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The effect of consuming bread contaminated with heavy metals on cardiovascular disease and calculating its risk assessment

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Heavy metals (HMs) may cause the generation of reactive oxygen species (ROS), which results in oxidative stress and eventually leads to an increase in cardiovascular diseases (CVD). The Hoveyzeh Cohort Study Center provided clinical data for cardiovascular cases. The collection of samples was done randomly. The association between CVD and HMs has been evaluated utilizing seven machine-learning techniques. The results showed that the effect coefficient (β) of bread consumption in the incidence of heart disease is 4.6908×10^{-02}. Consumption of bread contaminated with chromium (*P* value < 0.0217), cadmium (*P* value < 2.95×10^{-6}) and arsenic (P value < 1.15×10^{-07}) is significantly related to cardiovascular incidence. Each unit of bread consumption increases As intake by 0.494 (β = 4.940×10^{-01}) and CVD incidence by 11.9% (OR = 1.1190). Bread consumption increases Cd intake by 0.479 (β = 4.799×10^{-1}) and cardiovascular disease incidence by 11.97% (OR = 1.1197) per unit. The findings indicated that bread intake in the study region is not correlated with non-carcinogenic or carcinogenic risks, since the cancer risk and incremental lifetime cancer risk for both groups were below 1*10^-6. In the present investigation, bread had HMs included As, Cd, Cr, and Pb higher than the limit declared by WHO. The results of the present study showed that bread is a mediating factor (between HMs and the incidence of CVD).

Keywords Heart failure, Cohort study, Bread, Urinary

Metals with a density that is higher than 5 g/cm^3 are commonly referred to as HMs. They've got wide distribution in the crust of the Earth but are detected in the human body at comparatively low levels. Even small amounts of these in the soil, water, or environment are harmful to every living thing[1]. The main effect of these elements on human health occurs through exposure in the workplace, pollution of the atmosphere, and accumulation in food, especially wheat grown in soil that is contaminated. Arsenic (As), Cadmium (Cd), Lead (Pb), and Mercury (Hg) can be mentioned among the important heavy metals that have high toxicity[2].

Heavy metals can cause many disorders in the body of living organisms, including respiratory and cardiovascular diseases (CVD), types of cancer, etc.[3]. By the generation of ROS, such as radicals of superoxide, peroxide of hydrogen, and nitric oxide (NO), hazardous metals (As, Cd, Hg, and Pb) can lead to oxidative stresses[4]. Lipid peroxidation, or an oxidative alteration of the low-density lipoprotein (ox-LDL) caused by free radicals, is being proven to be increased by several metals. It is a known cause event that occurs early in the development of CVD[5]. Through oxidative damage, Cd can damage blood vessels, cause dysfunction in endothelial cells, and promote atherosclerotic. Proteins, nucleic acids, and oxidized lipids can all be damaged as a result of Pb-induced oxidative stress, which is known to cause the generation of ROS[6].

One of the most important ways of exposure to heavy metals is consuming food (such as bread). During each meal, both breakfast and dinner, bread plays an important role. Bread, which is full of carbohydrates, protein, vitamins, and minerals, has long been an essential component of our daily meals[7]. Bread provides an

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important part of a person's daily energy, though this differs depending on the national development level and socioeconomic structures of people[8]. The several steps involved in producing bread—from grain cultivation to storage, manufacturing to marketing and sales—increase the possibility of contracting a food-borne disease[9]. Based on ecological, commercial, and human causes such as rock erosion, increasing urbanization, industrial activity, waste products, and automobiles, HMs can move through the air, water, and soil and contaminate the food chain. Variables such as chemical usage in the cultivation of grains, food additive selection, machinery and equipment, and packaging contamination increase the risk of HMs. Consumption of food contaminated with heavy metals causes people to develop cardiovascular diseases. Heavy metals in food are well absorbed through digestion and can cause heart dysfunction (through reactive oxygen species and oxidative stress)[10].

No research has yet been undertaken about the impact of heavy metals in bread on the cardiovascular system, particularly in a study area characterized by elevated heavy metal contamination and a prevalence of cardiovascular disease among patients. This study aimed to investigate the concentrations of heavy metals in bread and the consequences for cardiovascular disease, utilizing urine as a biomarker.

Material and method

Sampling

The research study comprised two groups: one consisting of healthy people and another comprising of those with CVD. The participants were selected from a list of those with CVD at the cohort center. Samples of urine have been collected on the levels of different HMs, including Chromium (Cr), Cd, As, Pb, Ni, Cu, Selenium (Se), Zinc (Zn), Magnesium (Mg), antimony (Sb), Aluminum (Al), Sr, V, Fe, and Hg. The collection of samples was done randomly. Additionally, 180 participants (90 of whom were healthy and 90 of whom had CVD) had samples of their urine taken. The urine samples were taken in polypropylene tubes early in the morning, and after 1–2 h, all of them were frozen and transferred to the lab. Standard solutions with levels of 10, 100, 500, and 1000 ppb were injected into the analytical instrument to calibrate ICP-OES and produce a calibration curve. For each HM, the R^2 correlation coefficient, the wavelength, and the detection limit of all components were determined. The wavelengths for each of the elements As, Al, Cd, Cr, Fe, Hg, Ni, Pb, Sr, V, and Zn are 189.04 nm, 396.15 nm, 214.43 nm, 367.71 nm, 259.94 nm, 184.95 nm, 231.60 nm, 220.35 nm, 407.77 nm, 292.46 nm, and 213.85 nm, respectively. After diluting 1:10 with a 2% nitric acids solution, urine samples went directly into the ICP device. The HM concentrations in samples were measured using the method of ICP-OES. The device's LOD (Limit Of Detection) and LOQ (Limit Of Quantification) were identified for each of the metals of interest to assess the accuracy of the detection technique used for analyzing HMs. For V, Ni, Fe, Zn, Sr, Al, As, Cd, Sb, Hg, and Pb, the LODs (μg/l) are 1, 2, 2, 1, 0, 1, 0, 1, 0, 2, 1, while the LOQs (μg/l) were determined to be 3.3, 6.7, 6.7, 3.3, 0.3, 3.3, 6.7, 0.3,6.7,0.3 and 3.3, in that order.

Three samples of Rice bread, Tafton bread, and Baguette bread were collected from several bakeries in Susangerd, all of which sourced their flour from the same factory. Following the application of the samples onto clean paper, they were air-dried and subsequently subjected to an oven at 60 °C for 24 h to guarantee thorough desiccation. The dried samples were pulverized using a grinder and preserved in plastic containers. One gram of each sample was heated to an oven temperature of 450 °C to get white, carbon-free ash. Sample extraction was conducted via acid digestion utilizing 4 M nitric acid at 95 °C. The extracts were subsequently filtered using the Whatman 42 filter paper. The concentration of heavy metals in the sample was determined through injection into ICP.

