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ORIGINAL RESEARCH

Associations Between Metals and Nonmetals in Drinking Water, Cardiovascular Events, and Diet

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ABSTRACT

BACKGROUND Metals and nonmetals in drinking water could potentially influence cardiovascular health. The relationship between poor-quality drinking water, major adverse cardiovascular events (MACE), and diet is not well studied.

OBJECTIVES The aim of this study was to determine whether long-term exposure to metals (copper, manganese, aluminum, zinc, and cadmium) and nonmetals (selenium, sulfate, and nitrate-nitrogen) in drinking water was associated with MACE outcomes, and whether the dietary patterns could modify the association between long-term exposure to low-quality drinking water and MACE.

METHODS Data from a prospective population-based cohort from Yinzhou District, Ningbo (follow-up between 2016 and 2022) were linked to Yinzhou Health Information System. MACE endpoints included acute myocardial infarction (AMI), heart failure, stroke, angina, and cardiovascular death. Effect modification of the associations between exposure and MACE by dietary factors was determined.

RESULTS In the final cohort of 24,212 participants, 57 had an AMI; 886 developed heart failure; 733 had a stroke; 23 had angina; and 134 had a cardiovascular death. An increased risk of: 1) AMI was seen with exposure to copper, aluminum, cadmium, and selenium; 2) stroke with exposure to zinc, copper, and selenium; 3) angina with exposure to zinc and copper; and 4) cardiovascular death with exposure to zinc and aluminum in drinking water. Consuming fish, white meat, and grain products attenuated MACE outcomes induced by metals and nonmetals in drinking water.

CONCLUSIONS In this study, long-term exposure to higher metallic and nonmetallic elements in drinking water was associated with an increased risk of MACE. Specific dietary patterns modified the associations. Further studies are needed in this area. (JACC Adv. 2025;4:101669) © 2025 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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ABBREVIATIONS AND ACRONYMS

AMI = acute myocardial infarction

BMI = body mass index

CVD = cardiovascular disease

HF = heart failure

MACE = major adverse cardiovascular events

The majority of cardiovascular disease (CVD)-related deaths can be attributed to heart attacks and strokes.[1] China has witnessed a substantial rise in atherosclerotic CVDs, particularly ischemic stroke.[2,3] The incidence rate of ischemic stroke in China is 36% higher than the global average (240.5 per 100,000 population vs 176.4 per 100,000 population). Similarly, China is one of the countries with the highest burdens of hemorrhagic stroke.[3] Addressing factors associated with CVD is therefore very important in this population.

Metal elements, such as copper, zinc, cadmium, and manganese, are recognized as potential cardiovascular hazards. Humans can absorb metallic and nonmetallic elements from drinking water[4] and therefore screening for metallic elements is part of national water environmental standard testing.[5] One cross-sectional study showed that exposure to magnesium and arsenic in groundwater increased the risk of hypertension among U.S. populations.[6,7] Another study found that some metallic elements, such as manganese and copper, can concentrate in the left ventricle myocardium of individuals with cardiomyopathies.[8] However, the association between elements in drinking water and CVDs remains inconclusive, in part due to variations between study populations, exposure metrics, study designs, and study time periods.[6,9-14] Therefore, there is a need for studied focused on the association between drinking water quality and CVD.[15]

Dietary antioxidants (eg, vitamins, beta-carotene, and minerals) may influence the effects of metallic and nonmetallic elements in drinking water on CVD outcomes. These elements can trigger local and systemic responses through inflammatory and oxidative stress pathways.[16] One recent study suggested that specific diets could attenuate adverse health outcomes caused by metallic elements in drinking water;[17] however, further studies are needed.

The aim of this study was to examine the association between long-term exposure to metal (ie, copper, manganese, aluminum, zinc, and cadmium) and nonmetal elements (ie, selenium, sulfate, and nitrate-nitrogen) in drinking water and the risk of major adverse cardiovascular events (MACE) in a prospective cohort population in China. Additionally, we explored whether certain dietary components might influence the relationship between metallic and nonmetallic elements in drinking water and cardiovascular risk.

METHODS

STUDY POPULATION. We derived our study population from the prospective Yinzhou cohort study in Ningbo. Detailed information on the study design and data collection of the Yinzhou cohort has been published elsewhere.[18,19] The cohort initially included 48,908 participants, but 16,797 from 2 counties did not have follow-up as they belonged to another city. Among the remaining 32,111 participants enrolled in the Yinzhou cohort and available for analysis, those with MACE at baseline (N = 1,942), and those missing exposure data (N = 3,019), diet variables (N = 2,345), important sociodemographic, or socioeconomic variables (N = 593) were excluded. The final cohort included 24,212 participants (Supplemental Figure 1). The Zhejiang University School of Medicine Ethics Committee approved this study, and all participants were provided with written informed consent during the baseline investigation.

MACE ASCERTAINMENT. Yinzhou Health Information System consists of all health service data in Yinzhou District. In this system, the diagnoses of MACE were confirmed by the integration of the clinical, pathological, and imaging manifestations from professional doctors. We used the International Classification of Diseases, version 10 to record the specific types of CVDs, and subsequently categorized them into 5 major outcomes:[20] acute myocardial infarction (AMI) (I21), heart failure (HF) (I50), stroke (I60-I63), angina (I21), and cardiovascular death (I00-I99). Participants were followed from the time of their enrollment until they received a diagnosis of MACE, were lost to follow-up, died, or reached the end of follow-up (December 31, 2021), whichever occurred first.

