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RESEARCH ARTICLE

Drinking water quality and inflammatory bowel disease: a prospective cohort study

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Abstract
Environmental factors, such as drinking water and diets, play an important role in the development of inflammatory bowel disease (IBD). This study aimed to investigate the associations of metal elements and disinfectants in drinking water with the risk of inflammatory bowel disease (IBD) and to assess whether diet influences these associations. We conducted a prospective cohort study including 22,824 participants free from IBD from the Yinzhou cohort study in the 2016–2022 period with an average follow-up of 5.24 years. The metal and disinfectant concentrations were measured in local pipeline terminal tap water samples. Cox regression models adjusted for multi-level covariates were used to estimate adjusted hazard ratios (aHRs) and 95% confidence intervals (95% CIs). During an average follow-up period of 5.24 years, 46 cases of IBD were identified. For every 1 standard deviation (SD) increase in the concentration of manganese, mercury, selenium, sulfur tetraoxide (SO_4), chlorine, and nitrate nitrogen (NO_3_N) were associated with a higher risk of IBD with the HRs of 1.45 (95% CI: 1.14 to 1.84), 1.51 (95% CI: 1.24–1.82), 1.29 (95% CI: 1.03–1.61), 1.52 (95% CI: 1.26–1.83), 1.26 (95% CI: 1.18–1.34), and 1.66 (95% CI: 1.32–2.09), whereas zinc and fluorine were inversely associated with IBD with the HRs of 0.42 (95% CI: 0.24 to 0.73) and 0.68 (95% CI: 0.54–0.84), respectively. Stronger associations were observed in females, higher income groups, low education groups, former drinkers, and participants who never drink tea. Diets have a moderating effect on the associations of metal and nonmetal elements with the risk of IBD. We found significant associations between exposure to metals and disinfectants and IBD. Diets regulated the associations to some extent.

Keywords Inflammatory bowel disease · Heavy metals · Nonmetals disinfectants · Water pollution · Biochemical indices · Drinking water · Cohort study

Introduction

Inflammatory bowel disease (IBD), consisting of Crohn's disease (CD) and ulcerative colitis (UC), is a chronic and complex disease stemming from the synthetic effects of genetics, environmental factors, the intestinal barrier, and the immune response (Baumgart and Carding 2007; Ramos and Papadakis 2019). IBD is characterized by relapsing–remitting symptoms, resulting in physical disability and psychosocial stress for patients, causing high social and economic burdens (Jairath and Feagan 2020; Piovani et al. 2020). Recent years have witnessed rapid epidemiological changes in IBD (Ng et al. 2017). It was estimated that more than 6.8 million people were living with IBD in 2017 (Alatab et al. 2020), with high disease prevalence in high-income countries and rapidly increasing disease incidence in newly industrialized countries (Piovani et al. 2020). Previous studies predicted that the prevalence of IBD will increase by up to 1% in industrialized countries of the Western world, and newly industrialized and developing countries will transition from acceleration in the incidence stage to the compounding prevalence stage of IBD (Kaplan and Windsor

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Highlights
• We found significant associations between exposure to metals and disinfectants and inflammatory bowel disease (IBD).
• Stronger associations were observed in females, higher income groups, and low education groups.
• Diets have a moderating effect on the associations of metal and nonmetal elements with the risk of IBD.

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2021). Exploring the etiology and pathogenetic mechanism of IBD is urgent to alleviate the high burden of this costly and complex disease (Alatab et al. 2020).

The development of genome-wide association studies (GWASs) has largely contributed to understanding IBD at the genetic level (Abegunde et al. 2016). Although almost 200 genetic loci have been identified as associated with IBD (Jostins et al. 2012), the varied incidence of IBD in geographic distribution and the rapid increase in IBD incidence during the last decades reminds us of the importance of environmental factors for IBD (Lakatos 2009; Burisch et al. 2014). Environmental factors can disrupt the equilibrium between protective and detrimental gut bacteria, leading to a reduction in bacterial diversity, which has been implicated in the pathogenesis of inflammatory bowel disease (IBD) (Lakatos 2009). A growing number of epidemiologic studies have suggested that drinking water (Baron et al. 2005), diet (Yamamoto et al. 2009), smoking (Mahid et al. 2006), and hygiene (Klement et al. 2008) are critical environmental factors for IBD. However, the evidence is inconsistent with various study designs and populations. High-quality epidemiological studies with prospective design are needed to understand the etiology of IBD further and provide implications for prevention (Piovani et al. 2019).

Drinking water is consumed by more than 1 l daily by each adult in the daily diet. Previous studies have explored the associations between different microbiomes in drinking water and IBD (Abubakar et al. 2007; Forbes et al. 2016), while metal, nonmetal element, and disinfectant intake in drinking water can not be neglected. Taking up the metal elements and disinfectants in drinking water may alter the pathogenicity of microbial organisms in the intestinal tract and exacerbate immune system responses (Perl et al. 2004). Some observational studies have shown that iron in drinking water is associated with a higher incidence of IBD (Aamodt et al. 2008). Nitrate and sulfite may influence the regulatory mechanism of the gut and are toxic to micobiota (Jowett et al. 2004; Jädert et al. 2012). However, the association between metal elements and disinfectants in drinking water and IBD still needs to be better understood, especially in low- and middle-income countries. The concept of metal elements and disinfectants in drinking water as an etiological source of IBD may shed light on global variance in IBD incidence.

In this study, we aimed to estimate the association between long-term exposure to metal, nonmetal elements (mercury, iron, manganese, copper, aluminum, zinc, chromium, cadmium, and selenium) and disinfectants (fluorine, sulfur tetroxide (SO4), chlorine, nitrate nitrogen (NO3_N), and potential hydrogen (PH)) in drinking water and the risk of IBD in a prospective cohort population in southeast China. We also identified the susceptible population and examined the moderating effect of diet on the relationships. Metal and nonmetal elements may be enriched in diet. Diets may also metabolize them in an accelerated manner, which may have an impact on the associations between exposures and IBD in this study.

Materials and methods

Study population

The participants in our study were from the prospective Yinzhou cohort study in Ningbo, a major port city in southeastern China with a population of more than 9.5 million in 2021. The design and data collection details of the Yinzhou Cohort study have been published in a previous publication (Li et al. 2022). In the Yinzhou district, nine townships (comprising 25 towns) were selected based on the participants' coherence and nearby medical facilities' availability. All permanent residents who were 18 years old from these nine townships were invited to participate in the cohort study, with enrollment from January 2016 to December 2017. The trained medical staff conducted a face-to-face health survey to collect baseline information covering sociodemographic, lifestyles, and health conditions. The medical staff finished the questionnaire in approximately 15–20 min, and verifiers then checked it after completion. Follow-up was conducted via record linkage between the baseline database and the Yinzhou regional health information system (HIS) through the Wonders Big Data Management Platform, which integrates a hospital information system, medical insurance system, and other health surveillance systems.

A total of 25,490 participants were included in the baseline survey. We excluded patients with important control variables missing at baseline ($n = 473$), and participants with food variables missing ($n = 2193$). Eventually, 22,824 participants were included in this study with an average follow-up of 5.24 years (Supplement Fig. 1). The diagnosis of IBD was based on the consensus guideline of the European Crohn's and Colitis Organization and integrated the clinical, pathological, and imaging manifestations by the professional doctors. The Zhejiang University School of Medicine Ethics Committee approved this study (Approval no. 2015-ZJU-023). Written informed consent from participants was obtained before the baseline questionnaire investigation.

