



Co-exposure to iron, copper, zinc, selenium and titanium is associated with the prevention of gastric precancerous lesions

Tingting Wang · Fang Xu · Xiao Lin · Yaning Lv · Xiaohui Zhang · Wenli Cheng · Li Wang · Min Wang · Meng Zhang · Tao Xia · Shiqing Qian · Min Tang · Wanshui Yang · Ying Zhang · Daoming Zhang · Anla Hu · Qihong Zhao

Received: 5 March 2023 / Accepted: 8 May 2023 / Published online: 23 June 2023
© The Author(s), under exclusive licence to Springer Nature B.V. 2023

Abstract Gastric cancer is the third leading cause of cancer death, and gastric precancerous lesions (GPLs) are an important stage in the transformation of normal gastric mucosa to gastric cancer. Matched for age and sex, a total of 316 subjects were eventually included from our prospective observation population (including 1007 patients with GPLs and 762 normal controls), and a questionnaire survey was conducted. In total, 10 plasma elements (iron, copper, zinc, selenium, rubidium, strontium, titanium, aluminum, vanadium and arsenic) were measured by applying inductively coupled plasma–mass spectrometry (ICP–MS). A multivariate conditional logistic regression model and Bayesian kernel logistic regression

model (BKMR) were used to analyze the association between plasma element concentrations and GPLs. In the multimetal model, plasma titanium concentrations were significantly and positively associated with the prevalence of GPLs, with a fourth-quartile OR of 11.56 ([95% CI]: [2.78–48.13]). Plasma selenium and copper were negatively correlated with GPLs, with the highest quartiles of selenium and copper having an OR of 0.03 ([95% CI]: [0.01–0.15]; $P < 0.001$) and 0.24 ([95% CI]: [0.07–0.82]), respectively. In the BKMR model, there was a significant negative combined correlation of five metals on GPLs: iron, copper, zinc, selenium, and titanium. The results of this study showed that plasma concentrations of selenium and copper were negatively correlated with GPLs, while plasma concentrations of titanium were positively correlated with GPLs, and the combined action of the five elements was negatively correlated with GPLs.

Tingting Wang, Fang Xu, Xiao Lin and Yaning Lv authors contributed equally to the present study.

Supplementary Information The online version contains supplementary material available at <https://doi.org/10.1007/s10534-023-00509-6>.

T. Wang · F. Xu · X. Lin · X. Zhang · W. Cheng · L. Wang · M. Wang · M. Zhang · M. Tang · W. Yang · A. Hu (✉) · Q. Zhao (✉)
Department of Nutrition and Food Hygiene, School of Public Health, Anhui Medical University, Hefei, China
e-mail: huanla@ahmu.edu.cn

Q. Zhao
e-mail: qihong@ahmu.edu.cn

Y. Lv
Anhui Province, Hefei Customs Technology Center, Hefei, China

T. Xia · D. Zhang (✉)
Department of Gastroenterology, Anhui Province, Lujiang County People's Hospital, Hefei, China
e-mail: 20212177@qq.com

S. Qian
Department of Pathology, Anhui Province, Lujiang County People's Hospital, Hefei, China

Y. Zhang (✉)
Department of Gastroenterology and Hepatology, Anhui Province, Tongling Municipal Hospital, Tongling, China
e-mail: zhangy6042@163.com

Keywords Gastric precancerous lesions · Trace elements · Metallic elements · BKMR analysis

Abbreviations

GPLs	Gastric precancerous lesions
BMI	Body mass index
HP	Helicobacter pylori
Fe	Iron
Cu	Copper
Zn	Zinc
Se	Selenium
Rb	Rubidium
Sr	Strontium
Ti	Titanium
Al	Aluminum
V	Vanadium
As	Arsenic

Introduction

According to the latest GLOBOCAN statistics, the global number of new cases of gastric cancer was approximately 1.089 million, which accounted for 5.6% of the total number of new cancer cases in the world, and the death rate was approximately 769,100 (1/13), which accounted for 7.7% of the total global cancer-related deaths (with the global incidence rate ranked in fifth place in the tumor incidence parity and the death rate in fourth place) (Sung et al. 2020). Although the incidence and mortality rates of gastric cancer have been steadily declining, it remains one of the common causes of cancer-related deaths worldwide. There were approximately 479,000 new cases and 374,000 deaths from gastric cancer in China, which ranked third in the incidence and mortality rate of cancer in China (Cao et al. 2021). Gastric precancerous lesions (GPLs) are an important stage in the transformation of the normal gastric mucosa to gastric cancer, and they represent a major risk factor for gastric cancer and an important stage in preventing the occurrence of gastric cancer. Gastric carcinogenesis is a multistep process, and the currently accepted model proposed by Correa involves the transformation from normal mucosa to chronic nonatrophic gastritis, atrophic gastritis, and intestinal epithelial hyperplasia to heterogeneous hyperplasia, and further to gastric cancer (Correa 1992). Preventing the further progression of precancerous lesions in

the stomach is essential for the prevention of gastric cancer.

Environmental pollutants, especially heavy metals, are receiving increasing attention for their adverse association with the gastrointestinal tract and associated risk factors, such as a high-salt diet, Helicobacter pylori (*H. pylori*) infection, and smoking (Sohrabi et al. 2018). The reason for the growing concern about heavy metals is that they can enter the body's circulation through food, the respiratory tract and the skin, causing irreversible damage to multiple organs and tissues (Fonseca-Nunes et al. 2014). Previous reports have not only shown an association between exposure to single or multiple metals and gastric cancer incidence and mortality but also found a potential link between high concentrations of exposed heavy metals and gastric cancer (Yuan et al. 2016; Kim et al. 2019; Khazaei et al. 2020). Arsenic has been classified as a Class I carcinogen by the International Agency for Research on Cancer (IARC), and exposure to arsenic revealed an association with the incidence and mortality of gastric cancer (Yuan et al. 2016). A report by Kohzadi et al. showed that high levels of arsenic and iron accumulated in tissues over a long period of time increased the incidence and mortality of gastric cancer (Kohzadi et al. 2017). Consistent with previous reports, a recent study reported higher concentrations of aluminum and manganese in patients with colorectal tumors than in nontumor tissues (Sohrabi et al. 2018). There is only limited evidence exploring the association of certain essential trace elements with gastric cancer or precancerous lesions; for example, Wilk A et al. systematically addressed the association of vanadium with the gastrointestinal tract, where high concentrations of this metal can lead to irreversible damage to gastric tissues and organs (Wilk et al. 2017). The possible role of trace elements in cancer development or inhibition is not yet fully understood. Previous epidemiological evidence has shown a role for the trace elements iron, copper, zinc, and selenium in the occurrence of gastric cancer and gastric precancerous lesions, but the results have been inconsistent. Deficiencies in essential elements such as iron, zinc and selenium have been reported to be associated with an increased risk of esophageal, gastric, and colon cancers (Brandt et al. 2010; Taccioli et al. 2012; Torti and Torti 2013). However, a recent case–control study from Zambia showed no association between plasma selenium and gastric cancer or

precancerous lesions (Zyambo et al. 2022). A local case–control study from China showed a positive association between serum copper, the copper/zinc ratio and gastric cancer (Lin et al. 2020). However, in a recent Iranian study assessing trace element concentrations in esophageal and gastric cancers, copper levels were significantly lower than those in noncancerous tissues (Sohrabi et al. 2021). Animal studies have shown that decreased zinc levels and zinc-related enzyme activity are associated with the development of precancerous lesions (Christudoss et al. 2012). A meta-analysis including eight epidemiological studies showed a negative association between serum zinc and gastric cancer risk, but further evidence is needed to demonstrate this possible relationship due to mixed evidence (Fonseca-Nunes et al. 2014).

Anhui Province, southeast China, is a region with a high prevalence of gastric cancer. Because gastric precancerous lesions are a critical stage in the development of gastric cancer, the discovery of influencing factors associated with gastric precancerous lesions has important public health implications for the prevention of gastric cancer. Combining the current prevalence trend and high detection rate, it is necessary to focus on the association of multimetal exposure with gastric precancerous lesions as realistically as possible. To understand the association between plasma multiple-element exposure levels and gastric precancerous lesions, we established a matched case–control study in Anhui Province, China. Meanwhile, restricted cubic spline (RCS) was used to analyze the nonlinear relationship between elements in plasma and gastric precancerous lesions, and multivariate logistic analysis and Bayesian kernel machine regression model (BKMR) were used to explore the association between mixed exposure to multiple elements and gastric precancerous lesions.

Materials and Methods

Study population

This study was conducted in the affiliated hospitals of Anhui Medical University in Anhui Province from April 2019 to October 2021 using a random sampling method to complete the sample collection as well as the questionnaire survey. The inclusion criteria included the following: permanent residents who

were aged more than 18 (resided locally for more than 6 months) and were diagnosed by two histopathologists independently as having chronic atrophic gastritis, intestinalization, or heterogeneous hyperplasia. Patients who had a history of gastric cancer or metal-related illness, were diagnosed with other chronic wasting diseases, or were missing plasma samples and questionnaire data were excluded from our analysis. The control group included a healthy population older than 18 years with normal physical examination results, no liver or kidney function impairment, and no other diseases during the same period.