The article received approval from the ethical committee of Ahvaz Jundishapur University of Medical Sciences, with a recognized reference number. The study complies with all criteria and confirms informed consent. This research followed ethical criteria and acquired informed permission from individuals. IR.AJUMS. REC.1403.396 is the code.

Patients

The Hoveyzeh Cohort Study Center provided clinical data for cardiovascular cases. Patients with cardiovascular disorders have been included in the current study's patient data for inclusion. 90 cardiovascular patients and 90 healthy people participated in the study. Using Eq. 1, the sample size was calculated. We used the strategy described in the "Experimental Design and Statistical Analysis" section to solve the problem of an imbalanced data distribution.

The sample size was calculated using an average comparison formula:

$$n = \frac{(s_1^2 - s_2^2)^2 \left(z_{1-\frac{\alpha}{2}} + z_1 - \beta\right)^2}{(\overline{x}_1 - \overline{x}_2)^2} \tag{1}$$

Based on previous, similar study findings, these parameters have been taken into consideration:

$\alpha = 0.05$.
$\beta = 1/0$.
$\overline{x}_1 = 75.9$
$\overline{x}_2 = 80.6$
$S_1 = 11.5$
$S_2 = 10.7$

ADD (Average Daily Dose)

The ADDs of HMs derived from consuming bread can be calculated via Eq. 2. These doses are calculated in mg per kg per day. Table 1 presents the variables that are used to calculate ADDs[11].

Concentration	C	mg	Adults	Children
Ingestion rate	IR	(mg/day)	82	25
Exposure frequency	EF	(day)	365	365
Duration of human exposure	ED	(year)	60	6
Averaging time of human exposure	*At*	(day)	10,950	2190
Body weight	BW	(kg)	70	15

Table 1. ADDs calculation parameters.

$$ADD = \frac{C \times IR \times EF \times ED}{At \times BW}\left(\frac{mg}{Kg} \cdot day\right) \tag{2}$$

Non-carcinogenic risks

The non-hazardous impact (Eq. 3) is defined by HQ (Hazard Quotients), which stands for the exposure ratio for R_fD (Reference Dose) of HMs. RfD is the highest acceptable ingestion of a hazardous substance, under which no adverse non-carcinogenic consequences are expected from lifelong exposure. For example, the concentrations of As, Cd, Ni, and Pb eaten during digestion are 0.0003, 0.001, 0.046, and 0.02, respectively. The HI (Hazard Index) is calculated from the summing of the HQ stated in Eq. 4. In cases when the value is less than 1, there's no non-carcinogenic risk; nonetheless, when it is above 1, there is a non-carcinogenic potential[12].

$$\text{HQ} = \frac{ADD}{RfD} \tag{3}$$

$$\text{HI} = \sum_{1}^{i} HQ_s \tag{4}$$

CR (Carcinogenic Risks)

By dividing the ADD by the SF (Slope Factor)employing Eq. 5, one may calculate the CR of any given carcinogenic. As, Cd, Ni, and Pb have SF levels of 1.5, 0.38, 1.7, and 0.0085, respectively. To calculate the ILCR (Incremental Lifetime Cancer Risk), the total carcinogen hazards are added together[13] (Eq. 6).

$$\text{CR} = \text{ADD} \times \text{SF} \tag{5}$$

$$\text{ILCR} = \sum_{1}^{i} CR \tag{6}$$

ILCR $< 1 \times 10^{-6}$: The risk of developing cancer is incredibly low.

ILCR $> 1 \times 10^{-4}$: There is a likelihood of developing cancers.

$1 \times 10^{-6} <$ ILCR $< 1 \times 10^{-4}$: permitted level of risk.

Machine-learning model

The association between CVD and HMs has been evaluated utilizing several machine-learning techniques. The technique comprises entering clinical information of patients with CVD, along with their levels of urinary HMs, into a machine-learning model. The machine learning model can produce anticipated results from its input data, based on the specific algorithm used. Algorithms employed by machine learning methods enable it to predict and decide based on the input information. The GNB (Gaussian Naive Bayes), DT (Decision Tree), KNN (K-nearest Neighbors), SVM (Support Vector Machine), GB (Gradient Boosting), MLP (Multi-Layer Perceptron), LDA (Linear Discriminant Analysis), and LR (Linear regression) are the primary methods used in this study[14].

LR

LR involves identifying the line that most accurately represents the data. Variations of regression analysis encompass multiple regression, which identifies a plane of the best fit, and polynomial regression, as well, which determines a curve of best fit.

DT

DT is a commonly used approach to operations analysis, strategic planning, and machine learning. In a decision tree, each square is known as a node, and an increased number of nodes typically improves the precision of the decision tree. The final points of the decision tree, when a decision is made, are referred to as the branches of the tree. DT are simple to construct but lack accuracy in their forecasts.

SVM

SVM utilizes supervised approaches to classification that, although they can be quite complicated, are, at their most basic, quite simple.

GNB
GNB is a subset of Naive Bayes where the information features are distributed Gaussianically throughout the dataset and continuous characteristics are taken into consideration. A kind of classification algorithm based on the Naive Bayes approach, GNB acts on continuously normally distributed features.

KNN
KNN is a fundamental and essential method for classification in machine learning. It comes into the category of supervised learning and is frequently used in pattern identification, data extraction, and intrusion detection.

GB
GB is an effective boosting approach that amalgamates many poor learners into strong learners. Every new algorithm is trained using gradient descent to decrease the prior model's lost function, such as the mean squared error or cross-entropy.

LDA
LDA, occasionally referred to as Discriminant Function Evaluation, is a dimensionality reduction approach that is mostly used for supervised classification problems. It allows differentiation between categories, efficiently differentiating two or more groups.

MLP
MLP includes entirely linked dense layers that convert information entered from one dimension to another. It is known as "multi-layer" due to its inclusion of an input layer, one or more layers that are hidden, and an output layer. An MLP aims to simulate intricate interactions between inputs and outputs, making it an effective tool for diverse machine-learning scenarios.

