Dietary Iron Intake and Risk of Gastric Cancer

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ABSTRACT

Background. Iron is one of the essential elements for human life. Prior studies provided inconclusive results regarding the association between dietary iron intake and gastric cancer risk. We determined the association between dietary iron intake and risk of gastric cancer in a case-control study of 1,182 incident gastric cancer cases and 2,965 controls in Vietnam.

Methods. We used a validated, semi-quantitative food frequency questionnaire to obtain dietary information, including dietary iron intake. Unconditional regression model was used to calculate odds ratio (OR) and 95% confidence intervals (95% CI) of gastric cancer in relation to dietary iron intake, adjusted for potential confounders.

Results. We observed a U-shaped association between dietary iron intake and gastric cancer risk. Compared to category 2 (reference group), the ORs and 95% CIs of category 1 (lowest intake) and categories 3, 4, 5 and 6 were 1.64 (1.27-2.12), 1.17 (0.90-1.53), 1.35 (1.01-1.82), 1.65 (1.18-2.31) and 2.00 (1.36-2.95) (P_{trend}<0.001). This U-shaped association was also observed in both sexes, all types of dietary iron intake (i.e., heme- and non-heme) and among individuals with non-cardia gastric cancer. This pattern was more apparent among individuals with BMI<23 kg/m^2 ($P_{heterogeneity}$=0.02), never smokers ($P_{heterogeneity}$=0.02), without family history of cancer ($P_{heterogeneity}$=0.99), blood group O ($P_{heterogeneity}$=0.98); however, showed up in both alcohol-and coffee drinkers.

Conclusion. We found a U-shaped association between dietary iron intake and gastric cancer risk.

Impact. Results from our study also provide evidence for tailored dietary intervention program that would benefit most to specific populations and those living in similar settings.

INTRODUCTION

Gastric cancer remains a major global health concern, with an estimated 1.1 million new cases and 770,000 deaths each year.[1] While its prevalence is relatively low in North America and Europe, it is significantly higher in Asian countries.[2,3] More than two-thirds of gastric cancer cases in 2022 were reported in Eastern and South-Eastern Asia.[1] Eastern Asia shows the highest incidence rates—32.5 per 100,000 men and 13.2 per 100,000 women. In South-Eastern Asia, where Vietnam is located, the incidence is 7.3 per 100,000 men and 4.0 per 100,000 women. In Vietnam specifically, gastric cancer ranks as the fourth most commonly diagnosed cancer and the third leading cause of cancer-related mortality.[4] Although overall cancer incidence in Vietnam has shown a modest decline, gastric cancer remains widespread, largely due to the high prevalence of *Helicobacter pylori (H. pylori)* infection, affecting more than 70% of the population, and other lifestyle factors, including high-sail dietary pattern and tobacco use.[5] The prognosis for patients diagnosed at an advanced stage is poor, with a five-year survival rate of just 4.7%, despite recent advances in early detection and treatment options.[6] Risk and protective factors for gastric cancer are both non-modifiable elements—such as age, gender, and genetics—and modifiable factors, such as smoking, alcohol use, *Helicobacter pylori* infection, and dietary habits.[6,7]

Iron is one of the essential elements for human life, participating in different processes of metabolism, including electron transport, oxygen transport and DNA synthesis.[8] There are two main forms of dietary iron, including heme and non-heme. While heme iron is found only in seafood, poultry, fish, meat and other animal foods, non-heme is contained in plant-based food, including beans, vegetables, nuts, grains, fruits or seeds and/or in some animal products such as dairy and eggs.[9] Evidence from a meta-analysis found that excessive dietary iron intake is associated with increased risk of different cancers, such as colorectal cancer, breast cancer or lung cancer.[10] Several cohort studies suggest that iron deficiency or conditions such as iron-deficiency anemia may increase gastric cancer risk.[11,12] Different animal-model studies provided

evidence supporting the biological plausibility for the inverse association between dietary iron intake and gastric cancer risk. Accordingly, iron deficiency enhances *H. pylori* virulence and gastric inflammation by upregulating virulence factors such as CagA and by enhancing the assembly of its type IV secretion system, it also disrupts bile acid metabolism, particularly by increasing deoxycholic acid (i.e., DCA); consequently, promotes the carcinogenesis through DNA damage and a pro-inflammatory microenvironment. On the other hand, *H. pylori* exploit iron from its host through CagA and VacA, thus disrupting the polarity of gastric epithelial cells and facilitating bacterial adhesion and growth.[13] Yet, excessive dietary iron intake could potentially have carcinogenic effect, possibly due to the effect from heme, mainly found in red meat or other animal foods.[7,14] Other mechanism are also involved in the gastric carcinogenesis, including oxidative stress leading to DNA damage, oncogene activation, tumor suppressor gene inactivation, and formation of N-nitroso compounds.[15,16]