EXPOSURE ASCERTAINMENT. We collected terminal tap water samples from a total of 37 different sampling sites across the Yinzhou District from April of 2016 to October of 2022. These samples were taken 4 times annually, once for each season, and assigned to participants based on their residential addresses. We employed atomic absorption spectrophotometry or the atomic absorption method to measure metallic

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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(ie, copper, manganese, aluminum, zinc, and cadmium) and nonmetallic elements (ie, selenium, sulfate, and nitrate-nitrogen) in drinking water. We collected water sample from residential homes, community water systems, public water systems, etc (Supplemental Figure 2). We weighted daily metal and nonmetal exposures by age in 6 age strata, according to *The Manual of Drinking Water Exposure Parameters for Populations in Typical Cities of Key Basins in China (Adult Volume)*.[21] The equation is as follows:

$$Exposure_i = C_i \times \sum_{group=1}^{6} \left(\frac{N_{group}}{\sum_{j=1}^{6} N_j} \times V_{group} \right)$$

where $Exposure_i$ represented metal and nonmetal exposure, C_i represented the concentration of metal and nonmetal in drinking water, N_{group} and N_j represented the sample size of each age stratum in the manual data, and V_{group} represented the total daily drinking water intake of each naive age stratum in the manual data. We standardized the test results by calculating Z scores, which subtracted the mean of original measurement from each test value at individual sites, then divided by the original measurement SD.

DIET MEASUREMENT AND COVARIATES. Dietary information included information on intake of vegetables, fruits, marine fish, lakefish, red meat, white meat, and grain products and was obtained using a questionnaire. More detailed information and validation of the tool is reported in a previous study.[22] Diet consumption frequency was assessed with the question "What is the frequency you take vegetables, fruits, marine fish, lakefish, red meat, white meat, and grain products." Responses were categorized as "almost every day (more than 5 days per week)," "frequently (3-5 days per week)," and "occasionally (< 3 days per week)."

We identified potential covariates from previous literature and expert consultations within the field of epidemiology. These covariates included sociodemographics (ie, age, education level, and annual household income), lifestyle factors (ie, body mass index [BMI], smoking status, alcohol consumption, and tea consumption), and medical history (ie, diabetes and dyslipidemia). Current smokers were defined as participants who smoked at least one cigarette per day for over a year or at least 5 packs per month. Current alcohol drinkers were individuals consuming 100g of alcohol per week. Current tea consumers were individuals drinking more than 2 cups of tea per week for over 2 months.

STATISTICAL ANALYSIS. The associations of long-term exposure to metals and nonmetals in drinking water with the risk of MACE incidence were examined using Cox proportional hazards regression models. Regarding covariates and confounders, fully adjusted multivariable models based on a priori assumptions of the causal relationships, and then tested by a directed acyclic graph (Supplemental Figure 3), including age, educational level, BMI, annual household income, current smoking status, alcohol consumption status, current tea drinking status, and medical history of diabetes and dyslipidemia. Adjusted HRs and the corresponding 95% CIs were estimated for each endpoint associated with per 1 SD increase in metallic and nonmetallic element levels in drinking water.

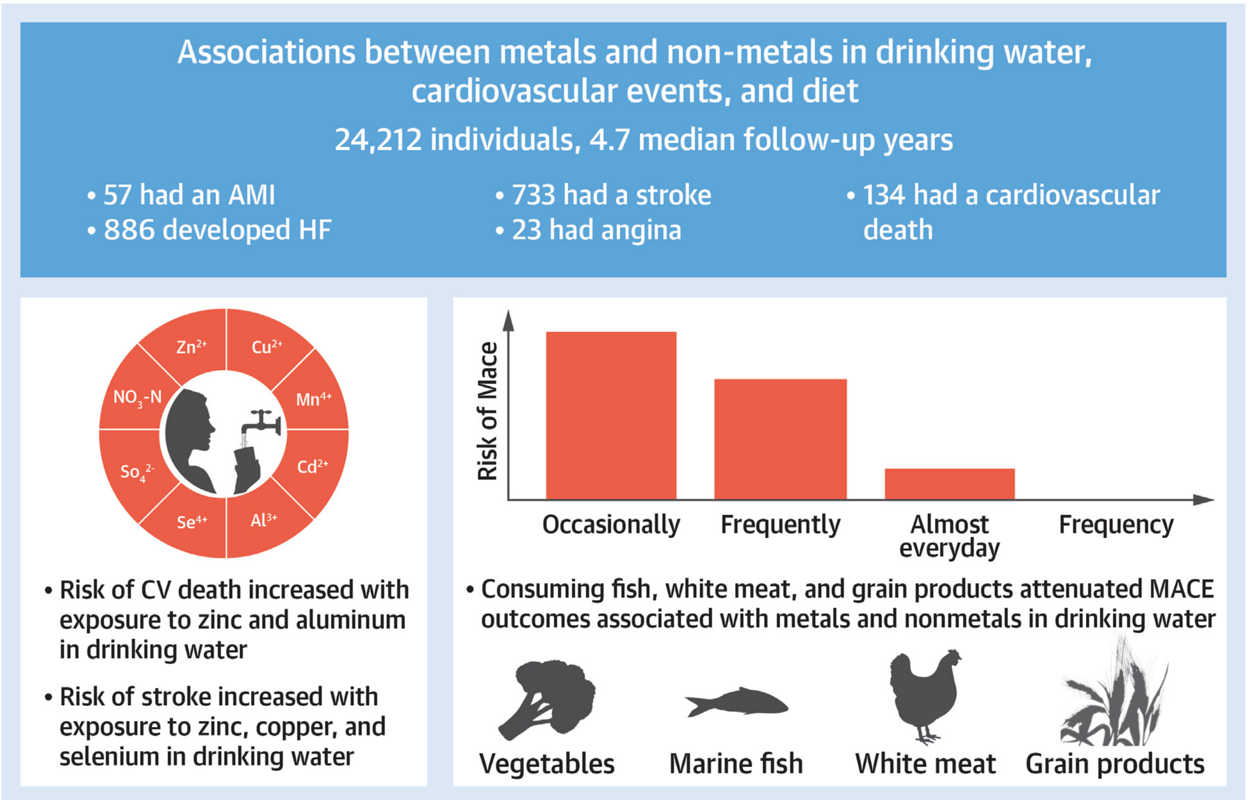
We conducted stratified analyses in prespecified subgroups defined by age, BMI group, education level, and annual income level.[23] Additionally, we explored the potential modification effect of diet on the associations between metals and nonmetals in drinking water exposure and MACE incidence. For each potential effect modifier, we evaluated effect modification by likelihood ratio tests comparing models that included an interaction term between metals, nonmetals exposure, and the effect modifier vs models without the interaction term. Stratum-specific HRs were obtained using the appropriate coefficients and variance-covariance matrix from the same interaction model.