Questionnaires and samples were collected from a total of 1769 residents, including 1007 patients with gastric precancerous lesions and 762 without disease. After excluding 266 who did not complete the questionnaire and after the performance of random sampling among the remaining 1507, Propensity score matching (PSM) was performed to match the GPL group and the normal control groups, and standardized mean difference (SMD) was used to evaluate the balance between groups after matching. $SMD \leq 0.15$ indicated balance, which could ensure the goodness of fit of the matching results. In this study, nearest neighbor matching algorithm was applied to match propensity scores. Ultimately, GPL group and normal controls were matched based on sex and age (within 3 years) with $SMD \leq 0.15$. Finally, a total of 316 people was included, 158 each in the case and control groups. The flowchart of study subject inclusion was shown in **Fig. S1**.

Data collection

Data were collected through face-to-face, one-on-one questionnaires administered by investigators. The questionnaires were used to collect data regarding general demographic characteristics, such as sex, age, marital status, household income, height, weight, and education level, and behavioral and lifestyle habits, including smoking, drinking and tea consumption, sleep status, labor intensity, etc.

Serum *H. pylori* infection history was defined as HP and presented as “positive” for “Hp infected” and “negative” for “Hp infection free”. Body mass index (BMI) was classified into three categories: underweight, “ $< 24.0 \text{ kg/m}^2$ ”; normal weight, “ $24.0\text{--}28.0 \text{ kg/m}^2$ ”; and obesity, “ $\geq 28.0 \text{ kg/m}^2$ ”. Smoking habits were defined as at least one cigarette

per day for more than 6 months. Alcohol, tea, and coffee drinking habits were defined as at least 3 times per week for more than 6 months. Education was divided into three groups: “illiterate”, “primary school”, and “junior high school or above”. Household income was classified as “low,” “medium,” and “high”. Sleep time was divided into four groups: “< 4 h”, “4–6 h”, “6–8 h”, and “> 8 h”. Sleep quality was divided into three groups: “poor”, “average” and “good”.

Sample collection

Subjects’ fasted venous blood was collected in 5 ml sodium heparin anticoagulation tubes, allowed to settle for one hour, centrifuged at $1500\times g$ for 10 min, and then assimilated into 2 ml EP tubes. On the same day, all blood samples were delivered to our laboratory on dry ice and stored at $-80\text{ }^{\circ}\text{C}$ until it was time for the analysis.

Measurement of plasma elements

Inductively coupled plasma–mass spectrometry (ICP–MS; Perkin Elmer NexION350X) was applied to measure elements in plasma. A Milli-Q water purification system (Millipore Co., USA) was used to produce the deionized water needed in the experimental process. Triton® X-100 and Up-s grade (ultra-pure) nitric acid (HNO_3) were purchased from Sigma–Aldrich Company and Suzhou Jingqing Chemical Company (Suzhou, China), respectively. Six standard stock solutions and a mixed internal standard were used: $1000\text{ }\mu\text{g/mL}$ of Fe, Cu, Zn, Rb stock solution and $10\text{ }\mu\text{g/mL}$ of Ti stock solution were purchased from the National Nonferrous Metals and Electronic Materials Analysis and Testing Center (Laiyike Experimental Technology Co., Ltd, Ahui, China); $10\text{ }\mu\text{g/mL}$ of 29 elements stock solution (PE#: N9300233) and mixed internal standards (PE#: N9303832) were obtained from Perkin Elmer Life and Analytical Sciences.

The frozen plasma was thawed in a refrigerator at $4\text{ }^{\circ}\text{C}$ before the assay; if there was flocculation in the serum after thawing, we filtered it with a Millex-HV filter head ($0.45\text{ }\mu\text{m}$ i.d.). After thawing, $200\text{ }\mu\text{l}$ of plasma was pipetted into a 15 ml centrifuge tube, diluted 25 times with a diluent solution containing 1% (v/v) nitric acid and 0.05% (v/v) Triton, vortexed and then measured on the machine.

By serially diluting the standard stock solution with a diluent solution containing 1% (v/v) nitric acid and 0.05% (v/v) Triton, a multielement working standard curve solution was prepared for each run. The ranges of calibration for each element were $0\text{--}5\text{ }\mu\text{g/L}$ Se, Sr, Al, V, As; $0\text{--}100\text{ }\mu\text{g/L}$ for Fe, Cu, Zn, Rb and $0\text{--}50\text{ }\mu\text{g/L}$ for Ti. The internal standard element for Al was Sc, and the internal standard element for iron, copper, zinc, selenium, rubidium, strontium, titanium, vanadium, and arsenic was Y.

For every 20 samples, a blank sample was tested as a quality control throughout the testing process. Recovery tests and precision tests were also performed to monitor the accuracy of the measurements. We randomly selected some blood samples from the population as mixed plasma samples for standard recovery addition experiments. We also randomly selected a sample for precision testing on the same day and different days of the sample treatment. The results of recovery experiments and precision tests are detailed in Table S1. According to the regulations of the International Union of Pure and Applied Chemistry (IUPAC), the formula for calculating the detection limit is $\text{CL}=3$. In our study, a diluent solution containing 1% (v/v) nitric acid and 0.05% (v/v) Triton was used for 11 determinations, and three times the standard deviation of the response value was used as the limit of detection (LOD) of the corresponding element to be measured. The LOD data of the instrument are shown in Table S2, which refer to the detailed procedural method of sample testing provided in a previous publication (Liang et al. 2017). After the pilot experiment, we found that 10 plasma elements (iron, copper, zinc, selenium, rubidium, strontium, titanium, aluminum, vanadium and arsenic) were detectable and stable by applying ICP–MS.

Helicobacter pylori testing

After undergoing C14 breath tests, the subjects were subjected to the Hp-IgG antibody detection kit (#20,163,400,552, Aibo Biomedical Co., Ltd, Hangzhou, China) to further confirm the results from the plasma samples using colloidal gold immunochromatography and strictly following the manufacturer’s instructions.

Statistical analysis

SPSS 25.0 and R 4.3.1 software were used for statistical analysis and graphing. A two-sided statistical significance level was set at $\alpha=0.05$. Categorical variables are presented as the number (percentage), and continuous variables are presented as the mean \pm standard deviation or median (25th percentile, 75th percentile). *T* tests, chi-square tests or Wilcoxon rank sum tests were used to analyze the differences in demographic characteristics between groups.

Given that the results of our plasma heavy metal concentration assays did not conform to a normal distribution, the data were log-transformed to improve their normality for better fit with the models. We used a Mann–Whitney U test to compare the concentrations of 10 metal elements in both groups, and Spearman's rank correlation analysis was used to determine their correlation coefficients. Multivariate conditional logistic regression analysis was used to evaluate the relationship between the metal elements and gastric precancerous lesions. Based on plasma metal element concentrations, participants were divided into quartiles, with the lowest concentration group as the reference. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated for the incidence of gastric precancerous lesions. Restricted Cubic Spline (RCS) analysis was used to explore the dose–response relationship between plasma metal elements and gastric precancerous lesions, with reference values set at the 10th percentile. In addition, given the nonlinear association of multiple metal element exposures on gastric precancerous lesions and interactions, a Bayesian kernel logistic regression model (BKMR) was performed to assess the combined associations of multiple elements. The univariate exposure responses for metal elements are shown by cross-sectional plots when other elements were fixed at the median. Differences in risk for individual metal elements were compared for gastric precancerous lesions at the 75th and 25th percentiles, where all other metal elements were fixed at a specific quantile. We also calculated the joint results of mixed metal element exposures by comparing exposure values when all elements were at the median to estimate the potential changes in the mode. In addition, we further discussed the interaction of multiple metallic elements with the risk of prevalent gastric precancerous lesions by fixing other

metallic elements at the median and exploring bivariate exposures of two metallic elements.

Results

Population characteristics

A total of 316 participants (198 males and 118 females) were included. The demographic characteristics of the study population are shown in Table 1. There were significant differences between the gastric precancerous lesion group and the normal control group in terms of BMI, education, marital status, occupation, economic income, family history of chronic gastritis, and tea consumption (all $P < 0.05$).

Elemental concentrations and GPL

The distributions of the 10 plasma elements are shown in Table 2. The plasma concentrations of selenium, iron, copper, and zinc were lower in the gastric precancerous lesion group than in the control group, while the concentrations of titanium and vanadium were higher in the gastric precancerous lesion group than in the control group; these differences were statistically significant ($P < 0.05$). The plasma concentrations of rubidium, strontium, and aluminum were slightly higher in the GPL group than in the control group, but the differences were not statistically significant.

Association between elements and GPLs

Based on the logistic stepwise regression method, we selected five elements for the next step of analysis. The association between plasma element concentrations and gastric precancerous lesions is presented in Table 3. Four elements (Fe, Cu, Zn, and Se) had a negative and significant association in the unadjusted single-element model. Furthermore, a positive association between Ti concentrations and gastric precancerous lesions was noticed in the unadjusted single-element model (OR [95% CI]: 3.30 [1.63–6.67]).

