).

In humans, blood Pb is positively associated with AST, while levels of blood Pb and Cd are positively correlated with AST activity and TBIL concentration in animals (Rey et al., 1997; Yuan et al., 2014). Several studies shows that Pb toxicity is firstly detected in bone, then in the liver. Toxic trace metals in food mostly affect the function of the liver and kidney (Nascimento et al., 2016; Samuel-Nakamura et al., 2017). Through multiple stepwise regression analysis, we found that one of the hazardous factors to abnormal liver function in humans was blood Pb (Table C).

Blood Pb commonly inhibits the activity of the ALAD enzyme in anemia (Feksa et al., 2012). Lead has a variety of hematological effects including anemia (Tomaszewska et al., 2015). However, we find there are significant increases in the Hb and RBC counts in response to exposure to Pb in our study (Table A.1). The present result is consistent with previous studies that blood Pb level is positively correlated with RBC ($r = 0.334$, $p < 0.01$) and hemoglobin ($r = 0.321$, $p < 0.01$) (Haider and Qureshi, 2013). There may be co-exposure of several toxic trace metals in the environment, such as Cu, Fe, and zinc (Zn), affecting the hematological toxicity of Pb and Cd (Roney et al., 2011; Massanyi et al., 2014).

In Table A.3, we find that blood Pb and Cd levels increase according to age. This has been reflected in animal research. It is found that older animals have higher Cd concentrations in the liver and kidney (Tomaszewska et al., 2015). One possible reason may be long-term of exposure, which is supported by the study of intestinal and liver toxicity of adult mice with long-term high Pb and Cd pollution (Butler Walker et al., 2006).

Some animal experiments suggest the exposure levels of toxic trace metals are affected by gender. Concentrations of Cd in the livers of female dogs are higher than that in male dogs, and the level of Cd in the liver, renal cortex and renal medulla and the concentration of Pb in the liver are higher than that in the male dogs. Female dogs have higher tissue concentrations of Pb and Cd in the liver than male dogs (Passlack et al., 2015). In the present study, blood Pb and Cd concentrations are differentiated by gender. The differences of blood lead, RBC and Hb were significantly distinguished by gender ($p < 0.05$).

The liver is the major target organ in long-term occupational or environmental exposure to pollutants. Previous studies have shown that the main cause of human exposure to Cd is smoking (Benedetti et al., 1992, 1994). Thus, this study excluded alcohol, smoking and drugs factors.

There are several limitations in this study. First, the general public was not sampled, instead local hospital patients. The present study was conducted in a cross-section design, and blood samples were limited to measure more pollutants. The variation in timing of measurements might have an impact on the findings. However, baseline blood levels were considered the most stable element of the exposure.

5. Conclusion

Blood Pb and Cd levels are at high levels and have affected the hematological and liver health of local residents. Although the local government was taken some measures to reduce emissions of toxic pollutants from the e-waste dismantling workshops, more work must be done to minimize the levels of exposure to local populations. The results suggest toxic trace metals may increase the burden of red blood cells and the liver. The exposure to Pb and Cd (especially from an e-waste-polluted area) could affect human hematological and hepatic functions. We now better understand the impact of toxic trace metals in the environment on the human liver health.

Author contributions

Y. Chen was involved in the study design, collected blood samples, conducted sample analysis, statistically analyzed the data, and drafted the manuscript. X. Xu and X. Huo assisted in the study design, helped in toxic trace metal measurements and revised the manuscript. X. Ling participated in analyzing the data. Z. Zeng and Qilin Qin revised the manuscript.

Conflicts of interest

The authors declare that they have no conflict of interests.