Prior studies provided inconclusive results, partly due to the difference in study design, measurement of iron and sources of iron as well as method of categorization. Indeed, a study from the Alpha-tocopherol, Beta-carotene Cancer Prevention Study (ATBC Cohort) suggested a potential U-shaped relationship between total iron binding capacity and gastric non-cardia cancer. According to the National Nutrition Survey of Vietnam, the average iron intake among Vietnamese individuals, predominantly non-heme iron, meets only about 72% of the recommended dietary allowance (RDA);[17] suggesting that iron insufficiency might partly contribute to the high incidence of gastric cancer in Vietnam. The objective of the current analysis was to further clarify the association between iron take and gastric cancer risk in Vietnamese population and to provide an optimal intake (or safe threshold) of this essential element.

MATERIALS AND METHODS

Study Population

Data used for the current analysis was generated from a hospital-based case-control study in Vietnam. The methods, study design, and initial results of this study were described elsewhere.[18–20] Briefly, study participants were recruited between 2003 and 2019 period from four hospitals in Hanoi, Vietnam, including Bach Mai Hospital, Viet Duc University Hospital, National Cancer Hospital, and Hanoi Medical University Hospital. Due to resource constraint, the long enrollment period was expanded into four sub-periods: 1) 2003-2006 (n=520 participants); 2) 2006-2007 (n=1,016 participants); 3) 2008 (n=402 participants); and 4) 2018-2019 (n=2,239 participants). All study participants provided written informed consent before participating into the study. Our study was approved by the participating Institutional Review Boards (IRBs) of Hanoi Medical University (#3918/HMUIRB) and the International University of Health and Welfare, Japan (#19-Ig-17).

Recruitment of Gastric Cancer Cases

The detail of our recruitment of patients with gastric cancer has been published in prior studies.[18–20] Briefly, gastric cancer patients were enrolled a few days or a week before the surgery. We identified potential gastric cancer cases by reviewing the list of patients who were scheduled for surgery and who met the inclusion criteria: 1) physically able to undergo surgery; 2) able to answer research questionnaire; 3) confirmed to have gastric cancer by pathologists; and 4) agreed to attend in the study. We used the following exclusion criteria to individuals who 1) refused to participate in the study; 2) unable to answer research questionnaire; and 3) changed their diet during the illness.

Recruitment of Controls

Individuals to be controls for the current study were 1) those who would receive different surgeries from the same hospital and while the gastric cancer patients were recruited. The following inclusion criteria was applied to these individuals, including 1) were cancer-free at the

time of enrolment and/or did not have a history of cancer; 2) able to answer research questionnaire; and 3) provided written informed consent. We excluded individuals from our study if they 1) refused to participate in the study; and 2) changed their diet during the illness.[18–20] We selected cases and controls prior surgery as they were newly diagnosed and did not have time to change their diet and/or lifestyle yet.

Information from Structured Questionnaire

A trained interview used a structure questionnaire to collect information from study participants on the day prior surgery. The following information was collected, including 1) sociodemographic factors, 2) body weight and height, 3) lifetime tobacco and alcohol use, 4) occupational exposure, 5) dietary information (see Dietary Assessment) 6) medical history, and 7) family history of cancer. A trained extractor extracted the following information from medical records: infection status of hepatitis B, hepatitis C, or HIV viruses, and/or *H. Pylori* (if any).

Dietary Assessment

Dietary information from study participants was collected using a a semi-quantitative food frequency questionnaire (FFQ), comprising 85 commonly consumed food items in Vietnam, which together accounted for 90% or more of essential nutrition. The FFQ was developed based on two household surveys conducted in the general population using 24-hour dietary records-one in 2009 and another in 2017. Participants were asked to report the frequency of their consumption of various foods and food groups during the past 12 months. Response options included six frequency categories: *"6-11 times/year", "1-3 times/month", "1-2 times/week", "3-4 times/week", "5-6 times/week"*, and *"1-3 times/day".* Following the frequency question, participants were asked to estimate portion sizes, categorized as small, medium or large. Nutrient intakes, including 95 nutrients and compounds such as dietary iron intake, was calculated using the Vietnamese Food Composition Database.[21] The FFQ was validated in a study conducted between October and November 2017, involving 1,327 participants, each completing two 24-hour dietary recalls (24-HDRs)-one on a weekday and another over three

consecutive non-weekdays. Pearson correlation coefficients (R^2) between the FFQ and 24-HDR ranged from 0.38 for protein to 0.53 for energy intake. The R^2 value for dietary iron intake was 0.18.[22] Reproducibility was additionally assessed in 150 healthy adults who completed the FFQ twice, 2-3 weeks apart, by independent interviewers. The test-retest correlation coefficient (R^2) was 0.78 for dietary iron intake.

