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ORIGINAL RESEARCH

Prospective Study on the Association Between Blood Heavy Metal Levels and Pulmonary Function in University Students from a Medical College in Shandong Province, China

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Background: This study aimed to examine the blood concentrations of selected heavy metals, their corresponding pulmonary functions, and their interrelationship with university students.

Methods: This prospective study, conducted from September 2019 to September 2020, encompassed 593 university students. Participants completed self-administered questionnaires regarding demographic factors and underwent lung function testing and blood mercury analysis at two distinct intervals: an initial assessment and a follow-up examination. Pulmonary function was assessed using Forced Vital Capacity, Forced Expiratory Volume in one second, and Peak Expiratory Flow. The blood concentrations of various heavy metals were determined through inductively coupled plasma mass spectrometry.

Results: Notable disparities in pulmonary function emerged among university students when categorized by gender, Body Mass Index, physical activity, and seafood consumption frequency, all showing statistical significance ($p<0.05$). Blood levels of Pb, Mn, Co, and Ni exhibited diverse patterns and extents of correlation with pulmonary function ($p<0.05$ in each instance). Specifically, a positive correlation was observed with blood Pb levels, while Mn, Co, and Ni levels were inversely correlated with pulmonary function ($p<0.01$ for both observations).

Conclusion: This study uncovered significant and complex relationships between the blood concentrations of individual heavy metals and pulmonary function in university students. These findings highlight the need for further research to elucidate these associations in greater detail.

Keywords: heavy metal, pulmonary function, students

Introduction

In the past two decades, environmental pollution has become increasingly severe, with heavy metal contamination posing a significant threat, especially in developing regions. In China, 15.87% of arable land's surface soil is tainted with heavy metals, a concern given the limited available area. Heavy metals, inherent chemical elements, can spread through air, water, soil, and other media. They enter the human body via diet and inhalation, among others, subsequently distributing across various tissues and organs, where they either participate in metabolic processes or exert toxic effects. Notable toxic heavy metals include Hg, Cd, and Pb. These metals are linked to a spectrum of adverse health effects, including respiratory, cardiovascular, and neurological disorders.[1–3] Understanding the trends in heavy metal pollution and their health impacts is thus critical.

Meanwhile, studies have shown that heavy metal exposure increases oxidative stress and inflammation in the lungs and damages the lung tissue cells; thus, the risk of lung diseases is increased.[4,5] The WHO Global Status Report on Non-Communicable Diseases (NCDs) lists chronic respiratory diseases as one of the diseases with the highest morbidity and

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mortality rates, with respiratory diseases accounting for 10.7% of all diseases,[6] which gives rise to a considerable disease burden.[7] The lung function level is one of the important methods to evaluate respiratory health in clinical medicine. Commonly used lung function indicators such as forced vital capacity (FVC), forced expiratory volume in the first second (FEV1), and peak expiratory flow (PEF) are essential for assessing the functional damage by respiratory diseases and monitoring the disease progression. At present, some studies have used the blood levels of heavy metals to represent their internal exposure and to assess their relationships with lung function, such as a cohort study performed in China, which indicates that the blood level of mercury was negatively correlated with the lung function, as indicated by FEV1, FVC, and PEF; for every two-fold increase in the blood concentration of mercury, the FEV1 decreased by 70.75 mL on average.[8] For every 2-fold increase in the blood concentration of selenium, FEV1 increased by an average of 91.14 mL.[9] A 2020 survey study on heavy metals in agricultural soils in the southern Shandong Peninsula in China indicates that the average concentrations of As, Cu, Ni, and Zn in the region are generally lower than the averages of the last five years for the whole Shandong Province, while the average concentration of Hg is relatively high.[10] Meanwhile, a study[11] shows that the average concentrations of heavy metals (Zn and Co) in the offshore waters of Yantai, Shandong Province, China, in 2019 and 2020 were slightly higher than those in the other coastal areas of China, with the order of the largest pollutants being Zn>Pb>Cd>Cr>Co. Consequently, our interest centered on the effects of internal heavy metal burdens on lung function in young individuals, typically devoid of pre-existing respiratory issues. A total of 26 heavy metal levels were measured in this study. We made several subgroups of it. The other heavy metals have been written or are underwriting, and the research on Mn, Pb, Co, and Ni is limited. Fish consumption is a typical lifestyle for coastal cities. Some studies show that fish intake is protective against childhood asthma. Other studies have reported neutral or detrimental effects on respiratory health. The reason is unclear; therefore, our study aimed to investigate whether frequency is an influential factor in lung function. This study aimed to examine selected heavy metals, including Mn, Pb, Co, and Ni, their corresponding pulmonary functions, influencing factors, and their interrelationship with university students.

