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# Long-Term Exposure to Nitrate and Trihalomethanes in Drinking Water and Gastric Cancer: A Multicase–Control Study in Spain (MCC-Spain)

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**Background:** Disinfection byproducts and *N*-nitroso compounds (NOC) formed endogenously after nitrate ingestion have been shown to be carcinogenic in animal studies, but epidemiological evidence is limited, especially in relation to gastric cancer.

**Objective:** We evaluated the association between drinking water exposure to nitrate and trihalomethanes (THMs) and gastric cancer in a multicase–control study conducted in Spain (MCC-Spain).

**Methods:** In 2008–2013, 254 hospital-based incident gastric cancer cases and 2,365 population-based controls were recruited, providing information on residential histories and type of water consumed. Adult lifetime average nitrate and THM levels in residences from age 18 until 2 years before the interview were estimated and linked with water consumption information to calculate waterborne ingested nitrate, brominated (Br)-THMs, and chloroform. Odds ratios (OR) and 95% confidence intervals (CI) were estimated using logistic regression, with adjustment for potential confounders. We assessed the effect modification by factors influencing endogenous NOC formation.

**Results:** Median [percentile 25th ($P_{25}$)–percentile 75 ($P_{75}$)] ($P_{25}$–$P_{75}$) lifetime waterborne ingested nitrate (mg/day), Br-THMs (μg/day), and chloroform (μg/day) were 2.7 (1.4–5.6), 3.8 (1.5–8.1), and 12.2 (4.0–23.7), respectively, in cases and 3.8 (1.8–8.5), 5.7 (2.6–19.2), and 12.9 (4.6–24.5) in controls, respectively. Adjusted OR (95% CI) for gastric cancer comparing nitrate intake >9.7 vs. ≤9.7 mg/day (percentile 80th, $P_{80}$) was 1.42 (0.88, 2.29). This association was more pronounced among participants with low consumption of vegetables [2.24 (1.02, 4.91)], vitamin C [2.10 (0.94, 4.71)], and vitamin E [2.81 (1.16, 6.78)] and among those with high consumption of alcohol [2.78 (0.98, 7.93)] or processed meat [1.91 (0.97, 3.75)]. When stratified by age, the association only remained in the >65 years of age group (median 73 years of age). OR for gastric cancer comparing Br-THM ingestion ≥ vs. 80th <80th percentile was 0.65 (0.33, 1.28) and for chloroform was 1.36 (0.87, 2.14). Comparable ORs were found for residential concentrations.

**Conclusions:** Long-term waterborne nitrate exposure below regulatory limits may increase gastric cancer risk among older adults and in those with poor dietary patterns. These findings need to be confirmed by cohort studies with larger sample sizes. https://doi.org/10.1289/EHP15039

## Introduction

Gastric cancer stands as a globally significant disease, ranking as the fifth most diagnosed malignancy worldwide.[1] Unfortunately, mortality rates from gastric cancer remain distressingly high.[1] *Helicobacter pylori* infection is the most extensively studied risk factor for gastric cancer.[2] Apart from genetic predisposition, other risk factors such as being male, older age, low socioeconomic status, smoking, alcohol consumption, processed/cured meat, and salt-preserved food including nitrite and nitrate-preserved meat intake contribute to gastric cancer, while a diet rich in fruits and vegetables may offer protection.[3,4] Conversely, the large geographic variability of gastric cancer incidence suggests the role of environmental factors in its etiology.[5]

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Nitrate and nitrite occur naturally in foods sourced from both plants and animals, are utilized as additives during meat processing, and can also be present in water. Thus, nitrate exposure mainly occurs through ingestion of food (vegetables and meat) and drinking water.[6] Although nitrate is a component of the nitrogen cycle and naturally occurs, the increasing use of nitrogen fertilizers in agriculture and intensive farming has led to increasing nitrogen levels in the water cycle[7] worldwide.

International Agency for Research on Cancer (IARC) classifies nitrate and nitrite as probable human carcinogens (group 2A) when ingested under conditions that result in endogenous nitrosation.[8] Approximately 5% of nitrate is converted to nitrite by the oral microbiome.[9] In the presence of nitrosating precursors, and with low antioxidant levels, nitrite can lead to the formation of *N*-nitroso compounds (NOCs) in the gastric acidic environment. NOCs are known to be carcinogenic,[8,10,11] and factors like heme iron in meat promote nitrosation, while antioxidants in vegetables inhibit it.[12]

Research in epidemiology reveals that nitrates affect human health differently depending on their source. Higher levels of nitrate/nitrite intake from drinking water and processed meat consumption have been linked to increased risks of developing various cancers.[13] A recent well-conducted Danish study found that while the consumption of naturally occurring animal-derived nitrate is not linked to cancer-related mortality, naturally occurring animal-derived nitrite, as well as nitrate and nitrite from additives in processed meat sources, are associated with cancer-related mortality.[13]

In epidemiological studies attempting to elucidate the relationship between nitrate exposure from drinking water and cancer, gastrointestinal cancer, including gastric cancer, has been the malignancy most consistently associated with such exposure.[14] However, in 2010, IARC concluded that there is inadequate human evidence on the carcinogenicity of nitrate in drinking water.[8] Additional research prioritizing studies examining source-dependent nitrate intakes and incorporating a precise characterization of factors influencing endogenous nitrosation (potential effect modifiers) is essential to establish stronger evidence regarding the risk of gastric cancer associated with ingested nitrate from water sources.[8]

The addition of disinfectants in drinking water to inactivate microbial pathogens leads to the generation of various disinfection byproducts (DBPs), which comprise a complex mixture of chemicals.[15] Chlorine, being the most commonly used disinfectant globally, gives rise to trihalomethanes (THMs) and haloacetic acids, which are the predominant DBPs formed following chlorination.[15] The presence of DBPs in public water systems poses potential health risks, as these chemicals can be absorbed into the body through drinking, breathing, and skin contact.[16] Laboratory testing has demonstrated the ability of various DBPs to damage DNA, while studies in animals have demonstrated their cancer-causing potential.[17,18] This has led the IARC to classify certain DBPs as potential human carcinogens.[19] Despite the evidence that THMs may contribute to carcinogenesis, there is a lack of epidemiological studies specifically exploring the association with gastric cancer.[20]

This study was set up to evaluate the association between gastric cancer and long-term exposure to nitrate and THMs in drinking water. Due to the known inhibitory capacity of antioxidants and vitamins in fruits and vegetables against endogenous nitrosation,[21–24] we further investigated the potential effect modification with high consumption of these foods and specific vitamins.

## Methods

### *Study Design and Population*

The MCC-Spain study (http://www.mccspain.org) is a multicase–control (MCC) study conducted in different provinces in Spain in 2008–2013. The design and the overall methodology have been previously described.[25] In brief, five cancer sites (breast, colorectal, leukemias, prostate, and gastric) were included in the MCC-Spain study. Cases were recruited from hospital settings, ensuring comprehensive case ascertainment in each participating hospital. Thus, cases were identified through active searches in regular visits to hospital departments and were interviewed closely after diagnosis (median of 58 d). No proxy interviews were conducted. For cases where patients had died before the interview, they were identified through registries but were not included in the study.