Exposure assessment

Terminal tap water samples were collected from a total of 37 different sampling sites in the Yinzhou district, with four measurements taken annually (one for each season), and matched to the participants based on their residential addresses (Fig. 1). The Yinzhou district has reached almost complete coverage in the tap water supply. The local Center

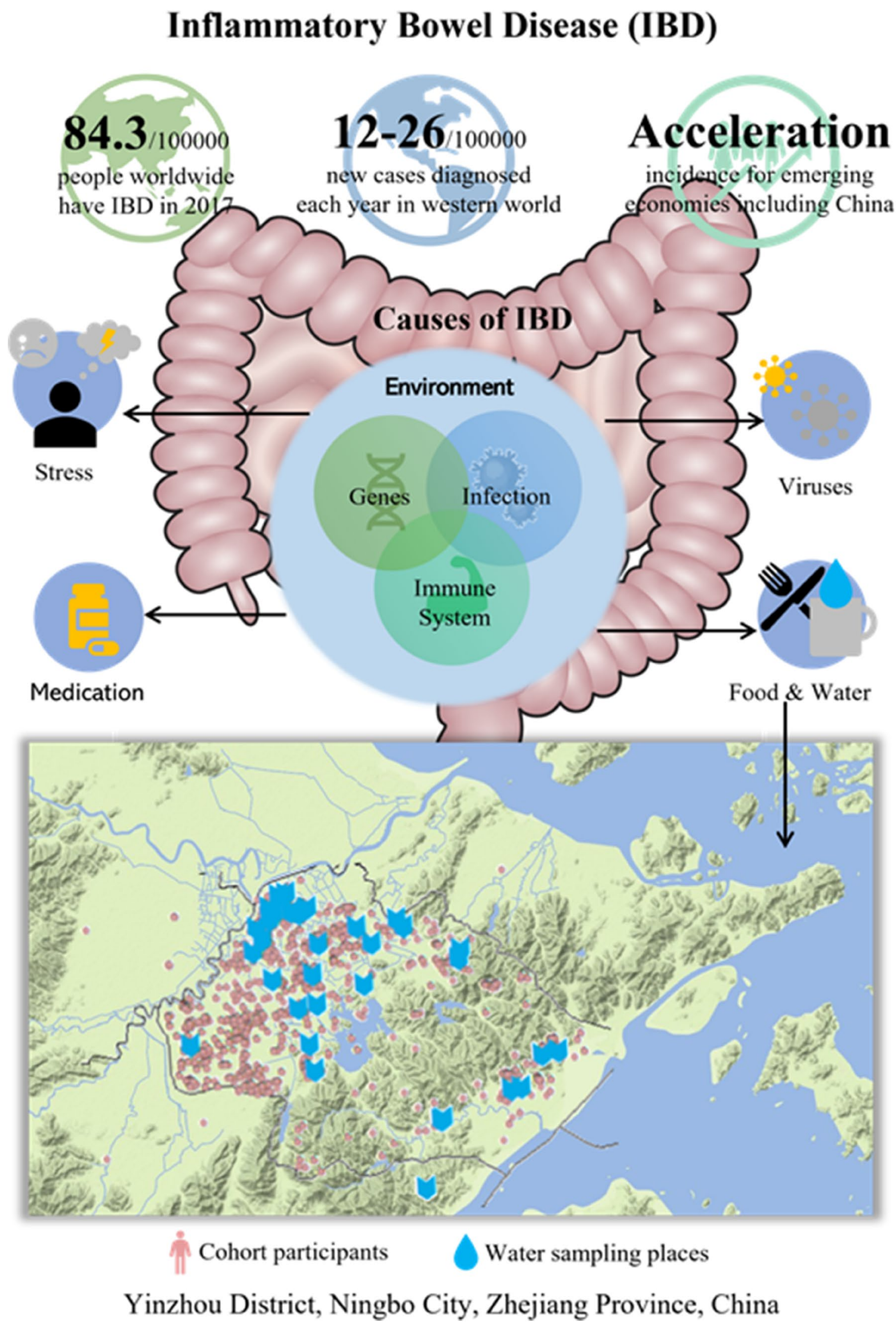

Fig. 1 The distribution of cohort participants and sampling places

for Disease Control and Prevention analyzed the terminal tap water samples for physicochemical indices. Metal, nonmetal elements, and disinfectants, including mercury, iron, manganese, copper, aluminum, zinc, chromium, cadmium, selenium, fluorine, sulfur tetraoxide (SO_4), chlorine, nitrate nitrogen (NO_3_N), and potential of hydrogen (PH) were measured by atomic absorption spectrophotometry or the atomic absorption method. During the analysis, replicates were introduced to ensure the accuracy of the analysis. The relative errors of the replicates were within ± 5%, indicating acceptable analytical accuracy. To aid in comparing exposure test results, we calculated standardized Z scores scaled to the regional measurements by subtracting the regional measurement mean from each measurement site's test values and dividing by the regional measurement standard deviation (SD).

Diets measurement

This study's primary diet measurement included green leafy vegetables, fruits, meat (red meat and white meat), and marine products (seafood and freshwater). In the baseline survey, participants were asked about the frequency of diet consumption every week. Frequent fruits, meat, and marine users were participants who responded, "more than four times every week" to "what's the frequency you take fruits, green leafy vegetables, meat, and marine products." The participants who responded 0 to 3 were classified as fruits, green leafy vegetables, meat, and marine products less users.

Covariates

We collected participant's sociodemographic status (age, sex, education level, and annual household income), lifestyle factors (body mass index, smoking status, alcohol drinking, and tea drinking), and medical history (stroke, diabetes, hypertension, cancer, and dyslipidemia) through a structured questionnaire at baseline. Body mass index (BMI) was computed by dividing weight in kilograms by height in meters squared. Current smoking was defined as smoking at least one cigarette per day for more than a year or consuming at least five packs per month. Current alcohol consumption was defined as consuming 100 g of alcohol per week. Tea consumption was defined as having more than two cups of tea per week for more than 2 months.

Statistical analysis

Descriptive analyses were conducted for all variables. Spearman's correlations between exposures were used to examine the covariance. We used Cox regression models to estimate metal and disinfectant exposure in drinking water and risk of the onset of IBD (Ozenne et al. 2017). This study specified three models to adjust for a set of variables considered sufficient for confounding adjustment. In the basic models, we adjusted for age, sex (male versus female), and educational attainment (illiteracy, primary school, or middle school and above). In the adjusted models, we further adjusted for BMI (underweight, normal, overweight, or obesity), annual household income (< 1400$ versus 1400$ ~), current smoking status (never, former, or current), alcohol consumption status (never, former, or current), current tea drinking status (never, former, or current), and medical history of stroke, diabetes, hypertension, cancer, and dyslipidemia (yes versus no). In the fully adjusted models, we additionally adjusted the consumption of green leafy vegetables, fruits, meat, and marine products. Cluster-robust standard errors were used to account for clustering by water sources.

We conducted subgroup analyses to explore the effect modifications of sex, age, education, annual household income, smoking status, alcohol consumption, tea consumption, and BMI by including interaction terms between exposures and potential modifiers. In addition, we explored the potential moderating effect of diet on the associations between metals, nonmetals, and disinfectants in drinking water exposure and the risk of IBD. 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 versus models without the interaction term. Stratum-specific HRs were obtained using the appropriate coefficients and variance–covariance matrix from the same interaction model. Sensitive analyses were conducted to test the robustness of our results by using the two-pollutant models. All associations were presented as HRs with corresponding 95% CIs. A 2-sided p-value < 0.05 was considered statistically significant. Stata version 16.0 for Mac (Stata Corp, College Station, TX, USA) and R Studio Version 1.2.5042 (The R Project for Statistical Computing, Vienna, Austria) were used for the statistical analyses.

