Heliyon 10 (2024) e24517

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon

Research article

Consumption of foods contaminated with heavy metals and their association with cardiovascular disease (CVD) using GAM software (cohort study)

Abdolkazem Neisi [a], Majid Farhadi [b,*], Bahman Cheraghian [c], Abdollah Dargahi [d], Mehdi Ahmadi [e], Afshin Takdastan [e], Kambiz Ahmadi Angali [f,**]

[a] *Department of Environmental Health, School of Public Health and Air Pollution and Respiratory Diseases Research Center, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran*
[b] *Student Research Committee, Department of Environmental Health Engineering, School of Public Health, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran*
[c] *Department of Biostatistics and Epidemiology, School of Public Health, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran*
[d] *Department of Environmental Health and Social Determinants of Health Research Center Khalkhal University of Medical Sciences, Khalkhal, Iran*
[e] *Environmental Technologies Research Center, and Department of Environmental Health Engineering, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran*
[f] *Department of Biostatistics and Epidemiology, School of Health, Social Determinants of Health Research Center, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran*

ARTICLE INFO

Keywords:
CVD
Heavy metal
Rice
Bread
Vegetable

ABSTRACT

Introduction: Heavy metals can enter the environment and food through industrial activities, acid rain, chemical fertilizers, pesticides, and sewage. A large amount of these metals is dangerous because they tend to bio accumulate. A concern with these metals is the long-term, low-dose exposure seen in the general population. HMs can cause disorders in the cardiovascular system through various mechanisms such as the production of free radicals, DNA damage, lipid peroxidation, and oxidative stress.
Material and method: Food items measured in the present study included rice, bread, and vegetables. 210 participants (105 controls and 105 patients) were randomly selected for this study. The demographic information of the subjects was obtained from the Hoveyzeh Cohort Center. The relationship between heavy metals in food and cardiovascular diseases is investigated by The Generalized Additive Model (GAM).
Result: The results of the present study showed that when urine Cd was smoothed based on rice Cd, there was a significant correlation between urine Cd and Cd consumed in vegetables and rice. The GAM coefficient for urinary Cd excreted in case-control groups and Cd consumed in vegetables were 479.79(SE: 6.49–73.87) and 818.56(SE: 11.96–68.43), respectively, and for rice consumed, it was 0.03(SE: 0.015–2.103) and 0.04(SE: 0.017–2.338), respectively. The GAM

* Corresponding author. Student Research Committee, Department of Environmental Health Engineering, School of Public Health, Ahvaz Jundishapur University of Medical Sciences, and Ahvaz, Iran.
** Corresponding author. Department of Biostatistics and Epidemiology, School of Health, Social Determinants of Health Research Center, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, *Iran*.
E-mail addresses: kazemneisi@gmail.com (A. Neisi), mirmajid100farhadi@gmail.com (M. Farhadi), Cheraghian2000@yahoo.com (B. Cheraghian), a.dargahi29@yahoo.com (A. Dargahi), ahmadi241@gmail.com (M. Ahmadi), afshin-ir@yahoo.com (A. Takdastan), kzfir4@gmail.com (K. Ahmadi Angali).

https://doi.org/10.1016/j.heliyon.2024.e24517
Received 23 September 2023; Received in revised form 6 January 2024; Accepted 10 January 2024
Available online 11 January 2024

coefficient for As consumption in vegetables and As in urine of case and control groups was 1.61 (SE: 9.48–0.16) and 22.36 (SE: 13.60–1.64), respectively. The same coefficient for rice consumption in case and control groups was 4.5 (SE: 0.62–7.22) and 10.48 (SE: 1.46–7.16), respectively. There was a very strong and significant correlation between the Sr in the urine of both groups and the Sr in the food consumed, so that the urinary Sr in the control group is excreted more than in the cardiovascular group.

Conclusion: GAM analysis indicates that As in vegetable and rice is more than the standard limitation value. Also, Sr and Cd in vegetables, rice, and bread were more than the standard limitation value. According to the GAM model As had a significant value in rice and vegetables indicating that As is more than the standard limitation value, therefore, it is associated with CVD.

1. Introduction

Heavy metals are those metals whose density is from 5.3 to 22 g per cubic centimeter; this term was later used for elements with high atomic weight or high atomic number. Heavy and relatively heavy metals are less reactive than light metals and have much less soluble sulfides and hydroxides [1]. A large amount of these metals is dangerous because they tend to bio accumulate. In fact, whenever compounds are absorbed and stored faster than decomposition (metabolism) or elimination, they accumulate in the bodies of living organisms. The body of a 70 kg human contains about 0.01 % heavy metal on average [2]. Heavy metals can enter the environment through industrial activities, acid rain, chemical fertilizers, pesticides, and sewage. Although a large amount of heavy metals is dangerous, their moderate amount is necessary for the body. For example, the presence of Fe, cobalt, Zn, vanadium, Cr, Ni, As, and selenium is required for oxygen transport, cell metabolism, hydroxylation, enzyme activity, glucose utilization, cell growth, metabolic growth, hormone production, respectively [3]. Different foods can be contaminated with heavy metals, but sometimes the possibility of some foods (such as vegetables, rice, and bread) being contaminated with heavy metals is high, due to the use of chemical fertilizers, their irrigation with sewage, and the use of pesticides [4].

Rice is a global product and a basic source of carbohydrates in the diet of Asian countries (90 % of the world's rice is produced and consumed in Asia), especially Iran. In Iran, the per capita consumption of rice is 30 kg, which is actually the second most consumed product in the country [5]. Rice can be contaminated with heavy metals through the roots or direct absorption of pollutants deposited from the atmosphere on the surface of aerial organs. All types of rice have the ability to absorb essential metals from the soil solution, but plants need different concentrations of other metals in addition to essential metals [6]. This ability allows plants to absorb unnecessary metals as well. Since these metals cannot be decomposed, when their concentration in the plant cell exceeds the threshold, they cause toxicity and plant damage due to cell destruction [7].

Plants are used as health indicators for the ecosystem. After legumes, fruits, and vegetables are an important part of the human diet. One of the important and effective factors for determining the health of vegetables is the concentration of heavy elements in them [8]. The contamination of vegetables with heavy metals can be caused by irrigation with sewage, fertilizers, and pesticides. The main sources of heavy metals in vegetables are their growth environment (soil, air, nutrients), which are absorbed by roots or leaves [9]. The absorption and bioaccumulation of heavy metals in plants are influenced by factors such as weather, atmospheric sediments, concentrations of heavy metals in the soil, the nature of the soil, and the amount of their growth. Atmospheric deposition is known as the main way of lead entry for leafy vegetables. The accumulation of metals mostly occurs in the roots of plants [10].

Cereals, especially wheat, are considered the basis of human nutrition and life and provide 70 % of the food for people on the planet. In the meantime, bread, as the main food item, has a major contribution to the nutrition pattern of families. The per capita consumption of bread in Iran is about 300 kg per year [11]. Investigating the amount of these metals in bread consumed by people can provide a suitable solution for the preparation and use of this valuable food source [12].