For sensitivity analysis, we evaluated the degree to which unmeasured confounding potentially affected our findings by calculating the E values.[24] We excluded participants who were followed <1 year to eliminate the prevalent effect, and set terminated time as December of 2019 (before starting COVID-19). Moreover, we also used a left censoring method to ensure the number of such cases would be comparable to the actual MACE observed in the study period. All the statistical analyses were conducted in Stata, version 16.0 (Stata Corp) and R Studio, Version 1.2.5042 (The R Project for Statistical Computing).

RESULTS

During the follow-up period (2016-2022), 57 participants had an AMI; 886 had HF; 733 had a stroke; 23 had angina; and 134 had a cardiovascular death (Central Illustration). The median age of patients with AMI, HF, stroke, angina, and cardiovascular death were 68.2, 69.5, 68.6, 64.1, and 77.5 years, respectively (Table 1). The majority of participants had a

CENTRAL ILLUSTRATION Diet Modified the Association of Metals and Nonmetals in Drinking Water With MACE



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Abbreviations as in Figure 1.

primary education or below. More than 55% had a normal range BMI. More than 50% of participants consumed vegetables almost every day, and approximately 50% to 70% of participants consumed fruit, fish, meat, and grain products frequently per week.

METAL AND NONMETALS IN DRINKING WATER AND MACE. The median concentrations of zinc, aluminum, selenium, sulfate, and nitrate nitrogen in drinking water were higher in patients with MACE than those in health status (Table 2). Moreover, the correlation matrix showed that no significant associations among the metals in drinking water (Supplemental Table 1).

In fully adjusted models, we observed an increased risk of incident AMI with exposure to copper, aluminum, cadmium, selenium, HRs (95% CI) of 1.42 (1.07-1.88), 1.41 (1.18-1.69), 1.36 (1.22-1.52), 1.47 (1.28-1.68), respectively (Table 3). We found an increased risk in incident stroke with exposure to zinc, copper, selenium, and a raised risk in incident angina with exposure to zinc and copper. We also found an elevated risk in cardiovascular death incidence with exposure to zinc and aluminum, HRs (95% CI) of 1.32 (1.03-1.68) and 1.31 (1.04-1.64).

Stratified analyses showed that long-term exposure to metal and nonmetal elements in drinking water in older populations, underweight participants, those with a primary education level, and low-income level was associated with higher risk of MACE outcomes compared with those young, normal-weight, those with higher education, and higher income level, respectively, except with exposure to aluminum, cadmium, selenium, and nitrate nitrogen (Figure 1, Supplemental Figure 4).

ASSOCIATION BETWEEN DIET, DRINKING WATER, AND MACE. Dietary intake modified the association between drinking water constituents and MACE outcomes. The manganese-, aluminum-, cadmium-,