The performance of ML methods was analyzed in our study utilizing a cross-validation five-fold strategy. To put it differently, we separated the data into five sections, using four for training and one for testing. Consequently, five equally sized groups were randomly selected from the original information. Since there weren't enough samples in the minority class for effective boundary learning, we were faced with the problem of unbalanced classification. We used SMOTE, an approach that generates synthetic minority class data and is intended to perform better than simple oversampling and to deal with issues. Based on our studies, SMOTE can significantly enhance performance when combined with the under-sampling of the majority class. Performance is improved by combining SMOTE with under-sampling of every class, as we mentioned earlier. Prediction precision, often calculated as follows, is a frequently utilized metric for evaluating machine learning systems. Using accuracy as a performance measurement makes logic when working with balanced data. Nevertheless, this method is inappropriate when the data set shows an imbalance. Thus, to evaluate the performance of the models suggested, balance accuracy, as stated in Eq. (9), and Area Under Curve (AUC) were utilized as markers of diagnosis[15].

$$\text{Accuracy} = \frac{\text{TP} + \text{TN}}{\text{TP} + \text{FP} + \text{TN} + \text{FN}} \tag{7}$$

$$\text{Sensitivity} = \frac{\text{TP}}{\text{TP} + \text{FN}} \tag{8}$$

$$\text{Specificity} = \frac{\text{TN}}{\text{TN} + \text{FP}} \tag{9}$$

$$\text{Balanced accuracy} = \frac{\text{Sensitivity} + \text{Specificity}}{2} \tag{10}$$

Statistical analysis
The association between response and independent variables is evaluated using the non-parametric statistical model known as GAM. Unlike linear regression models, this model lets the information determine the response variable's curve shape. It is considered that the distribution of the response variable Y is exponential. The variable that serves as a predictor (Xj) is linked to the outcome variable (Y) by making use of a link function (g), as can be seen in Eq. (11). The smoothing of data is one of the GAM model's main benefits. Using variable smoothing in this model has improved its ability to identify non-linear correlations. It differs significantly from parametric models because smoothed unknown functions are utilized instead of linear ones. These features can be collected[16]. Through smoothing the independent factors, the current research evaluates the association between HMs in bread and CVD.

$$\text{g}\ (\mu)\ =\ \alpha + \sum_{\text{j}=1}^{\text{p}} \text{fj}\ \ (\text{Xj}) \tag{11}$$

Fj = Smoothed unknown functions.
Xj = Predictor variables.

Q_A/Q_C
Quality assurance measures performed before data collection emphasize the standardization of activities. Training staff, creating procedures and surveys, analyzing measurement tools including stadiometers, standing

	Gender		Age	BMI	Smoking		Residence	
					Yes	No	Urban	Rural
Case	Male	42	42.91	29.98	11	79	38	52
	Female	48						
Control	Male	41	41.62	28.13	15	75	35	55
	Female	49						
p value	0.991		0.785	0.809	0.771		0.241	
	Wealth score				**Employment status**			
	Poorest	**Poor**	**Moderate**	**Rich**	**Employed**	**Housewife**	**Jobless**	**Retired**
Case	11	30	35	14	38	41	10	1
Control	15	26	45	4	43	37	8	2
p value	0.154				0.617			

Table 2. Demographic information of the participants in the Hoveyzeh cohort.

	HM (μg.lit^{-1})	Al	Cr	As	Pb	Sb	Sr	V	Zn	Ni	Cd
Groups											
Case (90)	Min–Max	22.67–39.74	19.11–54.2	12.57–33.38	11.3–19.57	0.16–2.68	50.17–87.4	0.09–16.35	196.93–357.12	0.00–1.18	9.12–36.44
	Mean ± sd	32.08 ± 5.15	40.7 ± 9.37	18.66 ± 7.71	15.78 ± 1.13	1.1 ± 0.75	63.18 ± 11.5	10.13 ± 3.61	298.17 ± 88.36	0.63 ± 0.3	20.25 ± 6.06
Control (90)	Min–Max	11.97–45.1	10.39–43.78	6.38–35.62	2.16–20.27	0.00–3.1	20.12–67.05	2.54–15.19	164.87–412.08	0.87–9.9	13.57–24.69
	Mean ± sd	25.17 ± 6.88	36.21 ± 8.19	15.68 ± 11.08	12.5 ± 8.4	0.93 ± 0.66	55.7 ± 22.11	11.7 ± 5.45	333.12 ± 166.47	0.57 ± 2.27	16.27 ± 4.46
p value		0.000	0.000	0.006	0.000	0.817	0.041	0.919	0.000	0.712	0.002

Table 3. The concentration of heavy metals in the urine of two case and control groups.

scales, and lab equipment, and carrying out pilot research are some of these actions. Following the start of data gathering and processing, quality control activities commence. Quality Control data monitoring forms the basis for possible corrective measures intended to reduce bias and improve dependability. To guarantee the precise execution of the study and data collecting in the Hoveyzeh cohort research plan, Quality Assurance and Quality Control teams have been instituted at both the national level (Persian cohort) and the university level. The Hoveyzeh cohort study team at the university comprises one epidemiologist, one biostatistician, and one laboratory scientist. The field quality control team comprises two individuals possessing master's degrees in epidemiological research, biostatistics, and lab sciences. The quality control team supervises all phases of data collection and result documentation. Furthermore, toward the conclusion of the questioning procedure, participants are randomly selected to attend the field supervisor's office to readdress a segment of the questionnaire (a minimum of two questions from each area). During this phase, the supervisor evaluates the precision of the data documented in the online system and the participants' replies.

Result and discussion

Demographic information

The present study included 180 participants with an equal number of controls (90 participants) and patients (90 participants). Both the case and control groups comprised a roughly similar proportion of males. However, the total number of female participants in both groups was higher than the number of male participants (*P* value = 0.991). The mean ages of the case and control groups, 42.91 and 41.62 years, respectively, were not significantly different (p-value = 0.785). Statistical analysis showed that although the BMI of the case group (29.98) was significantly higher than that of the control group (28.13), the differences were not close to significance (*P* value = 0.809). 42% of the patients were employed while the number of employed controls was 43 (47%); 41 of the cases (mostly female) were housewives (45%), while 37 of the female controls were housewives. Although most of the control and case group participants were housewives and employees, their employment status did not significantly affect the two groups (*P* value = 0.617). The location variable such as smoking did not appear to have a statistically significant effect. However, in both the control and case groups, the proportion of people living in rural areas was higher than that living in urban areas. The demographic information of the study volunteers is shown in Table 2.

Level of HMs in the urine

The levels of HMs in urine for both the control and case groups are shown in Table 3. Information on the minimum, maximum, mean, standard deviation, and p-value of HMs in urine for all the groups are given in the following table (Table 3). Some heavy metals in the urine of control subjects were significantly higher than those in the urine of case subjects; among them, Al (*P* value = 0.000), Fe (*P* value = 0.049), and Zn (*P* value = 0.000) can be mentioned. Ni (*P* value = 0.712) and Sb (*P* value = 0.817) were higher in the urine of the case group than in the control group, V (*P* value = 0.919), on the contrary, was higher in the urine of the control group but none of them was significant. Urine HMs (Cr, Pb, Sr, V, Cd, and As) were detected at higher levels in the research group's patients than in the other groups.