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Appendix

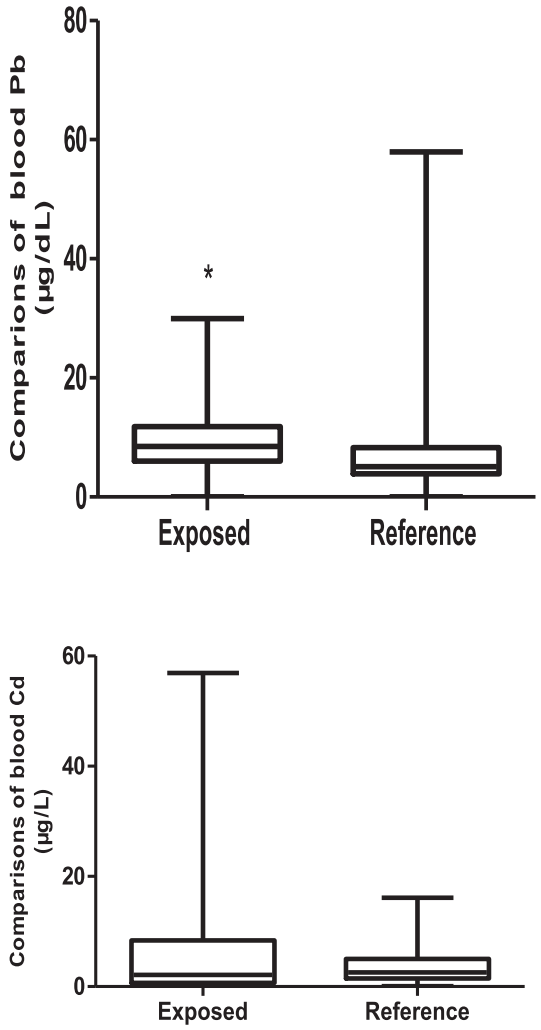

Fig. A. 1. Comparison of toxic trace metals in blood between exposed and reference subjects. Student's *t*-tests and Chi-square tests were used to assess the differences of blood toxic trace metal levels between exposed and reference groups. *Differences between exposed and reference groups are significant. The median level of parents' blood Pb is also higher in the exposed group than in the reference group (8.7 μg /dL versus 5.1 μg/dL, $p < 0.001$) (Fig A. 1).

Table A.1
Characteristics, clinical indexes and levels of toxic trace metals between the exposed and the reference subjects.

	Exposed group (n = 158)	Reference group (n = 109)	*p* value
Age (years)	44 ± 1.6	47 ± 1.9	0.144
Gender [n (%)]			
Male	86 (54%)	61 (56%)	0.489
Female	73 (46%)	48 (44%)	0.196
Liver Function			
AST (IU/L)	33.0 (20.0–92.0)	32.0 (21.0–66.5)	0.757
ALT (IU/L)	33.5 (18.0–108.5)	33.0 (17.0–96.0)	0.545
AST/ALT	1.0 (0.7–1.3)	1.0 (0.7–1.4)	0.834
GGT (IU/L)	68.0 (23.0–195.0)	26.0 (14.0–99.0)	0.001[a]
LDH (IU/L)	170.0 (137.0–232.3)	181.0 (137.0–267.0)	0.831
TBIL (μmol/L)	13.3 (10.8–19.6)	15.4 (10.4–33.6)	0.044[a]
Blood routine test			
RBC (× 10^3/μL)	4.5 (4.1–4.8)	4.2 (3.5–4.6)	0.001[a]
Platelets (× 10^3/μL)	234.0 (189.5–285.0)	231.0 (169.0–298 .5)	0.596
Hemoglobin (g/dL)	137.0 (119.5–150.0)	123.0 (107.0–143.0)	0.001[a]
Toxic trace metal			
Pb (μg/dL)	8.7 (6.2–12.2)	5.1 (3.9–8.4)	0.001[a]
Cd (μg/L)	2.1 (0.7–8.4)	2.6 (1.5–5.0)	0.460

Data are expressed as mean ± standard deviation (SD) or median (P_{25}-P_{75}).
RBC: Red blood cell; AST: Aspartate amino transferase; ALT: Alanine amino transferase.
LDH: lactic dehydrogenase; GGT: gamma glutamyl transpeptidase; TBIL: total bilirubin.
[a] Differences between exposed and reference groups are significant.

Table A.2
Comparisons of clinical indexes between the exposed and the reference subjects divided by gender.