Incident gastric cancer was histologically confirmed by medical records (codes C16 and D00.2, according to the International Classification of Diseases, 10th revision). Information on tumor location and Lauren classification was available.

Population-based controls for the entire MCC-Spain study (common to the five types of cancers) were randomly selected from the administrative records of the primary health care centers located within hospitals' catchment areas and were frequency matched to the overall distribution of all of the cases (gastric cancer and the others) by age (in 5-y age groups), province of residence, and sex.

Inclusion criteria required participants to be 20 to 85 years old, be able to understand and answer the recruitment questionnaire, and have lived for at least 6 months in the recruitment area. The overall response rate, calculated as the ratio of subjects interviewed to the sum of subjects interviewed and refusals, was 57% for gastric cancer cases and 53% for controls. This led to the enrollment of 459 cases of gastric cancer and 3,440 controls from 10 recruitment areas: Asturias, Barcelona, Cantabria, Granada, Huelva, Leon, Madrid, Murcia, Navarra, and Valencia.

The study protocol was approved by the ethics committee at all collaborating institutions, and participants signed an informed consent form prior to enrolment. For a comprehensive list of collaborating institutions, please refer to Castano-Vinyals et al.[25]

### *Data Collection*

Study participants answered a structured, computer-assisted questionnaire administered by trained personnel in a face-to-face interview to gather information on anthropometrics (self-reported), sociodemographics, and lifestyle factors, as well as personal and family medical history. Participants provided full address, year start and stop for the residences where they lived for at least 12 months from age 18 until the time of the interview, and the type of water consumed in each residence (municipal, bottled, well, other). The amount (glasses/d) of water ingested on average at home, work, and other places was ascertained. A final section evaluating the reliability of the interview was completed by the interviewer through a closed-ended question about the perceived general quality of the interview: unsatisfactory, questionable, reliable, or high-quality. Average dietary habits corresponding to the year before the interview were collected through a self-administered semiquantitative food frequency questionnaire, including a total of 140 food items, previously validated in Spain.[26] Questionnaires used are available online (http://mccspain.org).

### *Nitrate and THM Levels in Municipal Drinking Water*

We designed a structured questionnaire aimed at water utilities, local authorities, and/or health authorities to collect drinking

water source (surface/ground water proportion) and treatment in the study areas back to 1940. In addition, available data from routine monitoring in the drinking water treatment plants and the distribution network were collected for nitrate and THMs (chloroform, bromodichloromethane, dibromochloromethane, and bromoform). Given the high number of municipalities where study subjects had lived over a lifetime and the unfeasibility to collect information from all of them, we targeted data collection among MCC study municipalities that contributed up to 80% of person-years. Furthermore, for the years 2004–2010, the Spanish National Information System on Water for Consumption (SINAC) provided centralized routine monitoring data, which included information at the water zone level introduced by water supply operators from public or private companies or municipalities and public or private laboratories. The water zone was defined as a geographical area supplied by water with a homogeneous source and treatment and whose quality in the water distribution network can be considered homogeneous. Water zone corresponded to municipality except in the case of Barcelona city, which included three different water zones that were used separately to assign THM and nitrate concentrations. We linked each postal code from the residence to the corresponding water zone. We considered all residences where participants lived for more than 1 year. The proportion of person-years by source of water nitrate exposure data across years is presented in Table S1.

The distribution of the sampling points and the sampling frequency varied greatly depending on the population served, extension of the water zone, and the year and ranged from more than once a day (e.g., Madrid), to once every 3 months or once a year in less populated areas. Measurements below the analytical limit of quantification (QL) (5% of measurements) were substituted with half the QL (QL/2).[27] If the QL was missing, we imputed half of the most frequently reported value (1.0 mg/L for nitrate). In the case of THMs, QL values were always reported for chloroform, bromodichloromethane, bromodichloromethane, and bromoform.

### *Nitrate and THM Levels in Nonmunicipal Drinking Water*

We measured nitrate in the nine most-consumed bottled water brands in Spain using ultraviolet (UV) spectrophotometry, with 0.5/0.1 mg/L detection/quantification limit. Nitrate concentrations were in the range of 2.3–15.6 mg/L.[28] THMs were previously measured in 15 popular bottled water brands in Spain through purge-and-trap and gas chromatography. Mean concentrations for chloroform, bromodichloromethane, dibromochloromethane, and bromoform were $\leq$0.1 μg/L,[29] and limits of detection were, respectively, 0.015, 0.004, 0.005, and 0.011 μg/L. When water consumed was from private wells, we used THM data from 56 measurements in different Spanish areas that were supplied by chlorinated ground water, assuming chlorination practice among private well users. Average concentrations were 0.3, 0.3, 0.8, and 1.8 μg/L for chloroform, bromodichloromethane, dibromochloromethane, and bromoform, respectively. Nitrate data in private wells were not available.

### *Estimation of Long-Term Levels in Municipal Drinking Water*

We calculated the annual average levels of nitrate and THMs at the water zone level. Total THM (TTHM) levels were calculated by adding up chloroform, bromodichloromethane, dibromochloromethane, and bromoform concentrations. Years without measurements were assigned the average of all available measurements in the water zone if the water source and treatment did not change over the years. In the case of changes in the water source and/or treatment, procedures to back-extrapolate concentrations were applied. Thus, when water source changed, since THM concentrations in surface water are generally higher than in ground sources,[30] we used surface water percentage as a weight to back extrapolate THM concentrations through linear interpolation, assuming that concentrations increased proportionately to the percentage of surface water. Likewise, water zones with changes in treatment and THM measurements were used to estimate the change percentage of THM concentrations after introducing such treatments. These percentages were applied as a weight to back-extrapolate THM concentrations in areas with changes in these specific treatments when measurements were unavailable. Before chlorination started, THM concentrations were assumed to be zero. In the case of nitrate, the ground water percentage was used as a weight to back-extrapolate concentrations using linear interpolation, assuming that nitrate levels were higher in ground water.[31] In municipalities without any nitrate measurement (covering $\sim$0.5% of the total person-years), we imputed the levels of neighboring municipalities supplied with similar ground water proportion $\pm$10%.

### *Individual Exposures in the Study Population*

***Average nitrate and THM concentrations in residential tap water.*** We used municipality and year to link municipal levels in drinking water with residential histories of study participants from age 18 to 2 years before the interview. We estimated the average concentration of nitrate (mg/L) and THMs (μg/L) for this period, henceforth referred to as "lifetime" or "long-term exposure." Generally, participants had different water zones assigned as they lived in three residences, on average, during the exposure period, with the residence at the time of interview being the longest ($\approx$ 30 years). The average proportion of missing measurements per participant during the exposure period was $\sim$14.5%. There were no important differences between provinces, except for Asturias and Leon. The mean proportions of nitrate and THMs missing measurements in Asturias were 8% and 7%, respectively, while, in Leon they were 21% and 29%.