Thousands of chemicals comprising HMs enter the food chain through soil and water. Therefore, food has an important effect on the manifestation of adverse effects resulting from chemical pollutants. Metals are frequently absorbed into the body via the consumption of fish that were previously exposed to these metals in rivers with contaminants[17]. The findings of this research's mean level of HMs in the urine support the findings reported by researchers[18,19]. According to the investigation, humans can be exposed to several toxins such as Cd through contaminated vegetables and fruits, As through rice, Ni, and Pb through bread, which may cause organ abnormalities[20]. The gastrointestinal absorption rate of toxic metals reveals a negative association with the level of certain compounds in food. Pb and Cd are absorbed more quickly when the concentration of Fe is decreased. Insufficient dietary intake of Zn also enhances the uptake of Pb and Cd throughout the process of digestion[21]. The association between HMs and CVD has also been confirmed by prior research[22].

HMs in bread

The results of this study show that the highest concentration of heavy metals in bread is Fe (184.04 mg/kg) and the lowest is Sb (0.001 mg/kg). According to the results of Table 4, the mean concentration of Zn (33.11), Cd (0.22), As (1.54), and Pb (0.781) has exceeded the permissible limit declared by WHO, which is 27.4, 0.2, 0.1 and 0.3 mg/kg, respectively. The decreasing trend of heavy metal concentration in bread is as follows: Fe (125.97 ± 33.84) > Zn (33.11 ± 8.87) > Al (28.17 ± 22.71) > Sr (5.107 ± 2.062) > As (1.54 ± 0.64) > V (1.187 ± 0.77) > Pb (0.781 ± 1.12) > Ni (0.615 ± 0.310) > Sb (0.34 ± 0.27) > Cr (0.31 ± 0.18) > Cd (0.22 ± 0.09). Because wheat can be utilized for producing bread flour, differences in soil texture, frequency and quantity of fertilization, the type of chemical fertilizer, the origin of irrigation water, and human resources are all potential factors in the accumulation of HMs in wheat samples[23]. HMs get absorbed by grains like wheat from the soil, water, and atmosphere; nevertheless, the soil is the main source of HM contamination for these crops. Contamination of soil with HMs has two main reasons. The first reason is based on the region's geological structure. The soil in that place has organically formed HM elements due to its natural structure[24]. Human activity has a very small or negligible effect on this contamination. Another problem is the existence of HMs in the soil caused by humans or other non-natural sources. The main cause of HM contamination in places lack of naturally found HMs is human activity[25]. The absorption process can be affected by both the metal's concentration and its availability to the roots[26]. The main factor influencing the level of HMs in the grain in the study's region is human activity. For instance, the emissions from driving car exhaust are one of the reasons that HMs accumulate in the farmland of our study area[27]. Research conducted to assess the level of HMs in Hamadan bread shows that the deterioration of bakery tools has raised the mean concentrations of Cd, Pb, and Ni[28]. Several investigations showed that Zn, Cu, and Cd can enter the soil because of vehicle braking damage, car tire erosion, and oil loss from automobiles. Those s can also be used for the making of paints, fungicides, batteries, and different alloys like bronze[29]. The usage of animal and chemical fertilizers is an important factor contributing to the presence of these elements in cultivated soils and the contamination of crops with these toxic metals[30]. The nearness of the research region to the Ramin power plant can cause a high level of these elements.

Carcinogenic and non-carcinogenic risk assessment

Table 5 shows the results of the investigation on non-carcinogenic hazards. When the non-carcinogenic hazards of HMs were evaluated in two groupings—adults and children—it was found that the two groups' HI and HQ values were under 1. So, nothing is associated with the consumption of foods like bread in the study town with a non-carcinogenic likelihood of harmful HMs. The highest HQ values for children and adults were for Baguette bread contaminated with As, which were 0.00572 and 0.0033, respectively. The highest value of HI was related to Baguette bread (0.00616) in children and Tafton bread (0.0053) in adults.

The contamination of the bread consumed in the study area in terms of HI value is as follows:

For kids: Baguette (0.00616) > Tafton (0.00123) > Rice (0.0012).

For Adult: Baguette (0.0053) > Tafton (0.0035) > Rice (0.00072).

Heavy metal	Min	Max	Mean	SD	Acceptable limit
Al	6.27	55.95	28.17	22.71	–
As	0.64	2.27	1.54	0.64	0.1
Cd	0.02	0.29	0.22	0.09	0.2
Cr	0.025	0.148	0.31	0.18	0.02
Fe	87.15	184.04	125.97	33.84	–
Ni	0.147	1.44	0.615	0.310	1.63
Pb	0.13	2.63	0.781	1.12	0.3
Sr	1.64	9.89	5.107	2.062	–
Zn	7.73	40.19	33.11	8.87	27.4
V	0.01	6.65	1.187	0.77	–
Sb	0.00	1.56	0.34	0.27	–

Table 4. The concentration of heavy metals in Bread.

Food	Type	As	Cr	Cd	Cr	Ni	Pb	HI
	HQs (Kids)							
	Rice	0.00056	0.00049	0.0001	0.00049	4.9×10^{-5}	1.9×10^{-5}	0.0012
	Tafton	0.00049	0.00038	0.00018	0.00038	4.1×10^{-5}	0.00014	0.00123
	Baguette	0.00572	1.9×10^{-5}	0.00015	1.9×10^{-5}	8.13×10^{-5}	0.00019	0.00616
	Total		0.00088		0.00088			0.0085
Bread		0.00677		0.00043		0.00017	0.00034	HQs (Adult)
	Rice	0.00027	0.00035	7.1×10^{-5}	0.00035	2.6×10^{-5}	7.9×10^{-6}	0.00072
	Tafton	0.00019	0.00018	8.6×10^{-5}	0.00018	2×10^{-5}	5.9×10^{-5}	0.0053
	Baguette	0.0033	1.17×10^{-5}	0.00018	1.17×10^{-5}	3.9×10^{-5}	4.3×10^{-5}	0.0035
	Total	0.00376	0.00054	0.000337	0.00054	0.000085	0.0001	0.0048

Table 5. Non-carcinogenic risk results.

Food	Type	As	Cd	Cr	Ni	Pb	ILCR
	CRs (Kids)						
	Rice	2.4×10^{-8}	4.9×10^{-9}	7.2×10^{-8}	1.3×10^{-7}	4.6×10^{-11}	2.3×10^{-7}
	Tafton	1.6×10^{-8}	5.7×10^{-9}	5.6×10^{-8}	1×10^{-7}	3×10^{-10}	1.78×10^{-6}
	Baguette	1.9×10^{-7}	7.6×10^{-9}	2.8×10^{-9}	2×10^{-7}	2.3×10^{-10}	2.2×10^{-6}
	Total	5.9×10^{-8}	1.82×10^{-8}	1.3×10^{-7}	4.3×10^{-7}	5.76×10^{-10}	6.37×10^{-7}
Bread	CRs (Adult)						
	Rice	5.6×10^{-8}	1.1×10^{-8}	1.6×10^{-7}	3.1×10^{-7}	1×10^{-10}	1.08×10^{-7}
	Tafton	3.8×10^{-8}	1.3×10^{-8}	1.3×10^{-7}	2.4×10^{-7}	7.1×10^{-10}	1.84×10^{-6}
	Baguette	4.6×10^{-7}	1.7×10^{-8}	6.5×10^{-9}	4.7×10^{-7}	5.5×10^{-10}	1.91×10^{-6}
	Total	5.5×10^{-7}	4.1×10^{-8}	2.96×10^{-7}	1×10^{-6}	1.36×10^{-9}	9.54×10^{-7}

Table 6. Carcinogenesis risk results.