Results

We observed 119,600 person-years during the follow-up period, and 46 incidents of IBD were identified. There were no significant differences in baseline characteristics between healthy people and IBD patients. The baseline age was 60.8 years old for all the participants. Most participants had a relatively low education level (illiterate or primary school), and more than 60% were in the normal range of BMI. Most participants self-reported being never smokers and never alcohol and tea drinkers. Half of the participants tended to consume more vegetables, approximately 20% tended to consume more fruits, and more than 30% tended to consume more marine products and meat (Table 1). The

Table 1 Characteristics of study participants

Characteristics	Healthy people (*n* = 22,778)	IBD (*n* = 46)	*P value*
Age, *n* (%)			
Under 55	6513 (28.6%)	12 (26.1%)	0.71
55 +	16,265 (71.4%)	34 (73.9%)	
Sex, *n* (%)			0.10
Male	9175 (40.3%)	13 (28.3%)	
Female	13,603 (59.7%)	33 (71.7%)	
Education, *n* (%)			0.71
Primary school and below	16,412 (72.1%)	32 (69.6%)	
Middle school and above	6366 (27.9%)	14 (30.4%)	
BMI, *n* (%)			0.71
Underweight	913 (4.0%)	3 (6.5%)	
Normal	14,548 (63.9%)	30 (65.2%)	
Overweight	6616 (29.0%)	11 (23.9%)	
Obesity	701 (3.1%)	2 (4.3%)	
Smoking status, *n* (%)			0.19
Never	18,056 (79.3%)	41 (89.1%)	
Current	3867 (17.0%)	5 (10.9%)	
Former	855 (3.8%)	0 (0.0%)	
Alcohol drinking, *n* (%)			0.01
Never	18,913 (83.0%)	46 (100.0%)	
Current	3660 (16.1%)	0 (0.0%)	
Former	205 (0.9%)	0 (0.0%)	
Tea drinking, *n* (%)			0.76
Never	20,645 (90.6%)	43 (93.5%)	
Current	2031 (8.9%)	3 (6.5%)	
Former	102 (0.4%)	0 (0.0%)	
Annual income, *n* (%)			0.13
< \$1400	8406 (36.9%)	12 (26.1%)	
\$1400 ~	14,372 (63.1%)	34 (73.9%)	
Hypertension	14,323 (62.9%)	31 (67.4%)	0.53
Diabetes	3852 (16.9%)	11 (23.9%)	0.21
Dyslipidemia	7272 (31.9%)	16 (34.8%)	0.68
Cancer	636 (2.8%)	3 (6.5%)	0.13
Stroke	787 (3.5%)	3 (6.5%)	0.26
Vegetables			0.28
More	12,200 (53.6%)	21 (45.7%)	
Less	10,578 (46.4%)	25 (54.3%)	
Fruit			0.56
More	5294 (23.2%)	9 (19.6%)	
Less	17,484 (76.8%)	37 (80.4%)	
Seafood			0.83
More	5639 (24.8%)	12 (26.1%)	
Less	17,139 (75.2%)	34 (73.9%)	
Freshwater products			0.90
More	4779 (21.0%)	10 (21.7%)	
Less	17,999 (79.0%)	36 (78.3%)	
Marine products			0.69
More	8074 (35.4%)	15 (32.6%)	
Less	14,704 (64.6%)	31 (52.2%)	
Meat			0.44
More	8180 (35.9%)	14 (30.4%)	
Less	14,598 (64.1%)	32 (69.6%)	
Red meat			0.20
More	7456 (32.7%)	11 (23.9%)	
Less	15,322 (67.3%)	35 (76.1%)	
White meat			0.69
More	3019 (13.3%)	7 (15.2%)	
Less	19,759 (86.7%)	39 (84.8%)	

Abbreviations: *IBD*, inflammatory bowel disease; *BMI*, body mass index. Continuous variables are described as the mean ± standard deviation (SD), and categorical variables are expressed as counts and percentages. Differences in the distribution between healthy and IBD participants were tested using the Mann−Whitney *U* test for continuous variables and the chi-square test for categorical variables

concentrations of mercury, manganese, selenium, SO_4, chlorine, and NO_3_N in drinking water for participants with IBD were higher than those for healthy participants. In comparison, zinc and fluorine concentrations were lower than those in healthy participants (Table 2).

In general, no significant correlations between exposures in drinking water were observed (Supplement Table 1). In the fully adjusted model, for a 1 SD increase in the concentration of mercury, manganese, selenium, sulfur tetraoxide, chlorine, and nitrate nitrogen, the risk of IBD increased by 48% (*HR*: 1.48, 95% CI: 1.23 to 1.77), 47% (*HR*: 1.47, 95% CI: 1.13–1.72), 29% (*HR*: 1.29, 95% CI: 1.03–1.61), 51% (*HR*: 1.51, 95% CI: 1.10–2.06), 25% (*HR*: 1.25, 95% CI: 1.10–1.42), and 65% (*HR*: 1.65, 95% CI: 1.14–2.37), respectively (Table 3). In contrast, for a 1 SD increase in the concentration of zinc and fluorine, the risk of IBD decreased by 59% (*HR*: 0.41, 95% CI: 0.25 to 0.68) and 33% (*HR*: 0.67, 95% CI: 0.47–0.95), respectively. There was no significant association between exposure to copper, iron, aluminum, chromium, cadmium, and the potential of hydrogen in drinking water and IBD.

Stratified analyses demonstrated that the associations between manganese exposure and risk of IBD were higher in females and higher-income participants (Table 4). With 1 SD increase in long-term exposure to manganese, the risk for IBD increased by 53% (*HR*: 1.53, 95%: 1.20–1.96) in the females and 16% (*HR*: 1.16, 95%: 0.68–2.00) in males, and 50% (*HR*: 1.50, 95%: 1.10–2.03) for the high-income participants and 38% (*HR*: 1.38, 95%: 1.03–1.86) for the lower group. Similar results were found in the stratified analyses of the associations between mercury and IBD.

Table 2 Exposures component comparison in drinking water between healthy people and IBD patients

Exposures	Healthy participants (n = 22,778)	IBD (n = 46)	*P value*
Mercury (μg/L)	0.05 (0.05, 0.05)	0.05 (0.05, 0.28)	< 0.001
Manganese (μg/L)	15.00 (12.50, 16.25)	16.00 (15.00, 67.50)	0.01
Zinc (μg/L)	3.94 (2.50, 21.38)	3.13 (2.50, 4.00)	0.02
Copper (μg/L)	10.00 (10.00, 10.00)	10.00 (10.00, 10.00)	0.76
Iron (μg/L)	20.00 (20.00, 35.63)	29.00 (20.00, 37.15)	0.15
Aluminum (μg/L)	22.00 (15.50, 22.50)	21.00 (17.60, 22.00)	0.42
Chromium (μg/L)	2.00 (2.00, 2.00)	2.00 (2.00, 2.00)	0.87
Cadmium (μg/L)	0.10 (0.10, 0.22)	0.10 (0.10, 0.22)	0.22
Selenium (μg/L)	0.20 (0.15, 0.20)	0.20 (0.20, 0.20)	0.03
Fluorine (mg/L)	0.12 (0.11, 0.13)	0.12 (0.10, 0.12)	0.01
Sulfur tetraoxide (mg/L)	5.73 (5.0, 10.45)	9.63 (5.03, 11.26)	0.08
Chlorine (mg/L)	5.10(4.78, 6.35)	6.35 (5.10, 7.75)	< 0.001
Nitrate nitrogen (mg/L)	0.90 (0.90, 1.60)	1.35 (0.90, 1.78)	0.001
Potential of hydrogen	6.83 (6.80, 6.86)	6.83 (6.80, 6.86)	0.69

Abbreviations: *IBD*, inflammatory bowel disease; continuous variables are described as the median (q1, q3). Differences in the distribution between healthy and periodontitis participants were tested using the Wilcoxon rank-sum test

Table 3 Prospective association between long-term exposure to metal elements, disinfectants, and risk of IBD onset