***Average ingested nitrate and THMs.*** To calculate waterborne ingested nitrate (mg/d) and THMs (μg/d), we assigned levels in drinking water by year according to the reported water type consumed at home, including municipal (tap), bottled, and private well/other water. Nitrate and THM levels in municipal water were assigned for tap water consumption. Nitrate levels in the sampled bottled waters (range 2.3–15.6 mg/L)[28] were averaged using the sales frequency of each brand as a weight, leading to 6.1 mg/L of $NO_3^-$, which was assigned to study participants consuming bottled water. Since nitrate levels in well water were not available, waterborne ingested nitrate was considered missing for years when well water consumption was reported ($\approx$ 2%). A zero THM level was assigned to bottled water consumers according to a previous study.[29] THM values assigned for well water consumers were 0.3, 0.3, 0.8, and 1.8 μg/L for chloroform, bromodichloromethane, dibromochloromethane, and bromoform, respectively. The annual nitrate and THM estimates were averaged from age 18 to 2 years before the interview and multiplied by the average daily water intake at the residence, ascertained as the number of water glasses per day consumed on average at home (L/d, assuming 200 mL/glass). Water intakes = 0 and above the 99th percentile (4 L/day), considered implausible, were treated as missing values in the analyses.

### *Covariables*

Relevant data collected at enrollment included sex, age, education (less than primary school, primary school, secondary school, university), self-reported weight and height 1 year before the interview to compute body mass index (BMI) (kg/m$^2$), family history of gastric cancer (i.e., malignant tumors in first-degree relatives),

smoking (never, former, current), physical activity, and dietary habits including alcohol consumption. Smokers were defined as those smoking at least one cigarette/d for ≥6 months. Former smokers were defined as those who quit smoking ≥1 year before the interview. Physical activity was ascertained through open questions on any type of physical activity practiced in life, years, and frequency (h/wk), to calculate metabolic equivalents (METs) from age 16 to 2 years before the interview. Frequencies of food items in servings per day were converted to grams per day, and vitamin C and E intake was also estimated utilizing food composition tables.

### *Statistical Analysis*

From an initial sample of gastric cancer cases and controls of 3,899 (459 cases and 3,440 controls), we excluded participants from the recruitment areas and municipalities lacking data on water contaminants ($n = 367$ excluded). We further excluded individuals with nitrate or THM estimates covering <70% of the years between the age of 18 and 2 years before the interview ($n = 737$), those lacking data on the type of water consumed ($n = 57$), and those who reported no water consumption or provided implausible values ($n = 112$). Participants with interviews deemed unreliable by trained interviewers were also excluded ($n = 3$ cases). Finally, as the region of Murcia had only four controls and no cases, it was excluded to prevent biased estimates. The final sample included 2,619 participants, comprising 254 cases and 2,365 controls (Figure 1). Characteristics of the excluded participants from the study are displayed in Table S2.

Due to the differing genotoxicities of brominated THMs (Br-THMs) and chloroform, we assessed them separately.[32] Spearman correlations between tap water residential concentrations and waterborne ingested nitrate, Br-THMs (sum of bromodichloromethane, dibromochloromethane, and bromoform), and chloroform were examined. Estimated levels of nitrate (mg/L) and TTHMs, chloroform, and Br-THMs (μg/L) in drinking water at the residence and waterborne ingested level (mg/day, μg/day) were classified as below or at/above the 80th percentile, defined based on the distribution among controls.

We used unconditional logistic regression to estimate odds ratio (OR) and 95% confidence interval (CI) of gastric cancer associated with nitrate and THMs in drinking water exposure above the 80th percentile compared to below the 80th percentile. The decision to employ this cutoff point and compare two categories is driven by the restricted number of cases, the limited variability in exposure levels, and the nonlinearity of the associations (Figures S1 and S2). Nevertheless, we offer supplementary estimates derived from quartile categorizations (Table S3). The trend across quartiles reported in Table S3 was tested treating the median concentration within each category as a continuous variable in the model.

All models were adjusted for age, educational level, and recruitment area. Further adjustment included family history of gastric cancer, BMI, smoking, physical activity, alcohol consumption, meat consumption, and fruit and vegetables consumption using the categories reported in Table 1. An additional model was reported with mutual adjustments between nitrate, chloroform, and Br-THM levels. Multicollinearity was explored using the variance inflation factor (VIF). We employed stochastic regression, incorporating a random error term to accurately replicate the correlation between X and Y, for imputing missing values in meat consumption (10.9% of missing), fruit and vegetable consumption (10.9%), alcohol intake (10.9%), family history of gastric cancer (5.9%), BMI (3.9%), and physical activity (1.1%). The initial predictive model only included variables without missing data (age, sex, smoking, education, recruitment area, and case/control information), and as variables were imputed, they were subsequently incorporated as predictive variables in the following predictive models.

Based on previous findings, we conducted subgroup analyses for waterborne nitrate intake, stratifying (above and below the median among controls) by the following suspected effect modifiers: fruit consumption, vegetables consumption, vitamin C, vitamin E, processed/cured meat consumption, alcohol, smoking, sex, and age. Interaction $p$-value was obtained using the likelihood ratio test of the models with and without the multiplicative interaction term. Finally, associations accounting for localization (noncardias vs. cardias) and Lauren classification (intestinal vs diffuse) of the tumor were also explored, as these represent distinct biological and prognostic subtypes of gastric cancer that may respond differently to risk factors. All $p$-values presented are two-tailed; <0.05 was considered statistically significant. Analyses were performed using STATA version 16.0 (Stata Corp).

## Results

The recruitment area with the largest population contribution was Barcelona (34% of all subjects; $n = 883$), followed by Madrid (27%; $n = 746$), while Valencia (4.4%; $n = 114$) and Asturias (6.2%; $n = 161$) were the provinces with the lowest participant contribution. The average age was 64($\pm$11) years old for controls and 66($\pm$12) for cases. There were twice as many male cases as female cases. On average, cases had lower education, twice as often a family history of gastric cancer (first degree), a lower likelihood of being obese, engaged in lower levels of physical activity, and were more likely to have a history of alcohol consumption compared to controls. One-third of gastric cancers were noncardia. In terms of Lauren classification, 35% were intestinal type and 24% diffuse type, with the remainder being mixed or unclassified due to insufficient information (Table 1).

Median ($P_{25}$–$P_{75}$) values for average lifetime waterborne ingested nitrate (mg/day), Br-THMs (μg/day), and chloroform (μg/day) were 2.7 (1.4–5.6), 3.8 (1.5–8.1), and 12.2 (4.0–23.7), respectively, in cases, and 3.8 (1.8–8.5), 5.7 (2.6–19.2), and 12.9 (4.6–24.5) in controls (Table 1). Distribution of waterborne ingested and residential exposures of nitrate and trihalomethanes are displayed in Figure S1.