People Hoveyzeh cohort study are eating bread, vegetables, and rice more than other food and many participants who live in Hoveyzeh suffer from cardiovascular disease. For these reasons, The aim of the present study was to investigate the amount of heavy metals in high-consumption foods such as rice, bread, and vegetables in the food basket and its association with cardiovascular disease in the participants of the Hoveyzeh cohort (through the measurement of heavy metals in the urine of the control and patient groups).

2. Material and method

2.1. Study area

The Hoveyzeh cohort is a part of the Persian cohort and is a population-based prospective epidemiological study. The Hoveyzeh cohort study was conducted from 2016 to 2018. The main goal of the plan was the annual follow-up, for 15 years, to determine the prevalence and occurrence of chronic diseases in Hoveyzeh City. The general criteria for entering our study were living in Hoveyzeh and Sosangerd cities, having CVD, and being people aged 35–70 years in Hoveyzeh, and Susangerd cities [13]. The study complies with all regulations and confirmation that informed consent was obtained. These experiments were conducted according to established ethical guidelines, and informed consent was obtained from the participants. This article has been reviewed by the research ethics committee of Ahvaz University of Medical Sciences and has been approved with the special identifier IR.AJUMS.REC.1401.425.

Hoveyzeh city is located in Khuzestan province (southwest of Iran) with geographical coordinates of 31.46 North and 48.07 east. The geographical location of the studied area is shown in Fig. 1. According to the latest national divisions in 2015, this city includes two central and Nissan parts, two urban points, and 149 rural points. 61.56 % of its population are urban dwellers, and most of the population of this city lives in the two cities of Rafi and Hoveyzeh. Most of the people of this city are farmers, and most of them grow rice, vegetables, and wheat. The population of this city is 19,481 people. Dasht-e Azadegan city is also located in Khuzestan province with latitude and longitude coordinates of 31.44 North and 48.09 East. This city has four cities (Abu Hoveyzeh, Kut-e Seyyed Naim, Susangerd, and Bostan) and five villages (Allah-o Akbar, Howmeh-ye Gharbi, Howmeh-ye Sharqi, Bostan, and Saidiyeh). Most of the people of this city are farmers, and most of them grow rice, vegetables, and wheat. The population of this city is 107,989 people [14].

2.2. Sampling

Food items measured in the present study included rice, bread, and vegetables. 9 measured heavy metals included Fe, Zn, Al, Cr, Sr, Cd, As, Ni, and Pb. In order to sample them, bread was obtained from bakeries, vegetables from vendors, and rice from supermarkets in the city, and then they were taken to the laboratory. They were digested by nitric acid and finally injected into the ICP-MASS device and the amount of heavy metals in each was measured. The concentration of HMs in the samples was analyzed by ICP-OES. In order to check the validity of the detection method for the analysis of heavy metals, the Limit of Detection (LOD) and the Limit of Quantification (LOQ) of the device were calculated for the desired metals. LODs (μg/l) for Ni, Fe, Zn, Sr, Al, As, Cd, Hg and Pb are respectively 2, 2, 1, 0, 1, 0, 1, 2, 1 and LOQs (μg/l) was calculated 6.7, 6.7, 3.3, 0.3, 3.3, 0.3, 3.3, 0.3 and 3.30 were calculated respectively.

210 participants (105 controls and 105 patients) were randomly selected for this study. The demographic information of the subjects was obtained from the Hoveyzeh Cohort Center. Samples were taken from the urine of patients and controls in the morning. The amount of urine collected was 10 ml per person. They were transferred to the laboratory, and after acid digestion, they were injected into the ICP-MASS device and the amount of urinary heavy metals was measured.

2.3. Statistical analysis

GAM is a non-parametric statistical model that is presented to analyze the relationship between independent variables and response. In this model, unlike linear regression models, the data determine the curve shape of the response variables. It is assumed that the response variable Y has an exponential distribution. Y is connected to the predictor variable (Xj) through the link function (g) (Equation (1)). One of the most important advantages of the GAM model is the smoothing of variables. The smoothing of variables in this model has made it capable of identifying non-linear relationships. The important difference between this model and parametric models is that smoothed unknown functions replace linear functions. These functions are collectible [15]. In the present study, the relationship between heavy metals in food and cardiovascular diseases is investigated by smoothing the independent variables.

$$g(\mu) = \alpha + \sum_{j=1}^{p} f_j(X_j) \tag{1}$$

F_j = Smoothed unknown functions.
X_j = Predictor variables.

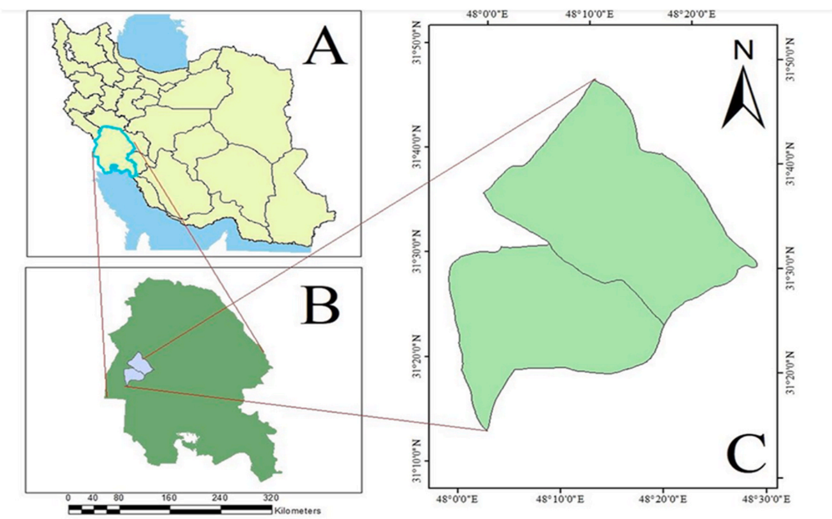

Fig. 1. Geographical location of Hoveyzeh and Dasht-e Azadegan.

3. Result and discussion

3.1. Demographic information of the cohort of participants

The demographic information of the participants in this study is shown in Table 1. In this table, information such as smoking, people's occupation, level of education, age, gender, wealth score, and BMI are reported. Except Wealth score, none of them were significant among the control and patient groups. Therefore, there was no need to adjust them in statistical analyses. The percentage of male (37.1 %) and female (62.9 %) participants in both case and control groups was equal, but in each group, the number of women (65) was more than the number of men [16]. As a result, the gender difference was not significant at all (p-value = 1). The number of smokers in both groups was small, so out of 210 participants, only 6 of them were smokers and the rest of the target population were not smokers. The age of the patients participating in this study (47.78) was higher than the control group (46.88), but this difference was not significant (p-value = 0.511). Although the BMI of the heart disease group (29.22) was higher than the control group (27.99), this factor was also not significant (p-value = 0.139). In the present study, Wealth score is statistically significant (p-value = 0.009). Therefore, this factor should be adjusted before conducting statistical studies, so as not to create bias. 37.1 % of the patient group are Poor and Poorest; while this rate is 30.3 % for the healthy group. 48.6 % of the healthy group were Rich and Richest; while this percentage for the group with cardiovascular disease was 36.2. The participants in this study were mostly urban dwellers. 62 % of the case group and 59 % of the healthy group were urban dwellers and the rest of the participants were rural. Residence was also not statistically significant (p-value = 0.422). Most of the participants in this study were illiterate; 65 % of the heart patient group and 60 % of the healthy group were not literate. Only 12 people had a university degree. Almost 91 % of participants with heart disease and healthy participants are employees (33 %) and housewives (58 %). It is necessary to explain that this factor is not statistically significant (p-value = 0.802).