We divided plasma element concentrations into quartiles and used the lowest quartile as the reference. Compared with that of the subjects in the lowest quartile of Ti, we noticed a higher odds ratio of gastric precancerous lesions in the multiple model

Table 1 Baseline characteristics of the paired case and control groups

Demographic characteristics		Number of people surveyed	Control (%)	GPL (%)	P value
Sex	Male	198 (62.7)	101 (63.9)	97 (61.4)	0.642
	Female	118 (37.3)	57 (36.1)	61 (38.6)	
Age (years)	≤ 45	27 (8.5)	12 (7.6)	15 (9.5)	0.265
	46–55	100 (31.6)	50 (31.6)	50 (31.6)	
	56–65	124 (39.2)	63 (39.9)	61 (38.6)	
	66–75	56 (17.7)	30 (19.0)	26 (16.5)	
	≥ 76	9 (2.8)	3 (1.9)	6 (3.8)	
BMI (kg/m ²)	< 24.0	185 (58.5)	100 (63.3)	85 (53.8)	0.008
	24.0–28.0	105 (33.2)	52 (32.9)	53 (33.5)	
	≥ 28.0	26 (8.2)	6 (3.8)	20 (12.7)	
Education level	Illiterate	101 (32.0)	48 (30.4)	53 (33.5)	0.012
	Primary School	73 (23.1)	47 (29.7)	26 (16.5)	
	Junior high school or above	142 (44.9)	63 (39.9)	79 (50.0)	
Marital Status	Single	4 (1.3)	0 (0.0)	4 (2.5)	0.019
	Married/unmarried/widowed	312 (98.7)	158 (100.0)	154 (97.5)	
Career	Farmers	151 (47.8)	88 (55.7)	63 (39.9)	0.006
	Non-Farmers	165 (52.2)	70 (44.3)	95 (60.1)	
Annual household income	Low	136 (43.0)	57 (36.1)	79 (50.0)	0.019
	Medium	92 (29.1)	58 (36.7)	34 (21.5)	
	High	88 (27.8)	43 (27.2)	45 (28.5)	
Smoking	Yes	118 (37.3)	62 (39.2)	56 (35.4)	0.491
	No	198 (62.7)	96 (60.8)	102 (64.6)	
Drinking	Yes	111 (35.1)	61 (38.6)	50 (31.6)	0.191
	No	205 (64.9)	97 (61.4)	108 (68.4)	
Family history of chronic gastritis	Yes	42 (13.3)	5 (3.2)	37 (23.4)	< 0.001
	No	274 (86.7)	153 (96.8)	121 (76.6)	
HP	Positive	132 (41.8)	59 (37.3)	73 (46.2)	0.112
	Negative	184 (58.2)	99 (62.7)	85 (53.8)	
Sleep time (hours)	< 4	8 (2.5)	3 (1.9)	5 (3.2)	0.143
	4–6	50 (15.8)	19 (12.0)	31 (19.6)	
	6–8	107 (33.9)	61 (38.6)	46 (29.1)	
	≥ 8	151 (47.8)	75 (47.5)	76 (48.1)	
Sleep quality	Good	69 (21.8)	36 (22.8)	33 (20.9)	0.212
	General	159 (50.3)	85 (53.8)	74 (46.8)	
	Difference	88 (27.8)	37 (23.4)	51 (32.3)	
Tea drinking	Yes	158 (50.0)	90 (57.0)	68 (43.0)	0.011
	No	158 (50.0)	68 (43.0)	90 (57.0)	

BMI body mass index; *HP* Helicobacter pylori

(OR [95% CI]: 11.56 [2.78 – 48.13]). Furthermore, two elements, Cu (OR [95% CI]: 0.24 [0.07 – 0.82]) and Se (OR [95% CI]: 0.03 [0.01 – 0.15]), remained significantly associated with gastric precancerous lesions. Spearman's rank correlations

between plasma elements and gastric precancerous lesions are shown in **Fig. S2**. Se and Zn were the most closely related ($r=0.52$), followed by Cu and Zn ($r=0.47$). The RCS plot showed a dose–response relationship between iron, copper, zinc,

Table 2 Concentrations of 10 elements in blood plasma

	Total population (µg/l)	People with GPLs (µg/l)	Normal Controls (µg/l)	^a P value
Fe	1053.789 (831.173–1368.608)	975.536 (742.307–1197.206)	1123.652 (895.691–1488.86)	<0.001
Cu	839.968 (731.012–972.43)	786.906 (684.798–850.334)	945.245 (813.252–1051.234)	<0.001
Zn	868.401 (766.921–1003.483)	812.525 (738.625–899.311)	943.725 (823.847–1094.481)	<0.001
Se	109.176 (84.599–136.028)	91.283 (74.656–112.031)	132.147 (108.26–154.62)	<0.001
Rb	134.659 (113.468–159.786)	138.64 (117.998–159.958)	129.655 (110.855–159.074)	0.313
Sr	35.762 (30.433–42.327)	36.399 (30.472–42.266)	35.246 (29.883–42.368)	0.496
Ti	22.853 (17.459–34.206)	26.786 (19.746–35.78)	21.335 (14.609–26.893)	<0.001
Al	151.364 (86.662–231.381)	155.13 (77.387–239.605)	145.02 (94.569–224.569)	0.906
V	1.438 (0.834–2.159)	1.833 (1.26–2.163)	0.834 (0.658–2.158)	<0.001
As	4.835 (2.900–4.835)	4.016 (3.027–4.772)	3.917 (2.84–4.917)	0.700

Fe, iron; Cu, copper; Zn, zinc; Se, selenium; Rb, rubidium; Sr, strontium; Ti, titanium; Al, aluminum; V, vanadium; As, arsenic. Element concentrations are presented as median (IQR)
^aP values were derived from Mann–Whitney U tests

selenium, and titanium and gastric precancerous lesions (Fig. 1).

BKMR

Figure 2 shows a linear relationship between single element exposure and gastric precancerous lesions when other element exposures were fixed at the median. The concentrations of iron, copper, zinc and selenium presented negative linear associations with the odds of gastric precancerous lesions, while the concentrations of titanium displayed positive linear associations with the odds of gastric precancerous lesions.

There was a combined correlation of five elements, iron (Fe), copper (Cu), zinc (Zn), selenium (Se), and titanium (Ti), on gastric precancerous lesions. Figure 3A shows that the overall results showed a significant negative correlation with outcome when the elements were simultaneously fixed at different percentile levels compared to the change in estimated potential outcome when fixed at the median. Figure 3B demonstrates that copper and selenium exposure were negatively associated with the risk of gastric precancerous lesions (75th vs. 25th), while we noticed a positive association between titanium

exposure and gastric precancerous lesions (75th vs. 25th) when the other four elements were fixed at different percentiles (25th, 50th, or 75th).

Finally, the bivariate exposure–response functions of the five elements are presented in Fig. 4. We found interaction correlations between selenium and titanium, copper and titanium, and selenium and copper for decreasing the risk of gastric precancerous lesions.

Discussion

Based on the results, five plasma elements that differed in concentration between the two groups were selected, and a polymetallic model was used to assess the correlation between plasma concentrations of the five elements and gastric precancerous lesions. We found that in the univariate model, plasma concentrations of iron, copper, zinc, and selenium were significantly and positively correlated with gastric precancerous lesions, and plasma concentrations of titanium were negatively correlated with gastric precancerous lesions. In contrast, in the multielement model, plasma selenium concentrations were significantly negatively correlated with gastric precancerous

Table 3 Correlations of plasma concentrations of five elements on the risk of developing precancerous lesions in the stomach

	Plasma metal	Quartile 1	Quartile 2	Quartile 3	Quartile 4	<i>p</i>
	Se	< 84.64	84.64–109.18	109.18–135.95	> 135.95	
	case/total	65/79	50/79	30/79	13/79	
	model1 ^a	1.00	0.53 (0.23–1.21)	0.16 (0.07–0.37)	0.06 (0.03–0.16)	< 0.001
	model2 ^b	1.00	0.54 (0.23–1.24)	0.14 (0.06–0.34)	0.06 (0.02–0.15)	< 0.001
	model3 ^c	1.00	0.66 (0.20–2.18)	0.10 (0.03–0.36)	0.03 (0.01–0.15)	< 0.001
	Fe	< 834.52	834.52–1053.79	1053.79–1368.42	> 1368.42	
	case/total	51/79	42/79	38/79	27/79	
	model1 ^a	1.00	0.61 (0.32–1.14)	0.44 (0.22–0.90)	0.27 (0.13–0.54)	0.001
	model2 ^b	1.00	0.61 (0.31–1.10)	0.44 (0.20–0.87)	0.27 (0.13–0.53)	0.003
	model3 ^c	1.00	0.51 (0.16–1.59)	0.59 (0.18–1.94)	1.88 (0.50–7.07)	< 0.001
	Cu	< 731.24	731.24–839.97	839.97–972.06	> 972.06	
	case/total	55/79	56/79	29/79	18/79	
	model1 ^a	1.00	0.83 (0.37–1.87)	0.25 (0.11–0.55)	0.12 (0.05–0.29)	< 0.001
	model2 ^b	1.00	0.83 (0.36–1.91)	0.24 (0.10–0.58)	0.13 (0.05–0.30)	< 0.001
	model3 ^c	1.00	1.18 (0.35–4.02)	0.16 (0.04–0.69)	0.24 (0.07–0.82)	< 0.001
Model 1 ^a was the crude odds ratio (95% CI)	Zn	< 766.52	766.52–867.64	867.64–1000.13	> 1000.13	
	case/total	51/79	51/79	39/79	17/79	
	model1 ^a	1.00	0.89 (0.43–1.83)	0.49 (0.24–1.03)	0.16 (0.07–0.35)	< 0.001
	model2 ^b	1.00	0.88 (0.43–1.83)	0.51 (0.24–1.09)	0.15 (0.07–0.34)	< 0.001
	model3 ^c	1.00	1.95 (0.63–6.04)	2.21 (0.63–7.73)	0.46 (0.11–1.88)	< 0.001
Model 2 ^b was adjusted for smoking, alcohol consumption, and hp infection	Ti	< 17.49	17.49–22.88	22.88–34.37	> 34.37	
	case/total	25/79	39/79	48/79	46/79	
	model1 ^a	1.00	2.34 (1.15–4.77)	3.70 (1.81–7.56)	3.30 (1.63–6.67)	< 0.001
	model2 ^b	1.00	2.30 (1.12–4.72)	3.90 (1.86–8.14)	3.39 (1.65–6.95)	0.001
	model3 ^c	1.00	6.38 (1.82–22.37)	11.21 (2.99–42.06)	11.56 (2.78–48.13)	< 0.001
Model 3 ^c was additionally adjusted for five metals (P < 0.05) except for the covariates in Model 2						