The proportion of person-years exposed to municipal, bottled, and well water consumption was ∼78%, 20%, and 2%, respectively, during the exposure window. The average water intake was 1.9 L/day for cases and 1.8 L/day for controls. Spearman correlations between residential tap water concentrations and waterborne ingested levels were moderate, rho 0.7 for nitrate, ∼0.5 for Br-THM, and 0.6 for chloroform. Likewise, Spearman correlations between residential concentration of contaminants were as follows: nitrate-chloroform, −0.3; nitrate-Br-THM, 0.8; chloroform-Br-THM, −0.3; and nitrate-total THMs, 0.6 (Figure S3).

### *Nitrate*

Exposure estimates for both residential and ingested nitrate did not appear to have a linear association with the risk of gastric cancer. Figure S2 revealed a U-shaped pattern; risk appears to decrease before increasing at ingestions of ∼15 mg/day and residential exposures of ∼10 mg/L. Considering the highest degree of OR adjustment, both lifetime average residential and waterborne ingested nitrate exposures showed positive but nonsignificant associations with gastric cancer when comparing the ≥80th vs. <80th percentile. OR (95% CI) comparing ≥10.5 vs. <10.5 mg/L of nitrate residential exposure was 1.52 (0.84, 2.73) (mean VIF, 2.2), and comparing ≥9.7 vs. <9.7 mg/day of waterborne nitrate ingestion was 1.42 (0.88, 2.29) (mean VIF, 2.7) (Table 2). The analysis

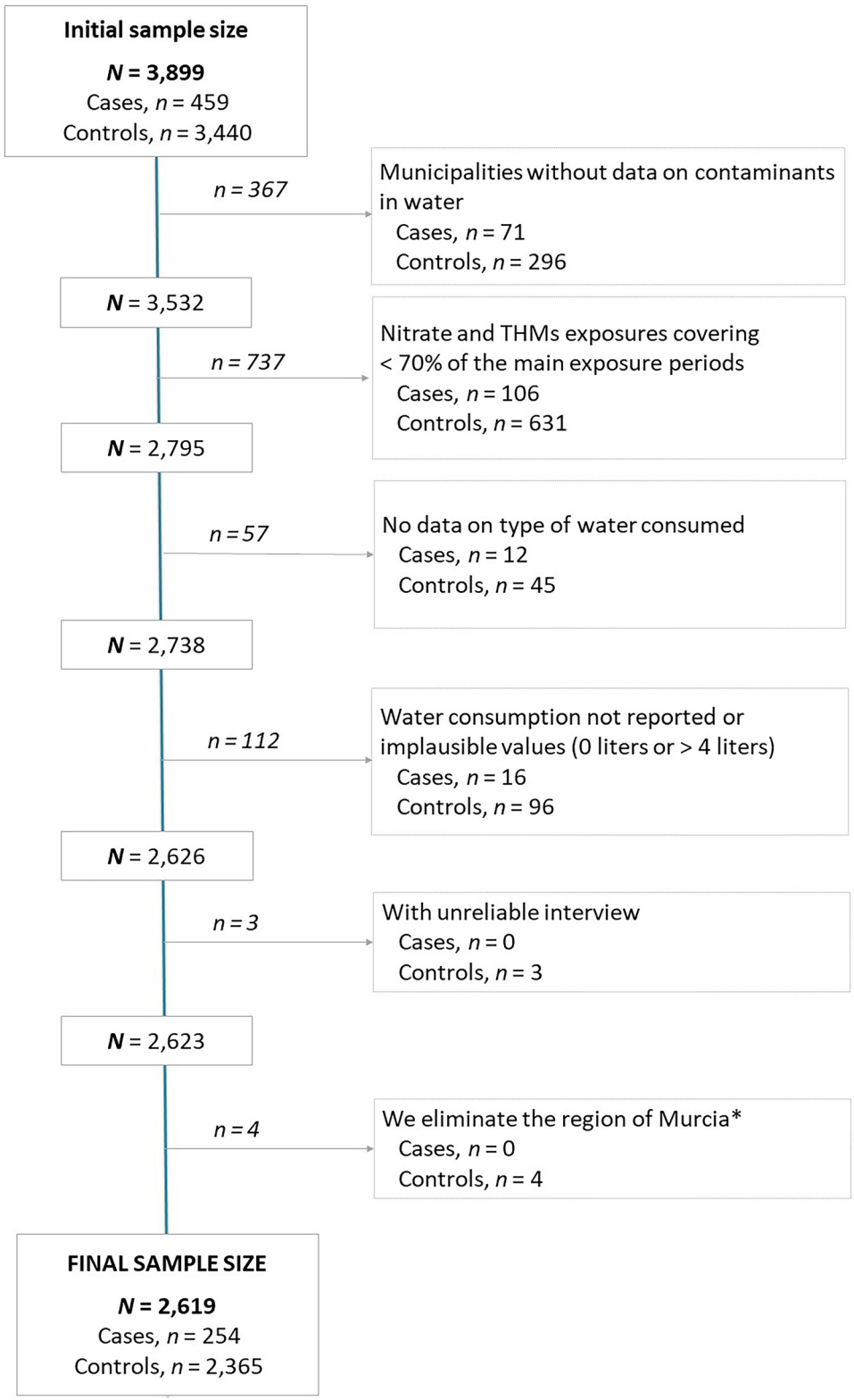


**Figure 1.** Flow chart showing exclusions of study participants from the multicase–control study in Spain (MCC-Spain). The main exposure periods were from 18 years of age to 2 years before the interview. The interviewers rated the quality of the interview, and those unreliable or inconsistent were excluded. A total of 653 participants were excluded from the study. *The region of Murcia was excluded as it contributed only four controls and no cases, potentially biasing estimates.

by quartiles of exposure did not show a monotonic increase in the association (Table S2).