3.2. Concentration of heavy metals in food

In the present study, the concentration of nine heavy metals (Fe, Al, Cr, Cd, Pb, Zn, As, Ni, and Sr) in food such as rice, vegetables, and bread was measured. Rice, bread, and vegetables are used in abundance in the diet of the people who live in Hoveyzeh and Dasht Azadegan. The types of rice used in these two cities are Anbar, Domsiah, Tarom, Hendi, and Pakistani. It tried to measure the concentration of heavy metals in these five types in this study. Table 2 shows the average concentration of heavy metals in various types of rice, vegetables, and bread. Since the standard limit declared in Iran for As is 0.15 mg/kg [17], its average concentration in the types of rice consumed in this study was higher than the standard limit. Some researchers reported that exposure to As even in concentrations lower than the standard can cause skin and urinary tract problems. One of the most important reasons for its high amount in rice is irrigation with well water. Consumed rice did not exceed the national standard of Iran (0.6 mg/kg) in the present study [18]. Pakistani rice had the lowest concentration (0.18 mg/kg) and Tarom rice had the highest concentration of Cd (0.55 mg/kg). Rice root has a high ability to absorb Cd (in divalent form) in water and soil. The highest average concentration of Ni and Cr in consumed rice was 0.061 and 0.37 mg/kg, respectively, considering that the national standard of Iran for the concentration of Ni and Cr in grains is 10 mg/kg [19]; none of the rice types exceeded the declared standard. Trivalent Cr is very necessary for the body, while hexavalent Cr and Ni

Table 1
Demographic information of the participants in the Hoveyzeh cohort.

Factors		Case	Control	p-value
Gender	Male (n)	40	40	1.00
	Female (n)	65	65	
Age (Mean ± sd)		47.78 ± 9.01	46.88 ± 9.11	0.511
BMI[a] (Mean ± sd)		29.22 ± 4.31	27.99 ± 5.01	0.139
Smoking	Yes	4	2	0.098
	No	101	103	
Wealth score	Poorest	19	25	0.009
	Poor	20	10	
	Moderate	30	20	
	Rich	25	30	
	Richest	11	20	
Residence	Urban	66	60	0.422
	Rural	39	45	
Last education	Illiterate	68	62	0.912
	Primary school	16	16	
	Secondary school	9	9	
	Diploma	6	10	
	University	6	6	
Employment status	Employed	34	35	0.803
	Housewife	62	60	
	Jobless	6	6	
	Broken-down	0	0	
	Retired	3	4	

[a] Body Mass Index.

Table 2
The concentration of heavy metals in foods.

Food	Type	As (PPM)	Cd	Cr	Ni	Fe	Al	Sr	Zn	Pb
Rice	Anbar	1.71	0.41	0.4	0.001	46	5.12	0.7	13	0.95
	Domsiah	2.49	0.51	0.31	0.014	63	6.31	0.96	26	0.35
	Tarom	2.69	0.55	0.009	0.008	114	6.52	0.18	7	0.24
	Hendi	1.49	0.19	0.006	0.004	83	3.2	0.26	5.5	0.012
	Pakistani	1.39	0.18	0.20	0.061	79	2.6	0.34	6.8	0.2
Vegetable	Cress	2.38	0.199	0.39	0.78	5188	2450	2000	679.27	0.163
	Chive	4.59	0.16	0.89	1.09	1616	3861	1989	46.74	0.321
	Basil	3.2	0.13	1.31	1.13	1508	670	3569	307.82	0.256
	Radish	5.4	0.254	1.41	2.5	2936	1488	2256	24.02	0.361
Bread	Barbari	0.20	0.13	1.39	0.8	129	42	9.89	18.14	0.054
	Sangak	0.11	0.15	1.2	0.61	221	26	1.64	23.54	0.41
	Lavash	1.29	0.19	0.049	1.2	316	51	2.33	36.14	0.30

metabolites are considered toxic. Ni can cause severe skin inflammation and cardiovascular disorders [20]. The average concentration of Pb in Indian rice was within the standard range, while the other types of rice exceeded the permissible limit. The concentration of Pb in Anbar rice was the highest (0.95 mg/kg). It should be explained that rice plants have a high ability to accumulate and absorb heavy metals (especially Pb). Among the important factors that increase the concentration of Pb in rice, we can mention irrigation with sewage and also the use of chemical fertilizers [21].

The participants consume vegetables most days because they are grown in the study area. The most consumed vegetables are Cress, Chive, Basil, and Radish. The World Health Organization (WHO) and the Food and Agriculture Organization (FAO) have announced the permissible limits of Cd, As, and Pb in consumed vegetables as 0.7, 0.05, and 0.1 mg/kg, respectively [22]. However, the average concentration of these three heavy metals in vegetables exceeds the standard limits, which can be dangerous. Radish has the highest concentration of As, Pb, Cr, and Ni, and Cress has the lowest concentration among vegetables. The use of chemical fertilizers to increase the yield of agricultural products, which transfers a large amount of Cd and lead to the soil, is one of the most important reasons for the contamination of vegetables with heavy metals. Another factor in the contamination of vegetables with heavy metals is the use of pesticides [23]. In their study, Cheng et al. reported that irrigation of vegetables using sewage effluent was the cause of heavy metal contamination [24].

Types of bread consumed in these areas are Barbari, Sangak, and Lavash.Considering that the national standard limit of As, Cd, Pb, and Ni in consumed bread is 0.15, 0.15, 0.15, and 10 mg/kg respectively; The average concentration of Pb in Sangak (0.41 mg/kg) and Lavash breads (0.30 mg/kg), the average concentration of Cd in Lavash bread (0.19 mg/kg), and the average concentration of As in Lavash (1.29 mg/kg) and Barbari breads (0.20 mg/kg) have exceeded the standard limits. The contamination of the studied breads with Cd, As and Pb in the current study can be due to soil contamination (the origin of the earth's texture) [25], excessive use of chemical fertilizers (especially phosphate fertilizers), insecticides, and irrigation with sewage effluent. A study was conducted in Iran to evaluate heavy metals in Hamadan bread؛ it was found that the average of Cd, Pb, and Ni has increased due to wear and tear of bakery equipment [26].

3.3. Concentration of urinary heavy metals

The concentration of urinary heavy metals is reported in Table 3. In this table, the concentration of metals of both groups is reported, including the minimum, maximum, mean, and standard deviation. In the end, the mean concentration of heavy metals in the urine between the patient group and the healthy group was statistically analyzed. Except for Ni, there was a significant correlation between urinary heavy metals in groups with heart disease and the healthy group (p.value < 0.05). The concentration of Al (28.18 ± 2.31), Fe (320.14 ± 10.29), and Zn (603.61 ± 105.99) in the control group was higher than the concentration of Al (23.91 ± 1.09), Fe (120.25 ± 11.25), and Zn (344.84 ± 90.18) in the patient group. However, the mean concentration of toxic metals such as As ($82.14 \pm$

Table 3
Concentration of urinary heavy metals.