Variable	Gender	Exposed group [β] Median (P_{25}, P_{75})	Reference group [δ] Median (P_{25}, P_{75})	*p* value
Liver Function				
AST (IU/L)	Male	35.0 (21.0, 82.0)	34.0 (21.0, 82.0)	0.757
	Female	27.0 (19.0, 108.0)	30.0 (21.0, 59.5)	0.938
ALT (IU/L)	Male	36.0 (17.0, 116.0)	39.0 (17.0, 111.0)	0.781
	Female	24.0 (18.0, 93.0)	28.0 (16.3, 82.0)	0.597
AST/ALT	Male	0.9 (0.6, 1.3)	0.9 (0.5, 1.4)	0.898
	Female	1.0 (0.9, 1.3)	1.1 (0.8, 1.6)	0.762
GGT (IU/L)	Male	102.0 (23.5, 217.5)	33.5 (16.0, 115.0)	0.003[a]
	Female	50.0 (17.5, 165.5)	20.0 (12.0, 81.0)	0.015[a]
LDH (IU/L)	Male	170.0 (135.5, 237.0)	181.0 (144.0, 233.8)	0.986
	Female	170.0 (137.5, 233.0)	180.0 (100.0, 275.0)	0.775
TBIL (μmol/L)	Male	14.5 (11.3, 22.1)	17.5 (11.6, 41.0)	0.069
	Female	12.5 (9.0, 17.8)	13.3 (9.6, 26.0)	0.277
Blood routine test				
RBC (× 10^3/μL)	Male	4.6 (4.3, 5.0)	4.2 (3.6, 4.7)	0.001[a]
	Female	4.3 (3.9, 4.6)	4.1 (3.5, 4.4)	0.022[a]
Platelets (× 10^3/μL)	Male	251.0 (189.8, 297.3)	203.0 (166.0, 293.0)	0.100
	Female	232.0 (175.0, 266.0)	251.5 (185.5, 300.8)	0.150
Hemoglobin (g/dL)	Male	148.1 (134.9, 156.7)	133.0 (112.0, 147.0)	0.001[a]
	Female	124.0 (111.0, 136.0)	119.0 (98.6, 129.0)	0.055
Toxic trace metal				
Pb (μg/dL)	Male	9.2 (6.8, 13.6)	5.3 (3.9, 8.6)	0.001[a]
	Female	7.8 (5.4, 9.9)	4.9 (4.0, 8.3)	0.003[a]
Cd (μg/L)	Male	2.4 (0.7, 8.9)	2.6 (1.5, 5.5)	0.387
	Female	1.9 (0.7, 8.2)	2.7 (1.5, 4.2)	0.959

Data are expressed as mean ± standard deviation (SD) or median (P_{25}-P_{75}).
RBC Red blood cells, AST Aspartate amino transferase, ALT Alanine amino transferase.
LDH lactic dehydrogenase, GGT gamma glutamyl transpeptidase, TBil total bilirubin.
[δ]Male unexposed: n = 61; [δ]Female unexposed: n = 48.
[β]Male exposed: n = 86; [β]Female exposed: n = 72.
[a] Differences between exposed and reference groups are significant.

Table A.3
Comparison of clinical indexes between the exposed and the reference groups divided by age

Variable	Age Group	Exposed group [β] Median (P_{25}, P_{75})	Reference group [δ] Median (P_{25}, P_{75})	*p* value
Liver Function				
AST (IU/L)	<40 years	37.0 (21.0, 87.3)	34.0 (21.0, 98.0)	0.856
	≥40 years	29.0 (19.0, 94.5)	30.0 (17.0, 85.3)	0.341
ALT (IU/L)	<40 years	40.5 (16.0, 114.5)	36.0 (17.0, 155.0)	0.635
	≥40 years	31.0 (18.8, 107.0)	30.5 (17.0, 85.3)	0.575
AST/ALT	<40 years	1.0 (0.7, 1.4)	1.1 (0.6, 1.6)	0.765
	≥40 years	0.9 (0.7, 1.3)	1.0 (0.7, 1.4)	0.625
GGT (IU/L)	<40 years	32.0 (12.0, 82.0)	18.0 (11.0, 42.0)	0.164
	≥40 years	129.0 (25.8, 227.5)	33.0 (17.0, 126.8)	0.001[a]
LDH (IU/L)	<40 years	184.0 (153.0, 267.0)	196.0 (159.0, 290.5)	0.867
	≥40 years	155.0 (134.0, 213.0)	218.0 (164.0, 276.5)	0.001[a]
TBIL (μmol/L)	<40 years	12.6 (9.6, 16.4)	12.6 (10.6, 25.0)	0.538
	≥40 years	13.8 (11.1, 23.1)	16.4 (10.2, 41.5)	0.124
Blood routine test				
RBC ($\times 10^3$/μL)	<40 years	4.53 (4.3, 4.9)	4.3 (3.7, 4.7)	0.083
	≥40 years	4.4 (4.0, 4.7)	4.1 (3.5, 4.5)	0.003[a]
Platelets ($\times 10^3$/μL)	<40 years	245.0 (177.0, 296.0)	248.0 (200.0, 292.0)	0.763
	≥40 years	233.1 (191.9, 277.5)	229.5 (152.8, 302.8)	0.164
Hemoglobin (g/dL)	<40 years	135.0 (116.9, 152.7)	123.0 (108.0, 145.0)	0.319
	≥40 years	137.0 (121.0, 149.3)	122.0 (105.8, 142.0)	0.004[a]
Heavy metal levels				
Pb (μg/dL)	<40 years	7.8 (5.6, 10.2)	4.9 (3.5, 7.9)	0.001[a]
	≥40 years	9.3 (6.7, 13.1)	5.4 (4.0, 8.5)	0.001[a]
Cd (μg/L)	<40 years	1.2 (0.4, 6.5)	2.3 (1.3, 5.2)	0.021[a]
	≥40 years	2.8 (0.9, 9.3)	2.7 (1.5, 4.9)	0.030[a]