TABLE 1 Baseline Characteristics of the Study Participants

	Healthy People (n = 22,404)	Acute Myocardial Infarction (n = 57)	Heart Failure (n = 886)	Stroke (n = 773)	Angina (n = 23)	Cardiovascular Death (n = 134)
Age, y	61.39 (54.10-67.14)	68.22 (63.91-73.17)	69.53 (62.86-76.47)	68.64 (63.13-75.16)	64.07 (58.80-66.92)	77.45 (71.01-82.32)
Sex						
Male	8,932 (39.9%)	39 (68.4%)	398 (44.9%)	365 (49.8%)	13 (56.5%)	71 (53.0%)
Female	13,472 (60.1%)	18 (31.6%)	488 (55.1%)	368 (50.2%)	10 (43.5%)	63 (47.0%)
Education level						
Primary school and below	16,132 (72.0%)	49 (86.0%)	761 (85.9%)	609 (83.1%)	14 (60.9%)	124 (92.5%)
Middle school and above	6,272 (28.0%)	8 (14.0%)	125 (14.1%)	124 (16.9%)	9 (39.1%)	10 (7.5%)
Annual income						
<$4,200	8,528 (38.1%)	33 (57.9%)	515 (58.1%)	444 (60.6%)	8 (34.8%)	107 (79.9%)
≥$4,200	13,876 (61.9%)	24 (42.1%)	371 (41.9%)	289 (39.4%)	15 (65.2%)	27 (20.1%)
BMI[a]						
Underweight	862 (3.8%)	4 (7.0%)	44 (5.0%)	35 (4.8%)	1 (4.3%)	15 (11.2%)
Normal	14,271 (63.7%)	35 (61.4%)	523 (59.0%)	427 (58.3%)	18 (78.3%)	89 (66.4%)
Overweight	6,610 (29.5%)	17 (29.8%)	269 (30.4%)	248 (33.8%)	3 (13.0%)	28 (20.9%)
Obesity	661 (3.0%)	1 (1.8%)	50 (5.6%)	23 (3.1%)	1 (4.3%)	2 (1.5%)
Smoking status						
Never	17,818 (79.5%)	33 (57.9%)	701 (79.1%)	561 (76.5%)	17 (73.9%)	102 (76.1%)
Current	3,835 (17.1%)	19 (33.3%)	133 (15.0%)	134 (18.3%)	5 (21.7%)	27 (20.1%)
Former	751 (3.4%)	5 (8.8%)	52 (5.9%)	38 (5.2%)	1 (4.3%)	5 (3.7%)
Alcohol drinking						
Never	18,516 (82.6%)	39 (68.4%)	735 (83.0%)	571 (77.9%)	18 (78.3%)	101 (75.4%)
Current	3,690 (16.5%)	17 (29.8%)	141 (15.9%)	154 (21.0%)	5 (21.7%)	28 (20.9%)
Former	198 (0.9%)	1 (1.8%)	10 (1.1%)	8 (1.1%)	0 (0.0%)	5 (3.7%)
Tea consumption						
Never	20,237 (90.3%)	49 (86.0%)	800 (90.3%)	636 (86.8%)	18 (78.3%)	120 (89.6%)
Current	2,072 (9.2%)	7 (12.3%)	79 (8.9%)	91 (12.4%)	5 (21.7%)	13 (9.7%)
Former	95 (0.4%)	1 (1.8%)	7 (0.8%)	6 (0.8%)	0 (0.0%)	1 (0.7%)
Diabetes mellitus	3,642 (16.3%)	11 (19.3%)	243 (27.4%)	159 (21.7%)	8 (34.8%)	27 (20.1%)
Dyslipidemia	7,176 (32.0%)	19 (33.3%)	379 (42.8%)	263 (35.9%)	12 (52.2%)	50 (37.3%)
Vegetable consumption[b]						
Almost everyday	11,406 (50.9%)	33 (57.9%)	487 (55.0%)	390 (53.2%)	13 (56.5%)	73 (54.5%)
Frequently	10,314 (46.0%)	22 (38.6%)	383 (43.2%)	330 (45.0%)	9 (39.1%)	53 (39.6%)
Occasionally	684 (3.1%)	2 (3.5%)	16 (1.8%)	13 (1.8%)	1 (4.3%)	8 (6.0%)
Fruit consumption[b]						
Almost everyday	5,242 (23.4%)	7 (12.3%)	154 (17.4%)	149 (20.3%)	6 (26.1%)	14 (10.4%)
Frequently	14,826 (66.2%)	43 (75.4%)	629 (71.0%)	473 (64.5%)	13 (56.5%)	93 (69.4%)
Occasionally	2,336 (10.4%)	7 (12.3%)	103 (11.6%)	111 (15.1%)	4 (17.4%)	27 (20.1%)
Marine fish consumption[b]						
Almost everyday	5,449 (24.3%)	14 (24.6%)	178 (20.1%)	148 (20.2%)	4 (17.4%)	24 (17.9%)
Frequently	13,567 (60.6%)	39 (68.4%)	543 (61.3%)	447 (61.0%)	14 (60.9%)	81 (60.4%)
Occasionally	3,388 (15.1%)	4 (7.0%)	165 (18.6%)	138 (18.8%)	5 (21.7%)	29 (21.6%)
Lakefish consumption[b]						
Almost everyday	4,791 (21.4%)	14 (24.6%)	125 (14.1%)	114 (15.6%)	3 (13.0%)	15 (11.2%)
Frequently	13,484 (60.2%)	35 (61.4%)	567 (64.0%)	456 (62.2%)	12 (52.2%)	92 (68.7%)
Occasionally	4,129 (18.4%)	8 (14.0%)	194 (21.9%)	163 (22.2%)	8 (34.8%)	27 (20.1%)
Red meat consumption[b]						
Almost everyday	6,904 (30.8%)	20 (35.1%)	259 (29.2%)	188 (25.6%)	4 (17.4%)	37 (27.6%)
Frequently	12,342 (55.1%)	30 (52.6%)	482 (54.4%)	411 (56.1%)	13 (56.5%)	72 (53.7%)
Occasionally	3,158 (14.1%)	7 (12.3%)	145 (16.4%)	134 (18.3%)	6 (26.1%)	25 (18.7%)
White meat consumption[b]						
Almost everyday	3,190 (14.2%)	12 (21.1%)	70 (7.9%)	82 (11.2%)	1 (4.3%)	13 (9.7%)
Frequently	15,044 (67.1%)	39 (68.4%)	622 (70.2%)	486 (66.3%)	14 (60.9%)	89 (66.4%)
Occasionally	4,170 (18.6%)	6 (10.5%)	194 (21.9%)	165 (22.5%)	8 (34.8%)	32 (23.9%)

Continued on the next page

TABLE 1 Continued

	Healthy People (n = 22,404)	Acute Myocardial Infarction (n = 57)	Heart Failure (n = 886)	Stroke (n = 773)	Angina (n = 23)	Cardiovascular Death (n = 134)
Grain products[b]						
Almost everyday	3,131 (14.0%)	6 (10.5%)	100 (11.3%)	88 (12.0%)	2 (8.7%)	14 (10.4%)
Frequently	17,143 (76.5%)	45 (78.9%)	679 (76.6%)	545 (74.4%)	17 (73.9%)	103 (76.9%)
Occasionally	2,130 (9.5%)	6 (10.5%)	107 (12.1%)	100 (13.6%)	4 (17.4%)	17 (12.7%)

Values are median (IQR) or n (%). [a]BMI: underweight indicates below 18.5 kg/m^2; normal indicates 18.5 to 24.9 kg/m^2; overweight indicates 25.0 to 29.9 kg/m^2; obesity indicates over 30.0 kg/m^2. [b]Vegetable consumption, Fruit consumption, Marine fish consumption, Lakefish consumption, Red meat consumption, White meat consumption, Grain products: Almost every day indicates over than 5 days per week; frequently indicates 3 to 5 days per week; occasionally indicates <3 days per week.