HM (mg. lit^{-1})	Case (n = 105)				Control (n = 105)				p value
	Min	Max	Mean	SD[a]	Min	Max	Mean	SD	
Al	19.04	26.18	23.91	1.09	19.12	35.04	28.18	2.31	.000
Cr	36.33	39.27	38.16	0.89	9.87	58.61	31.29	12.34	.000
As	49.01	99.26	82.14	8.98	6.16	20.14	10.89	2.03	.000
Fe	80.15	139.02	120.25	11.25	289.22	340.79	320.14	10.29	.000
Pb	28.16	31.96	29.98	0.88	7.2	12.69	10.42	1.78	.000
Sr	26.93	31.25	30.01	1.11	7.13	13.59	10.86	0.99	.000
Zn	138.2	539.12	344.84	90.18	346.89	803.75	603.61	105.99	.000
Ni	.02	11	1.03	1.52	.03	5.96	0.96	1.64	.669
Cd	9.69	23.1	16.13	2.47	1.08	12.59	7.35	2.51	.000

[a] Standard Deviation.

Table 4
Association of heavy metals in food and uninary heavy metals (using GAM software).

Group 1	Food	Coefficients	SE[a]	p.value	Group 2	Food	Coefficients	SE	p.value
U_{Al}.V[c]	Al_V[b]	1.082452	0.04–26.49	0.000	U_{Al}.V	Al_V	0.6927866	0.024–28.351	0.000
	Al_B[d]	0.422980	0.27–1.54	0.125		Al_B	0.1363539	0.184–0.739	0.462
	Al_R[e]	−0.002271	0.009–0.24	0.810		Al_R	0.0002465	0.002–0.109	0.913
U_{Al}.B[f]	Al_V	−0.030202	0.037-(-0.802)	0.425	U_{Al}.B	Al_V	−0.0219356	0.024-(−0.877)	0.382
	Al_B	8.074969	0.331–24.39	0.000		Al_B	5.3377511	0.188–28.366	0.000
	Al_R	−0.002407	0.009-(-0.256)	0.798		Al_R	0.0002465	0.002–0.109	0.913
U_{Al}.R[g]	Al_V	−0.030142	0.037-(-0.799)	0.426	U_{Al}.R	Al_V	−0.021947	0.024-(-0.885)	0.378
	Al_B	0.422980	0.273–1.546	0.125		Al_B	0.156948	0.183–0.855	0.395
	Al_R	0.257377	0.009–26.73	0.000		Al_R	0.191849	0.005–38.328	0.000
U_{As}.V	As_V	1.6100	0.169–9.481	0.000	U_{As}.V	As_V	22.365	1.645–13.60	0.000
	As_B	−27.1469	15.67-(-1.732)	0.0863		As_B	−101.285	104.41-(−0.97)	0.334
	As_R	4.5092	0.624–7.225	0.000		As_R	10.481	1.464–7.16	0.000
U_{As}.B	As_V	−3.6102	2.557-(-1.411)	0.161	U_{As}.B	As_V	−6.6223	16.45-(-0.403)	0.688
	As_B	0.2419	0.031–7.802	0.000		As_B	3.5810	0.289–12.362	0.000
	As_R	4.6503	0.629–7.382	0.000		As_R	10.4807	1.4637–7.160	0.000
U_{As}.R	As_V	−4.2410	2.604-(-1.628)	0.1067	U_{As}.R	As_V	−11.114	16.26-(-0.683)	0.496
	As_B	−26.5097	15.90-(-1.667)	0.0986		As_B	−102.926	103.52-(-0.994)	0.323
	As_R	6.4824	0.390–16.61	0.000		As_R	39.413	2.196–17.948	0.000
U_{Cd}.V	Cd_V	0.11208	0.011–9.874	0.000	U_{Cd}.V	Cd_V	0.401	0.016–24.452	0.000
	Cd_B	−98.47588	63.77-(-1.544)	0.126		Cd_B	−631.7	63.07-(-10.015)	0.000
	Cd_R	−7.50436	4.570-(-1.642)	0.104		Cd_R	−2.010	1.584-(-1.269)	0.207
U_{Cd}.B	Cd_V	479.79977	73.87–6.495	0.000	U_{Cd}.B	Cd_V	818.56925	68.43–11.96	0.000
	Cd_B	0.03310	0.015–2.103	0.0381		Cd_B	0.04190	0.017–2.338	0.021
	Cd_R	−7.88330	4.537-(-1.737)	0.0855		Cd_R	−1.99642	1.578- (−1.265)	0.208
U_{Cd}.R	Cd_V	446.4225	71.92–6.207	0.000	U_{Cd}.R	Cd_V	813.4886	68.55–11.87	0.000
	Cd_B	−102.3330	65.01-(-1.574)	0.1186		Cd_B	−631.729	63.07-(-10.02)	0.000
	Cd_R	0.4803	0.177–2.706	0.007		Cd_R	2.2465	0.143–15.69	0.000
U_{Cr}.V	Cr_V	2.50157	0.026–93.66	0.000	U_{Cr}.V	Cr_V	1.3209	0.683–1.932	0.0561
	Cr_B	−2.96024	5.324-(-0.556)	0.579		Cr_B	110.3361	87.53–1.260	0.2104
	Cr_R	−0.24350	4.781-(-0.051)	0.959		Cr_R	62.8237	27.89–2.252	0.0265
U_{Cr}.B	Cr_V	−0.56434	5.765-(-0.098)	0.922	U_{Cr}.B	Cr_V	−81.8347	93.12-(-0.879)	0.381
	Cr_B	2.49665	0.031–79.90	0.000		Cr_B	2.8109	0.7313–3.84	0.000
	Cr_R	−0.24350	4.781-(-0.051)	0.959		Cr_R	63.0832	27.87–2.263	0.025
U_{Cr}.R	Cr_V	−0.56434	5.765-(-0.098)	0.922	U_{Cr}.R	Cr_V	−84.7850	93.11-(-0.911)	0.365
	Cr_B	−2.96024	5.324–0.556	0.579		Cr_B	110.3361	87.53–1.260	0.210
	Cr_R	3.24345	0.034–92.81	0.000		Cr_R	2.2984	0.479–4.797	0.000
U_{Fe} .V	Fe_V	30.12687	0.432–69.60	0.000	U_{Fe} .V	Fe_V	7.70263	0.532–14.45	0.000
	Fe_B	−0.10394	0.225-(-0.460)	0.646		Fe_B	0.57451	0.313–1.833	0.0698
	Fe_R	−0.05533	0.100-(−0.548)	0.585		Fe_R	0.03787	0.049–0.764	0.4468
U_{Fe}.B	Fe_V	0.38997	0.401–0.972	0.334	U_{Fe}.B	Fe_V	−0.885	0.552-(-1.604)	0.112
	Fe_B	17.64417	0.300–58.76	0.000		Fe_B	5.71866	0.341–16.74	0.000
	Fe_R	−0.05825	0.100-(-0.577)	0.565		Fe_R	0.03172	0.050–0.633	0.528
U_{Fe}.R	Fe_V	0.4434	0.401–1.104	0.272	U_{Fe}.R	Fe_V	−0.9732	0.551-(-1.764)	0.0807
	Fe_B	−0.1141	0.224-(-0.508)	0.612		Fe_B	0.5402	0.316–1.708	0.0906
	Fe_R	6.9871	0.104–67.131	0.000		Fe_R	2.3839	0.110–21.55	0.000
U_{Ni} .V	Ni_V	0.15514	0.062–2.480	0.0148	U_{Ni} .V	Ni_V	0.2040	0.115–1.761	0.0813
	Ni_B	7.93948	9.112–0.871	0.3857		Ni_B	−8.2757	11.17-(-0.741)	0.4607
	Ni_R	−135.06255	72.29-(-1.868)	0.0646		Ni_R	−0.1381	0.196-(-0.704)	0.4831
U_{Ni} .B	Ni_V	2.02287	7.253–0.279	0.7809	U_{Ni} .B	Ni_V	13.945871	8.688–1.605	0.11157
	Ni_B	0.11913	0.056–2.098	0.0384		Ni_B	−0.057415	0.090-(-0.635)	0.52692
	Ni_R	−126.02130	71.90-(-1.753)	0.0827		Ni_R	0.016965	0.005–3.176	0.00198
U_{Ni}.R	Ni_V	1.193875	7.206–0.166	0.869	U_{Ni}.R	Ni_V	13.9962203	8.689–1.611	0.110
	Ni_B	7.951988	9.118–0.872	0.385		Ni_B	−7.7125579	11.191-(-0.689)	0.492
	Ni_R	0.003252	0.006–0.476	0.635		Ni_R	−0.0004513	0.006-(-0.065)	0.949
U_{Pb}.V	Pb_V	0.140999	0.007–18.06	0.000	U_{Pb}.V	Pb_V	0.67148	0.015–44.04	0.000
	Pb_B	0.531860	20.71–0.026	0.980		Pb_B	35.28637	27.16–1.299	0.197
	Pb_R	3.331463	2.130–1.564	0.121		Pb_R	−0.12520	0.980-(-0.128)	0.899
U_{Pb}.B	Pb_V	4.363656	22.57–0.193	0.847	U_{Pb}.B	Pb_V	−18.68087	28.14-(-0.664)	0.508
	Pb_B	0.140927	0.008–16.01	0.000		Pb_B	0.69950	0.015–43.92	0.000
	Pb_R	2.544436	2.165–1.175	0.243		Pb_R	−0.36184	0.979-(-0.369)	0.713
U_{Pb}.R	Pb_V	7.39227	22.62–0.327	0.745	U_{Pb}.R	Pb_V	−23.72408	27.88-(-0.851)	0.397
	Pb_B	−0.39913	21.19-(-0.019)	0.985		Pb_B	31.85912	26.87–1.186	0.239
	Pb_R	1.63716	0.084–19.405	0.000		Pb_R	5.25377	0.088–59.18	0.000
U_{Sr}.V	Sr_V	1.55885	0.062–24.89	0.000	U_{Sr}.V	Sr_V	5.63746	0.147–38.18	0.000
	Sr_B	−4.81946	0.917-(-5.252)	0.000		Sr_B	5.27511	1.464–3.603	0.000
	Sr_R	4.84525	1.380–3.510	0.0006		Sr_R	0.08788	0.774–0.113	0.90987
U_{Sr}.B	Sr_V	−1.4274	2.174-(−0.656)	0.51318	U_{Sr}.B	Sr_V	−7.50646	3.268-(-2.296)	0.0237
	Sr_B	2.6582	0.166–16.01	0.000		Sr_B	11.88681	0.285–41.70	0.000