Contamination of bread consumed in the study area in terms of As (the highest amount of heavy metals in all types of bread) is as follows:

For kids: Baguette (0.00572) > Rice (0.00056) > Tafton (0.00049).

For adults: Baguette (0.0033) > Rice (0.00027) > Tafton (0.00019).

Table 6 indicates the findings of the investigation on CR. The assessment of the cancer-causing risk associated with HM in both the adult and kid groups indicated that the CRs and ILCR were estimated to be below 1×10^{-6} for both groups. So, eating pieces of bread polluted with hazardous HMs in the studied region has no relation to CR. The highest CR values for children and adults were for Baguette bread contaminated with As, which were 1.9×10^{-7}, and 4.6×10^{-7}, respectively. The highest value of ILCR was related to Rice bread (2.3×10^{-7}) for kids, and Baguette bread (1.91×10^{-6}) for adults.

The contamination of the bread consumed in the study area in terms of ILCR value is as follows:

For kids: Baguette (2.2×10^{-6}) > Tafton (1.78×10^{-6}) > Rice (2.3×10^{-7}).

For Adult: Baguette (1.91×10^{-6}) > Tafton (1.84×10^{-6}) > Rice (1.08×10^{-7}).

The presence of HMs in breads and foods is affected by various circumstances. One of the main factors of contaminants in bread is environmental pollution, particularly the poisoning of farmland with HMs. In these regions, HMs accumulate by the roots of crops, such as rice, wheat, and other cereals. HM contamination may happen during the bread's production and baking. Certain ingredients, including polluted water, salt, yeast, and soda for baking, may pollute bread with HMs during processing and preparation[31]. An investigation by Nazmara et al. calculated daily amounts of Cd, Pb, Cr, Ni, and Co based on the daily intake of various breads using a market basket method. Based on the eating habits of baguette, Sangak, Lavash, and Berberi bread, the daily intake of Cd was 0.5 µg/kg on the mean, and 0.4, 0.8, 0.1, and 0.6 µg/kg on average[32]. The estimated daily consumption of Cd from the nutrition, measured for a mean person, was 15.66 µg per day. The daily pb consumption from the bread types was 4.7, 4.1, 2.1, and 5.8 µg/kg, yielding an average of 4.2 µg/kg. According to research, the average individual intakes 28.37 µg of pb daily, with grains accounting for the highest possess of this eating at 4.94 µg/kg. The maximum daily intake of the metals As, Cd, Hg, and Pb from Catalan foods has been determined by Llobet et al. to be 223.6, 15.7, 21.2, and 28.4 µg/day, respectively. The average daily calculated intake of Cr, Ni, and Co from various breads was 6, 4.7, and 1.6 µg/kg, respectively, based on this study[33]. Basaran revealed that the THQ levels for HM exposed from bread intake among individuals in Turkey were less than 1, but the HI values were above 1, respectively[7]. Woldetsadik et al. showed that the THQ levels of Al, As, Co, Cr, and Pb exposure from wheat eating among pregnant and lactating women aged eighteen and older were 0.04, 0.01, < 0.00, < 0.00, and < 0.00, respectively, with the HI being under 1[34].