	HR (95% CI)*		
IBD	Model 1	Model 2	Model 3
Mercury	1.43 (1.22, 1.67)	1.40 (1.20, 1.63)	1.48 (1.23, 1.77)
Manganese	1.27 (0.94, 1.72)	1.39 (1.03, 1.86)	1.47 (1.13, 1.92)
Zinc	0.50 (0.33, 0.76)	0.47 (0.30, 0.73)	0.41 (0.25, 0.68)
Copper	1.00 (0.93, 1.06)	0.99 (0.93, 1.06)	0.99 (0.93, 1.06)
Iron	1.19 (0.90, 1.58)	1.28 (0.97, 1.68)	1.28 (1.00, 1.68)
Aluminum	1.23 (0.91, 1.67)	1.28 (0.99, 1.64)	1.25 (0.93, 1.69)
Chromium	0.97 (0.85, 1.10)	0.97 (0.85, 1.11)	0.92 (0.76, 1.13)
Cadmium	1.15 (0.86, 1.53)	1.16 (0.85, 1.58)	1.12 (0.80, 1.58)
Selenium	1.32 (0.94, 1.66)	1.34 (1.09, 1.64)	1.29 (1.03, 1.61)
Fluorine	0.70 (0.51, 0.97)	0.68 (0.49, 0.93)	0.67 (0.47, 0.95)
Sulfur tetraoxide	1.44 (1.02, 2.03)	1.49 (1.09, 2.02)	1.51 (1.10, 2.06)
Chlorine	1.26 (1.11, 1.43)	1.25 (1.09, 1.43)	1.25 (1.10, 1.42)
Nitrate nitrogen	1.52 (1.05, 2.21)	1.58 (1.14, 2.20)	1.65 (1.14, 2.37)
Potential of hydrogen	0.83 (0.61, 1.14)	0.79 (0.56, 1.10)	0.77 (0.55, 1.07)

Model 1 adjusted for age, sex, and education. Model 2 was further adjusted for BMI, annual household income, current smoking status, current alcohol consumption status, current tea consumption, medical history of stroke, diabetes, hypertension, cancer, and dyslipidemia. Model 3 further adjusted for current vegetable consumption, current fruit consumption, current seafood consumption, current freshwater product consumption, current marine product consumption, current meat consumption, current red meat consumption, and current white meat consumption. * HRs were calculated based on one standard deviation (SD) increase in each element

The associations between disinfectants and IBD were higher in older females, higher-income participants, and participants with relatively lower education levels. With 1 SD increase in long-term exposure to selenium, the risk for IBD increased by 40% (*HR*: 1.40, 95%: 1.07–1.81) in the older participants and 6% (*HR*: 1.06, 95%: 0.77–1.48), 36% (*HR*: 1.36, 95%: 1.07–1.74) in the females and 7% (*HR*: 1.07, 95%: 0.72–1.60) in males, 32% (*HR*: 1.32, 95%: 1.04–1.68) for the high-income participants and 12% (*HR*: 1.12, 95%: 0.61–2.06) for the lower group, and 44% (*HR*: 1.44, 95%: 1.13–1.83) for the primary school and below, while 3% (*HR*: 1.03, 95%: 0.71–1.50) for the participants with middle school and above education. Similar results were found in the stratified analyses of the associations

Table 4 Subgroup analysis for the prospective association between metal elements and IBD

	Mercury	Manganese	Zinc	Copper	Iron	Aluminum	Chromium	Cadmium
Age								
< 55	1.78 (1.32, 2.39)	1.60 (0.98, 2.63)	0.21 (0.06, 0.72)	1.10 (1.04, 1.16)	1.29 (0.74, 2.24)	0.89 (0.54, 1.47)	0.88 (0.57, 1.34)	1.06 (0.77, 1.45)
55 ~	1.40 (1.09, 1.79)	1.45 (1.14, 1.84)	0.45 (0.26, 0.79)	0.97 (0.94, 1.00)	1.28 (0.94, 1.73)	1.30 (1.04, 1.63)	0.98 (0.64, 1.51)	1.17 (0.86, 1.59)
Sex								
Male	1.36 (0.89, 2.10)	1.16 (0.68, 2.00)	0.63 (0.28, 1.40)	0.97 (0.93, 1.01)	1.12 (0.66, 1.90)	1.18 (0.83, 1.69)	-	0.87 (0.56, 1.36)
Female	1.55 (1.25, 1.91)	1.53 (1.20, 1.96)	0.33 (0.17, 0.65)	1.00 (0.97, 1.03)	1.35 (0.98, 1.85)	1.25 (0.94, 1.66)	0.98 (0.72, 1.35)	1.21 (0.93, 1.56)
Income								
< 1400$	1.04 (0.59, 1.86)	1.38 (1.03, 1.86)	0.82 (0.42, 1.60)	0.94 (0.88, 1.00)	1.43 (0.91, 2.24)	1.33 (0.83, 2.15)	-	0.87 (0.41, 1.84)
140 0$ ~	1.65 (1.33, 2.04)	1.50 (1.10, 2.03)	0.24 (0.11, 0.53)	1.00 (0.97, 1.02)	1.17 (0.83, 1.66)	1.21 (0.91, 1.60)	0.93 (0.68, 1.27)	1.18 (0.92, 1.51)
Education								
Primary and below	1.37 (0.96, 1.95)	1.38 (1.07, 1.79)	0.40 (0.22, 0.70)	0.96 (0.94, 0.99)	1.17 (0.86, 1.61)	1.26 (0.99, 1.61)	1.00 (0.65, 1.53)	1.25 (0.95, 1.66)
Middle and above	1.78 (1.32, 2.39)	2.05 (1.37, 3.07)	0.53 (0.17, 1.58)	1.04 (1.00, 1.09)	1.77 (1.02, 3.07)	1.11 (0.71, 1.73)	0.87 (0.57, 1.32)	0.96 (0.67, 1.37)
Smoking status								
Never	1.98 (1.19, 3.31)	1.59 (1.00, 2.52)	0.72 (0.22, 2.39)	0.92 (0.86, 0.99)	2.19 (1.19, 4.06)	1.37 (0.67, 2.80)	-	1.23 (0.90, 1.68)
Current	0.94 (0.57, 1.57)	1.12 (0.94, 1.33)	1.02 (0.80, 1.31)	0.96 (0.90, 1.03)	1.07 (0.58, 1.99)	0.97 (0.80, 1.18)	0.80 (0.59, 1.09)	0.92 (0.67, 1.25)
Former	1.45 (1.19, 1.78)	1.43 (1.10, 1.85)	0.39 (0.22, 0.68)	1.00 (0.97, 1.02)	1.18 (0.86, 1.61)	1.22 (0.95, 1.57)	0.96 (0.70, 1.30)	1.11 (0.86, 1.44)
Alcohol drinking								
Never	1.08 (0.90, 1.31)	1.25 (0.98, 1.58)	0.83 (0.48, 1.44)	0.99 (0.97, 1.02)	1.13 (0.85, 1.49)	1.07 (0.84, 1.35)	0.89 (0.66, 1.22)	0.97 (0.77, 1.22)
Current	1.05 (0.87, 1.27)	1.10 (0.85, 1.44)	1.39 (0.80, 2.41)	-	0.85 (0.64, 1.12)	0.71 (0.43, 1.16)	0.95 (0.69, 1.29)	0.91 (0.72, 1.15)
Former	1.51 (1.24, 1.82)	1.45 (1.14, 1.84)	0.42 (0.24, 0.73)	0.99 (0.97, 1.02)	1.28 (0.97, 1.69)	1.23 (0.97, 1.56)	0.92 (0.68, 1.26)	1.13 (0.89, 1.42)
Tea drinking								
Never	1.54 (1.27, 1.87)	1.50 (1.18, 1.89)	0.38 (0.20, 0.70)	0.99 (0.97, 1.02)	1.35 (1.01, 1.80)	1.25 (0.97, 1.61)	0.82 (0.53, 1.27)	1.11 (0.88, 1.41)
Current	-	-	1.03 (0.45, 2.36)	0.94 (0.82, 1.07)	0.25 (0.04, 1.52)	0.97 (0.34, 2.78)	1.27 (0.76, 2.14)	1.23 (0.52, 2.95)
Former	0.97 (0.80, 1.18)	1.15 (0.81, 1.63)	1.08 (0.57, 2.01)	0.84 (0.82, 0.86)	1.21 (0.80, 1.82)	1.10 (0.86, 1.42)	-	1.09 (0.53, 2.22)
BMI								
Normal	1.37 (1.06, 1.78)	1.49 (1.15, 1.93)	0.43 (0.23, 0.82)	0.99 (0.96, 1.02)	1.30 (0.91, 1.85)	1.28 (1.07, 1.53)	1.02 (0.74, 1.39)	1.20 (0.89, 1.61)
Underweight	-	1.31 (0.69, 2.47)	0.72 (0.17, 3.13)	0.96 (0.88, 1.06)	1.24 (0.38, 4.07)	0.78 (0.33, 1.88)	-	-
Overweight	1.69 (1.20, 2.39)	1.48 (0.95, 2.31)	0.33 (0.10, 1.14)	0.99 (0.96, 1.02)	1.27 (0.76, 2.11)	1.30 (0.78, 2.16)	-	1.03 (0.72, 1.47)
Obesity	-	0.30 (0.20, 0.44)	0.21 (0.16, 0.28)	1.03 (0.88, 1.22)	1.11 (0.94, 1.31)	0.57 (0.45, 0.72)	-	1.44 (1.25, 1.66)