In the stratified analyses by dietary factors, no significant interactions were found for any of the dietary variables explored. However, the nitrate–gastric cancer association appeared to be modified by three independent factors: higher vegetable consumption and higher intakes of vitamins C and E. The OR (95% CI) for gastric cancer among individuals with the lowest vegetable

**Table 1.** Characteristics of the study population. Cases of gastric cancer and controls from the multicase–control study in Spain (MCC-Spain).

| Characteristic ($n = 2{,}619$) | Cases ($n = 254$) | Controls ($n = 2{,}365$) |
|---|---|---|
| Residential area [*n* (%)] | | |
| Asturias | 12 (4.7) | 149 (6.3) |
| Barcelona | 57 (22.4) | 826 (34.9) |
| Cantabria | 14 (5.5) | 241 (10.2) |
| Leon | 42 (16.5) | 201 (8.5) |
| Madrid | 84 (33.1) | 662 (26.3) |
| Navarra | 36 (14.2) | 221 (9.3) |
| Valencia | 9 (3.5) | 105 (4.4) |
| Age (years) [*n* (%)] | | |
| <55 | 56 (22.0) | 530 (22.4) |
| 55–64 | 46 (18.1) | 564 (23.8) |
| 65–69 | 48 (18.9) | 444 (18.8) |
| 70–74 | 34 (13.4) | 395 (16.7) |
| ≥75 | 70 (27.6) | 432 (18.3) |
| Males [*n* (%)] | 176 (69.3) | 1,248 (52.8) |
| Females [*n* (%)] | 78 (30.7) | 1,117 (47.2) |
| Educational level [*n* (%)] | | |
| Less than primary school | 62 (24.4) | 411 (17.4) |
| Primary school | 100 (39.4) | 777 (32.9) |
| Secondary school | 58 (22.8) | 685 (29.0) |
| University | 34 (13.4) | 492 (20.8) |
| Family history of gastric cancer [*n* (%)] | | |
| No | 189 (74.4) | 1,974 (83.5) |
| Yes | 65 (25.6) | 391 (16.5) |
| Body mass index ($kg/m^2$) [*n* (%)] | | |
| <25 | 134 (52.8) | 866 (36.6) |
| 25 to <30 | 90 (35.4) | 1,052 (44.5) |
| ≥30 | 30 (11.8) | 447 (18.9) |
| Smoking, [*n* (%)] | | |
| Never | 96 (37.8) | 1,021 (43.2) |
| Former | 119 (46.9) | 893 (37.8) |
| Current smoker | 39 (15.4) | 451 (19.1) |
| Physical activity [*n* (%)] | | |
| Inactive (0 METS h/wk) | 127 (50.0) | 942 (39.8) |
| Low (>0 to 8 METS h/wk) | 29 (11.4) | 345 (14.6) |
| Moderate (>8 to 16 METS h/wk) | 17 (6.69) | 286 (12.1) |
| Very active (>16 METS h/wk) | 81 (31.9) | 792 (33.5) |
| Alcohol consumption [*n* (%)] | | |
| Never | 58 (22.8) | 507 (21.4) |
| Former | 66 (26.0) | 223 (9.40) |
| Current moderate consumption (≤20 g/d men; ≤10 g/d women) | 81 (31.9) | 1,082 (45.8) |
| Current high consumption (>20 g/d men; >10 g/d women) | 49 (19.3) | 553 (23.4) |
| Meat consumption [*n* (%)] | | |
| Low (28 ± 11 g/d) | 80 (31.5) | 819 (34.6) |
| Moderate (57 ± 8 g/d) | 83 (32.7) | 797 (33.7) |
| High (109 ± 37 g/d) | 91 (35.8) | 749 (31.7) |
| Fruit and vegetables consumption [*n* (%)] | | |
| Low (266 ± 94 g/d) | 85 (33.5) | 797 (33.7) |
| Moderate (515 ± 61 g/d) | 103 (40.6) | 812 (34.3) |
| High (828 ± 252 g/d) | 66 (26.0) | 756 (32.0) |
| Vitamin C (mg/d) | 161.1 (84.9) | 165.8 (96.3) |
| Vitamin E (mg/d) | 11.5 (5.7) | 10.9 (5.5) |
| Gastric cancer type | | |
| Localization of tumor | | |
| Non-cardias | 183 (72.1) | — |
| Esophagogastric junction | 65 (25.6) | — |
| Gastric not specified/overlapping areas | 6 (2.4) | — |
| Lauren classification | | |
| Intestinal | 88 (34.7) | — |
| Diffuse | 62 (24.4) | — |
| Mixed | 10 (3.9) | — |
| Not available | 94 (37.0) | — |
| Average lifetime residential tap water [median ($P_{25}$–$P_{75}$)] | | |
| Nitrate (mg/L) | 2.4 (2.3–9.0) | 5.3 (2.3–10.1) |
| Total trihalomethanes[a] (μg/L) | 30.5 (24.3–37.5) | 33.5 (27.2–66.0) |
| Brominated trihalomethanes[b] (μg/L) | 6.1 (3.8–17.2) | 9.4 (4.1–51.9) |
| Chloroform (μg/L) | 22.1 (15.5–26.8) | 22.0 (16.2–25.8) |
| Average lifetime waterborne ingestion [median ($P_{25}$–$P_{75}$)] | | |
| Nitrate (mg/d) | 2.7 (1.4–5.6) | 3.8 (1.8–8.5) |
| Total trihalomethanes[a] (μg/d) | 18.4 (6.9–33.9) | 23.6 (10.5–47.0) |
| Brominated trihalomethanes[b] (μg/d) | 3.8 (1.5–8.1) | 5.7 (2.6–19.2) |
| Chloroform (μg/day) | 12.2 (4.0–23.7) | 12.9 (4.6–24.5) |

Note: The following variables had missing values: meat consumption (55 cases, 230 controls), fruit and vegetable consumption (55 cases, 230 controls), alcohol consumption (55 cases, 230 controls), family history of gastric cancer (14 cases, 141 controls), BMI (11 cases, 91 controls), and physical activity (29 controls). —, no data; BMI, body mass index; METS, metabolic equivalents; THM, trihalomethane.
[a]Total THMs (TTHMs) includes chloroform, bromodichloromethane, dibromochloromethane, and bromoform.
[b]Brominated THMs includes bromodichloromethane, dibromochloromethane, and bromoform.

consumption (≤169 g/day) was 2.24 (1.02, 4.91) for ingested nitrate ≥80th vs. <80th percentile. Conversely, for those with the highest vegetable consumption (>169 g/day), the OR was 1.03 (0.45, 2.34). Similarly, associations were stronger with higher intake of processed meat and alcohol. The OR (95% CI) for those with the lowest consumption of processed meat (≤10.5 g/day) was 1.06 (0.38, 2.93), while it was 1.91 (0.97, 3.75) for those with the highest consumption. Likewise, the OR for those with no-to-moderate alcohol consumption (i.e., never, former, and current consumers of ≤20 g/day in men and 10 g/day in women) was 1.15 (0.59, 2.23), while it was 2.78 (0.98, 7.93) for those consuming >20 g/day in men and 10 g/day in women (Table 3).

While no meaningful differences were found based on sex or smoking, there were differences by age. The association between nitrate and stomach cancer was observed in older individuals (>65 years of age; median, 73 years of age) [OR of 1.69 (0.89, 3.19)] but not in younger individuals (median, 57 years of age) [1.33 (0.59, 2.97)] with an interaction *p*-value of 0.089 (Table 3). Furthermore, no significant differences were observed when stratifying by tumor location or Lauren classification (Table S4).