(continued on next page)

Table 4 (*continued*)

Group 1	Food	Coefficients	SE[a]	p.value	Group 2	Food	Coefficients	SE	p.value
	Sr_R	4.3304	1.371–3.158	0.0021		Sr_R	0.08787	0.774–0.113	0.9099
U_{Sr}.R	Sr_V	0.2948	2.131–0.138	0.89	U_{Sr}.R	Sr_V	−7.5065	3.268-(-2.296)	0.02372
	Sr_B	−4.8815	0.928-(-5.260)	0.000		Sr_B	5.2751	1.464–3.603	0.000
	Sr_R	2.7877	0.099–27.96	0.000		Sr_R	6.8018	0.127–53.54	0.000
Uzn.V	Zn_V	30.925	2.644–11.696	0.000	Uzn.V	Zn_V	16.547	2.728–6.065	0.000
	Zn_B	10.083	19.895–0.507	0.613		Zn_B	−4.257	23.29-(-0.183)	0.855
	Zn_R	1.731	6.872–0.252	0.802		Zn_R	−4.087	2.847-(-1.435)	0.154
U_{Zn}.B	Zn_V	0.3170	2.448–0.129	0.897	U_{Zn}.B	Zn_V	2.675	2.793–0.957	0.341
	Zn_B	230.7388	23.45–9.837	0.000		Zn_B	102.227	22.00–4.645	0.000
	Zn_R	0.4883	6.748–0.072	0.942		Zn_R	−4.087	2.847-(-1.435)	0.154
U_{Zn}.R	Zn_V	1.594	2.437–0.654	0.515	U_{Zn}.R	Zn_V	2.675	2.793–0.957	0.341
	Zn_B	9.714	19.907–0.488	0.627		Zn_B	−4.257	23.29-(-0.183)	0.855
	Zn_R	77.750	6.895–11.277	0.000		Zn_R	37.335	6.159–6.062	0.000

[a] Standard Error.
[b] Aluminum in vegetables.
[c] Urinary aluminum when smoothed by vegetables.
[d] Aluminum in bread.
[e] Aluminum in rice.
[f] Urinary aluminum when smoothed by bread.
[g] Urinary aluminum when smoothed by rice.

8.98), Pb (29.98 ± 0.88), Sr (30.01 ± 1.11), Cd (16.13 ± 2.47), and Cr (38.16 ± 0.89) in the group with cardiovascular disease was higher than As (10.89 ± 2.03), Pb (10.42 ± 1.78), Sr (10.86 ± 0.99), Cd (7.35 ± 2.51), and Cr (31.29 ± 12.34) in the healthy group. Although the mean concentration of urinary Ni in the patient group was higher than the control group, it was not statistically significant (P value > 0.669). Since heavy metals enter the human food chain through water, soil, and air; Food consumption is one of the most important routes of human exposure to heavy metals [27]. For example, Cd enters the human body through contaminated vegetables, As through rice, and Pb through bread, and causes disorders in the body's organs. The absorption rate of toxic metals from the digestive tract is inversely proportional to the concentration of some elements in the diet. Depletion of Fe accelerates the absorption of Pb and Cd [28]. Also, the lack of Zn in the diet increases the absorption of Pb and Cd through the digestive system. Previous studies have also confirmed the link between HMs and cardiac disorders [29].

3.4. Association of heavy metals in food and urinary heavy metals

In order to model the regression of the present study, the GAM statistical model should be used to create a correlation between the response variables (urinary heavy metals) and the independent variables (heavy metals in food). In this model, each urinary heavy metal must be smoothed separately to have a suitable regression correlation. Finally, the correlation between them and heavy metals in food will be investigated (Table 4).