Materials and Methods

Data Collection

The research subjects were undergraduate students recruited from the Binzhou Medical University in Yantai City, Shandong Province, China, in 2019. They were subjected to blood heavy metal and lung function measurements for the baseline (September 1, 2019) and follow–up data (September 5, 2020). The geographical distribution of the participants' current residences is shown in Figure 1. This study follows the STROBE guidelines.

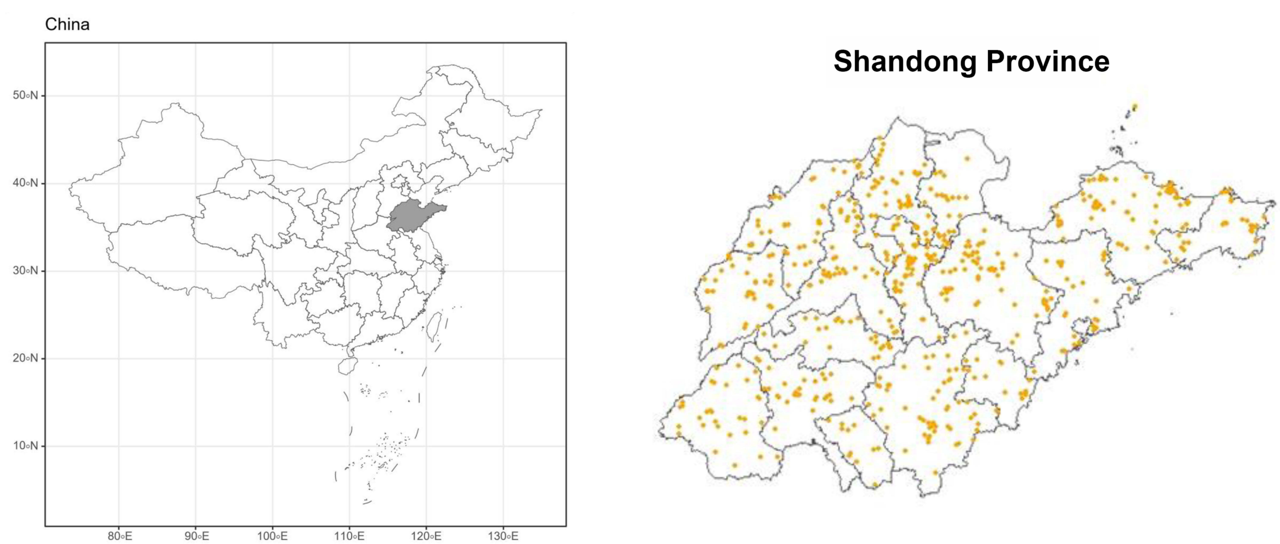

Figure 1 Geographical distribution of participants' current residence.

The inclusion criteria were as follows: (1) their home addresses were registered before university enrollment; (2) at ages >18 years, in the sophomore or higher college year; (3) voluntary participation — completion of self–answered questionnaire, lung function test, and blood heavy metal measurement.

General Demographic Data

General demographic characteristics of the participants, including age, gender, educational level, active and passive smoking status, alcohol consumption, physical activity, family income, and seafood consumption frequency, were collected using questionnaires.