Model adjusted for age, sex, and education, BMI, annual household income, current smoking status, current alcohol consumption status, current tea consumption, medical history of stroke, diabetes, hypertension, cancer, and dyslipidemia, current vegetable consumption, current fruit consumption, current seafood consumption, current freshwater product consumption, current marine product consumption, current meat consumption, current red meat consumption, and current white meat consumption. "-": the aHRs were omitted due to a few observations between fluorine, sulfur tetraoxide, chlorine, nitrate nitrogen, and IBD (Table 5).

We found that the associations between metal elements, disinfectants, and IBD were higher in participants who never drank tea. With a 1 SD increase in long-term exposure to manganese, the risk for IBD increased by 50% (*HR*: 1.50, 95%: 1.18–1.89) in the participants who never drank tea and 15% (*HR*: 1.15, 95%: 0.81–1.63) in the participants who ever drank tea. Similar results were observed for other metal elements and disinfectants (Tables 4 and 5).

We found significant modification effects on the associations between metal elements, nonmetal elements, and IBD between different diet groups. Long-term exposure to manganese was a significant risk factor for IBD for participants who ate fewer vegetables, fruits, marine products (seafood, freshwater products), and meat (red meat, white meat). The association between zinc, fluorine, and IBD was higher in participants who ate fewer vegetables, fruits, marine products (seafood, freshwater products), and meat (red meat, white meat). One SD increase in long-term exposure to aluminum, the risk for IBD increased by 38% (*HR*: 1.38, 95%: 1.16–1.64) for those who eat fewer fruit, while aluminum served as a protective factor for participants who eat more fruit (*HR*: 0.41, 95%: 0.17–0.96). The association between selenium and IBD was higher in participants who ate fewer vegetables, fewer fruits, and more marine products (seafood and freshwater) and meat (red meat, white meat) (Fig. 2).

Sensitive analyses showed that the associations between the majority of metal elements, disinfectants in drinking water, and IBD still exist. In contrast, the associations between long-term selenium intake and IBD were not

Table 5 Subgroup analysis for the prospective association between disinfectants and IBD

	Selenium	Fluorine	Sulfur tetraoxide	Chlorine	Nitrate nitrogen	Potential of hydrogen
Age						
< 55	1.06 (0.77, 1.48)	0.60 (0.44, 0.82)	1.41 (1.01, 1.98)	1.27 (1.16, 1.39)	1.60 (1.07, 2.40)	1.00 (0.60, 1.67)
55 ~	1.40 (1.07, 1.81)	0.69 (0.54, 0.89)	1.56 (1.24, 1.97)	1.25 (1.16, 1.35)	1.68 (1.27, 2.23)	0.69 (0.47, 1.03)
Sex						
Male	1.07 (0.72, 1.60)	0.77 (0.50, 1.17)	1.09 (0.66, 1.81)	1.29 (0.97, 1.72)	1.25 (0.75, 2.07)	0.84 (0.42, 1.68)
Female	1.36 (1.07, 1.74)	0.65 (0.51, 0.82)	1.66 (1.36, 2.03)	1.25 (1.17, 1.34)	1.84 (1.41, 2.40)	0.74 (0.52, 1.07)
Income						
< 140 0$	1.12 (0.61, 2.06)	0.83 (0.50, 1.39)	1.61 (0.99, 2.61)	1.60 (1.00, 2.54)	1.75 (1.05, 2.94)	0.43 (0.24, 0.77)
1400$ ~	1.32 (1.04, 1.68)	0.63 (0.50, 0.79)	1.49 (1.20, 1.85)	1.24 (1.17, 1.32)	1.63 (1.24, 2.13)	0.94 (0.67, 1.33)
Education						
Primary and below	1.44 (1.13, 1.83)	0.69 (0.54, 0.88)	1.62 (1.30, 2.01)	1.25 (1.17, 1.34)	1.75 (1.32, 2.31)	0.83 (0.59, 1.18)
Middle and above	1.03 (0.71, 1.50)	0.64 (0.43, 0.95)	1.31 (0.89, 1.92)	1.26 (1.09, 1.46)	1.48 (0.97, 2.27)	0.59 (0.22, 1.61)
Smoking status						
Never	0.98 (0.54, 1.78)	0.50 (0.30, 0.82)	2.09 (1.22, 3.56)	3.01 (1.32, 6.85)	2.72 (1.28, 5.81)	0.73 (0.18, 3.00)
Current	0.91 (0.50, 1.66)	0.98 (0.59, 1.62)	1.02 (0.60, 1.75)	1.05 (0.46, 2.38)	1.04 (0.84, 1.28)	0.95 (0.23, 3.93)
Former	1.33 (1.06, 1.66)	0.71 (0.56, 0.89)	1.47 (1.19, 1.80)	1.23 (1.16, 1.32)	1.57 (1.23, 2.01)	0.78 (0.56, 1.08)
Alcohol drinking						
Never	1.03 (0.82, 1.28)	0.89 (0.71, 1.10)	1.13 (0.93, 1.36)	1.13 (1.06, 1.20)	1.15 (0.92, 1.45)	0.92 (0.66, 1.28)
Current	0.82 (0.65, 1.02)	1.04 (0.77, 1.40)	1.18 (0.98, 1.42)	1.16 (0.79, 1.72)	1.18 (0.81, 1.71)	0.88 (0.64, 1.23)
Former	1.29 (1.03, 1.61)	0.68 (0.54, 0.84)	1.52 (1.26, 1.83)	1.26 (1.18, 1.34)	1.66 (1.32, 2.09)	0.77 (0.55, 1.07)
Tea drinking						
Never	1.28 (1.02, 1.62)	0.66 (0.52, 0.82)	1.55 (1.29, 1.86)	1.26 (1.18, 1.34)	1.71 (1.35, 2.16)	0.76 (0.53, 1.07)
Current	1.34 (0.51, 3.53)	1.25 (0.44, 3.56)	1.15 (0.40, 3.30)	0.86 (0.30, 2.42)	1.12 (0.38, 3.25)	0.98 (0.70, 1.38)
Former	1.12 (0.89, 1.41)	0.88 (0.54, 1.43)	1.33 (1.10, 1.59)	1.14 (1.07, 1.21)	1.25 (0.99, 1.57)	1.01 (0.71, 1.43)
BMI						
Normal	1.38 (1.06, 1.80)	0.68 (0.53, 0.87)	1.44 (1.12, 1.85)	1.24 (1.13, 1.35)	1.59 (1.20, 2.10)	0.74 (0.49, 1.12)
Underweight	0.96 (0.39, 2.36)	1.75 (0.71, 4.34)	1.29 (0.47, 3.53)	0.95 (0.44, 2.04)	1.23 (0.44, 3.42)	0.42 (0.19, 0.93)
Overweight	1.12 (0.78, 1.60)	0.63 (0.40, 0.98)	1.66 (1.16, 2.38)	1.27 (1.14, 1.42)	1.80 (1.11, 2.91)	0.92 (0.49, 1.72)
Obesity	1.32 (1.10, 1.58)	0.42 (0.35, 0.51)	2.68 (2.29, 3.13)	8.57 (5.93, 12.39)	4.13 (3.39, 5.03)	1.04 (0.88, 1.22)