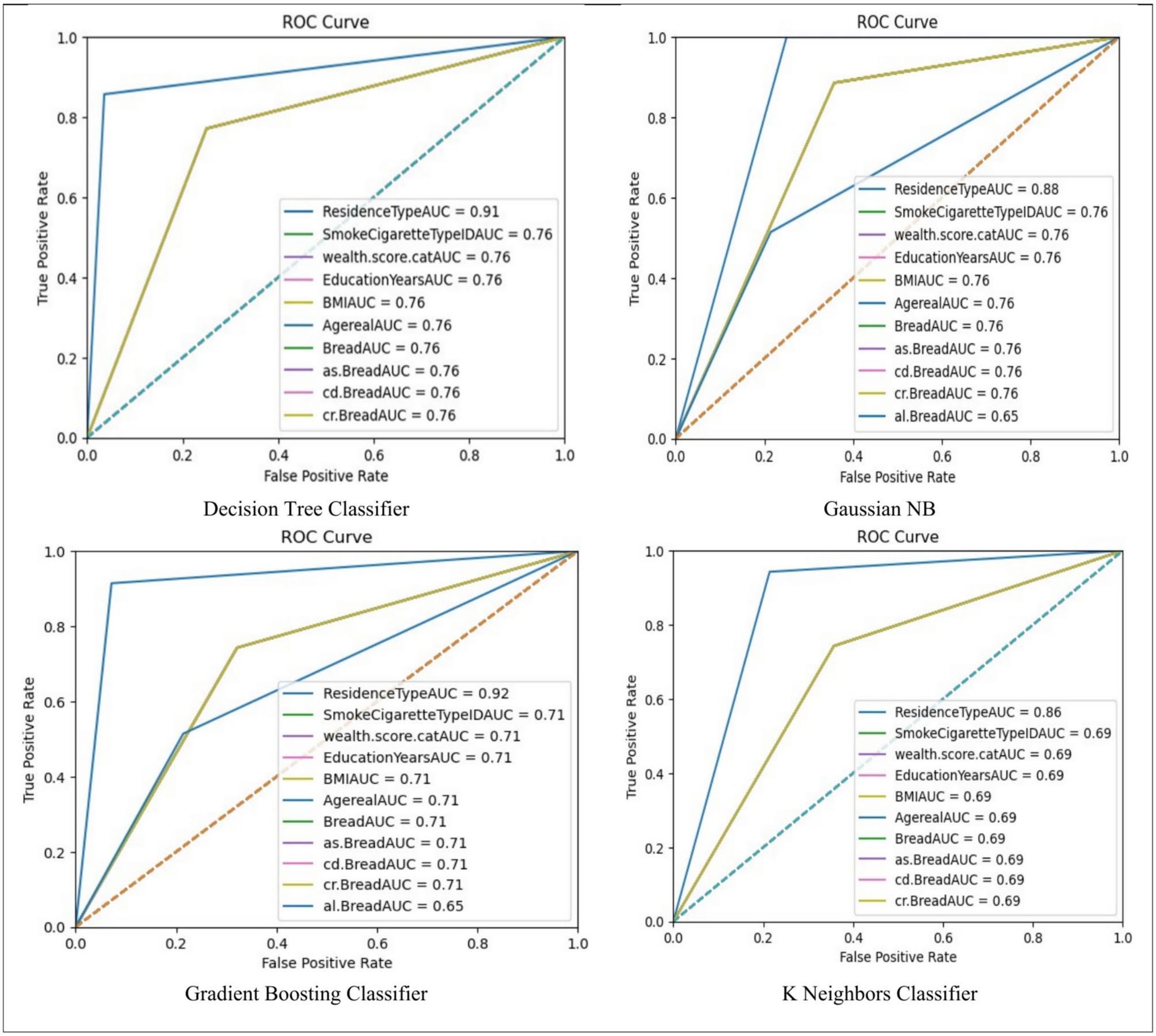

Fig. 1. The ROC of the seven machine-learning models. Seven machine learning modes have been demonstrated in Fig. 1 to extract variables that have the highest effects on cardiovascular incidence. CVD is affected by characteristics like residence type, age, BMI, smoking, and wealth score. Besides these, four other HMs are affected by Al, Cr, Cd, and As. Residence type, age, BMI, smoking, and wealth score are important variables affecting CVD in the DTC, GNB, GB, KN, LDA, LR, and MLP models. Nevertheless, each of these factors was adjusted for in the evaluation. The research aimed to find out the effects of HMs on CVD. The findings of the measurements of HMs in consumption bread revealed that Al(0.65) was effective in models GB and GNB, while As, Cr, and Cd had the highest effects in DTC, GNB, GB, KN, LDA, LR, and MLP models. Finally, the elements with the greatest effects (as determined by various ML models) were As, Cr, and Cd, which have been added to the GAM statistical model.

ML models and CVD

The ML model's aim in this research is to determine the effect of variables (such as HMs, age, residence, education, and BMI) on CVD. Figure 1 shows the influence of each variable in neural network models. This means the level to which the variable has affected the incidence of CVD. Variables with coefficients closer to 1 in the model have a more significant effect on heart disease. As reported in Table 7, among all the heavy metals in bread, As, Cd, Cr, and Al were associated with cardiovascular disease. Cd, Cr, and As were the elements associated with CVD in all ML models that were used to extract effective HMs. Besides HMs, several variables influenced heart disease within the Hoveyzeh cohort. The parameters included variables such as residential type, smoking, wealth score, BMI, age, and amount of bread consumption.

However, to find out the effect of HMs on the incidence of CVD, these parameters were adjusted. The influence coefficient of Residence type in DTC, GNB, GB, KN, LDA, LR, and MLP models was 0.91(CI 0.83–0.98), 0.88(CI 0.78–0.96), 0.92(CI 0.85–0.98), 0.86(CI 0.77–0.95), 0.84(CI 0.74–0.93), 0.88(CI 0.78–0.96), and

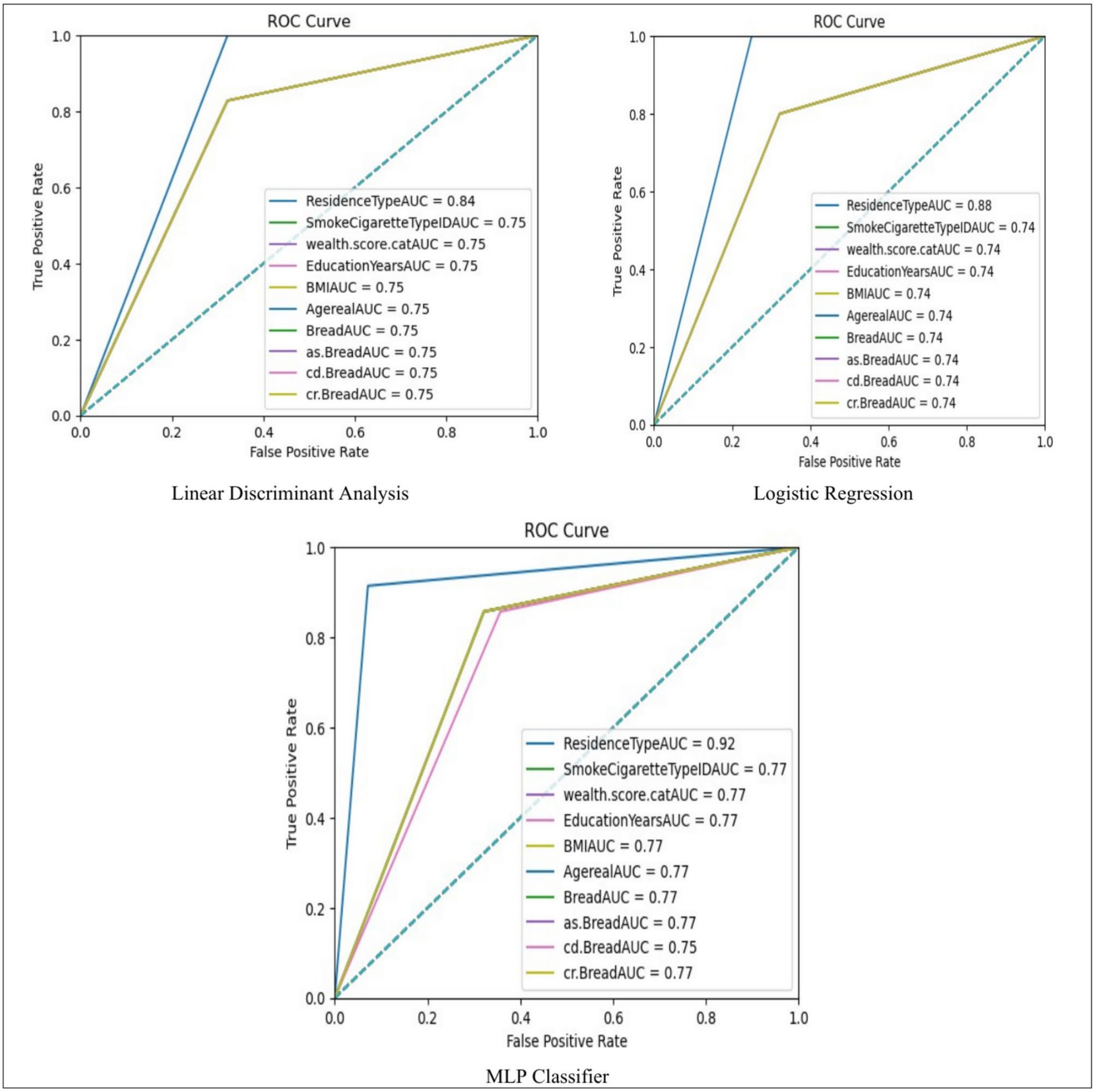

Figure 1. (continued)

0.92(CI 0.85–0.98), respectively. The same coefficient for smoking in DTC, GNB, GB, KN, LDA, LR, and MLP models was 0.76(CI 0.64–0.87), 0.76(CI 0.64–0.88), 0.71(CI 0.58–0.83), 0.69(CI 0.56–0.82), 0.75(CI 0.63–0.87), 0.74(CI 0.61–0.86), and 0.77(CI 0.65–0.88), respectively. The wealth score, age, BMI, and consumption of bread had an influence coefficient of 0.76(CI 0.64–0.87), 0.76(CI 0.64–0.88), 0.71(CI 0.58–0.83), 0.69(CI 0.56–0.82), 0.75(CI 0.63–0.87), 0.74(CI 0.61–0.86), and 0.77(CI 0.65–0.88) in the DTC, GNB, GB, KN, LDA, LR, and MLP models, respectively. In DTC, GNB, GB, KN, LDA, LR, and MLP models, the influence coefficients of As, Cd, and Cr were, respectively, 0.76(CI 0.64–0.87), 0.76(CI 0.64–0.88), 0.71(CI 0.58–0.83), 0.69(CI 0.56–0.82), 0.75(CI 0.63–0.87), 0.74(CI 0.61–0.86), and 0.77(CI 0.65–0.88).