Determination of Blood Heavy Metals

(1) A fasting blood sample of 10 mL was collected from each participant, with each 1 mL of blood distributed into one tube, 4 tubes for the preparation of serum, and 5 tubes for that of plasma. The aliquots of each sample were promptly stored at –80°C for further laboratory use. (2) Element concentrations were measured using inductively coupled plasma mass spectrometry at the Laboratory of Biogenic Elements in the Medical School of Peking University. The blood samples were placed at room temperature for 2 h, then transferred to a microwave digestion system (Ultra WAVE, Milestone Co., Italy) and treated for 50 min. After that, 0.1 mL of 2 ng/mL indium was added to each sample and diluted to 8 mL with ultrapure water. The blood heavy metals were measured by inductively coupled plasma mass spectrometer (ICP–MS, ELAN DRC II, PerkinElmer, USA).[9] Blood levels of Pb, Mn, Co, and Ni were measured.

Pulmonary Function Testing

Pulmonary function tests were conducted by skilled technicians per European Respiratory Society guidelines, utilizing a spirometer (Chestgraph HI–101, CHEST Ltd., Japan). The primary indicators of pulmonary function included Forced Vital Capacity (FVC, mL), Forced Expiratory Volume in one second (FEV1, mL), and Peak Expiratory Flow (PEF, mL). The spirometer was calibrated before and after each day's lung function tests. Participants were required to produce at least three acceptable spirograms, with the best result selected for analysis. Follow-up pulmonary function assessments were carried out one year after the initial measurements for each individual.

Statistical Analysis

Statistical analysis was executed utilizing R software (version 4.0.3) and SPSS 23.0. A two-tailed test significance threshold was established at $p<0.05$. Categorical data are represented as frequencies and percentages and graded data as means and standard deviations. When required by the distribution of data, logarithmic transformation of blood heavy metal concentrations was applied to achieve normal distribution.

Ethical Considerations

This study was approved by the Binzhou Medical University Ethics Committee (approval no. 2019.45) and was performed in compliance with the Declaration of Helsinki. Written informed consent was obtained from each participant. Participation in the study was voluntary. The survey was anonymous, all participants' personal data were kept confidential, and all sets of information were coded and preserved throughout all data collection and analysis stages.

Results

General Information

A total of 593 subjects were included in the investigation. General information is presented in Table 1.

Univariate Analysis of Pulmonary Function Levels in University Students

Lung function levels of college students during the study were normally distributed. The results of *t*-test and one-way ANOVA analysis showed that after stratification of the data by gender and lifestyle factors revealed statistically significant differences in pulmonary function levels regarding several factors, such as gender, physical activity, and

Table 1 Baseline Characteristics of Study Participants

Characteristics		2019	2020
Gender	Female	361	361
	Male	232	232
Height (cm)		168.19±8.41	168.07±8.49
Weight (kg)		62.96±13.95	62.91±14.38
Age		18.44±0.63	19.48±0.67
BMI		22.12±3.84	22.10±3.80
Smoking status (n,%)	Yes	12	14
	No	581	579
Passive smoking (n,%)	Yes	64	35
	No	529	558
Alcohol consumption (n,%)	Yes	21	19
	No	572	574
Physical activity (n,%)	<1 hour/day	76	172
	1~3 hours/day	316	315
	3~5 hours/day	110	65
	>5 hours/day	91	41
Lung diseases (n,%)	Yes	114	266
	No	479	327
Fish consumption frequency (n,%)	≥ 2 times/day	44	63
	1 time/day	36	46
	2~6 times/week	131	133
	1 time/week	164	165
	1~3 times/month	152	130
	Never	66	56
FVC (L)		2.73±0.85	3.39±0.77
FEV1 (L)		2.65±0.79	3.14±0.65
PEF (L)		5.52±1.72	6.26±1.74
FEV1/ FVC (n,%)	<70%	1	164
	≥70%	592	428
Pb(ng/mL)		13.42±8.12	11.21±4.37
Mn(ng/mL)		16.63±5.59	13.26±5.26
Co(ng/mL)		0.44±0.22	0.45±0.43
Ni(ng/mL)		4.97±5.56	3.79±4.32

seafood consumption ($p<0.05$), with the female participants, physically active participants and seafood consumers (≥2 times/day) showed higher pulmonary function levels. The Body Mass Index (BMI), smoking status/passive smoking, lung disease, and alcohol consumption did not seem influential in lung function, as shown in Table 2.