lesions, while the opposite was true for plasma titanium concentrations. Bayesian logistic regression analysis showed that mixed exposure to five elements in the plasma had a negative combined correlation on gastric precancerous lesions, and there was an interaction between plasma selenium and titanium.

Gastric cancer accounts for approximately 6% of cancers worldwide and is the fifth most commonly diagnosed malignancy. Although the incidence and mortality rates of gastric cancer have steadily declined over the past 15 years, the absolute incidence of gastric cancer continues to rise due to the prevalence of *Helicobacter pylori* infection, poor dietary habits, and the aging of the world population (Gullo et al. 2020). Prevention of the development of gastric cancer remains crucial. As a result, gastric cancer remains one of the most significant health burdens in developing countries. According to the Correa cascade response model proposed by Correa in 1992, gastric cancer does not occur overnight but is

a multistage, multifactorial and precancerous gastric process (Correa 1992). *Helicobacter pylori* infection, bile reflux, age, dietary habits, and family history of gastric cancer are all independent risk factors for gastric precancerous lesions and gastric carcinogenesis, and the combined presence of multiple risk factors may cause a higher risk (Zhang et al. 2021).

A review found that trace element and heavy metal levels may influence cancer development and progression (Mulware in review). The long-term development of industry and manufacturing has had a huge impact on the environment and has increased the risk of human exposure to various types of metals (Sanaei et al. 2021). Different types of metals may have some biological action on the human body. Co, Cu, Ni, Fe, Mn, Zn, Mo, and Se are essential elements for living organisms, and their absence may cause health problems, but they can have adverse health effects when ingested in amounts above the safe limit (Giri et al. 2021).

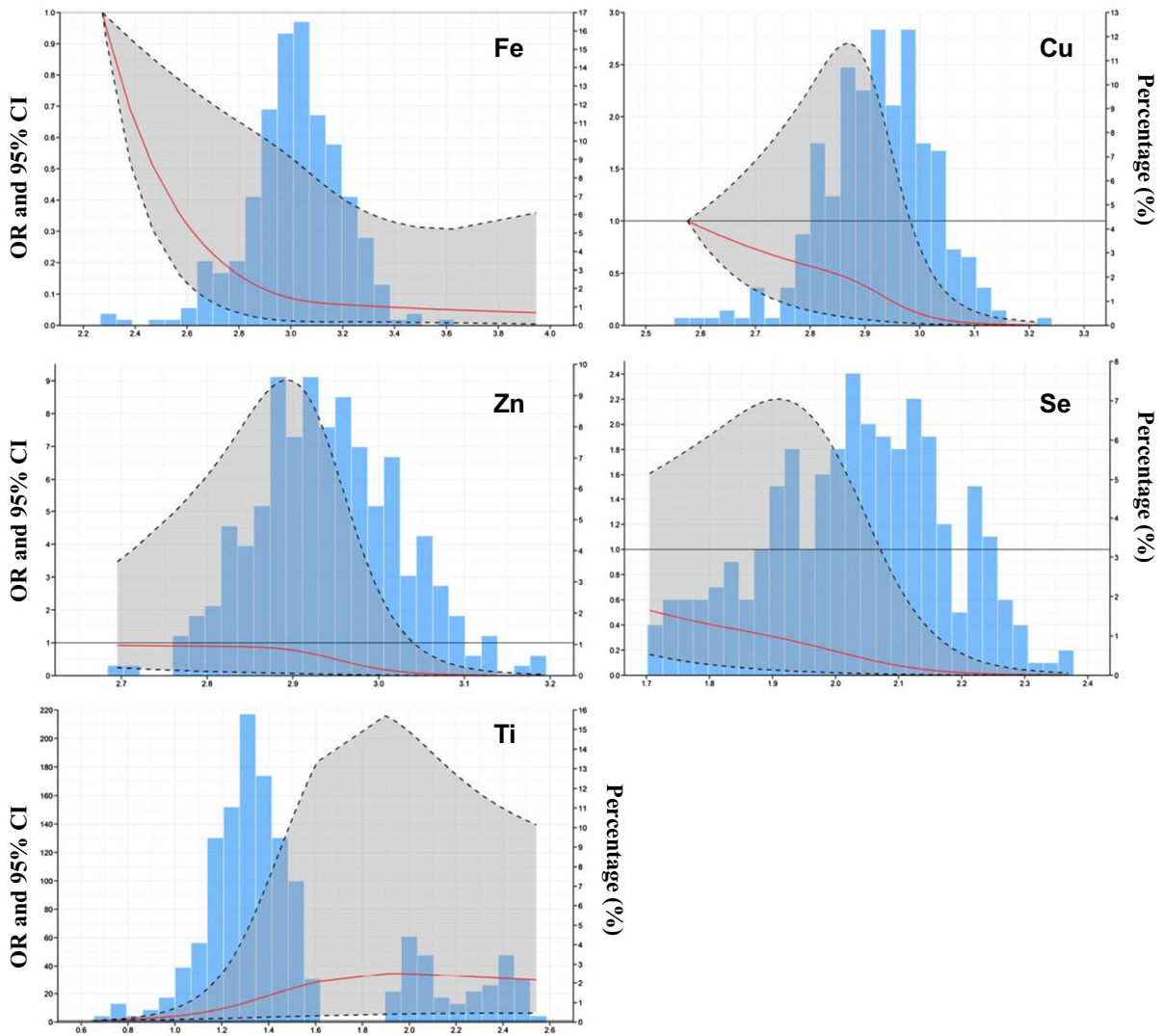


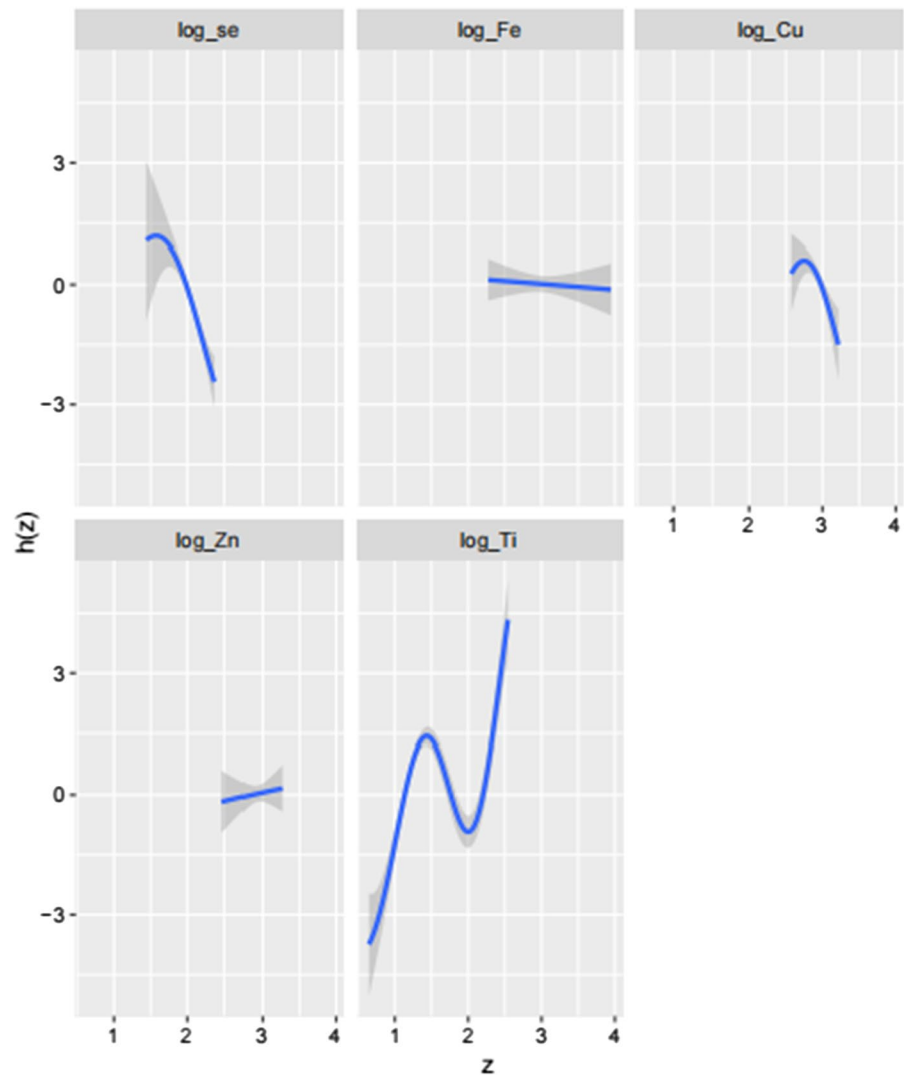
Fig. 1 Adjusted restricted cubic spline (RCS) analysis for the relationship between plasma elements and GPLs. The two dashed lines represent the [95% confidence interval (CI)] of the OR of the RCS based on log-transformed levels of iron (Fe), copper (Cu), zinc (Zn), selenium (Se), and titanium (Ti) from the polymetallic model with the reference value set at the 10th