In the present study, when UAl was smoothed separately by vegetables, bread, and rice, the p-value was significant for vegetables, bread, and rice respectively. The GAM coefficient for UAl excreted in the case group was higher than the control group. This means that people with cardiovascular disease excreted more Al than the control group. It seems that Al is considered a protective factor for the heart. Although the effects of aluminum metal on heart diseases have not yet been determined and the research done in this case is limited, Zhen Liu and his colleagues conducted a study titled the effects of Aluminum on the Heart, and the results of this research showed that high levels of aluminum have a significant correlation with heart disorders [30]. Unlike the results of the present study, it was shown in an epidemiological and clinical study that the exposure of pregnant mothers to high levels of aluminum causes heart disorders in babies [31].

When urinary As was smoothed in terms of vegetable As, there was a significant correlation between As consumed in food (vegetables and rice) and urinary As of both groups. So the GAM coefficient for As consumption in vegetables and As in the urine of case and control groups was 1.61(SE: 0.16–9.48) and 22.36(SE: 1.64–13.60), respectively. The same coefficient for rice consumption in the case and control groups was 4.5(SE: 0.62–7.22) and 10.48(SE: 1.46–7.16), respectively. When urinary As was smoothed in terms of bread As, there was a significant relationship between bread and rice As consumed and the urinary As of both groups. So the GAM coefficient for bread As consumption and urinary As in the case and control groups was 0.24(SE: 0.03–7.8) and 3.58(SE: 0.28–12.36), respectively. The same coefficient for rice consumption was 4.65(SE: 0.62–7.38) and 10.48(SE: 1.46–7.16) respectively. When urinary As was smoothed by rice As, there was only a significant correlation between urinary As and rice As. The GAM coefficient for As consumed in rice and urinary As excreted in the case and control groups were 6.48(SE: 0.39–17.94) and 39.41(SE: 2.19–17.94), respectively. This means that the excretion rate of the toxic metal As in the urine of the controls is higher than that of the patient group. As a result, in the patient group, the rate of As absorption is high and this factor can increase cardiovascular disorders. As causes dysfunction of the heart by causing oxidative stress and endothelial damage [32]. Also, it can cause inflammatory atherosclerosis by increasing mRNA transcripts. Researchers have obtained conflicting results on As exposure and CVD. Most researchers believe that exposure to As increases the risk of heart disease; While Lewis and Gular did not find any correlation between urinary As and cardiovascular disorders [33].

When urinary Cd was smoothed based on Cd in vegetables, there was only a significant correlation between excreted urinary Cd and the amount of Cd consumed in vegetables. But when urinary Cd was smoothed based on Cd in bread, there was a significant correlation between urinary Cd excreted by both groups and Cd consumed in bread and vegetables. Also, when urinary Cd was smoothed based on rice Cd, there was a significant correlation between urinary Cd and Cd consumed in vegetables and rice. The GAM coefficient for urinary Cd excreted in case-control groups and Cd consumed in vegetables were 479.79(SE: 6.49–73.87) and 818.56(SE: 11.96–68.43), respectively, and for rice consumed, it was 0.03(SE: 0.015–2.103) and 0.04(SE: 0.017–2.338), respectively. The researchers presented evidence that shows that Cd causes severe cardiac arrhythmia by affecting the vascular endothelium; As a result, it is known as a risk factor for cardiovascular disease [34]. They also reported that an increase in urinary Cd causes an increase in heart rate and an increase in the chance of CVD. Kane et al. conducted a study on Australian women and the results of their research showed that the higher the amount of urinary Cd, the higher the chance of developing cardiovascular diseases. However, Fagerberg et al. believe that no correlation was observed between urinary Cd and cardiac disorders [35].

In the present study, there was no significant correlation between Cr and Ni consumed in food and their concentration in the urine of individuals, when each of them was smoothed. No synergistic effect between food Ni and Cr was observed.

In this research, there was a significant correlation between Fe consumed in food and urinary Fe. So the GAM coefficient for urinary Fe excreted by case people (30.12), when the Fe of vegetables was smoothed, was higher than the urinary Fe of the control group (7.70). The GAM coefficient for the urinary Fe excretion of the case and control group, when it was based on the Fe in smoothed bread, was 17.64 (SE: 0.30–58.76) and 5.71(SE: 0.34–16.74), respectively. The GAM coefficient for the excreted urinary Fe of the patient and control groups when it was smoothed based on the Fe in rice was 6.98 (SE: 0.10–67.13) and 2.38 (SE: 0.11–21.55), respectively. It can be concluded that the urinary Fe excreted in the case group is more than the control group and the control group has a higher absorption of Fe in their body. Mitochondria need Fe in order to function better, if the Fe they need is not supplied, their activity will be disturbed. One of the problems caused by the lack of proper functioning of mitochondria is cardiovascular disease [36]. The results of Benedikt Schrage et al.'s studies showed that people with low levels of Fe in their bodies developed CVD [37]. Fe deficiency causes many cardiovascular problems. Among these problems, we can mention cardiac ischemia, death caused by CVD, acute coronary syndrome, heart attack, myocardial necrosis, and myocardial infarction [38]. In their study, Samar et al. found that women (before menopause) have fewer cardiovascular problems than men of the same age, but after menopause, these women suffer more cardiovascular problems than men of the same age, and he stated that the cause of this problem is Fe deficiency in postmenopausal women [39].

The results of the table above show that there is a significant correlation between the Pb consumed in food and the urinary Pb excreted, so the GAM coefficient for urinary Pb in people with cardiovascular disease, when it was smoothed in terms of vegetables (0.14) was lower than the control group (0.67). The same coefficient was 0.14(SE: 0.008–16.01) and 0.69(SE: 0.015–43.92) for the case and control groups, respectively, when the Pb in bread was smoothed. Also, when it was smoothed based on rice Pb, it was 1.63 (SE: 0.08–19.40) and 5.25(SE: 0.08–59.18) in the case and control groups, respectively. The increase in blood pressure occurs in two stages; The first stage occurs with the reduction of ATP enzyme activity and the stimulation of Ca/Na pumping, which causes the contraction of vascular smooth fibers, and the second stage occurs due to the release of renin from the kidney cortex, which many researchers consider the possible cause of both stages to be exposure to Pb [40]. Researchers believe that the increase in diastolic blood pressure is due to the high exposure of the body to Pb. In a study conducted on 166 Pb factory workers, researchers found that workers with high urinary Pb levels had higher diastolic blood pressure than the healthy group [16].

There was a very strong significant correlation between the urinary Sr of people of both groups and the Sr of consumed food, so whenever we smooth the urinary Sr based on the Sr of food, most of them become significant. The results of this research showed that urinary Sr is excreted in the control group more than the cardiovascular group; That is, the patient group absorbs Sr as a risk factor more than the control group, which can ultimately have harmful effects on the heart. The creation of fluctuating potentials, long-term depolarization in heart Purkinje fibers, and apoptosis of stem cells are the mechanisms of the destructive effect of Sr on the heart [41]. Sr, which is found in food, soil, and water, has a half-life of fewer than 3 years and belongs to the alkaline earth group [42]. The most important way to bury it from the body is through urine; As a result, urine is an important biomarker for measuring the amount of calcium received by the body. Sr is considered one of the important risk factors for cardiovascular diseases; therefore, there is a positive correlation between the amount of urinary Sr and heart diseases [43].