Assessment of Other Covariates

We collected additional information using the structured questionnaire and included them in the multivariable analysis. Body mass index (BMI) was calculated by dividing weight in kilograms by height in meters squared and then categorized into four groups: <18.5 kg/m², 18.5–22.9 kg/m², 23–24.9 kg/m², and ≥25 kg/m². Following the World Health Organization (WHO) guidelines for Asian populations, individuals with a BMI ≥23 kg/m² were classified as overweight or obese.[23,24] Age was grouped into six categories: 15–39, 40–49, 50–59, 60–69, 70–79, and ≥80 years. Education levels were classified as primary, secondary, and high school or higher. Smoking status was categorized as never smokers and ever smokers. Similarly, alcohol and coffee consumption were each classified as never drinkers and ever drinkers. History of type 2 diabetes was recorded as a binary variable as yes and no.

Statistical Analysis

In the current analysis, means and standard deviations (SDs) were calculated for continuous variables whereas counts and proportions were calculated for categorical variables. Differences in characteristics between cases and controls were assessed using t-tests (or ANOVA for multiple groups) for continuous variables and chi-square (χ^2) tests for categorical variables. We selected category 2 of dietary iron intake as the reference group because the mean dietary iron intake of this group was the closest to the recommended daily allowance (RDA) of 7.9mg/day for the 50-69 age group, as recommended by the Vietnam National Institute of Nutrition.[25] This age group constituted the majority of our study population.

Unconditional logistic regression was used to estimate odds ratios (ORs) and 95% confidence intervals (CIs) for the associations between dietary iron intake and gastric cancer risk. The multivariable regression models included the following covariates: (1) age (i.e., 15–39, 40–49, 50–59, ≥60 years), (2) sex (i.e., male versus female), (3) enrollment period (2003–2006, 2006–2007, 2008, and 2018–2019, to account for temporal variation), (4) education level (i.e., primary, secondary, high school or higher), (5) BMI (<18.5, 18.5–22.9, ≥23 kg/m²), (6) smoking status (never vs. ever smoker), (7) coffee consumption (never vs. ever drinker), (8) alcohol consumption (never vs. ever drinker), (9) family history of cancer (yes vs. no), (10) blood group (A, B, AB, O), (11) history of type 2 diabetes (yes vs. no), (12) total energy intake (in ninths, kcal/day), and (13) *H. pylori* infection status.

We performed stratified analyses by sex, histologic subtype (non-cardia vs. cardia), BMI (<23 vs. ≥23 kg/m²), smoking status, alcohol consumption, history of diabetes, *H. pylori* status, and blood group. Tests for linear trends were performed using ordinal values for six categories of dietary iron intake. We also tested for interaction by adding product terms between dietary iron intake and stratifying variables in the multivariable models.

All analyses were conducted using Stata version 14.0 (StataCorp, College Station, TX, USA). Two-sided tests were used, and a *P*-value <0.05 was considered statistically significant.

Data Availability Statement

Data of the current study will be available to the corresponding authors upon reasonable request.

RESULTS

Compared to cancer cases, control subjects were more likely to be male, younger age, higher education levels, more likely to have fridge at home, higher BMI, less likely to have a family history of cancer, less likely to be smokers and alcohol drinkers, more likely to be coffee drinkers, more likely to have a history of type 2 diabetes, more likely to have blood groups B and/or O, higher intakes of vitamins B_1, B_2 and B_6, and higher intakes of beans, vegetables, fruits, meats and fish (all *P's* <0.05). No difference was observed between cases and controls with respect to the level of energy intake and *H. Pylori* infection status (**Table 1**).

Among controls, individuals with higher intake of iron were more likely to be younger, to be male, higher education levels, less likely to use fridge, more likely to be alcohol drinkers and coffee drinkers, more likely to have family history of cancer, but less likely to have history of diabetes and higher intakes of and other food group or selected micronutrient (all *P's* <0.05). No difference was found between different levels of dietary iron intake regarding BMI, blood group and *H. pylori* infection status (**Table 2**).