Correlation Between Blood Heavy Metal Levels and Pulmonary Function in University Students

This study observed that the blood concentrations of heavy metals (Pb, Mn, Co, Ni) in university students did not follow a normal distribution. Spearman correlation analysis showed varying modes/degrees of correlation between these blood metal levels and pulmonary function. Specifically, blood Pb levels exhibited a positive correlation with pulmonary function ($p<0.01$), while blood Mn and Co concentrations showed a negative correlation with pulmonary function ($p<0.01$). Blood Ni content was also negatively correlated with FVC moderately ($p<0.05$), as presented in Table 3.

Table 2 The Analysis of Potential Influencing Factors on the Lung Function Levels in College Students

Gender/lifestyles		FVC (L)	FEV1 (L)	PEF (L)
Gender (%)	Female	2.67±0.80	2.60±0.75	5.49±1.62
	Male	2.82±0.91*	2.74±0.86*	5.57±1.86*
Smoking status (%)	Yes	2.85±0.63	2.68±0.52	5.40±1.54
	No	2.72±0.85	2.65±0.80	5.53±1.72
Passive smoking (%)	Yes	2.63±0.79	2.58±0.77	5.34±1.53
	No	2.74±0.85	2.66±0.79	5.54±1.73
Alcohol consumption (%)	Yes	2.58±0.69	2.51±0.67	5.79±1.94
	No	2.74±0.86	2.66±0.80	5.51±1.71
Physical activity (%)	Yes	2.78±0.85*	2.69±0.80*	5.54±1.72
	No	2.59±0.83	2.53±0.79	5.51±1.71
Lung disease (%)	Yes	2.71±0.88	2.65±0.83	5.72±1.79
	No	2.73±0.84	2.66±0.79	5.48±1.70
Fish consumption frequency (%) (2020)	≥ 2 times/day	3.78±0.74**	3.45±0.64**	6.86±1.70
	1 time/day	3.47±0.82	3.15±0.67	6.13±1.53
	2~6 times/week	3.43±0.76	3.18±–0.66	6.36±1.83
	1 time/week	3.36±0.77	3.11±0.62	6.11±1.70
	1~3 times/month	3.24±0.71	3.02±0.62	6.18±1.72
	never	3.27±0.73	3.03±0.63	6.06±1.78

Notes: The results were performed, *p<0.05, **p<0.01.

Table 3 Association Between Blood Levels of Heavy Metals and Lung Function

Heavy Metals	FVC (L)	FEV1 (L)	PEF (L)
Pb	0.16**	0.15**	0.11**
Mn	–0.12**	–0.14**	–0.09*
Co	–0.23**	–0.20**	–0.20**
Ni	–0.08*	–0.07	–0.03

Notes: Spearman correlation analysis was performed, *p<0.05, **p<0.01.

Associations of Several Variables with Pulmonary Function Levels in University Students by Multivariate Analysis

Multivariate analysis was employed to investigate the relationship between pulmonary function levels (FVC, FEV1, PEF) as dependent variables and a set of independent variables. These included gender, BMI, physical activity, blood concentrations of Pb, Mn, Co, and Ni, as well as seafood consumption—each demonstrating significant differences in both univariate and correlation analyses. Multiple regression models were constructed for this purpose. The analysis identified gender, BMI, and blood concentrations of Co, Pb, and Mn as primary determinants influencing the pulmonary function levels in university students, with all indicated cases showing statistical significance (p<0.01), as detailed in Tables 4–6.

Multivariate Analysis of Factors Affecting Changes in Pulmonary Function in University Students

Multivariate regression analysis indicated that blood Co level and fish consumption frequency were significant factors influencing changes in pulmonary function (FVC) (p<0.05), as displayed in Table 7.