Model adjusted for age, sex, education, BMI, annual household income, current smoking status, current alcohol consumption status, current tea consumption, medical history of stroke, diabetes, hypertension, cancer, dyslipidemia, current vegetable consumption, current fruit consumption, current seafood consumption, current freshwater product consumption, current marine product consumption, current meat consumption, current red meat consumption, and current white meat consumption

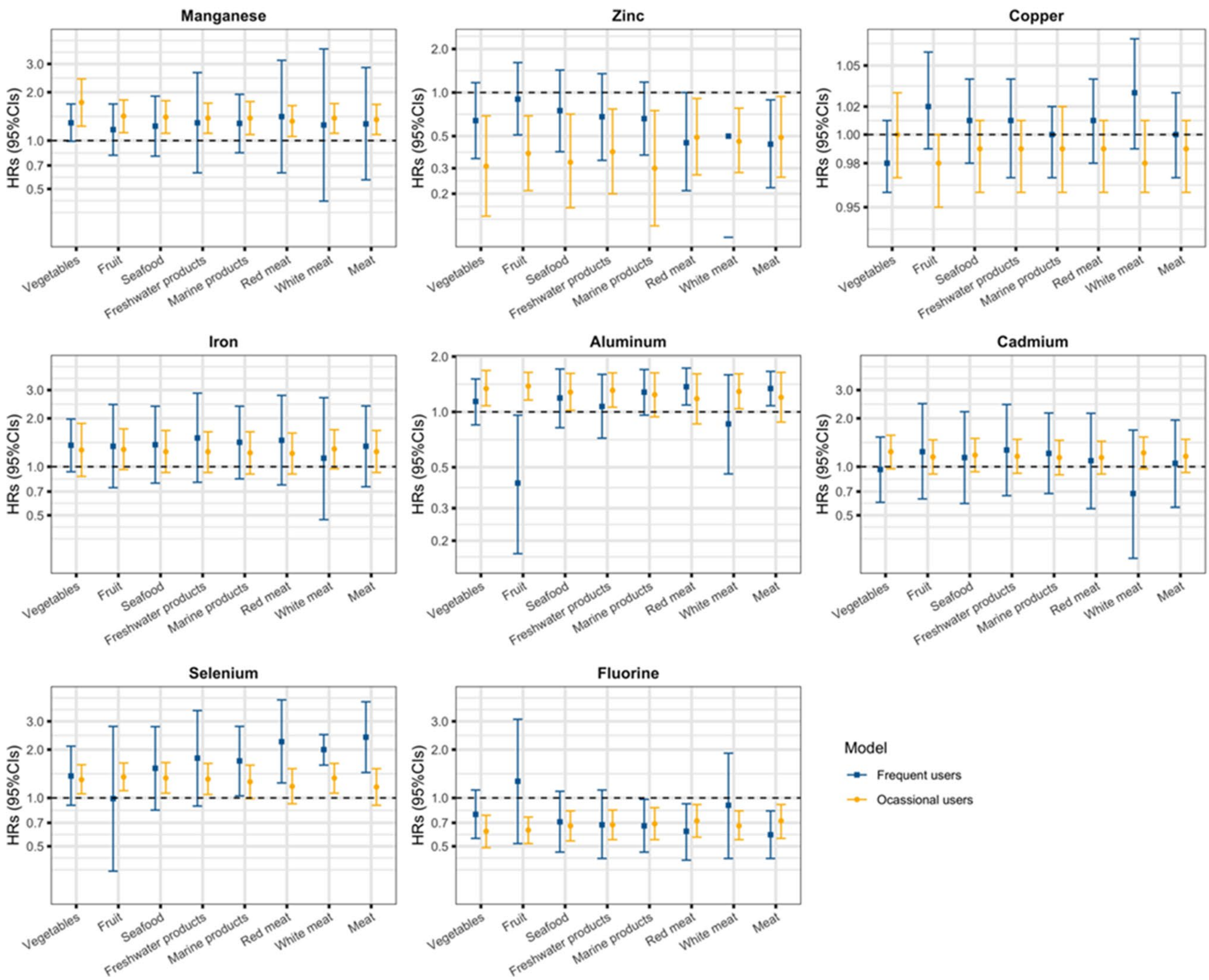

Fig. 2 The moderating effect of food consumption on the prospective associations between metal elements and IBD. Model adjusted for age, sex, education, BMI, annual household income, current smoking status, current alcohol consumption status, current tea consumption, medical history of stroke, diabetes, hypertension, cancer, dyslipidemia, current vegetable consumption, current fruit consumption, current seafood consumption, current freshwater product consumption, current marine product consumption, current meat consumption, current red meat consumption, and current white meat consumption

significant when adjusted for other pollutants (Supplement Table 2).

Discussion

In this prospective cohort study, 46 IBD cases were identified from 22,824 participants during 5.24 follow-up years with a higher incidence rate than the average level in Asia (Park and Cheon 2021). We have shown that long-term exposure to manganese, mercury, selenium, sulfur tetroxide, chlorine, and nitrate nitrogen from drinking water was associated with higher risk of IBD over follow-up. In addition, long-term exposure to zinc and fluorine from drinking water was associated with lower risk of IBD. The associations were more pronounced in females, high-income residents, and participants with lower education levels. In addition, we identified the moderating effects of diets on the relationships. Improving drinking water quality may alleviate the disease burden of IBD, especially in countries progressing into a high prevalence stage of IBD.

The underlying mechanisms underlying the relationship between metals and disinfectants from drinking water and risk of IBD are unknown. Hypotheses are that metals and disinfectants absorbed through gastrointestinal macro, and transported through the blood to various tissues (Engwa et al. 2019). Exposure to heavy metals alters the innate and adaptive immune systems by inducing inflammatory reactions (Anka et al 2022). Heavy metal exposure can also inhibit the growth of intestinal flora and lead to dysbiosis of intestinal flora (Jin et al. 2017). The absorption of mercury in the intestine inhibits the production of digestive enzymes, affects the work of digestive enzymes, disrupts the intestinal flora, causes immune-mediated reactions, and increases the risk of IBD (Vojdani et al. 2003; Rice et al. 2014). Long-term exposure to manganese could lead to neurotoxicity, and manganese stimulates glial cells to produce inflammatory mediators that trigger neuroinflammation (Harischandra et al. 2019). Epidemiological studies have shown that blood manganese levels are significantly higher in patients with confirmed IBD than in healthy individuals (Stochel-Gaudyn et al. 2019). Zinc is a cofactor of intestinal proteases that regulate the function of innate immune cells (Lahiri and Abraham 2014; Ananthakrishnan et al. 2018). Zinc inhibits the transcription of inflammatory mediators and is essential for autophagy and bacterial clearance (El-Tawil 2012). Zinc deficiency decreases the integrity of the cantorial barrier, and epidemiological studies have shown a significant negative association between a high zinc diet and the prevalence of IBD in women (Ananthakrishnan et al. 2015).

Although the relationship was not significant, the present study suggests that iron, aluminum, and cadmium may be risk factors for the development of IBD. A prospective Norwegian study found that iron in drinking water was associated with an increased risk of IBD (Aamodt et al. 2008). Excessive iron accumulation increases metabolic oxidative stress and contributes to cellular mutations and death (Wang et al. 2019). The increase in iron stimulates bacterial virulence, which triggers the immune response disorders (Hantke et al.). Previous studies pointed out that aluminum alters its pathogenicity and host response to infection by entering mycobacteria (Perl et al. 2004; Lerner 2007). Exposure to high concentrations of cadmium causes irritation and erosion of the digestive tract (Singh et al. 2012), and animal studies have shown that cadmium causes colonic inflammation in rats (Adegoke et al. 2017). More prospective cohort and experimental studies are needed to explore the underlying mechanisms.