Overall, both lower and higher intakes of iron were associated with increased risk of gastric cancer. Compared to category 2, the reference group, the ORs and respective 95% CI of category 1 (lowest intake) and categories 3, 4, 5 and 6 (the highest intake) were 1.64 (1.27-2.12), 1.17 (0.90-1.53), 1.35 (1.01-1.82), 1.65 (1.18-2.31) and 2.00 (1.36-2.95) (P_{trend}<0.001) **(Table 3 and Figures 1A-C)**. This U-shaped association was also observed in both sexes ($P_{heterogeneity}$<0.001) **(Figures 1A-C)** and both in heme- and non-heme iron intakes (**Table 3** and **Figures 2A-C and 3A-C**) as well as non-cardia gastric cancer (**Table 3**).

In stratified analysis, the U-shaped association was more apparent among individuals with BMI<23 kg/m^2 ($P_{heterogeneity}$=0.02), never smokers ($P_{heterogeneity}$=0.02), without family history of cancer ($P_{heterogeneity}$=0.99), blood group O ($P_{heterogeneity}$=0.98); however, appeared in both never- and ever alcohol drinkers and coffee drinkers ($P_{heterogeneity}$=0.33 and 0.17, respectively), and did not show up in stratified analysis by history of diabetes ($P_{heterogeneity}$=0.25). Only those with lower

intake or iron was associated with higher risk of gastric cancer in stratified analysis by family history of cancer. The ORs and respective 95% CIs for individuals with- and without family history of cancer, compared with individuals with dietary iron intake at category 2 (reference category) were 4.11 (1.50, 11.31) and 1.49 (1.14, 1.95) (**Supplementary Table 1**).

DISCUSSION

In a case control study of 1,182 gastric cancer cases and 2,995 controls, we observed a U-shaped association between dietary iron intake and gastric cancer risk and this pattern was consistently found in both sexes, in heme-and non-heme iron intakes and patients diagnosed with non-cardia gastric cancer only. In stratified analysis, the U-shaped association was more obvious among individuals with BMI<23 kg/m^2 never smokers, without family history.

In a nested case-control study of 341 gastric cancer cases 86 cardia, 172 noncardia, and 83 non-specified), accrued during 22 years of follow-up, and 341 individually matched controls of the ATBC Cancer Prevention Study, Cook et al.[9] found a results of suggestive u-shaped association between TIBC and risk of gastric non-cardia cancer, which is consistent with results from our study, a U-shaped relationship between dietary iron intake and risk of gastric non-cardia cancer (P_{trend}<0.001). Prior studies reported linear association, either positive or negative, depend on sources of iron and its bioavailability. For instance, in 2022, Collatuzzo et al.[26] used data from the Stomach Cancer Pooling (StoP) Project, a consortium of more than xxx case-control studies, comprising 4,658 gastric cancer cases and 12,247 controls, and reported that iron intake was inversed associated with gastric cancer risk ($OR_{perquartile}$=0.88, 95% CI: 0.83-0.93) and the results were similar between cardia (OR=0.85, 95% CI: 0.77-0.94) and non-cardia (OR=0.87, 95% CI: 0.81-0.94) as well as for diffuse (OR=0.79, 95% CI: 0.69-0.89) versus intestinal type (OR=0.88, 95% CI: 0.79-0.98). Similar, a meta-analysis of three studies, which also included the study by Cook et al.,[9] conducted by Deng et al.,[27] also reported an inverse associations between both serum ferritin iron and serum iron levels with risk of gastric cancer (OR=0.62, 95% CI: 0.38-1.00, I^2=72%; and OR=0.97, 95% CI: 0.94-1.00, I^2=49%, respectively). Our study, to our knowledge, might be the first effort reporting a U-shaped association between iron intake and risk of gastric cancer, overall, in all histologic sites (i.e., cardia vs. non-cardia) and types of iron (i.e., heme vs. non-heme).

Our finding that the U-shaped association between iron intake and risk of gastric cancer in the current study is interesting because it is inconsistent with prior studies in which higher BMI appears strengthen this association, thus increasing risk of gastric cancer.[28,29] In our analysis, the association between BMI and gastric cancer risk among individuals with BMI≥23kg/m^2 was diminished, a finding that was consistent with results from a meta-analysis of 24 prospective cohort studies, involving 10 million participants in which Chen et al.[30] reported that high BMI (or BMI≥25kg/m^2) was not a risk factor for gastric cancer in a combined analysis of gastric non-cardia cancer and gastric cardia cancer or gastric non-cardia cancer alone. This, coupled with suggestion from prior animal model studies which showed plausible mechanism the in individuals with overweight or obese, this leads to triggering chronic inflammation and increasing levels of hepcidin, a hormone regulating iron absorption,[31,32] we postulated that in our analysis BMI was a true effect modifier of the association between iron intake and risk of gastric cancer ($P_{heterogeneity}$=0.02).