Table 4 Multivariate Regression Analysis of Several Variables Potentially Influencing the FVC Volume

Variable	Beta	B (95% Confidence Limits)	*p* value
Pb	0.11	0.02 (0.00, 0.03)	0.028*
Mn	–0.17	–0.02 (–0.01, –0.03)	0.001**
Co	–0.14	–0.48 (–0.79, –0.17)	0.002**
Gender	0.08	0.14 (0.00, 0.27)	0.000**
BMI	0.23	0.05 (0.03, 0.06)	0.000**

Notes: Multivariate regression analysis was performed, *p<0.05, **p<0.01.

Table 5 Multivariate Regression Analysis of Several Variables Potentially Influencing the FEV1 Volume

Variable	Beta	B (95% Confidence Limits)	*p* value
Pb	0.18	0.03 (0.02, 0.05)	0.000*
Mn	–0.16	–0.02 (–0.00, –0.03)	0.000**
Co	–0.16	–0.46 (–0.73, –0.28)	0.001**
BMI	0.24	0.04 (0.03, 0.05)	0.000**

Notes: Multivariate regression analysis was performed, *p<0.05, **p<0.01.

Table 6 Multivariate Regression Analysis of Several Variables Potentially Influencing the PEF Volume

Variable	Beta	B (95% Confidence Limits)	*p* value
Pb	0.14	0.06 (0.03, 0.08)	0.000*
Co	–0.14	–0.57 (–0.89, –0.25)	0.001**
BMI	0.26	0.11 (0.08, 0.15)	0.000**

Notes: Multivariate regression analysis was performed, *p<0.05, **p<0.01.

Table 7 Multivariate Regression Analysis of Factors Influencing Changes of FVC

Variable	OR (95% Confidence Limits)	*p* value
Co (2020)	0.35 (0.12, 0.99)	0.04*
Fish consumption (%) (2020)	1.19 (1.03, 1.36)	0.01**

Notes: Multivariate regression analysis was performed, *p<0.05, **p<0.01.

Discussion

Analysis of Influencing Factors on Pulmonary Function Levels in College Students

This study highlighted gender, BMI index, physical activity, and frequency of seafood consumption as pivotal factors affecting pulmonary function levels in college students. Notably, individuals consuming seafood at least twice daily exhibited significantly elevated FVC and FEV1 compared to other groups (p<0.01). Meanwhile, except for consuming seafood at least twice daily, there is no difference between the other groups. Aligning with a study from Australia,[12] which suggested a protective role of fish intake against childhood asthma, our findings indicate a similar trend. However, contrasting research[13] has reported neutral or detrimental effects of fish consumption on respiratory health. Fish, a low-fat, high-quality protein source rich in essential unsaturated fatty acids and vitamin D, benefits human health. Our study delved into the effect of seafood consumption frequency on pulmonary function in college students, theorizing that the benefits might stem from the intake of high-quality proteins like fish, which improve the overall physical constitution. The study showed that the frequency of fish intake is a potential influencing factor. Adequate seafood intake every day may have positive effects on lung function. Interestingly, the blood levels of heavy metals between seafood and non-seafood consumers did not show significant statistical differences. However, the allergenic properties of fish could account for its potential adverse respiratory effects. The mechanisms through which fish consumption impacts pulmonary function levels merit further investigation.

Correlation Analysis of Blood Heavy Metal Levels and Pulmonary Function in College Students

Our results indicated varying modes/degrees of correlations between the concentrations of Pb, Mn, Co, and Ni in the blood and pulmonary function in college students. Specifically, the blood Pb concentration showed a positive correlation with pulmonary function. However, this is not consistent with any existing biological and medical knowledge, so the result should be verified in further studies. Analyzing the data using the blood lead exceedance according to the diagnostic criterion for non-occupational adults (blood lead level ≥ 0.100 mg/L), the group with elevated blood lead levels demonstrated significantly higher pulmonary function compared to those with normal lead levels. Most studies, from either China or other countries, on blood Pb[14] have indicated its relevance to mortality from cardiovascular diseases, and bronchial and lung cancers, etc. Furthermore, a study conducted in the United States[15] suggests a significant correlation between the serum Pb and FEV1/FVC% predicted values for all participants, suggesting that lead exposure negatively impacts the pulmonary function of non–smoking American adults. Surprisingly, in this study, elevated blood Pb levels positively affected pulmonary function indicators. This result contradicts previous research findings from China and other countries/regions. However, regression analysis indicated that the impact of blood Pb levels on pulmonary function was relatively small, FVC (0–30 mL), FEV1 (20–50 mL), and PEF (30–80 mL). This discrepancy could be attributed to a potential protective dose of blood Pb or the presence of confounding factors. However, the specific mechanisms behind this have to be explored by further studies.