### *Trihalomethanes*

The associations found between THMs and gastric cancer were not linear; rather, they resemble an inverted U-shape based on Figure S2. However, quartile analyses revealed a nonsignificant inverse trend without linear pattern (Table S3). Lifetime average residential exposure to Br-THMs exhibited a nonsignificant inverse association with gastric cancer when comparing at or above vs. below the 80th percentile (≥58.3 vs. <58.3 μg/L) [OR (95% CI) of 0.67 (0.38, 1.20) and mean VIF of 4.2] as did waterborne ingested Br-THMs (≥29.0 vs. <29.0 μg/day) [OR (95% CI) of 0.65 (0.33, 1.28) and mean VIF of 2.5].

However, individuals with the highest chloroform exposure (≥80th percentile) compared to those with the lowest exposure showed a positive association with gastric cancer, although the association did not reach statistical significance. The OR (95% CI) of gastric cancer for residential chloroform (≥27 vs. <27 μg/L) was 1.32 (0.82, 2.13) with a mean VIF of 4.2 and for waterborne ingestion (≥27 vs. <27 μg/day) was 1.36 (0.87, 2.14) with a mean VIF of 2.4 (Table 2). Subgroup analyses by tumor site and Lauren classification showed similar results (Table S3).

## Discussion

In this case–control study, long-term intake of waterborne nitrate was linked to an increased OR of gastric cancer. This association was modified by the consumption of fruits, vegetables, vitamin C, vitamin E, alcohol, and processed/cured meat consumption.

**Table 2.** Association of residential concentrations and estimated waterborne ingestion of nitrate and trihalomethanes with gastric cancer in the multicase–control study in Spain (MCC-Spain).

| | Cases | Controls | OR (95% CI)[a] | OR (95% CI)[b] | OR (95% CI)[c] |
|---|---|---|---|---|---|
| Nitrate | | | | | |
| Residential (mg/L) | | | | | |
| <80th percentile (0.5–10.5 mg/L) | 215 | 1,904 | Ref | Ref | Ref |
| ≥80th percentile (10.5–38.0 mg/L) | 39 | 470 | 1.35 (0.78, 2.32) | 1.27 (0.72, 2.24) | 1.52 (0.84, 2.73) |
| Estimated waterborne ingestion (mg/d) | | | | | |
| <80th percentile (0.1–9.7 mg/day) | 215 | 1,876 | Ref | Ref | Ref |
| ≥80th percentile (9.8–42.5 mg/day) | 39 | 489 | 1.13 (0.73, 1.76) | 1.19 (0.75, 1.88) | 1.42 (0.88, 2.29) |
| Total trihalomethanes | | | | | |
| Residential (μg/L) | | | | | |
| <80th percentile (0.71–78.9 μg/L) | 231 | 1,892 | Ref | Ref | Ref |
| ≥80th percentile (79.0–139.4 μg/L) | 23 | 473 | 0.65 (0.37, 1.13) | 0.58 (0.33, 1.02) | 0.54 (0.30, 0.97) |
| Estimated waterborne ingestion (μg/d) | | | | | |
| <80th percentile (0–54.3 μg/day) | 227 | 1,892 | Ref | Ref | Ref |
| ≥80th percentile (50.4–348.8 μg/day) | 27 | 473 | 0.59 (0.38, 0.93) | 0.56 (0.35, 0.89) | 0.55 (0.33, 0.92) |
| Brominated THMs | | | | | |
| Residential (μg/L) | | | | | |
| <80th percentile (0.3–58.3 μg/L) | 227 | 1,892 | Ref | Ref | Ref |
| ≥80th percentile (58.4–121.8 μg/L) | 27 | 473 | 0.83 (0.49, 1.38) | 0.72 (0.42, 1.22) | 0.67 (0.38, 1.20) |
| Estimated waterborne ingestion (μg/d) | | | | | |
| <80th percentile (0–29.0 μg/day) | 232 | 1,892 | Ref | Ref | Ref |
| ≥80th percentile 29.1–300.5 μg/day) | — | — | — | — | — |
| Chloroform | | | | | |
| Residential (μg/L) | | | | | |
| <80th percentile (0.2–26.9 μg/L) | 193 | 1,892 | Ref | Ref | Ref |
| ≥80th percentile (26.9–41.0 μg/L) | 61 | 473 | 1.17 (0.75, 1.83) | 1.29 (0.82, 2.05) | 1.32 (0.82, 2.13) |
| Estimated waterborne ingestion (μg/d) | | | | | |
| <80th percentile (0–27.4 μg /day) | 203 | 1,892 | Ref | Ref | Ref |
| ≥80th percentile (27.4–116.2 μg/day) | 51 | 473 | 0.92 (0.65, 1.30) | 0.93 (0.65, 1.34) | 1.36 (0.87, 2.14) |

Note: Brominated THMs includes bromodichloromethane, dibromochloromethane, and bromoform. Total THMs includes chloroform, bromodichloromethane, dibromochloromethane, and bromoform. —, no data; CI, confidence interval; OR, odds ratio; Ref, reference; THM, trihalomethane.
[a]Model adjusted for age, sex, educational level, and recruitment area.
[b]Model further adjusted for family history of gastric cancer, body mass index, smoking, physical activity, alcohol consumption, meat consumption, and fruit and vegetables consumption.
[c]Model further mutually adjusted for the other corresponding components, i.e., total THMs (nitrate model), nitrate (THMs model), chloroform and nitrate (brominated THMs model), and brominated THMs and nitrate (chloroform model).

Likewise, the association between nitrate and gastric cancer was observed in older individuals (>65 years of age; median, 73 years of age) but not in younger individuals (median, 57 years). This may suggest that gastric cancer development in younger individuals may be more influenced by factors other than nitrate exposure in water. However, it does not appear to be due to genetic predisposition, as there was no correlation between family history of gastric cancer and early onset diagnosis (rho = 0.01). This observation requires further in-depth investigation. A significant inverse association was suggested between gastric cancer and total THMs. Further analyses revealed a nonsignificant positive correlation with chloroform, contrasted by an inverse relationship with brominated THM. Nitrate and THMs analysis based on tumor site and Lauren classification yielded no statistically significant variations.