Data are expressed as mean ± standard deviation (SD) or median (P_{25}-P_{75}).
RBC Red blood cells, AST Aspartate amino transferase, ALT Alanine amino transferase.
LDH lactic dehydrogenase, GGT gamma glutamyl transpeptidase, TBil total bilirubin.
[δ]Male unexposed: n = 61; [δ]Female unexposed: n = 48.
[β]Male exposed: n = 86;[β]Female exposed: n = 72.
[a] Differences between exposed and reference groups are significant.

Table B
Spearman's rank correlation analysis of toxic trace metals and clinical indexes in blood from the exposed and reference groups

		Pb	Cd	AST	ALT	GGT	LDH	TBIL	RBC	Hb	PLT
Pb	r	1	0.117	0.069	0.119	−0.107	0.025	−0.080	0.170	0.121	−0.062
	p	–	0.048*	0.247	0.046*	0.074	0.718	0.181	0.004**	0.042*	0.302
Cd	r	–	1	0.223	0.213	−0.085	0.072	0.097	0.102	0.030	-0.059
	p	–	–	0.001**	0.001**	0.152	0.302	0.105	0.088	0.612	0.320
AST	r	–	–	1	0.837	0.522	0.394	0.361	0.002	0.023	−0.157
	p	–	–	–	0.001**	0.001**	0.001**	0.001**	0.974	0.701	0.008**
ALT	r	–	–	–	1	0.544	0.341	0.348	0.036	0.065	−0.132
	p	–	–	–	–	0.001**	0.001**	0.001**	0.542	0.278	0.027*
GGT	r	–	–	–	–	1	0.231	0.523	−0.176	−0.096	−0.074
	p	–	–	–	–	–	0.001**	0.001**	0.003**	0.107	0.219
LDH	r	–	–	–	–	–	1	0.108	−0.090	−0.099	−0.106
	p	–	–	–	–	–	–	0.801	0.197	0.156	0.128
TBIL	r	–	–	–	–	–	–	1	−0.074	0.033	−0.146
	p	–	–	–	–	–	–	–	0.219	0.585	0.014*
RBC	r	–	–	–	–	–	–	–	1	0.628	−0.047
	p	–	–	–	–	–	–	–	–	0.001**	0.429
Hb	r	–	–	–	–	–	–	–	–	1	−0.137
	p	–	–	–	–	–	–	–	–	–	0.022*
PLT	R	–	–	–	–	–	–	–	–	–	1
	P	–	–	–	–	–	–	–	–	–	–

*$p < 0.05$, **$p < 0.01$.

Table C
Logistic regression analysis of influencing factors for people of abnormal liver function from the two groups

Influencing factors	Cases (N)	OR (95%CI)	*p* value
Age (years)			
<40	100	1.00	
≥ 40	167	0.777(0.428, 1.411)	0.408
Gender			
Male	156	1.00	
Female	111	1.278 (0.708, 2.307)	0.417
Hepatic disease			
No	196	1.00	
Yes	71	12.392 (5.202, 29.521)	0.001[a]
RBC ($\times 10^3/\mu L$)			
< 3.5	37	1.00	
3.5–5.5	221	12.945 (1.208, 138.656)	0.034[a]
> 5.5	9	9.841 (1.271, 76.213)	0.029[a]
Hemoglobin (g/dL)			
< 110	52	1.00	
110-160	195	1.383 (0.274, 6.977)	0.695
> 160	20	1.022 (0.279, 3.745)	0.973
Platelets ($\times 10^3/\mu L$)			
< 100	14	1.00	
100-300	193		
> 300	60	1.152 (0.583, 2.279)	2.279
Toxic trace metal			
Blood Pb (μg/dL)			
< 5	59	1.00	
≥ 5	208	1.936 (1.004, 3.732)	0.049[a]
Blood Cd (μg/L)			
< 2.4	140	1.00	
≥ 2.4	127	0.345 (0.194, 0.614)	0.001[a]

More than two kinds of transaminases (AST、ALT、GGT) elevating above normal range or one kind of transaminases at least twice higher than normal range were considered as abnormal liver function in clinic.
$p < 0.05$ was considered statistically significant.
[a] Adjusted with the age, gender, hepatic disease, RBC, Hb and PLT variable.

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