percentile. Adjustment factors were smoking, alcohol consumption, and hp infection. The histogram represents the histogram of the distribution of metal elements in the plasma of the study subjects. The unit for the concentration of each metal was $\mu\text{g/L}$

Other metals, such as arsenic, cadmium, chromium, lead, and cobalt, are not essential to the human body and can cause health problems even at low concentrations (Giri et al. 2020; Jalili et al. 2020). Related studies have shown that there are four possible mechanisms by which heavy metals cause gastric cancer. First, heavy metals damage the gastric mucosal barrier by reducing gastric mucosal thickness, mucus content and basal acid output, thus

affecting the function of E-cadherin and causing reactive oxygen species (ROS) damage. Second, heavy metals directly or indirectly induce ROS production, causing gastric mucosal and DNA damage, which in turn alters gene regulation, signal transduction and cell growth, eventually leading to carcinogenesis, and exposure to heavy metals also promotes the invasion and metastasis of gastric cancer cells. Third, heavy metals can inhibit DNA damage

Fig. 2 Univariate exposure–response function and 95% confidence interval (CI) for the association between single element exposure and gastric precancerous lesions when other element exposures were fixed at the median



repair or lead to inefficient DNA damage repair. Fourth, heavy metals can cause other genetic abnormalities (Yuan et al. 2016).

For many organisms, selenium is an essential trace element which is necessary to sustain life, and its properties are intermediate between those of the elements sulfur and tellurium; selenium performs its biological functions through selenoproteins (Kurokawa and Berry 2013). People consume selenium primarily through food but may also be exposed to it through air, drinking water, and dietary supplements (Selenium 2021). Early epidemiological studies have shown that selenium exposure is inversely associated with the risk of various cancers (Vinceti et al. 2017). It has been shown that selenium has an anticancer

association which may be related to the redox mechanisms of selenium metabolites (Kim et al. 2021), such as eliminating reactive oxygen species (Cai et al. 2016), preventing DNA and chromosome breaks, and preventing the loss of chromosomes, DNA and even mitochondrial DNA, thus improving overall genomic stability (Ferguson et al. 2012). The relationship between selenium and gastric cancer has been evaluated through several studies that highlight the protective correlations of this micronutrient against gastric cancer. A meta-analysis of selenium and gastric cancer showed a negative association between selenium levels and gastric cancer risk and that low selenium levels may increase an individual's risk of gastric cancer or decrease survival in gastric cancer patients

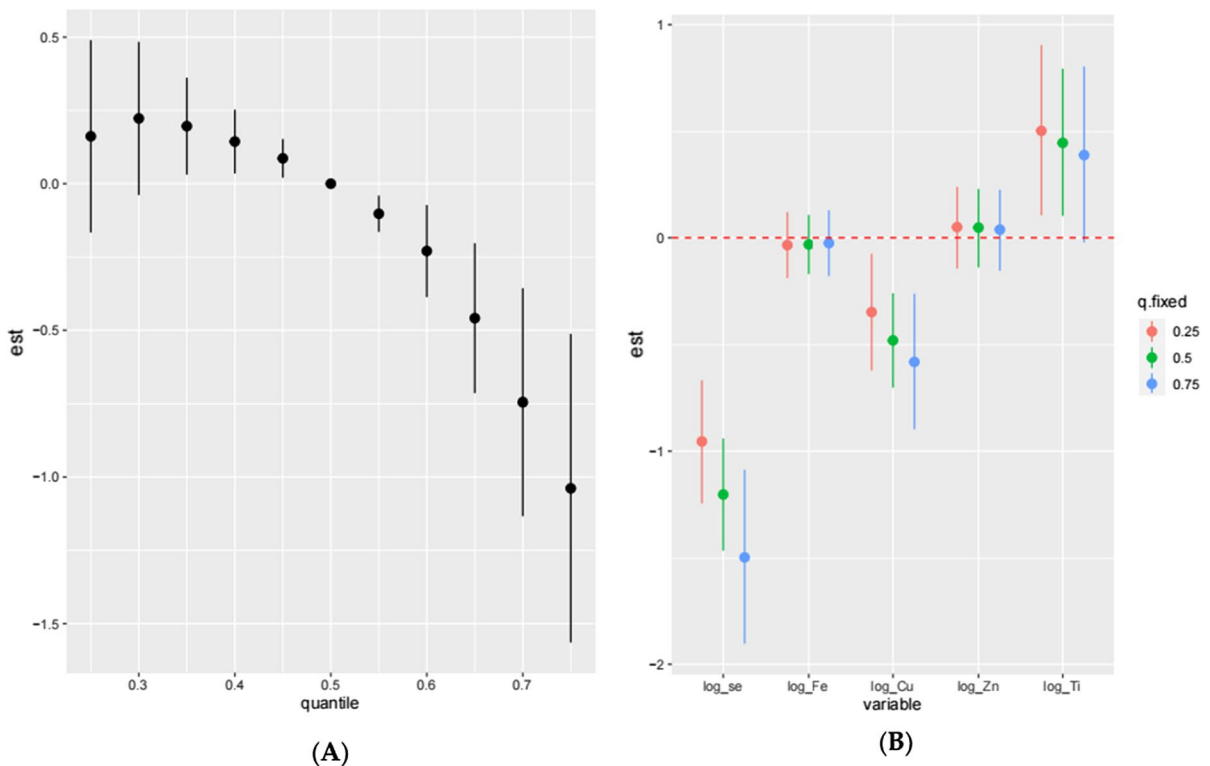


Fig. 3 The joint correlations of five elements, iron (Fe), copper (Cu), zinc (Zn), selenium (Se), and titanium (Ti), on GPLs was determined using a Bayesian kernel function regression model (BKMR). Adjusted factors included smoking, alcohol consumption and hp infection. (A) Overall action of the mixtures [95% confidence interval (CI)], the plot indicated the estimated change in the risk of gastric precancerous lesions by comparing a particular percentile (from the 25th per-

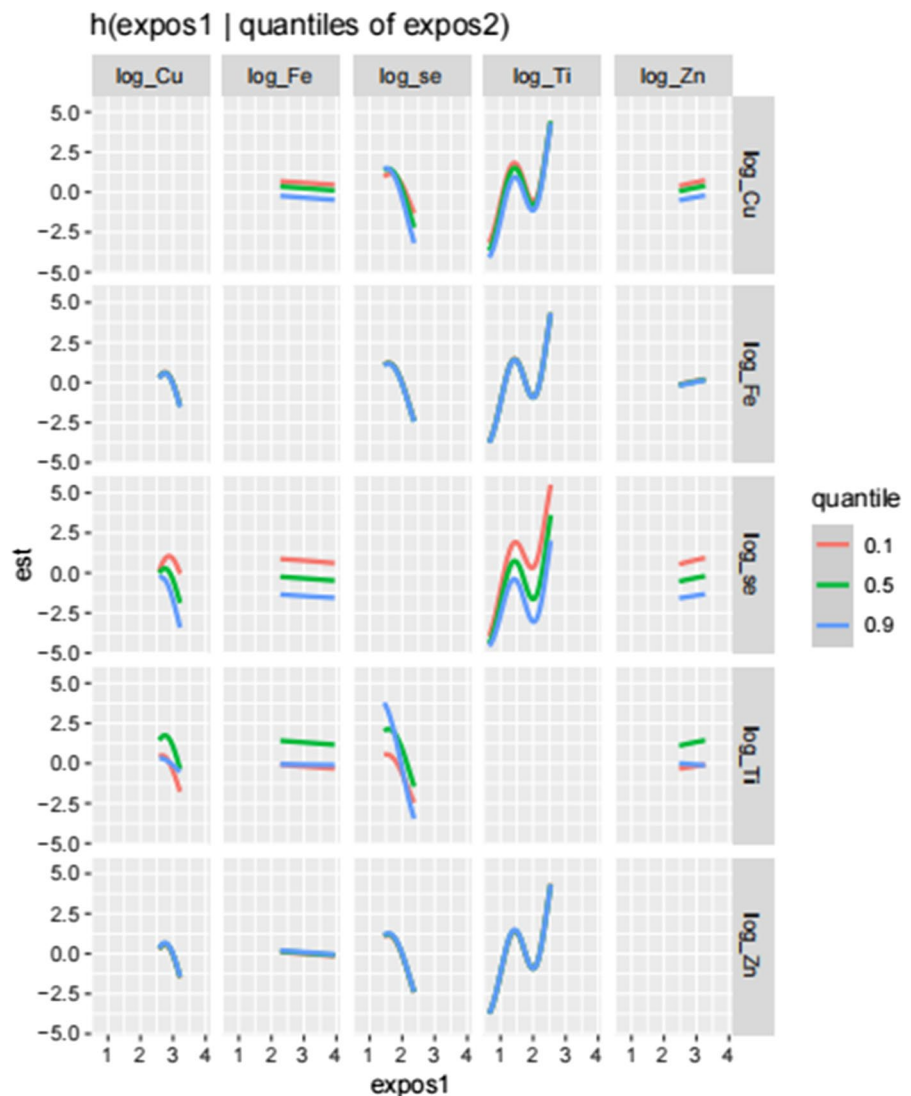
tile to 75th percentiles) of all elements level with their median value the 50th percentile). (B) Single element association [95% confidence interval (CI)]. The right plot indicated the results of single element by comparing the 75th of the element concentrations with its 25th percentile, when concentrations of all the other elements were held at the 25th (red line), 50th (green line) or 75th (blue line) percentiles