On the other hand, the blood Mn and Co concentrations in college students showed a negative correlation with pulmonary function. Notably, in this study, where blood Co was included in the regression equation, the results indicated that for every doubling of blood Co levels, FVC and FEV1 decreased by an average of 200–800 mL. As Co is an essential component of vitamin B12, some studies[16] have suggested that a blood Co concentration of 700–800 µg/L may pose a significant risk of cardiovascular effects. Additionally, a study[17] demonstrated an exposure–response relationship between cobalt exposure and Clara cell protein 16 (CC16) levels in the blood, and combined with causal analysis of plasma CC16 concentration and pulmonary function decline,[18] blood Co concentration may be associated with lung damage. This finding is consistent with the results of our study. Moreover, a study on metalworkers' pulmonary function and respiratory symptoms in both smokers and non–smokers, similarly asserted that even low levels of cobalt exposure could impair lung function.[19] The influence of blood Mn on pulmonary function changes was relatively small in this study. The regression analysis demonstrated that a two-fold increase in blood Mn concentration caused fluctuations of about 20 mL decrease in pulmonary function. A study on children's respiratory symptoms and blood levels of heavy metals showed a correlation between elevated blood manganese levels and coughing and wheezing symptoms.[20] This might partially explain the impact of blood Mn on pulmonary function. However, no literature can currently be found regarding the association between blood Mn level and pulmonary function–related indicators, and the underlying mechanisms remain unclear, warranting further investigation.

Multifactorial Analysis of Pulmonary Function Changes in College Students

This study also conducted a multivariate regression analysis of pulmonary function changes in college students. The pulmonary function level of the students in 2020 was significantly improved compared to 2019 (p<0.01). Physical exercise and fish consumption were verified for their association with values of the lung function indicators, where no other factors demonstrated significance. Factors influencing pulmonary function changes were analyzed, and the results indicated that blood Co and fish consumption significantly affected the changes in pulmonary function (FVC). Fish consumption seemed to play a protective role in pulmonary function, which is consistent with a systematic review in which fish consumption was also confirmed as a protective factor against lung cancer risk.[21]

Limitations

Despite being a prospective study, its limitation lies in the singular follow-up assessment conducted over a relatively extended period. Given the varying metabolic cycles of these heavy metals, our preliminary findings may not be robust enough to draw definitive conclusions, and there is a risk of introducing bias that could mislead future research. Future studies should consider expanding participant numbers and incorporating intermittent monitoring of blood heavy metal concentrations to improve result accuracy.

Conclusion

The study showed that gender, BMI index, physical activity, and frequency of seafood consumption are pivotal factors. Adequate seafood intake every day may positively affect lung function. Meanwhile, the current study explored the link between blood heavy metal levels and lung function among college students in a northern city in China. It revealed a significant, yet minor, positive correlation between blood lead (Pb) levels and lung function, suggesting a protective effect. However, this finding is at odds with established biological and medical knowledge, underscoring the need for further verification in subsequent research. In contrast, Mn, Co, and Ni blood concentrations were negatively correlated with lung function, particularly with Co levels showing a more pronounced impact.

Clinical Relevance

Our findings indicate potential risks associated with heavy metal exposure leading to human lung function impairment, underscoring the need for further investigation to clarify these associations.

Data Sharing Statement

The datasets generated and analyzed during the current study are available from the corresponding author upon reasonable request.

Ethical approval and informed consent

This study was approved by the Binzhou Medical University Ethics Committee (approval no. 2019.45) and was performed in compliance with the Declaration of Helsinki. Written informed consent was obtained from each participant.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work. All authors read and approved the final version of the manuscript.

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Disclosure

The authors have no conflicts of interest to declare in this work.

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