BMI = body mass index.

sulfate-, and nitrate-MACE associations were significantly attenuated among participants who consumed a higher quantity of fish, white meat, and grain products (**Figure 2** and Supplemental Figure 5). Specifically, the associations of manganese and aluminum with HF and cardiovascular death were less pronounced in participants consuming higher amounts of white meat, fish, and grain products. Participants who consumed more fish and white meat experienced a diminished correlation between cadmium, nitrate, and sulfate and HF, cardiovascular death.

In the sensitivity analyses, the E-value calculation showed that this study had no potential unmeasured confounding bias due to the e values of significant exposure were all more than 1.20 (Supplemental Table 2). These additional analyses revealed that long-term exposure to metals (ie, copper, manganese, aluminum, zinc, and cadmium) and nonmetals (ie, selenium, sulfate, and nitrate-nitrogen) in drinking water increased the risk of MACE outcomes, aligning with the main analyses (Supplemental Tables 3 and 4). Results from left censoring were consistent with those of the primary analysis (Supplemental Table 5).

DISCUSSION

In this well-characterized prospective cohort study, we found that long-term exposure to metals and nonmetals in drinking water was associated with higher risk of MACE during the follow-up period. Stronger associations were observed in older and underweight populations. Additionally, we identified modification effects of dietary intake on the associations between metal and nonmetals in drinking water and MACE.

METALLIC ELEMENTS IN DRINKING WATER AND MACE OUTCOMES. Metal elements such as copper, zinc, cadmium, and manganese, commonly encountered in daily life, are recognized as potential cardiovascular hazards. These elements sequestrate within arterial wall macrophages and lead to oxidative stress mediation, which has been identified as a novel contributing risk factor in the advancement of vascular diseases.[25-30] Abnormal copper levels impacted the activity of superoxide dismutase activity, thus facilitating the formation of hydroxyl free radicals, a central factor in the pathophysiology of atherosclerosis.[27] Zinc played a crucial role in essential proteins like protein kinase C, producing C-reactive protein and inflammatory cytokines, and entrapping particles in macrophages and monocytes.[28] Studies, such as Messner et al[29], provided an explanation of cadmium-caused CVDs which cadmium impaired endothelial barrier functionality, primarily by the breaking down endothelial cell-cell adhesions and instigating endothelial cell death, leading to the release of cellular remnants. Cadmium led to the initiation and promotion of atherosclerosis due to the crucial roles of monocytes and macrophages in trans-differentiation into foam cells and necrotic foam cell death in endothelial dysfunction.[30] In the current study, we found manganese was associated with stroke, aligning with theories suggesting that manganese-induced neurotoxicity stimulates glial cells to produce inflammatory mediators that triggered neuroinflammation.[31]

In our study, exposure to copper and cadmium and MACE outcomes were aligned with previous studies. Epidemiological studies have shown that patients who suffered from HF, atherosclerosis, or other confirmed CVDs might have higher serum copper concentration compared to health individuals.[32] A cohort study among elderly Australian populations and found that exposure to higher cadmium was associated with an elevated risk of CVDs.[33] A population-based study by Peters et al[34] among 12,049 participants from National Health and Nutrition Examination Survey showed that increases in blood and urine cadmium levels were associated with an elevated risk of stroke and HF.

TABLE 2 Water Constituents of Study Participants

	Healthy People (n = 22,404)	Acute Myocardial Infarction (n = 57)	Heart Failure (n = 886)	Stroke (n = 733)	Angina (n = 23)	Cardiovascular Death (n = 134)
Metal constituents						
Zinc (mg/d)	0.02 ± 0.02	0.03 ± 0.02	0.03 ± 0.02	0.03 ± 0.02	0.03 ± 0.03	0.04 ± 0.02
Copper (mg/d)	0.02 ± 0.002	0.02 ± 0.002	0.02 ± 0.002	0.02 ± 0.002	0.02 ± 0.002	0.02 ± 0.002
Manganese (mg/d)	0.05 ± 0.05	0.06 ± 0.08	0.05 ± 0.06	0.06 ± 0.07	0.05 ± 0.05	0.07 ± 0.08
Aluminum (mg/d)	0.04 ± 0.01	0.04 ± 0.02	0.03 ± 0.01	0.04 ± 0.01	0.04 ± 0.01	0.04 ± 0.02
Cadmium (μg/d)	0.54 ± 0.15	0.58 ± 0.16	0.52 ± 0.12	0.54 ± 0.13	0.56 ± 0.13	0.55 ± 0.13
Nonmetal constituents						
Selenium (μg/d)	0.36 ± 0.06	0.38 ± 0.05	0.36 ± 0.05	0.36 ± 0.05	0.37 ± 0.05	0.36 ± 0.04
Sulfate (mg/d)	12.46 ± 5.66	13.48 ± 5.82	12.67 ± 5.28	13.08 ± 5.78	12.16 ± 4.44	13.22 ± 5.09
Nitrate nitrogen (mg/d)	1.96 ± 0.72	2.11 ± 0.84	1.97 ± 0.73	2.03 ± 0.78	1.95 ± 0.53	2.07 ± 0.78

Values are mean ± SD. The units in milligrams or microgram per day were based on a food frequency questionnaire.