(Gong et al. 2016). An analysis by Xu Ce et al. showed that serum selenium levels were significantly and negatively associated with the risk of developing gastric cancer and the risk of death in gastric cancer patients (Xu 2017). A Dutch cohort study showed that total selenium levels were negatively associated with gastric and esophageal cancers (Brandt et al. 2010). Two other studies in Chinese and Finnish populations with relatively low selenium levels found a negative association between serum selenium levels and total gastric cancer (Mark et al. 2000). Those studies also indirectly support our finding that selenium exposure is negatively associated with gastric precancerous lesions.

Iron, copper, and zinc, the three most abundant essential trace elements, are components of several key enzyme systems in the human body and play a

key role in preventing oxidative DNA damage and affecting gene mutations to maintain DNA integrity (Grzeszczak et al. 2020). Some related studies reported that low levels of iron may be associated with gastric cancer: a study conducted by Kohzadi et al. showed low levels of iron in gastric cancer tissues (Kohzadi et al. 2017), and a case–control study in Korea showed that the risk of gastric cancer was significantly lower in people with high total dietary iron intake than in those with low total dietary iron intake (Tran et al. 2021). On the other hand, several other studies have shown that increased body iron concentrations are associated with an increased risk of gastric cancer (Jakszyn et al. 2012; Khayyat-zadeh et al. 2015). Zinc alone is associated with the risk of gastric cancer, but epidemiological findings are limited and controversial: an analysis by Sayyed

Fig. 4 Bivariate exposure response functions for elemental mixture exposure associated with GPLs. For example: bivariate exposure Zn—Cu response function when copper is fixed at the 10th, 50th, or 90th percentile and other elements are fixed at intermediate values (Fig. 1 on the right); Zn—Fe response function when iron is fixed at the 10th, 50th, or 90th percentile and other elements are fixed at intermediate positions (second panel on the right); Zn—Se response function when selenium is fixed at the 10th, 50th, or 90th percentile and Zn reaction function when other elements are fixed at the middle position (third panel on the right); Zn—Ti when titanium is fixed at the 10th, 50th, or 90th percentile and other elements are fixed at the middle position (fourth panel on the right)



et al. showed that high serum zinc levels may have a protective correlation against gastric cancer (Khayatzadeh et al. 2015), while Zhang et al. observed higher serum zinc concentrations in patients with gastric cancer than in healthy controls (Zhang et al. 2012); a detailed systematic review and meta-analysis conducted by Li et al. showed no statistical association between zinc intake and the risk of gastric and esophageal cancers (Li et al. 2014). An Iranian study assessing trace element concentrations in gastric cancer and normal tissues found that copper concentrations were higher in noncancerous tissues of cancer patients (Kohzadi et al. 2017). However, a previous study found that hair copper levels were significantly

higher in gastric cancer patients than in controls (Afzal et al. 2020). Our study found that plasma concentrations of iron, copper, and zinc in the population with gastric precancerous lesions were lower than those in the normal group. However, as seen from the aforementioned study, iron, copper, and zinc were associated with the development of gastric cancer, and thus the evidence is conflicting and is not sufficient to draw conclusions. We cannot provide a precise and comprehensive interpretation of the obtained results, which are pending further research findings.

Titanium is a common metal, usually in the form of titanium dioxide (TiO₂) (Jin et al. 2021). Titanium is a nonessential trace element in the human body. It

can be absorbed into the human body through various routes, including oral, dermal, and inhalation exposure (Musial et al. 2020). Titanium is now widely used in medical applications such as artificial joints, cochlear implants and heart valves (Xu et al. 2020). There are already researchers who are concerned about the biosafety of titanium. Studies have reported that the presence of titanium particles may be harmful, and the release of titanium particles may cause an inflammatory response in the surrounding tissue (Moran et al. 2017; Zhang et al. 2020). Studies have reported that titanium exposure may be associated with adverse health consequences, such as diabetes, colonic inflammation, low birth weight, congenital heart disease and cardiopulmonary disease (Jin et al. 2021; Grande and Tucci 2016; Sun et al. 2022; Zhao et al. 2018). Several experimental studies have shown that titanium exposure leads to oxidative stress, cytotoxicity, and damage to DNA and lipid metabolism (Ren et al. 2019; Fadoju et al. 2019; Trouiller et al. 2009; Shinohara et al. 2014). Currently, there are few studies on the relationship between titanium and precancerous lesions in the stomach. An animal study found that titanium had gastric toxicity in mice and suggested potential adverse consequences on digestive health (Hong et al. 2017). The mechanism of titanium leading to the development of gastric precancerous lesions may be related to titanium causing oxidative stress damage, genotoxicity, etc. (Fadoju et al. 2019). The results of this study suggested that plasma titanium concentrations may be positively associated with gastric precancerous lesions. However, considering that for the titanium-implanted or occupationally exposed population, the blood concentration of titanium is much higher than that of the normal population (Lukina et al. 2016; Sarmiento-González et al. 2008), further investigation is needed to explore the association between titanium exposure and gastric precancerous lesions.

This study was a case–control study, which had some advantages for exploring the association between elements and gastric precancerous lesions. First, we conducted a one-to-one evaluation of the study subjects using a questionnaire in a standard and rigorous manner to ensure the authenticity and validity of the data. We not only explored the association between individual elements and gastric precancerous lesions but also explored the association of multiple elements acting in combination on

gastric precancerous lesions. These results may help in the prevention of gastric cancer. On the other hand, there are some limitations in our study. There may be some information bias based on the determination of elements in single plasma samples, and further studies can detect different biological samples from patients with gastric precancerous lesions. Patients with gastric precancerous lesions may have taken laparoscopic drugs (under the advice of their doctors), such as omeprazole or other types of gastric drugs, and may have also underwent dietary interventions to prevent further disease progression; those factors may affect plasma element levels.

Conclusion

The results of this study showed that plasma levels of selenium and copper were negatively correlated with GPLs, while plasma concentrations of titanium were positively correlated with GPLs. Mixed exposure to iron, copper, zinc, selenium, and titanium was negatively associated with the risk of gastric precancerous lesions, and there may be some interaction between selenium and titanium metals. Therefore, a reasonable increase in the intake of the trace elements iron, copper, zinc, and selenium, as well as a decrease in the exposure of titanium metal, may have a positive impact on gastric precancerous lesions.

Acknowledgements We appreciate all patients and doctors participated in the present study. We also appreciate the funding aforementioned supported for this study. The funding agencies had no role in the design and conduct of the study; collection, management, analysis, or interpretation of the data; preparation, review, or approval of the manuscript; or decision to submit the manuscript for publication. And we also appreciate the advice from Dr. Gengsheng He, School of Public Health, Fudan University.

Author contributions Study concept and design: YZ, DZ, AH and QZ; data acquisition: TW, FX, YL, XZ, WC, DZ, YZ, YL, LW, MW, XL, MZ, TX, SQ, MT, WY; data analysis: TW, FX; data interpretation: TW, FX; article drafting: TW, FX; manuscript review and editing: QZ.

Funding This study was supported from the National Natural Science Foundation of China (No. 81973049), Anhui Province Peak Discipline Construction Plan (Grant No. 0301001861), and Basic and Clinical Cooperative Research Promotion Program of Anhui Medical University (No. 2020xkjT031).

Data availability The data generated during and analyzed during the current study are not publicly available due to the nature of this research, participants of this study did not agree for the data to be shared publicly, so supporting data is not available, but are available from the corresponding author on reasonable request.

Declarations

Conflict of interest The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Ethical approval The present study obtained ethics approval from the ethics committee of Anhui Medical University. All participants also provided written informed consent for the current study.