Over the years, there has been a growing number of epidemiological studies examining the relationship between nitrate in drinking water and various cancers affecting different organs of the gastrointestinal tract. However, reaching a definitive conclusion remains challenging as most cancer types have been investigated by four studies or fewer, leading to a high uncertainty. Analysis combining four case–control studies,[33–36] including nearly 20,000 participants, found that each 10-mg/L increase in drinking water nitrate levels was linked to a 91% higher risk of stomach cancer [relative risk (RR) = 1.91; 95% CI: 1.09, 3.33]. While there was considerable variation between studies ($I^2 = 76.64\%$), all studies pointed toward increased risk.[14] However, previous cohort studies, including two early ones and a recent one, found no nitrate–gastric cancer association in drinking water.[37–39] In virtually all studies, including the present one, the level of nitrate in residential drinking water was below the World Health Organization (WHO) recommended limit of 50 mg/L. Several reasons may explain this heterogeneity and discrepancy, including significant differences in nitrate ranges, lack of water intake data, different exposure windows considered, and the fact that some studies assessed cancer mortality instead of incidence. Likewise, the transformation of nitrate into NOCs is influenced by several factors: the types of bacteria in our gut, stomach acid levels, and how much nitrate, nitrite, and proteins/amino acids we consume through food and water.[12,40]

Differential health effects have been suggested based on the dietary source of nitrate. Nitrate and nitrite occur naturally in water and soil, with plant- and animal-sourced foods being the primary sources of exposure. Certain green leafy vegetables and root vegetables, such as beetroot, contain the highest absolute concentrations.[41] Despite the smaller contribution from nitrate-based food additives and drinking water, these sources are the only ones consistently demonstrating health risks.[13] This is likely because antioxidants, vitamins, and polyphenols naturally present in fruits and vegetables, which are also sources of natural nitrate and nitrite, act as inhibitors of NOC formation and may reduce the carcinogenic potential of nitrate and nitrite from these natural sources.[21–24]

Phytochemicals derived from fruits and vegetables have also demonstrated effectiveness against *Helicobacter pylori*, a bacterium directly associated with chronic gastritis and considered the primary risk factor for gastric cancer.[42] Likewise, vitamin C has shown significant antitumor activity, and a high vitamin C dose has been proposed as a cancer treatment.[43,44] We were able to take these dietary factors into account and observe the potential effect of fruits and vegetables, which contain antioxidants and vitamins, in inhibiting or reducing the carcinogenicity effect of

**Table 3.** Association of estimated nitrate via waterborne ingestion (≥80th vs. <80th percentile) with gastric cancer by categories of potential effect modifiers among participants in the multicase–control study in Spain (MCC-Spain).

| Nitrate[a] (mg/d) | Cases/controls | OR (95% CI) | *p*-Value | Cases/controls | OR (95% CI) |
|---|---|---|---|---|---|
| By fruit consumption | ≤328 g/d (median, 193 g/d) ($n = 1,165$) | | — | >328 g/d (median, 457 g/d) ($n = 1,169$) | |
| <80th percentile | 81/836 | Ref | — | 89/857 | Ref |
| ≥80th percentile | 16/232 | 1.64 (0.74, 3.66) | 0.377 | 13/210 | 1.21 (0.55, 2.65) |
| By vegetables consumption | ≤169 g/d (median, 111 g/day) ($n = 1,178$) | | — | >169 g/d (median, 239 g/day) ($n = 1,156$) | |
| <80th percentile | 94/870 | Ref | — | 76/823 | Ref |
| ≥80th percentile | 16/198 | 2.24 (1.02, 4.91) | 0.411 | 13/244 | 1.03 (0.45, 2.34) |
| By vitamin C | ≤150 mg/d (median, 102 mg/d) ($n = 1,170$) | | — | >150 mg/d (median 211 mg/d) ($n = 1,164$) | |
| <80th percentile | 85/846 | Ref | — | 85/847 | Ref |
| ≥80th percentile | 17/222 | 2.10 (0.94, 4.71) | 0.482 | 12/220 | 1.03 (0.46, 2.33) |
| By vitamin E | ≤10 mg/d (median, 7.3 mg/day) ($n = 1,159$) | | — | >10 mg/d (median, 13.2 mg/day) ($n = 1,175$) | |
| <80th percentile | 76/848 | Ref | — | 94/845 | Ref |
| ≥80th percentile | 15/220 | 2.81 (1.16, 6.78) | 0.375 | 14/222 | 0.83 (0.39, 1.78) |
| By alcohol | No-to-moderate consumption[b] ($n = 1,736$) | | — | High consumption[b] ($n = 598$) | |
| <80th percentile | 131/1,250 | Ref | — | 39/443 | Ref |
| ≥80th percentile | 19/336 | 1.15 (0.59, 2.23) | 0.538 | 10/106 | 2.78 (0.98, 7.93) |
| By processed/cured meat consumption | ≤10.5 g/d (median, 4.6 g/d) ($n = 1,151$) | | — | >10.5 g/d (median, 20 g/d) ($n = 1,183$) | |
| <80th percentile | 76/869 | Ref | — | 94/824 | Ref |
| ≥80th percentile | 7/199 | 1.06 (0.38, 2.93) | 0.262 | 22/243 | 1.91 (0.97, 3.75) |
| By smoking | Never ($n = 1,117$) | | — | Ever ($n = 1,501$) | |
| <80th percentile | 81/792 | Ref | — | 134/1.083 | Ref |
| ≥80th percentile | 15/229 | 1.33 (0.59, 2.97) | 0.475 | 24/260 | 1.69 (0.89, 3.19) |
| By sex | Female ($n = 1,195$) | | — | Male ($n = 1,424$) | |
| <80th percentile | 63/895 | Ref | — | 152/981 | Ref |
| ≥80th percentile | 15/222 | 1.58 (0.66, 3.77) | 0.525 | 24/267 | 1.42 (0.77, 2.60) |
| By age | ≤65 years of age (median, 57 years of age) ($n = 1,344$) | | — | >65 years of age (median, 73 years of age) ($n = 1,275$) | |
| <80th percentile | 101/1,014 | Ref | — | 114/862 | Ref |
| ≥80th percentile | 18/211 | 0.98 (0.49, 1.96) | 0.089 | 21/278 | 2.19 (1.07, 4.48) |

Note: OR (95% CI) adjusted for age, sex, educational level, recruitment area, family history of gastric cancer, body mass index, smoking, physical activity, alcohol consumption, meat consumption, fruit and vegetables consumption, and total THMs. Interaction *p*-value was obtained using the likelihood ratio test with and without the multiplicative interaction term. —, no data; CI, confidence interval; OR, odds ratio; Ref, reference; THM, trihalomethane.

[a]<80th percentile: 0–29.0 μg/day; ≥80th percentile: 27.4–116.2 μg/day.

[b]Includes never and former consumers as well as current consumption ≤20 g (men)/10 g (women); High consumption means current consumption >20 g (men)/10 g (women).

ingested nitrate. Participants with lower intake of total fruits and vegetables, as well as vitamin C and E, showed a stronger positive association, while participants with intakes above the median exhibited smaller nonsignificant or nonassociations between waterborne ingested nitrate and gastric cancer.

By contrast, heme iron in meat and smoking are well-documented enhancers of endogenous nitrosation (as demonstrated in controlled human studies).[8] We also observed a stronger link between ingested nitrate and gastric cancer among participants with higher processed meat consumption, whereas the association diminishes in those with lower consumption (≤10.5 g/day). However, no differences were observed based on smoking. We also wanted to explore the potential modifying effect of alcohol, as the consumption of large quantities of alcoholic beverages leads to disturbances in the gut microbiota, mucosal damage, increased gut permeability, and altered intestinal absorption of nutrients, including several vitamins.[45,46] Our data suggested that high alcohol consumption may increase the risk of gastric cancer, potentially associated with nitrate exposure in drinking water.