NONMETALLIC ELEMENTS IN DRINKING WATER AND MACE OUTCOMES. Our study suggested that exposure to selenium, sulfate, and nitrate in drinking water was positively associated with the incidence of AMI, stroke, and cardiovascular death. Previous evidence focused on the benefits of dietary selenium sources on CVDs.[35,36] However, the association of excessive selenium intake on the risk of MACE has not yet been conclusively determined. Sulfate in drinking water was a risk factor for MACE in this study. This could be attributed to the production of endotoxins triggered by sulfate enrichment, which in turn incites human immune responses and inflammation.[37] A population-based analysis in the United Kingdom that showed at moderate-to-high sulfate concentrations, nitrate in drinking water was positively associated with blood pressure-related CVDs.[38] These findings imply that the long-term effects of nitrate on cardiovascular events were influenced by concurrent sulfate intake.

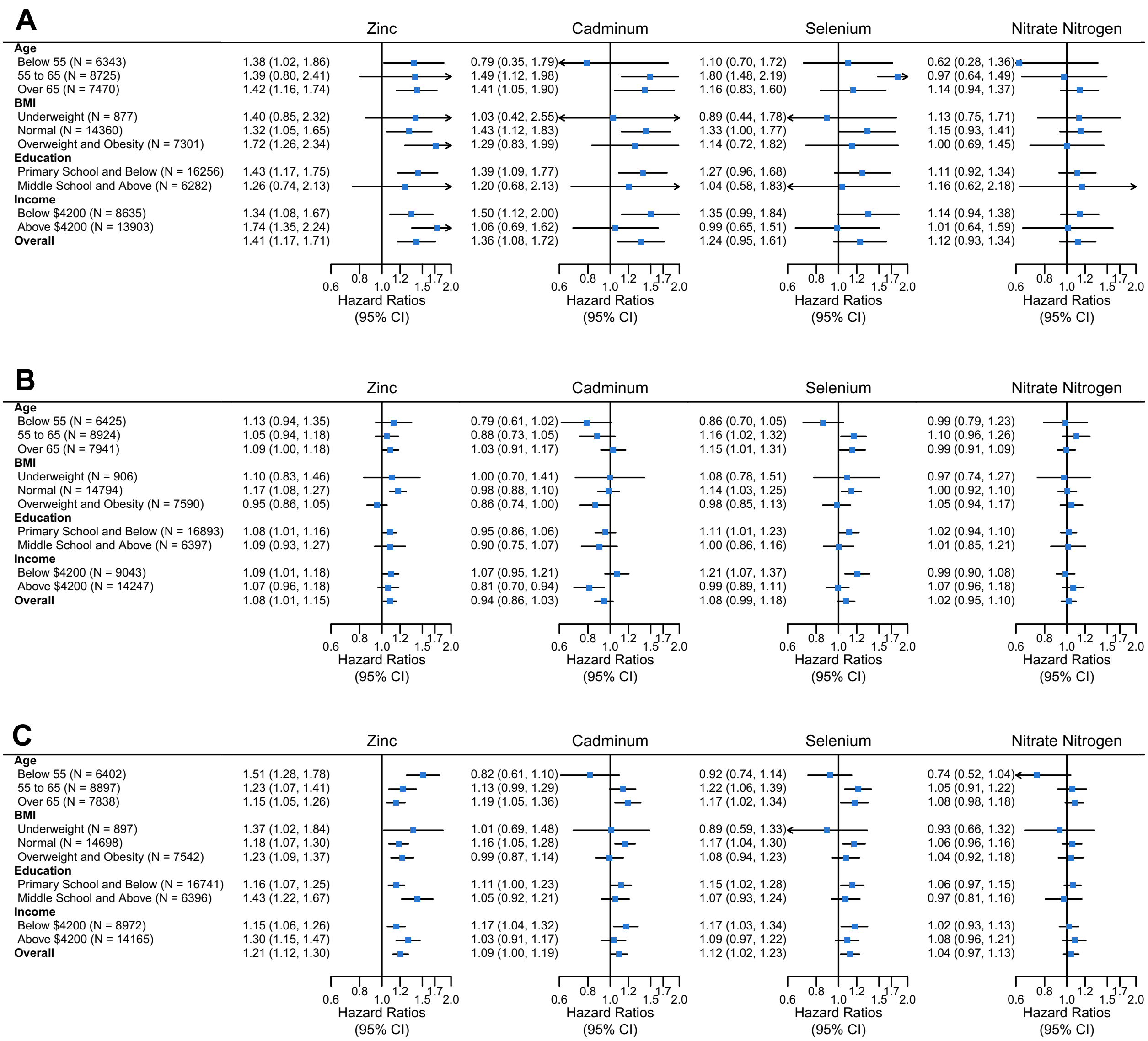
STRATIFIED ANALYSIS AND DIET MODIFICATION EFFECTS. In stratified analysis, a higher risk of MACE incidence when exposed to metals and nonmetals in drinking water in older populations, underweights, primary education level, and low-income level was observed. Possible explanations include in vivo exposure level and health services utilization. Previous literature suggested that vulnerable groups, such as the elderly, malnourished, low education degree, and low socioeconomic status, were more susceptible to the effects of exposure to metals and nonmetals in drinking water.[39] This observation may be attributed to the fact that older individuals are typically more susceptible to noncommunicable diseases. Additionally, malnourished individuals often correlate with

TABLE 3 Associations of Long-Term Exposure to Metals and Nonmetals in Drinking Water With Major Adverse Cardiovascular Events