Human subjects' statement The study was reviewed and approved by the Ethics Committee of Anhui Medical University, and all participants signed written informed consent (Approval No: 20190292).

References

- Afzal A, Qayyum MA, Shah MH (2020) Study of trace metal imbalances in the scalp hair of stomach cancer patients with different types and stages. *Biol Trace Elem Res* 196:365–374. <https://doi.org/10.1007/s12011-019-01926-w>
- Cai X, Wang C, Yu W, Fan W, Wang S, Shen N, Wu P, Li X, Wang F (2016) Selenium exposure and cancer risk: an updated meta-analysis and meta-regression. *Sci Rep* 6:19213. <https://doi.org/10.1038/srep19213>
- Cao W, Chen HD, Yu YW, Li N, Chen WQ (2021) Changing profiles of cancer burden worldwide and in China: a secondary analysis of the global cancer statistics 2020. *Chin Med J (engl)* 134:783–791. <https://doi.org/10.1097/CM9.0000000000001474>
- Christudoss P, Selvakumar R, Pulimood AB, Fleming JJ, Mathew G (2012) Zinc and zinc related enzymes in precancerous and cancerous tissue in the colon of dimethyl hydrazine treated rats. *Asian Pacific J Cancer Prev* 13:487–492. <https://doi.org/10.7314/apjcp.2012.13.2.487>
- Correa P (1992) Human gastric carcinogenesis: a multistep and multifactorial process—First American Cancer Society Award Lecture on Cancer Epidemiology and Prevention. *Cancer Res* 52:6735–6740
- Fadoju O, Ogunsuyi O, Akanni O, Alabi O, Alimba C, Adaramoye O, Cambier S, Eswara S, Gutleb AC, Bakare A (2019) Evaluation of cytogenotoxicity and oxidative stress parameters in male Swiss mice co-exposed to titanium dioxide and zinc oxide nanoparticles. *Environ Toxicol Pharmacol* 70:103204. <https://doi.org/10.1016/j.etap.2019.103204>
- Ferguson LR, Karunasinghe N, Zhu S, Wang AH (2012) Selenium and its' role in the maintenance of genomic stability. *Mutat Res* 733:100–110. <https://doi.org/10.1016/j.mrfmmm.2011.12.011>
- Fonseca-Nunes A, Jakszyn P, Agudo A (2014) Iron and cancer risk—a systematic review and meta-analysis of the epidemiological evidence., *Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive. Oncology* 23:12–31. <https://doi.org/10.1158/1055-9965.EPI-13-0733>
- Giri S, Singh AK, Mahato MK (2020) Monte Carlo simulation-based probabilistic health risk assessment of metals in groundwater via ingestion pathway in the mining areas of Singhbhum copper belt, India. *Int J Environ Heal R* 30:447–460. <https://doi.org/10.1080/09603123.2019.1599101>
- Giri S, Mahato MK, Singh AK (2021) Multivariate linear regression models for predicting metal content and sources in leafy vegetables and human health risk assessment in metal mining areas of Southern Jharkhand, India. *Environ Sci Pollut R* 28:27250–27260. <https://doi.org/10.1007/s11356-021-12494-9>
- Gong H, He J, Li B (2016) Meta-analysis of the association between selenium and gastric cancer risk. *Oncotarget* 7(13):15600–15605
- Grande F, Tucci P (2016) Titanium dioxide nanoparticles: a risk for human health? *Mini Rev Med Chem* 16:762–769. <https://doi.org/10.2174/138955751666616032114341>
- Grzeszczak K, Kwiatkowski S, Kosik-Bogacka D (2020) The role of Fe, Zn, and Cu in pregnancy. *Biomolecules*. <https://doi.org/10.3390/biom10081176>
- Gullo I, Grillo F, Mastracci L, Vanoli A, Carneiro F, Saragoni L, Limarzi F, Ferro J, Parente P, Fassan M (2020) Precancerous lesions of the stomach, gastric cancer and hereditary gastric cancer syndromes. *Pathologica* 112:166–185. <https://doi.org/10.32074/1591-951X-166>
- H. Sung, J. Ferlay, R.L. Siegel, M. Laversanne, I. Soerjomataram, A. Jemal, F. Bray, *Global Cancer Statistics (2020) GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin* 71(2021):209–249. <https://doi.org/10.3322/caac.21660>
- Hong F, Wu N, Zhou Y, Ji L, Chen T, Wang L (2017) Gastric toxicity involving alterations of gastritis-related protein expression in mice following long-term exposure to nano TiO₂ (2). *Food Res Int* 95:38–45. <https://doi.org/10.1016/j.foodres.2017.02.013>
- Jakszyn P, Agudo A, Lujan-Barroso L, Bueno-de-Mesquita HB, Jenab M, Navarro C, Palli D, Boeing H, Manjer J, Numans ME, Igalí L, Boutron-Ruault MC, Clavel-Chapelon F, Morois S, Grioni S, c. Panico, R. Tumino, C. Sacerdote, J.R. Quirós, E. Molina-Montes, J.M. Huerta Castaño, A. Barricarte, P. Amiano, K.T. Khaw, N. Wareham, N.E. Allen, T.J. Key, S.M. Jeurnink, P.H. Peeters, C. Bamia, E. Valanou, A. Trichopoulou, R. Kaaks, A. Lukanova, M.M. Bergmann, B. Lindkvist, R. Stenling, I. Johansson, C.C. Dahm, K. Overvad, A. Olsen, A. Tjønneland, G. Skeie, A.R. Broderstad, E. Lund, D.S. Michaud, T. Mouw, E. Riboli, C.A. González, (2012) Dietary intake of heme iron and risk of gastric cancer in the European prospective