Association between HMs and CVD

Table 8 shows the results of the GAM statistical model. In this study, by adjusting the parameters of BMI, Age, Gender, Smoke, Wealth Score, and Resident, it was tried to investigate the effect of HMs in bread on CVD. The significance levels for BMI, Age, Gender, Smoke, Wealth Score, and Resident parameters were 0.9510, 0.5326, 0.2853, 0.4734, 0.5666, and 0.1865, respectively. Since the *P* value of the above parameters was more than 0.05, none of them had a significant relationship with CVD. Only bread consumption had a significant relationship with the incidence of CVD (*P* value < 0.0217). The results showed that the effect coefficient (β) of

AUC						
Parameters	MLP	DTC	GNB	KNC	LDA	LR
Education. Y	0.77	076	0.76	0.69	0.75	0.74
Residence. T	0.92	0.91	0.88	0.86	0.84	0.88
Bread AUC	0.77	0.76	0.76	0.69	0.75	0.74
Smoke cigarette	0.77	0.76	0.76	0.69	0.75	0.74
Wealth score	0.77	0.76	0.76	0.69	0.75	0.74
Age	0.76	0.76	0.76	0.69	0.75	0.74
BMI	0.77	0.76	0.76	0.69	0.75	0.74
Al	-	-	0.65	-	0.75	0.74
Cd	0.75	0.76	0.76	0.69	0.75	0.74
Cr	0.77	0.76	0.76	0.69	0.75	0.74
As	0.77	0.76	0.76	0.69	0.75	0.74

Table 7. Comparison of discrimination characteristics among eight ML models.

	Estimate (β)	Standard error	Z value	P (>|Z|)
Intercept	− 0.2113	3.4409	− 0.061	0.9510
Z BMI	0.1694	0.2715	0.624	0.5326
Z Age	0.2512	0.2351	1.068	0.2853
Z Bread	4.6908×10^{-02}	2.0441	2.295	0.0217*
Z Gender	0.3881	0.5413	0.717	0.4734
Z Smoke	− 0.7899	1.3784	− 0.573	0.5666
Z Wealth	− 0.2777	0.2103	− 1.321	0.1865
Z Resident	0.4839	0.5854	0.827	0.4084

Table 8. Relationship between different parameters and CVD (GAM model).

	Estimate (β)	Standard Error	Z value	P (>|Z|)	OR[1]
Intercept $_{(ZCrBread)}$	3.735×10^{-16}	3.578×10^{-02}	0.000	1	–
Z Cr $_{Bread}$	4.621×10^{-01}	2.0441	2.295	0.0217*	1.1051
Intercept $_{(Z\ Cd\ Bread)}$	3.102×10^{-05}	5.602×10^{-02}	0.001	1	–
Z Cd_{Bread}	4.799×10^{-1}	9.981×10^{-02}	4.808	2.95×10^{-6}***	1.1197
Intercept $_{(Z\ As\ Bread)}$	3.193×10^{-05}	3.902×10^{-02}	0.001	0.999	–
Z As_{Bread}	4.940×10^{-01}	8.986×10^{-02}	5.497	1.15×10^{-07}***	1.1190

Table 9. Relationship between HMs and bread (GAM model). [1]Odds ratio.

bread consumption in the incidence of heart disease is 4.6908×10^{-02}. This means that the consumption of each unit of bread causes an increase of 0.046 CVD.

The results of the present study showed that bread is a mediating factor (between HMs and the incidence of CVD). This means that HMs can affect bread and bread consumption can cause heart disease. It was stated earlier that by using different machine learning models, among all the HMs found in bread, As, Cr, and Cd are the most effective metals in CVD incidence. Consumption of bread contaminated with Cr (*P* value < 0.0217), Cd (*P* value < 2.95×10^{-6}) and As (*P* value < 1.15×10^{-07}) is significantly related to cardiovascular incidence. Baseline concentration (β) for Cr, Cd, and As in bread was 3.735×10^{-16}, 3.102×10^{-05}, and 3.193×10^{-05}, respectively.

As reported in Table 9, the increase in each unit of bread consumption causes an increase of 0.464 ($\beta = 4.621 \times 10^{-01}$) in Cr intake, and the increase of each Cr unit causes an increase of 0.1 (OR = 1.1051) in the incidence of CVD. Supplementing with Cr has been shown to affect both the prevention and treatment of CVDs[35]. Studies proved that people with CVDs had reduced amounts of Cr in their bloodstream plasma compared with healthy people[36]. Increased inflammation markers have been correlated with a higher probability of death from CVDs in all people. It has been claimed that these markers are novel risk factors that may be applied to forecast CVD[37]. Cr supplementation could be important in reducing inflammatory and immunity activation, based on studies[38]. Prior studies have investigated the use of Cr supplementation to reduce inflammation markers in humans as well as animals. Additionally, as main risk factors for CVDs, hs-CRP, tumor necrosis factor-alpha (TNF-α), and interleukin-6 (IL-6) have been reported to have a negative correlation with the level of these inflammatory biomarkers when supplemented with Cr[39]. Abnormalities of TNF-α have been correlated to CVD such as atherosclerotic. TNF-α is a key cytokine implicated in the acute phase response. The other factor operating an acute reaction is IL-6, a kind of cytokine that plays a role in several biological processes including inflammatory responses, malignancy, immunity, and hypertrophic[40]. High blood pressure, elevated plasma angiotensin II levels, and vascular hypertrophy have all been associated with the level of IL-6 in plasma[41]. Farrokhian et al. did a research study that investigated the effect of Cr administration on inflammation indicators in diabetic individuals with CHD. Following an intervention period of twelve weeks that involved a daily dose of 200 µg Cr picolinate, a significant reduction in blood hs-CRP was seen, which was comparable to the group receiving the placebo[42]. The results of the present study (about the relationship between Cr and cardiovascular incidence) do not match the results of other studies. It has been reported in other studies that Cr has a protective effect on the heart, while the results of our studies show that Cr is a dangerous factor for the heart; Considering that the permissible limit of urinary Cr is 2 µg/liter by WHO[43], the reason for the harmful effect of chromium on the heart and blood vessels is probably the excessive amount of urinary Cr.