The GAM coefficient for Zn in urine when smoothed based on vegetable Zn for the patient group and the control group was 30.92 and 16.54, respectively. This coefficient was 230.73 and 102.22 for cardiovascular patients and the control group when it was smoothed based on Zn bread. Finally, when it was smoothed based on Zn in rice, this coefficient was 77.75 and 37.33 for patients and the healthy group, respectively. Cytokine increase has destructive effects on heart efficiency. Therefore, if cytokines are reduced, heart function improves [44]. Zn with its anti-inflammatory properties can reduce cytokines; As a result, the presence of Zn in the body is a key factor in maintaining heart health. In addition, it can cause fetal heart growth and endothelial adhesion. Researchers found that Zn deficiency in the diet causes cardiovascular problems. Also, in another study, researchers reported that those suffering from heart failure have low levels of Zn in their serum [45].

4. Conclusion

GAM analysis indicates that As in vegetable and rice is more than the standard limitation value. Also, Sr and Cd in vegetables, rice, and bread were more than the standard limitation value. According to the GAM model, As had a significant value in rice and vegetables, indicating that As is more than the standard limitation value therefore, it is associated with CVD. It can be concluded that the urinary Fe excreted in the case group is more than the control group and the control group has a higher absorption of Fe in their body. People with cardiovascular disease absorb more Pb than the control group, which indicates that Pb is a risk factor for the heart. Sr in food has a synergistic effect, which means that eating vegetables, rice and bread together reduces the excretion of Sr from the body and increases its absorption in the body. There was a significant correlation between Zn in urine and Zn in food. In such a way that the amount of urinary Zn excreted from the body of patients was higher than that of control subjects. The results of the present study showed that Zn has a protective effect on the cardiovascular system.

Based on the results of this study, the authors recommend to the people of the Hoveyzeh region the authority to supervise rice cultivated to reduce heavy metal concentrate under standard limitations. Also, we recommend that vegetables be cultivated far from roads and highways or vehicles should use lead-less fuel.

4.1. *Limitations*

Due to financial limitations, we could not sample and analysis of heavy metals in air, soil, and water. Also, we could not sample and analyze in blood, hair, and nails of the study population.

We suggest that researchers study the above media and exposure root for future research.

Data availability

Data will be made available on request.

Declarations: Experiments were conducted according to established ethical guidelines, and informed consent obtained from the participants.

CRediT authorship contribution statement

Abdolkazem Neisi: Validation, Supervision, Project administration, Funding acquisition, Conceptualization. **Majid Farhadi:** Writing – review & editing, Writing – original draft, Project administration, Methodology, Formal analysis, Data curation, Conceptualization. **Bahman Cheraghian:** Software, Data curation. **Abdollah Dargahi:** Data curation, Conceptualization. **Mehdi Ahmadi:** Validation, Supervision, Software. **Afshin Takdastan:** Visualization, Validation. **Kambiz Ahmadi Angali:** Supervision, Resources, Project administration.

Declaration of competing 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.

References

[1] S.A. Razzak, M.O. Faruque, Z. Alsheikh, L. Alsheikhmohamad, D. Alkuroud, A. Alfayez, et al., A comprehensive review on conventional and biological-driven heavy metals removal from industrial wastewater, Environmental Advances 7 (2022) 100168.

[2] J. Liu, L. Cao, S. Dou, Bioaccumulation of heavy metals and health risk assessment in three benthic bivalves along the coast of Laizhou Bay, China, Mar. Pollut. Bull. 117 (1–2) (2017) 98–110.

[3] M. Jaishankar, T. Tseten, N. Anbalagan, B.B. Mathew, K.N. Beeregowda, Toxicity, mechanism and health effects of some heavy metals, Interdiscip Toxicol 7 (2) (2014) 60–72.

[4] V. Kazemi Moghaddam, P. Latifi, R. Darrudi, S. Ghaleh Askari, A.A. Mohammadi, N. Marufi, et al., Heavy metal contaminated soil, water, and vegetables in northeastern Iran: potential health risk factors, J Environ Health Sci Eng 20 (1) (2022) 65–77.

[5] K. Sharafi, R.N. Nodehi, M. Yunesian, A.H. Mahvi, M. Pirsaheb, S. Nazmara, Human health risk assessment for some toxic metals in widely consumed rice brands (domestic and imported) in Tehran, Iran: uncertainty and sensitivity analysis, Food Chem. 277 (2019) 145–155.

[6] Z. Zakaria, N.S. Zulkafflee, N.A. Mohd Redzuan, J. Selamat, M.R. Ismail, S.M. Praveena, et al., Understanding potential heavy metal contamination, absorption, Translocation and accumulation in rice and human health risks, Plants 10 (6) (2021) 1070.

[7] A. Bhargava, F.F. Carmona, M. Bhargava, S. Srivastava, Approaches for enhanced phytoextraction of heavy metals, J. Environ. Manag. 105 (2012) 103–120.

[8] H. El-Ramady, P. Hajdú, G. Törős, K. Badgar, X. Llanaj, A. Kiss, et al., Plant nutrition for human health: a pictorial review on plant bioactive compounds for sustainable agriculture, Sustainability 14 (14) (2022) 8329.

[9] A. Alengebawy, S.T. Abdelkhalek, S.R. Qureshi, M.Q. Wang, Heavy metals and pesticides toxicity in agricultural soil and plants: ecological risks and human health implications, Toxics 9 (3) (2021).

[10] J. Briffa, E. Sinagra, R. Blundell, Heavy metal pollution in the environment and their toxicological effects on humans, Heliyon 6 (9) (2020) e04691.

[11] F. Aalipour, Evaluation of salt, sodium, and potassium intake through bread consumption in chaharmahal and bakhtiari province, International Journal of Epidemiologic Research 6 (2019) 60–64.

[12] S.M. Khodaei, Z. Esfandiari, M. Sami, A. Ahmadi, Determination of metal(oids) in different traditional flat breads distributed in Isfahan city, Iran: health risk assessment study by Latin hypercube sampling, Toxicol Rep 10 (2023) 382–388.

[13] H. Poustchi, S. Eghtesad, F. Kamangar, A. Etemadi, A.-A. Keshtkar, A. Hekmatdoost, et al., Prospective epidemiological research studies in Iran (the Persian Cohort Study): rationale, objectives, and design, Am. J. Epidemiol. 187 (4) (2018) 647–655.

[14] B. Cheraghian, S.J. Hashemi, S.A. Hosseini, H. Poustchi, Z. Rahimi, S. Sarvandian, et al., Cohort profile: the Hoveyzeh Cohort Study (HCS): a prospective population-based study on non-communicable diseases in an Arab community of Southwest Iran, Med. J. Islam. Repub. Iran 34 (2020) 141.

[15] S.N. Wood, Inference and computation with generalized additive models and their extensions, TEST 29 (2) (2020) 307–339.

[16] W. Qu, G.L. Du, B. Feng, H. Shao, Effects of oxidative stress on blood pressure and electrocardiogram findings in workers with occupational exposure to lead, J. Int. Med. Res. 47 (6) (2019) 2461–2470.