Previous studies suggested that serum selenium levels are lower in patients with IBD than in healthy subjects, and animal studies indicated that dietary selenium supplementation might be beneficial in IBD (Vaghari-Tabari et al. 2021). However, the causal relationship is difficult to establish, and intestinal inflammation can affect the ability of IBD patients to absorb nutrients (Kudva et al. 2015). The effect of excessive selenium intake on the risk of IBD has yet to be conclusively determined. Our study showed that fluorine was associated with a lower risk of IBD. More animal and interventional studies are needed to verify the validity of the findings further. In this study, sulfur tetraoxide, chlorine, and nitrate nitrogen were significant risk factors for IBD. Sulfate reducing bacteria (SRB) levels in humans are elevated when excessive sulfur oxides are consumed in the daily diet, and SRB is a contributing factor to the development of IBD (Kushkevych et al. 2019, 2020). The level of serum nitrate nitrogen was higher in IBD patients than in healthy people, indicating the potential pathogenesis of IBD (Oudkerk Pool et al. 1995). Chlorine in disinfectants destroys bacteria in the water, but excessive chlorine enrichment may produce new compounds that trigger intestinal inflammation and human immune responses (Li and Mitch 2018).

In the current study, we further suggested that a higher association between exposure to metals such as mercury and manganese and the development of IBD was more pronounced in females and high-income residents. In addition, the associations between disinfectants and IBD were higher in older individuals, females, higher-income participants, and participants with lower education levels. The potential explanations for the findings include in vivo exposure level and health services utilization. Earlier studies found that higher income was more prevalent in IBD patients (Lakatos 2009; Hu et al. 2014), with higher income people tending to consume more Western food (high fat food) (Ananthakrishnan et al. 2018). Improving drinking water quality might reduce the incidence of IBD, especially in vulnerable groups such as women, older adults, and people with low education levels. We recommend implementing a dynamic update mechanism for drinking water standards that considers the latest research on the link between drinking water and health. Further prospective studies are necessary to generate stronger evidence that can guide ongoing improvements in Chinese drinking water standards (Supplement Table 3).

We found that vegetables and fruits significantly modulate the relationship between metallic and nonmetallic elements and IBD. Numerous studies have shown that fruits and vegetables are significant protective factors for the development of IBD (Hansen et al. 2011). Soluble fiber from fruits and vegetables inhibits the transcription of inflammatory mediators and maintains the integrity of the epithelial barrier (Galvez et al. 2005; Rose et al. 2007). For meat and fish, which are rich in protein, total protein intake is positively associated with IBD development (Jantchou et al. 2010). The results of this study further support the protective effect of vegetables and fruits on IBD. Increasing the intake of vegetables and fruits in the daily diet and consuming moderate amounts of meat and aquatic products has a potential impact on reducing the development of IBD.

Our study results should be interpreted with several limitations. First, exposures to metals and disinfectants in our study were at the regional level rather than the individual level. Even though we used the measurement values from the nearest tap water pipeline from the participants' residential addresses as the surrogate of the individual exposure level, exposure levels may still vary across the drinking habits and the volume. Second, we could not discriminate the effects of exposures on the onset of UC and CD due to the limited number of IBD cases. Third, due to elderly participant nature of this study, our findings might not be generalizable to the general population. In terms of strengths, this study is the first prospective study to examine the association between metal and disinfectant exposure and the risk of IBD in low- and middle-income countries. The hospital-based clinical diagnosis of IBD and professional exposure measurement alleviated the measurement bias. Finally, this study followed strict quality control methods in data collection, collation, and data analysis to ensure the scientific validity of the results.

Conclusions

In conclusion, this study provides novel evidence that long-term exposure to higher metal elements and disinfectants levels in drinking water increases the risk of IBD. Given the growing burden of IBD, our study sheds light on tailored public health policies for improving drinking water standards to alleviate IBD impairment.

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Data availability Please get in touch with the corresponding author for more information.

Declarations

Consent to participate Written informed consent from participants was obtained before they completed the questionnaires. All methods were carried out in accordance with relevant guidelines and regulations of Declaration of Helsinki.

Consent for publication All the authors have reviewed and approved the manuscript for publication.

Conflict of interest The authors declare no competing interests.

References

Aamodt G, Bukholm G, Jahnsen J, Moum B, Vatn MH (2008) The association between water supply and inflammatory bowel disease based on a 1990–1993 cohort study in southeastern Norway. Am J Epidemiol 168(9):1065–1072

Abegunde AT, Muhammad BH, Bhatti O, Ali T (2016) Environmental risk factors for inflammatory bowel diseases: evidence based literature review. World J Gastroenterol 22(27):6296–6317

Abubakar I, Myhill DJ, Hart AR, Lake IR, Harvey I, Rhodes JM et al (2007) A case-control study of drinking water and dairy products in Crohn's disease–further investigation of the possible role of Mycobacterium avium paratuberculosis. Am J Epidemiol 165(7):776–783

Adegoke A, Salami A, Olaleye S (2017) Cadmium exacerbates acetic acid induced experimental colitis in rats. J Exp Biol 7(5):27

Alatab S, Sepanlou SG, Ikuta K, Vahedi H, Bisignano C, Safiri S et al (2020) The global, regional, and national burden of inflammatory bowel disease in 195 countries and territories, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet Gastroenterol Hepatol 5(1):17–30

Ananthakrishnan AN, Khalili H, Song M, Higuchi LM, Richter JM, Chan AT (2015) Zinc intake and risk of Crohn's disease and ulcerative colitis: a prospective cohort study. Int J Epidemiol 44(6):1995–2005

Ananthakrishnan AN, Bernstein CN, Iliopoulos D, Macpherson A, Neurath MF, Ali RAR et al (2018) Environmental triggers in IBD: a review of progress and evidence. Nat Rev Gastroenterol Hepatol 15(1):39–49

Anka AU, Usman AB, Kaoje AN, Kabir RM, Bala A, KazemArki M (2022) Potential mechanisms of some selected heavy metals in the induction of inflammation and autoimmunity. Eur J Inflamm 20:1721727X221122719

Baron S, Turck D, Leplat C, Merle V, Gower-Rousseau C, Marti R et al (2005) Environmental risk factors in paediatric inflammatory bowel diseases: a population based case control study. Gut 54(3):357–363

Baumgart DC, Carding SR (2007) Inflammatory bowel disease: cause and immunobiology. Lancet 369(9573):1627–40

Burisch J, Pedersen N, Cukovic-Cavka S, Turk N, Kaimakliotis I, Duricova D, Bortlik M et al (2014) Environmental factors in a population-based inception cohort of inflammatory bowel disease patients in Europe—an ECCO-EpiCom study. J Crohns Colitis 8(7):607–616

El-Tawil AM (2012) Zinc supplementation tightens leaky gut in Crohn's disease. Inflamm Bowel Dis 18(2):E399

Engwa GA, Ferdinand PU, Nwalo FN, Unachukwu MN (2019) Mechanism and health effects of heavy metal toxicity in humans. In: Karcioglu O, Arslan B (eds) Poisoning in the modern world-new tricks for an old dog?, vol 10. Intechopen, London, pp 70–90

Forbes JD, Van Domselaar G, Sargent M, Green C, Springthorpe S, Krause DO, Bernstein CN (2016) Microbiome profiling of drinking water in relation to incidence of inflammatory bowel disease. Can J Microbiol 62(9):781–793

Galvez J, Rodríguez-Cabezas ME, Zarzuelo A (2005) Effects of dietary fiber on inflammatory bowel disease. Mol Nutr Food Res 49(6):601–608