The group of THMs comprising chloroform, bromodichloromethane, dibromochloromethane, and bromoform represents a significant proportion of DBPs. As a result, the total THM, encompassing the sum of all these compounds, is widely regarded as an indicator of DBP exposure. Total cancer incidence has been dose-dependently associated with the concentration of total THM in drinking-water, cumulative total THM intake, and duration of exposure.[20] A recent meta-analysis suggested a dose threshold for cancer risk from drinking water total THM levels of 55 μg/L in females and 40 μg/L in males.[20] However, the exact biomechanisms of DBP carcinogenicity remain unclear.

The few epidemiologic studies of DBP exposures and digestive cancers have not found associations.[39,47,48] Similarly, our study showed no consistent THM–gastric cancer associations, with Br-THMs showing an inverse association while chloroform showed a nonsignificant positive association. We speculate that Br-THMs might exhibit antibiotic properties, potentially mitigating the presence of *Helicobacter pylori*, thus indirectly offering protection against gastric cancer.[49] However, there is currently insufficient data to substantiate the validity of this hypothesis. Likewise, as there is no prior study assessing the relationship between DBPs and gastric cancer, making comparisons is not possible. Nevertheless, in our previous case–control MCC-study assessing prostate cancer, residential levels of Br-THMs also showed an inverse association, while chloroform showed a nonlinear positive association.[20]

Although THMs have been widely used in epidemiological research as DBP exposure surrogates, they have limitations. THMs are not the most toxic DBP family,[50] and the correlation with other DBPs are site-dependent.[51] In the present study, we measured DBPs other than THMs in drinking water collected in the study areas.[51] Chloroform concentrations were positively correlated with 3-chloro-4-(dichloromethyl)-5-hydroxy-2(5H)-furanone (MX), a major mutagenic constituent of DBPs,[52] that occurred at a median (range) concentration of 16.7 (0.8–54.1) ng/L. Conversely, Br-THM concentrations were negatively correlated with MX.[51] This

might partly explain the inverse association that we observed between residential Br-THMs and gastric cancer and the positive trend with chloroform.

Exposure measurement error is a main concern. There was a small exposure difference between cases and controls, and there was a limited number of historical measurements, especially before 1980. To minimize exposure measurement error, we limited the statistical analysis among study participants with exposure data at least for 70% of the exposure window. Conversely, we analyzed historical nitrate concentrations in two municipalities with the longest historical record in order to explore eventual temporal trends due to, e.g., agricultural practices. No changes were identified in the annual average over 17 years, suggesting that temporal trends are unlikely in the study areas. Although domestic wells may be linked to unregulated carcinogens (e.g., arsenic), the expect impact on results is minimal given the low percentage of well water users (<2% of person-years), there are no identified arsenic hotpots in the study areas, and arsenic has not been shown to be linked to gastric cancer. In addition, we did not account for exposure outside home or domestic filter use, which may have led to nondifferential measurement error in the waterborne ingested exposure estimates. However, the reported amount of water consumed at work ($0.2 \pm 0.3$ L/day) and other places ($0.01 \pm 0.05$ L/day) was smaller than that consumed at home ($1.2 \pm 0.7$ L/day). In a previous case–control study on bladder cancer in Spain, we evaluated THM ingestion at home and the workplace.[53] Correlation between both (Pearson correlation coefficient, 0.74) suggests minor error expected from omitting workplace exposure. Thus, minor and nondifferential exposure misclassification bias, attenuating the OR toward the null, is expected.[54] Regarding domestic filters that could potentially reduce THM exposure,[55] we believe their use was likely infrequent during the study period.

Personal information was collected retrospectively postdiagnosis, introducing the possibility of differential recall between cases and controls. However, the questionnaire was administered through face-to-face interviews by trained research personnel. The questions about water consumption patterns were unrelated to gastric cancer diagnosis, minimizing potential differential recall between cases and controls. We implemented quality control measures, excluding interviews deemed unreliable or inconsistent by our interviewers. This approach likely resulted in comparable interview quality across cases and controls, thus limiting potential attenuation bias in our findings on nitrate/THM exposure through water consumption. Selection bias might be a concern due to control sampling methods and the high proportion of participant exclusions. Response rates were moderate, especially among controls, partly explained by the population-based source as opposed to hospital-based cases. We lacked information on nonparticipants to ascertain whether their drinking water sources and city of residence differed from those of participating cases and controls. However, the probability of participation can be assumed to be independent from the exposure, and nondifferential bias is expected, if any. Because controls had a slightly higher educational level compared to cases, all risk estimates were adjusted for education. To ensure that we avoid selection bias from the high exclusion rate of participants, we examined the descriptive characteristics of excluded participants and compared them with those included in the study (Table S1). We found no significant differences in key characteristics between these groups, suggesting that selection bias was not a concern.

We cannot disregard the possibility that, despite adjusting for recruitment area, there may still be some influence from regions with the highest participant numbers, namely Barcelona and Madrid. Also, residual confounding by unmeasured factors, such as environmental exposures like air pollution, green spaces, or other drinking water contaminants, cannot be ruled out. Unfortunately, it was not feasible to conduct analyses based on recruitment areas due to the restricted exposure variability within each area and the limited number of cases.

A key limitation of this study is the small number of cases included in the analyses. While nitrate–gastric cancer associations emerged when stratifying by nitrosation-promoting factors using the 80th percentile approach, the small sample size prevented quartile-stratified analyses. Results from stratified analyses using the 80th percentile approach should also be interpreted cautiously due to the limited number of cases in some categories. Larger studies are needed to further explore these relationships and investigate potential dose–response patterns in participant subgroups. Nevertheless, the consistency of associations in stratified analyses strengthens the validity of our findings. Although chance cannot be completely ruled out, the observed effect modification by dietary factors aligns with previous research and provides biological plausibility to our results. Strengths of this study include the following: *a*) the long-term exposure approach (from 18 years of age to 2 years before the study interview); *b*) the detailed individual information on a range of covariables that allowed the assessment of several potential confounders and coexposure to two main water contaminants; *c*) the ability to assess the effect modification by certain dietary factors on the association between waterborne nitrate and gastric cancer; *d*) the inclusion of analysis based on tumor site and Lauren classification; and *e*) the availability of data on various water-contaminants, allowing us to address potential confounding effects among them. This approach helps mitigate the influence of one pollutant on another, enhancing the robustness of the findings.

## Conclusions

The study findings suggest that long-term waterborne ingested nitrate, even at concentrations well below the regulatory limits, could potentially pose a risk factor for gastric cancer, and this association is strongly modified by dietary intake of fruits, vegetables, vitamin C, vitamin E, processed/cured meat, and alcohol. Total THMs exhibit an inverse and nonsignificant association with the risk of gastric cancer. Further research is warranted to establish more definitive conclusions.

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