[17] S. Nemati, M. Mosaferi, A. Ostadrahimi, A. Mohammadi, Arsenic intake through consumed rice in Iran: markets role or government responsibility, Health Promot. Perspect. 4 (2) (2014) 180–186.

[18] K. Sharafi, R.N. Nodehi, M. Yunesian, A. Hossein Mahvi, M. Pirsaheb, S. Nazmara, Human health risk assessment for some toxic metals in widely consumed rice brands (domestic and imported) in Tehran, Iran: uncertainty and sensitivity analysis, Food Chem. 277 (2019) 145–155.

[19] Y. Fakhri, G. Bjørklund, A.M. Bandpei, S. Chirumbolo, H. Keramati, R. Hosseini Pouya, et al., Concentrations of arsenic and lead in rice (Oryza sativa L.) in Iran: a systematic review and carcinogenic risk assessment, Food Chem. Toxicol. 113 (2018) 267–277.
[20] G. Genchi, A. Carocci, G. Lauria, M.S. Sinicropi, A. Catalano, Nickel: human health and environmental toxicology, Int. J. Environ. Res. Publ. Health 17 (3) (2020).
[21] J. Martínez-Cortijo, A. Ruiz-Canales, Effect of heavy metals on rice irrigated fields with waste water in high pH Mediterranean soils: the particular case of the Valencia area in Spain, Agric. Water Manag. 210 (2018) 108–123.
[22] R. Tajik, A. Alimoradian, M. Jamalian, M. Shamsi, R. Moradzadeh, B. Ansari Asl, et al., Lead and cadmium contaminations in fruits and vegetables, and arsenic in rice: a cross sectional study on risk assessment in Iran, Iranian Journal of Toxicology 15 (2) (2021) 73–82.
[23] P. Atitsogbey, E. Kyereh, H. Ofori, P.-N.T. Johnson, M. Steiner-Asiedu, Heavy metal, microbial and pesticides residue contaminations are limiting the potential consumption of green leafy vegetables in Ghana: an overview, Heliyon 9 (4) (2023) e15466.
[24] S. Cheng, Heavy metal pollution in China: origin, pattern and control, Environ. Sci. Pollut. Res. 10 (2003) 192–198.
[25] D. Naghipour, A. Amouei, S. Nazmara, A comparative evaluation of heavy metals in the different breads in Iran: a case study of rasht city, Health Scope 3 (4) (2014).
[26] S. Kianpoor, S. Sobhanardakani, Evaluation of Zn, Pb, Cd and Cu concentrations in wheat and bread consumed in Hamedan city, Food Hygiene 7 (4) (2017) 83–92, 28.
[27] P.B. Tchounwou, C.G. Yedjou, A.K. Patlolla, D.J. Sutton, Heavy metal toxicity and the environment, Exp Suppl 101 (2012) 133–164.
[28] J.P. Goff, Invited review: mineral absorption mechanisms, mineral interactions that affect acid–base and antioxidant status, and diet considerations to improve mineral status, J. Dairy Sci. 101 (4) (2018) 2763–2813.
[29] I.W. Fong, New perspectives of infections in cardiovascular disease, Curr. Cardiol. Rev. 5 (2) (2009) 87–104.
[30] Z. Liu, C. He, M. Chen, S. Yang, J. Li, Y. Lin, et al., The effects of lead and aluminum exposure on congenital heart disease and the mechanism of oxidative stress, Reprod. Toxicol. 81 (2018) 93–98.
[31] Y. Ou, M.S. Bloom, Z. Nie, F. Han, J. Mai, J. Chen, et al., Associations between toxic and essential trace elements in maternal blood and fetal congenital heart defects, Environ. Int. 106 (2017) 127–134.
[32] A. Ceriello, New insights on oxidative stress and diabetic complications may lead to a "causal" antioxidant therapy, Diabetes Care 26 (5) (2003) 1589–1596.
[33] F.L. Facco, W.A. Grobman, K.J. Reid, C.B. Parker, S.M. Hunter, R.M. Silver, et al., Objectively measured short sleep duration and later sleep midpoint in pregnancy are associated with a higher risk of gestational diabetes, Am. J. Obstet. Gynecol. 217 (4) (2017) 447, e1-. e13.
[34] K.E. Cosselman, A. Navas-Acien, J.D. Kaufman, Environmental factors in cardiovascular disease, Nat. Rev. Cardiol. 12 (11) (2015) 627–642.
[35] B. Fagerberg, L. Barregard, Review of cadmium exposure and smoking-independent effects on atherosclerotic cardiovascular disease in the general population, J. Intern. Med. 290 (6) (2021) 1153–1179.
[36] R. Gordan, S. Wongjaikam, J.K. Gwathmey, N. Chattipakorn, S.C. Chattipakorn, L.H. Xie, Involvement of cytosolic and mitochondrial iron in iron overload cardiomyopathy: an update, Heart Fail. Rev. 23 (5) (2018) 801–816.
[37] B. Schrage, N. Rübsamen, F.M. Ojeda, B. Thorand, A. Peters, W. Koenig, et al., Association of iron deficiency with incident cardiovascular diseases and mortality in the general population, ESC Heart Failure 8 (6) (2021) 4584–4592.
[38] I.S. Anand, P. Gupta, Anemia and iron deficiency in heart failure: current concepts and emerging therapies, Circulation 138 (1) (2018) 80–98.
[39] S.R. El Khoudary, B. Aggarwal, T.M. Beckie, H.N. Hodis, A.E. Johnson, R.D. Langer, et al., Menopause transition and cardiovascular disease risk: implications for timing of early prevention: a scientific statement from the American Heart Association, Circulation 142 (25) (2020) e506–e532.
[40] F.V. Brozovich, C.J. Nicholson, C.V. Degen, Y.Z. Gao, M. Aggarwal, K.G. Morgan, Mechanisms of vascular smooth muscle contraction and the basis for pharmacologic treatment of smooth muscle disorders, Pharmacol. Rev. 68 (2) (2016) 476–532.
[41] R.W. Tsien, D.O. Carpenter, Ionic mechanisms of pacemaker activity in cardiac Purkinje fibers, Fed. Proc. 37 (8) (1978) 2127–2131.
[42] X. Cheng, C. Chen, Y. Hu, X. Guo, J. Wang, Photosynthesis and growth of Amaranthus tricolor under strontium stress, Chemosphere 308 (2022) 136234.
[43] H. Peng, F. Yao, S. Xiong, Z. Wu, G. Niu, T. Lu, Strontium in public drinking water and associated public health risks in Chinese cities, Environ. Sci. Pollut. Res. Int. 28 (18) (2021) 23048–23059.
[44] M.N. Amin, S.A. Siddiqui, M. Ibrahim, M.L. Hakim, M.S. Ahammed, A. Kabir, et al., Inflammatory Cytokines in the Pathogenesis of Cardiovascular Disease and Cancer, vol. 8, SAGE Open Med, 2020 2050312120965752.
[45] H. Rosenblum, B. Bikdeli, J. Wessler, A. Gupta, D.L. Jacoby, Zinc deficiency as a reversible cause of heart failure, Tex. Heart Inst. J. 47 (2) (2020) 152–154.