- investigation into cancer and nutrition study. *Int J Cancer* 130:2654–63. <https://doi.org/10.1002/ijc.26263>
- Jalili C, Kazemi M, Taheri E, Mohammadi H, Boozari B, Hadi A, Moradi S (2020) Exposure to heavy metals and the risk of osteopenia or osteoporosis: a systematic review and meta-analysis. *Osteoporos Int* 31:1671–1682. <https://doi.org/10.1007/s00198-020-05429-6>
- Jin Y, Li Z, An H, Pang Y, Li K, Zhang Y, Zhang L, Yan L, Wang B, Ye R, Li Z, Ren A (2021) Environmental titanium exposure and reproductive health: Risk of low birth weight associated with maternal titanium exposure from a nested case-control study in northern China. *Ecotox Environ Safe* 208:111632. <https://doi.org/10.1016/j.ecoenv.2020.111632>
- Khayatzadeh SS, Maghsoudi Z, Foroughi M, Askari G, Ghiasvand R (2015) Dietary intake of Zinc, serum levels of Zinc and risk of gastric cancer: a review of studies. *Adv Biomed Res* 4:118–118. <https://doi.org/10.4103/2277-9175.157849>
- Khazaei S, Mohammadbeigi A, Jenabi E, Asgarian A, Heidari H, Saghaifpour A, Arsang-Jang S, Ansari H (2020) Environmental and ecological factors of stomach cancer incidence and mortality: a systematic review study on ecological studies. *Rev Environ Health* 35:443–452. <https://doi.org/10.1515/reveh-2020-0022>
- Kim H, Lee J, Woo HD, Kim DW, Choi IJ, Kim Y, Kim J (2019) Association between dietary cadmium intake and early gastric cancer risk in a Korean population: a case-control study. *Eur J Nutr* 58:3255–3266. <https://doi.org/10.1007/s00394-018-1868-x>
- Kim SJ, Choi MC, Park JM, Chung AS (2021) Antitumor effects of selenium. *Int J Mol Sci*. <https://doi.org/10.3390/ijms222111844>
- Kohzadi S, Sheikhesmaili F, Rahehagh R, Parhizkar B, Ghaderi E, Loqmani H, Shahmoradi B, Mohammadi E, Maleki A (2017) Evaluation of trace element concentration in cancerous and non-cancerous tissues of human stomach. *Chemosphere* 184:747–752. <https://doi.org/10.1016/j.chemosphere.2017.06.071>
- Kurokawa S, Berry MJ (2013) Role of the essential metalloid in health. *Met Ions Life Sci* 13:499–534. https://doi.org/10.1007/978-94-007-7500-8_16
- Li P, Xu J, Shi Y, Ye Y, Chen K, Yang J, Wu Y (2014) Association between zinc intake and risk of digestive tract cancers: a systematic review and meta-analysis. *Clin Nutr (Edinburgh, Scotland)* 33:415–420. <https://doi.org/10.1016/j.clnu.2013.10.001>
- Liang C, Li Z, Xia X, Wang Q, Tao R, Tao Y, Xiang H, Tong S, Tao F (2017) Determine multiple elements simultaneously in the sera of umbilical cord blood samples—a very simple method. *Biol Trace Elem Res* 177:1–8. <https://doi.org/10.1007/s12011-016-0853-6>
- Lin Y, Wu C, Yan W, Guo S, Liu B (2020) Five serum trace elements associated with risk of cardia and noncardia gastric cancer in a matched case-control study. *Cancer Manag Res* 12:4441–4451. <https://doi.org/10.2147/CMAR.S250592>
- Lukina E, Laka A, Kollerov M, Sampiev M, Mason P, Wagstaff P, Noordeen H, Yoon WW, Blunn G (2016) Metal concentrations in the blood and tissues after implantation of titanium growth guidance sliding instrumentation. *Spine J* 16:380–388. <https://doi.org/10.1016/j.spinee.2015.11.040>
- Mark SD, Qiao YL, Dawsey SM, Wu YP, Katki H, Gunter EW, Fraumeni JF Jr, Blot WJ, Dong ZW, Taylor PR (2000) Prospective study of serum selenium levels and incident esophageal and gastric cancers. *J Natl Cancer Inst* 92:1753–1763. <https://doi.org/10.1093/jnci/92.21.1753>
- Moran MM, Wilson BM, Ross RD, Viridi AS, Sumner DR (2017) Arthroscopy-based preclinical models of particle-induced osteolysis: a systematic review. *J Orthop Res* 35:2595–2605. <https://doi.org/10.1002/jor.23619>
- Mulware SJ (2013) Trace elements and carcinogenicity: a subject in review. *3 Biotech* 3:85–96. <https://doi.org/10.1007/s13205-012-0072-6>
- Musial J, Krakowiak R, Mlynarczyk DT, Goslinski T, Stanisz BJ (2020) Titanium dioxide nanoparticles in food and personal care products—what do we know about their safety? *Nanomaterials (Basel, Switzerland)*. <https://doi.org/10.3390/nano10061110>
- Ren Y, Zhang Y, Wang Z, Wang C, Zhang H, Wang Y, Zhao Z (2019) Role of Brd4 in the production of inflammatory cytokines in mouse macrophages treated with titanium particles. *Can J Physiol Pharmacol* 97:1028–1034. <https://doi.org/10.1139/cjpp-2019-0142>
- Steevens J, van den Brandt PA, Goldbom RA, Leo SJ (2010) Selenium status and the risk of esophageal and gastric cancer subtypes: the Netherlands cohort study. *Gastroenterology* 138:1704–13. <https://doi.org/10.1053/j.gastro.2009.12.004>
- Sanaei F, Amin MM, Alavijeh ZP, Esfahani RA, Sadeghi M, Bandarrig NS, Fatehizadeh A, Taheri E, Rezakazemi M (2021) Health risk assessment of potentially toxic elements intake via food crops consumption: Monte Carlo simulation-based probabilistic and heavy metal pollution index. *Environ Sci Pollut Res Int* 28:1479–1490. <https://doi.org/10.1007/s11356-020-10450-7>
- Sarmiento-González A, Marchante-Gayón JM, Tejerina-Lobo JM, Paz-Jiménez J, Sanz-Medel A (2008) High-resolution ICP-MS determination of Ti, V, Cr Co, Ni, and Mo in human blood and urine of patients implanted with a hip or knee prosthesis. *Anal Bioanal Chem* 391:2583–2589. <https://doi.org/10.1007/s00216-008-2188-4>
- Selenium KM (2021) *Adv Food Nutr Res* 96:417–429. <https://doi.org/10.1016/bs.afnr.2021.02.019>
- Shinohara N, Danno N, Ichinose T, Sasaki T, Fukui H, Honda K, Gamo M (2014) Tissue distribution and clearance of intravenously administered titanium dioxide (TiO₂) nanoparticles. *Nanotoxicology* 8:132–141. <https://doi.org/10.3109/17435390.2012.763001>
- Sohrabi M, Gholami A, Azar MH, Yaghoobi M, Shahi MM, Shirmardi S, Nikkha M, Kohi Z, Salehpour D, Khoonsari MR, Hemmasi G, Zamani F, Sohrabi M, Ajdarkosh H (2018) Trace element and heavy metal levels in colorectal cancer: comparison between cancerous and non-cancerous tissues. *Biol Trace Elem Res* 183:1–8. <https://doi.org/10.1007/s12011-017-1099-7>
- Sohrabi M, Nikkha M, Sohrabi M, Rezaee Farimani A, Mirasgari Shahi M, Ziaie H, Shirmardi S, Kohi Z, Salehpour D, Safarnezhad Tameshkel F, Hajibaba M, Zamani F, Ajdarkosh H, Sohrabi M, Gholami A (2021) Evaluating tissue levels of the eight trace elements and heavy metals

- among esophagus and gastric cancer patients: A comparison between cancerous and non-cancerous tissues. *J Trace Elements Med Biol* 68:126761. <https://doi.org/10.1016/j.jtemb.2021.126761>
- Sun J, Mao B, Wu Z, Jiao X, Wang Y, Lu Y, Ma X, Liu X, Xu X, Cui H, Lin X, Yi B, Qiu J, Liu Q (2022) Relationship between maternal exposure to heavy metal titanium and offspring congenital heart defects in Lanzhou, China: a nested case-control study. *Front Public Health* 10:946439. <https://doi.org/10.3389/fpubh.2022.946439>
- Taccioli C, Chen H, Jiang Y, Liu XP, Huang K, Smalley KJ, Farber JL, Croce CM, Fong LY (2012) Dietary zinc deficiency fuels esophageal cancer development by inducing a distinct inflammatory signature. *Oncogene* 31:4550–4558. <https://doi.org/10.1038/onc.2011.592>
- Torti SV, Torti FM (2013) Iron and cancer: more ore to be mined. *Nat Rev Cancer* 13:342–355. <https://doi.org/10.1038/nrc3495>
- Tran TT, Gunathilake M, Lee J, Choi IJ, Kim Y, Kim J (2021) The Associations of Dietary Iron Intake and the Transferrin Receptor (TFRC) rs9846149 Polymorphism with the Risk of Gastric Cancer: A Case-Control Study Conducted in Korea. *Nutrients* 13:2600. <https://doi.org/10.3390/nu13082600>
- Trouiller B, Reliene R, Westbrook A, Solaimani P, Schiestl RH (2009) Titanium dioxide nanoparticles induce DNA damage and genetic instability in vivo in mice. *Cancer Res* 69:8784–8789. <https://doi.org/10.1158/0008-5472.CAN-09-2496>
- Vinceti M, Filippini T, Cilloni S, Crespi CM (2017) The epidemiology of selenium and human cancer. *Adv Cancer Res* 136:1–48. <https://doi.org/10.1016/bs.acr.2017.07.001>
- Wilk A, Szypulska-Koziarska D, Wiszniewska B (2017) The toxicity of vanadium on gastrointestinal, urinary and reproductive system, and its influence on fertility and fetuses malformations. *Postepy Hig Med Dosw* (online) 71:850–859. <https://doi.org/10.5604/01.3001.0010.4783>
- Xu C (2017) Meta-analysis of the correlation between selenium levels in vivo and gastric cancer. *China Medical Innovation* 14:69–73
- Xu J, Aoki H, Kasugai S, Otsuka M (2020) Enhancement of mineralization on porous titanium surface by filling with nano-hydroxyapatite particles fabricated with a vacuum spray method. *Mater Sci Eng C Mater Biol Appl* 111:110772. <https://doi.org/10.1016/j.msec.2020.110772>
- Yuan W, Yang N, Li X (2016) Advances in understanding how heavy metal pollution triggers gastric cancer. *Biomed Res Int* 2016:7825432. <https://doi.org/10.1155/2016/7825432>
- Zhang WH, Wu XJ, Niu JX, Yan H, Wang XZ, Yin XD, Pang Y (2012) Serum zinc status and Helicobacter pylori infection in gastric disease patients. *Asian Pacific Journal of Cancer Prevention: APJCP* 13:5043–5046. <https://doi.org/10.7314/apjcp.2012.13.10.5043>
- Zhang L, Haddouti EM, Welle K, Burger C, Wirtz DC, Schildberg FA, Kabir K (2020) The effects of biomaterial implant wear debris on osteoblasts. *Front Cell Dev Biol* 8:352. <https://doi.org/10.3389/fcell.2020.00352>
- Zhang LY, Zhang J, Li D, Liu Y, Zhang DL, Liu CF, Wang N, Wu SR, Lu WQ, Guo JZ, Shi YQ (2021) Bile reflux is an independent risk factor for precancerous gastric lesions and gastric cancer: An observational cross-sectional study. *J Digest Dis* 22:282–290. <https://doi.org/10.1111/1751-2980.12986>
- Zhao L, Zhu Y, Chen Z, Xu H, Zhou J, Tang S, Xu Z, Kong F, Li X, Zhang Y, Li X, Zhang J, Jia G (2018) Cardiopulmonary effects induced by occupational exposure to titanium dioxide nanoparticles. *Nanotoxicology* 12:169–184. <https://doi.org/10.1080/17435390.2018.1425502>
- Zyambo K, Kelly P, Kayamba V (2022) Evaluation of the association between gastric cancer and plasma selenium in Zambian adults: a case-control study. *Ecancermedicalscience* 16:1351. <https://doi.org/10.3332/ecancer.2022.1351>

Publisher's Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Springer Nature or its licensor (e.g. a society or other partner) holds exclusive rights to this article under a publishing agreement with the author(s) or other rightsholder(s); author self-archiving of the accepted manuscript version of this article is solely governed by the terms of such publishing agreement and applicable law.