	Acute Myocardial Infarction (51 Cases/108,854.8 Person-Years)	Heart Failure (749 Cases/110,697.6 Person-Years)	Stroke (663 Cases/110,276.7 Person-Years)	Angina (20 Cases/108,785.9 Person-Years)	Cardiovascular Death (134 Cases/109,134.9 Person-Years)
Metal constituents					
Zinc	1.24 (1.01-1.51)	1.03 (0.94-1.13)	1.18 (1.11-1.25)	1.28 (1.03-1.59)	1.32 (1.03-1.68)
Copper	1.42 (1.07-1.88)	1.02 (0.96-1.08)	1.16 (1.05-1.28)	1.41 (1.01-1.97)	1.14 (0.87-1.50)
Manganese	1.07 (0.81-1.40)	0.99 (0.90-1.08)	1.05 (1.00-1.11)	0.93 (0.84-1.02)	1.09 (0.92-1.30)
Aluminum	1.41 (1.18-1.69)	0.91 (0.82-1.01)	1.12 (0.99-1.28)	1.14 (0.93-1.40)	1.31 (1.04-1.64)
Cadmium	1.36 (1.22-1.52)	0.94 (0.82-1.07)	1.09 (0.95-1.26)	1.10 (0.82-1.46)	1.30 (0.94-1.81)
Nonmetal constituents					
Selenium	1.47 (1.28-1.68)	1.04 (0.96-1.13)	1.10 (1.02-1.18)	1.24 (0.83-1.86)	1.05 (0.78-1.40)
Sulfate	1.05 (0.83-1.32)	0.99 (0.85-1.16)	1.02 (0.97-1.07)	0.81 (0.59-1.11)	1.03 (0.73-1.45)
Nitrate nitrogen	1.09 (0.86-1.39)	1.00 (0.87-1.16)	1.03 (0.97-1.09)	0.82 (0.59-1.14)	1.08 (0.80-1.45)

Values are HR (95% CI). Model adjusted for age, education, BMI, annual household income, current smoking status, current alcohol consumption status, current tea consumption, medical history of diabetes and dyslipidemia, vegetable consumption, fruit consumption, marine fish consumption, lake fish consumption, red meat consumption, white meat consumption, and grain product consumption. HRs were calculated based on 1 SD increase in each element.

FIGURE 1 Stratified Analyses for Associations of Long-Term Exposure to Metals and Nonmetals in Drinking Water With MACE Incidence by Age, BMI, Education Level, and Income Level