The increase in each unit of bread consumption causes an increase of 0.494 ($\beta = 4.940 \times 10^{-01}$) in As intake, and the increase of each As unit causes an increase of 0.11 (OR = 1.1190) in the incidence of CVD. As the concentration of As in the urine, used as a biological indication, increases, the probability of developing CVD also increases. The permissible limit of arsenic in urine is 50 µg per liter[43]. Consuming food exposes people to As most of the day; an average daily intake of 50 mg is common. Breathing in polluted air, eating contaminated water, and having into encountering soil with As levels ranging from 1 to 40 mg/kg are other routes of exposure[44]. Oxidative stress, inflammation, and damage to endothelial cells may cause CVD[45]. Research done with animals proves that oxidization of triglycerides occurs at every stage of cardiovascular disease. Furthermore, have been demonstrated to decrease the formation of lesions associated with atherosclerosis. Oxidized lipids produce many bioactive compounds, such as reactive oxygen compounds (ROS), peroxides, and isoprostanes. Among these, aldehydes are the main product of oxidation[46]. Both of the most common unsaturated and saturated aldehydes produced through the oxidization of LDL are malondialdehyde (MDA) and 4-hydroxy-trans-2-nonenal (HNE)[47]. In human and laboratory animal lesions caused by atherosclerosis, protein additives of MDA and HNE were identified. The findings reported that rats who were exposed to As had an increased buildup of protein additives of MDA and HNE in their early as well as severe lesions. Higher levels of free MDA and HNE have been observed in the bloodstreams of rats who were exposed to As[48]. Aldose reductase, a main enzyme found in CVD cells that decreases lipid-derived aldehydes, is also observed to be released in response to As. The enzyme itself is an effective catalyst for this reaction[49]. As mentioned before, a study indicates that genetic variation of GSTP1, an enzyme involved in As metabolism, is significantly associated with the development of atherosclerosis of the carotid artery[50]. Given the highly reactive nature of lipid aldehydes and their ability to improve leukocyte adherence, cytokine production, and lipid uptake through scavenge receptors, it is possible that a high synthesis of these aldehydes or a reduced detoxifying mechanism after being exposed to As might aggravate the process of atherosclerosis[51]. The results of the study showed that there is a 30% chance of getting CVD and a 23% risk of having coronary artery disease when As exposure was present. Nevertheless, there wasn't any association found between exposure to As and stroke[52]. Low and moderate concentrations of As are correlated to an elevated likelihood of CVD, as reported in research by Lynda, Medrano, Gong, Milkier, Versant, and Engel[53–55].

The increase in each unit of bread consumption causes an increase of 0.479 ($\beta = 4.799 \times 10^{-1}$) in Cd intake, and the increase of each Cd unit causes an increase of 0.11 (OR = 1.1197) in the incidence of CVD. As the concentration of Cd in the urine, used as a biological indication, increases, the probability of developing CVD also increases. The main causes that lead to increased Cd intake in the body include the inhalation of smoking, eating a poor diet, or occupational exposure in an environment that is contaminated[56]. Cd has a deleterious adverse effect on the heart. A potential reason for the phenomenon is the antagonistic interaction between this HM and Ca in the circulatory system. Cd causes arrhythmia and impacts the heart's rhythm[57]. The cellular uptake mechanism and Cd are uncertain, requiring more study to clarify the level of Cd present in the circulatory and the pathway by which it is taken in by cellular[58]. Many cell transporters and channels for ions are being proven to help with the transportation of Cd through the cell membranes, including the calcium channel. Cd can also be accumulated by cells of the immune system and enter the vessels with monocytes containing Cd[59]. Cd-induced hyperproduction of both macrophages and monocytes could be a key player in the occurrence and progression of atherosclerosis. Endothelium death of cells resulting from Cd can occur as well as endothelium integrity disturbance. Cd can enter the media layer from the circulatory system through holes formed among endothelial cells[60]. Cd mainly accumulates in the soft cells of muscles after its transportation through vascular cells. Cytotoxic effects, interacting with Ca ion flow and ion homeostasis, and stimulation of cell proliferation in smooth muscles at low levels of Cd are some of the effects it has on cells of the smooth muscle. These reactions result in the following accumulation of lipids in vessels and a change of the cholesterol profile toward an increased atherogenic state[61]. Cd has been shown to lead to endothelium death of cells, and this is the key process by which it results in coronary artery disease rupturing the endothelium of the arteries and thus exacerbating inflammation in the arteries[62]. Atherosclerosis is significantly affected by cytokine and hyperactivated inflammatory reactions. Interleukin (IL)-6, IL-8, IL-1β, and tumor necrosis factor-alpha are among the key pro-inflammatory cytokines that are increased by Cd buildup and can affect inflammation in atherosclerotic[63]. Cd accumulates in the capillary wall. With similarities in risk factors between coronary artery disease (CAD) and peripheral arterial disease (PAD), it is conceivable that Cd accumulation might affect PAD[64]. The research done by NHANES found that PAD may be associated with a high level of Cd in both the urine and serum. This indicates that there's a significant association between the consumption of Cd and CVD[65]. Kane et al. did a study in Australia investigating the effect of Cd on the increased risk of cardiovascular diseases (CVD), with emphasis on women as participants. Their results showed that an increase in UCd led to a 36% rise in the chance of death caused by heart failure and a 17% increase in the risk of associated coronary failure[66].

Conclusion

This research aims to monitor the levels of HMs in bread consumed in Hoveyzeh City and evaluate the association between these levels and the incidence of CVD. The results of this study showed that the concentration of heavy metals such as As, Cd, Cr, and Pb exceeded the permissible limit declared by WHO. The reason for the high concentration of heavy metals in consumer bread can be due to soil contamination, the use of chemical fertilizers, and the irrigation of crops with sewage effluent. Different machine learning models were used to find out the relationship between heavy metals in consumer bread and cardiovascular disease. As, Cd, and Cr were associated with the incidence of CVD out of the nine HMs that were evaluated. In such a way the increase in the concentration of these three elements in the consumed bread caused a rise in the incidence of heart disease. Continuously HM monitoring and crop irrigation and fertilization management are two corrective actions that can be done to reduce the effect of HMs on consumer bread.

Data availability

All data is available in the article.

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Author contributions
MF: Data collection, writing original draft preparation; BC and MA: Formal analysis; AD and KAA: Formal analysis; AN and AT: Conceptualization, methodology, supervision, acquisition, project administration.

Declarations

Competing interests
The authors declare no competing interests.

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

Additional information

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