Hansen TS, Jess T, Vind I, Elkjaer M, Nielsen MF, Gamborg M, Munkholm P (2011) Environmental factors in inflammatory bowel disease: a case-control study based on a Danish inception cohort. J Crohns Colitis 5(6):577–584

Harischandra DS, Ghaisas S, Zenitsky G, Jin H, Kanthasamy A, Anantharam V, Kanthasamy AG (2019) Manganese-induced neurotoxicity: new insights into the triad of protein misfolding, mitochondrial impairment, and neuroinflammation. Front Neurosci 13:654

Hu D, Ren J, Wang G, Gu G, Liu S, Wu X et al (2014) Geographic mapping of Crohn's disease and its relation to affluence in Jiangsu province, an eastern coastal province of china. Gastroenterol Res Pract 2014:590467

Jädert C, Petersson J, Massena S, Ahl D, Grapensparr L, Holm L et al (2012) Decreased leukocyte recruitment by inorganic nitrate and nitrite in microvascular inflammation and NSAID-induced intestinal injury. Free Radical Biol Med 52(3):683–692

Jairath V, Feagan BG (2020) Global burden of inflammatory bowel disease. Lancet Gastroenterol Hepatol 5(1):2–3

Jantchou P, Morois S, Clavel-Chapelon F, Boutron-Ruault MC, Carbonnel F (2010) Animal protein intake and risk of inflammatory bowel disease: the E3N prospective study. Am J Gastroenterol 105(10):2195–2201

Jin Y, Wu S, Zeng Z, Fu Z (2017) Effects of environmental pollutants on gut microbiota. Environ Pollut 222:1–9

Jostins L, Ripke S, Weersma RK, Duerr RH, McGovern DP, Hui KY et al (2012) Host–microbe interactions have shaped the genetic architecture of inflammatory bowel disease. Nature 491(7422):119–124

Jowett SL, Seal CJ, Pearce MS, Phillips E, Gregory W, Barton JR, Welfare MR (2004) Influence of dietary factors on the clinical course of ulcerative colitis: a prospective cohort study. Gut 53(10):1479–1484

Kaplan GG, Windsor JW (2021) The four epidemiological stages in the global evolution of inflammatory bowel disease. Nat Rev Gastroenterol Hepatol 18(1):56–66

Klement E, Lysy J, Hoshen M, Avitan M, Goldin E, Israeli E (2008) Childhood hygiene is associated with the risk for inflammatory bowel disease: a population-based study. Am J Gastroenterol 103(7):1775–1782

Kudva AK, Shay AE, Prabhu KS (2015) Selenium and inflammatory bowel disease. Am J Physiol Gastrointest Liver Physiol 309(2):G71–G77

Kushkevych I, Leščanová O, Dordević D, Jančíková S, Hošek J, Vítězová M et al (2019) The sulfate-reducing microbial communities and meta-analysis of their occurrence during diseases of small–large intestine axis. J Clin Med 8(10):1656

Kushkevych I, Castro Sangrador J, Dordević D, Rozehnalová M, Černý M, Fafula R, Vítězová M, Rittmann SKR (2020) Evaluation of physiological parameters of intestinal sulfate-reducing bacteria isolated from patients suffering from IBD and healthy people. J Clin Med 9(6):1920

Lahiri A, Abraham C (2014) Activation of pattern recognition receptors up-regulates metallothioneins, thereby increasing intracellular accumulation of zinc, autophagy, and bacterial clearance by macrophages. Gastroenterology 147(4):835–846

Lakatos PL (2009) Environmental factors affecting inflammatory bowel disease: have we made progress? Dig Dis 27(3):215–225

Lerner A (2007) Aluminum is a potential environmental factor for Crohn's disease induction: extended hypothesis. Ann N Y Acad Sci 1107:329–345

Li XF, Mitch WA (2018) Drinking water disinfection byproducts (DBPs) and human health effects: multidisciplinary challenges and opportunities. Environ Sci Technol 52(4):1681–1689

Li T, Yu Z, Xu L, Wu Y, Yu L, Yang Z (2022) Residential greenness, air pollution, and incident ischemic heart disease: a prospective cohort study in China. Sci Total Environ 838:155881

Mahid SS, Minor KS, Soto RE, Hornung CA, Galandiuk S (2006) Smoking and inflammatory bowel disease: a meta-analysis. Mayo Clin Proc 81(11):1462–1471

Ng SC, Shi HY, Hamidi N, Underwood FE, Tang W, Benchimol EI et al (2017) Worldwide incidence and prevalence of inflammatory bowel disease in the 21st century: a systematic review of population-based studies. Lancet 390(10114):2769–2778

Oudkerk Pool M, Bouma G, Visser JJ, Kolkman JJ, Tran DD, Meuwissen SG, Peña AS (1995) Serum nitrate levels in ulcerative colitis and Crohn's disease. Scand J Gastroenterol 30(8):784–788

Ozenne B, Sørensen AL, Scheike T, Torp-Pedersen C, Gerds TA (2017) riskRegression: predicting the risk of an event using Cox regression models. R Journal 9(2):440–460

Park J, Cheon JH (2021) Incidence and prevalence of inflammatory bowel disease across Asia. Yonsei Med J 62(2):99–108

Perl DP, Fogarty U, Harpaz N, Sachar DB (2004) Bacterial-metal interactions: the potential role of aluminum and other trace elements in the etiology of Crohn's disease. Inflamm Bowel Dis 10(6):881–883

Piovani D, Danese S, Peyrin-Biroulet L, Bonovas S (2020) Inflammatory bowel disease: estimates from the global burden of disease 2017 study. Aliment Pharmacol Ther 51(2):261–270

Piovani D, Danese S, Peyrin-Biroulet L, Nikolopoulos GK, Lytras T, Bonovas S (2019) Environmental risk factors for inflammatory bowel diseases: an umbrella review of meta-analyses. Gastroenterology 157(3):647–659. e4

Ramos GP, Papadakis KA (2019) Mechanisms of disease: inflammatory bowel diseases. Mayo Clin Proc 94(1):155–165

Rice KM, Walker EM Jr, Wu M, Gillette C, Blough ER (2014) Environmental mercury and its toxic effects. J Prev Med Public Health 47(2):74–83

Rose DJ, DeMeo MT, Keshavarzian A, Hamaker BR (2007) Influence of dietary fiber on inflammatory bowel disease and colon cancer: importance of fermentation pattern. Nutr Rev 65(2):51–62

Singh P, Mogra P, Bano H, Sankhla V, Deora K, Barolia S, Javeria S (2012) Protective and preventive effects of curcumin against cadmium chloride induced gastrointestinal toxicity in Swiss albino mice. World J Sci Technol 2(12):10–17

Stochel-Gaudyn A, Fyderek K, Kościelniak P (2019) Serum trace elements profile in the pediatric inflammatory bowel disease progress evaluation. J Trace Elem Med Biol 55:121–126

Vaghari-Tabari M, Jafari-Gharabaghlou D, Sadeghsoltani F, Hassanpour P, Qujeq D, Rashtchizadeh N, Ghorbanihaghjo A (2021) Zinc and selenium in inflammatory bowel disease: trace elements with key roles? Biol Trace Elem Res 199(9):3190–3204

Vojdani A, Pangborn JB, Vojdani E, Cooper EL (2003) Infections, toxic chemicals and dietary peptides binding to lymphocyte receptors and tissue enzymes are major instigators of autoimmunity in autism. Int J Immunopathol Pharmacol 16(3):189–199

Wang W, Green M, Choi JE, Gijón M, Kennedy PD, Johnson JK et al (2019) CD8+ T cells regulate tumour ferroptosis during cancer immunotherapy. Nature 569(7755):270–274

Yamamoto T, Nakahigashi M, Saniabadi AR (2009) Review article: diet and inflammatory bowel disease–epidemiology and treatment. Aliment Pharmacol Ther 30(2):99–112

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