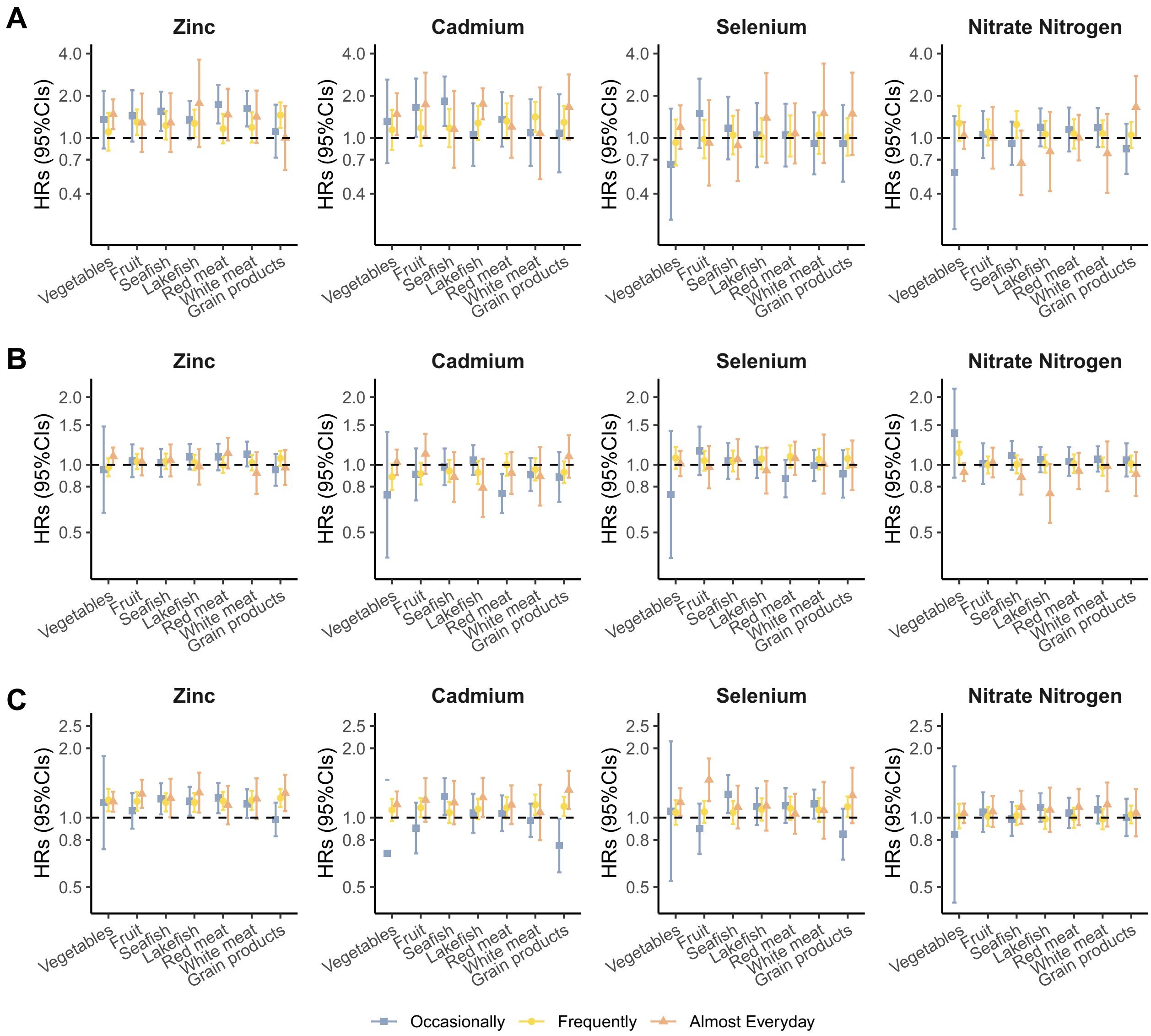


(A) HRs for cardiovascular death; (B) HRs for HF; (C) HRs for stroke. The model adjusted for age, education, BMI, annual household income, current smoking status, current alcohol consumption status, current tea consumption, medical history of diabetes and dyslipidemia, vegetable consumption, fruit consumption, marine fish consumption, lake fish consumption, red meat consumption, white meat consumption, and grain product consumption. The dashed line represents HR of 1. AMI and angina were not shown in Figure 1 due to limited cases. AMI = acute myocardial infarction; BMI = body mass index; HF = heart failure; MACE = major adverse cardiovascular events.

lower socioeconomic status, resulting in limited opportunities for proper health care access. Consequently, these individuals are more prone to experience adverse cardiovascular events related to inferior health care quality.

Recent evidence had several potential biological pathways by which diet could modify the association of metals and nonmetals in drinking water and health outcomes. Studies such as the one by Tortosa-Caparros et al[17], found an inverse association between omega-3 fatty acids from marine fish and white meat and CVD outcomes due to their anti-inflammatory properties. Therefore, consuming high amounts of marine fish and white meat may benefit

FIGURE 2 **The Moderating Effects of Dietary Supplementation on the Prospective Associations of Long-Term Exposure to Metals and Nonmetals in Drinking Water With MACE Incidence**



(A) HRs for cardiovascular death; (B) HRs for HF; (C) HRs for stroke. The model adjusted for age, education, BMI, annual household income, current smoking status, current alcohol consumption status, current tea consumption, medical history of diabetes and dyslipidemia, vegetable consumption, fruit consumption, marine fish consumption, lake fish consumption, red meat consumption, white meat consumption, and grain product consumption. AMI and angina were not shown in Figure 1 due to limited case. Abbreviations as in Figure 1.

those exposure to metals and nonmetals in drinking water by reducing inflammation-related CVDs onset and progression.[40] Nevertheless, marine fish also contained abundant selenium, which could adversely affect vascular health due to excessive daily intakes of selenium, particularly in the areas with low-quality drinking water.[17]

Several studies have shown that the consumption of vegetables, fruit, and grain products can prevent CVDs, as soluble fiber, polyphenols, and flavonoids from these foods had their antioxidant and anti-inflammatory properties to inhibit the transcription of inflammatory mediators and maintain the integrity of the epithelial barrier.[41,42] Thus, eating such foods could alleviate inflammation-related CVDs in individuals who used low-quality drinking water. However, Sakellari et al[43] conducted a population-based study in Greece that showed a higher blood cadmium level was observed in populations who consumed more leafy and green vegetables. This might increase the risk of MACE outcomes in individuals with long-term exposure to cadmium in drinking water. Furthermore, an epidemiological study reported that cadmium was positively associated with hypertension, stroke, and coronary heart disease in Chinese population who consumed grain products contaminated with cadmium.[44] Furthermore, the risk of CVDs could be mitigated by consuming nitrates from natural food sources due to their beneficial effect on endothelial function and decrease of blood pressure.[45] This suggests that a natural diet might help reduce CVDs triggered by low-quality drinking water.

STRENGTH AND LIMITATIONS. The strengths of our study included the prospective design with information on divergent potential sociodemographics, lifestyles, and socioeconomic confounders collected at enrollment, preventing the risk of recall bias. Furthermore, this study identified participants using strict inclusion/exclusion criteria, data analysis strategies, and validation.

The present study also had some limitations. First, this study used regional-level exposures to metallic and nonmetallic elements in drinking water rather than the individual level, though the measurement values from the nearest tap water pipeline from the participants' residential addresses as the surrogate of the individual exposure level was used, and exposures were weighted by sex in 6 age stratifications. Second, we were unable to collect data related to filtered drinking water in households, which could affect the concentrations of elements in drinking water. Third, this study had limited information about the bottled water intake among participants since bottled water might contain some mineral elements, though consumption of bottled water in China is low. Fourth, information of metallic or nonmetallic (eg, cadmium) from foodstuffs was not collected in this study. Fifth, we focused solely on the initial event that individuals experienced and did not account for any subsequent events thereafter. Finally, we assumed the diet patterns were fixed and only had the availability of only one baseline measurement of dietary intake pattern.

IMPLICATIONS OF FINDINGS. It is crucial to understand the relationship between drinking water and health. The findings of this study suggested that metal and nonmetal in drinking water are associated with MACE and that diet may modify drinking water-induced adverse cardiovascular health outcomes. Individual-level prevention strategies and population-wide policy efforts could be used to promote healthier diets, in concert with improving drinking water quality standards. To achieve this, a multifaceted approach is essential and would include a collaborative effort between individuals, health care providers, policymakers, and public health authorities.

CONCLUSIONS

Our study found that long-term exposure to higher levels of metallic (copper, manganese, aluminum, zinc, and cadmium) and nonmetallic (selenium, sulfate, and nitrate-nitrogen) elements in drinking water was associated with an elevated risk of MACE. Specific dietary patterns modified the associations. Given the growing burden of MACE, our study suggests public health policies for improving drinking water standards could impact CVD health. Further studies are needed.

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APPENDIX For supplemental tables and figures, please see the online version of this paper.