Though the U-shape pattern association found in both men and women in the current study, the estimate appeared stronger in women. One important note is that in our population, the age group was primarily distributed among those of 50-59 years of age, an age range that often correspond to menopause among women. Furthermore, due to lack of knowledge, Vietnamese men are often less likely to come for regular health check than Vietnamese women,[33] leading to have a higher rates of detection and diagnosis of gastric cancer among women.

We also found that the U-shaped association between iron intake and gastric cancer risk was particularly pronounced among non-diabetic individuals while it was not among diabetic individuals. Although the mechanism remains unclear, several studies have demonstrated a positive association between diabetes and an increased risk of gastric cancer. For instance, meta-analysis (11 prospective cohort studies and 6 case-control studies) (relative risk-RR = 1.19, 95% CI: 1.08-1.31)[34] or two other prospective cohort studies in Asia, one in Korea among

195,312 study participants (hazard ratio-HR=1.66, 95% CI: 1.04-2.68),[35] and one in Taiwan among 19,625 individuals (HR=1.24, 95% CI: 1.06-2.91).[36] Diabetic individuals often experience heightened oxidative stress and altered iron homeostasis, which may influence the impact of dietary iron on gastric carcinogenesis. The presence of insulin resistance, impaired glucose metabolism, and increased systemic inflammation in diabetes might shift the threshold at which iron becomes either protective or carcinogenic, thereby disrupting the U-shaped relationship observed in non-diabetic individuals.[37,38]

Our study has several limitations. First, selection bias is possible because this is a hospital-based case-control study in which control subjects were not representative the general population, possibly leading to the scenario that obtained estimates were away from the null. Also, study participants were recruited from provinces located in Northern Vietnam, our results were also not generalized to other geographical locations in Vietnam or Asian countries. In addition, control subjects, though considered cancer-free individuals, were still have medical issues and needed surgeries, thus they were not considered healthy controls. The other limitation is that the dietary habits and lifestyle of study participants from one period might be different from others due to a long enrollment period (between 2003 and 2019). We, however, minimized this possibility in the multivariable analysis by including this variable (i.e., enrollment periods) in the model. Also, our study population included 88 participants (or 7.4% total gastric cancer cases) who were younger than 40 years of age that might have different carcinogenic mechanisms. Due to small sample size, we were unable to conduct stratified analysis in this subpopulation. In addition, the interview was, on average, conducted within a week from the diagnosis date of cancer to the date of completion of the FFQ survey, information collected might be “over-recall”, resulting in the estimates be away from the null (or inflated). Finally, residual confounding might also occur from unmeasurable factors despite our effort to employ a comprehensive set of covariates in the multivariable regression models.

Our study also has several strengths. The employment of comprehensive set of covariates also helped minimize potential confounding effects. This also might be the first effort, to our knowledge to determine the association between iron intake and gastric cancer risk in a sizable study. Finally, the use of validated semi-quantitative FFQ to collect detailed information of diet from study participants and generated nutrients, both macro-and micro ones, from Vietnamese food using Food Composition Database would provide accurate information of nutrition intake.

In summary, we found a U-shaped association between iron intake and gastric cancer risk and this pattern was consistently observed in both sexes, in all types of iron (i.e., heme-and non-heme) and in patients diagnosed with non-cardia gastric cancer only. Further studies are thus warranted to replicate our results in other study design (i.e., cohort study) and diverse populations as well as better understand the underlying mechanisms of such association. Results from our study also provide evidence for tailored and personalized dietary intervention program that would benefit most to specific populations and in similar settings in low-and - middle income countries.

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Table 1. Characteristics of Study Participants in the Current Case-Control Study

Characteristics	Total (N=4.117)	Cancer (n=1,182)	Controls (n=2,995)	*P-value*
Age, mean (SD), range, years old	55.36 (12.13) (15-82)	57.6 (11.5) (22-88)	54.5 (12.2) (15-92)	<0.001
10-39	455 (11.0)	88 (7.4)	367 (12.3)	<0.001
40-49	811 (19.4)	189 (16.0)	622 (20.8)	
50-59	1,279 (30.6)	363 (30.7)	916 (30.6)	
60-69	1,150 (27.5)	369 (31.2)	781 (26.1)	
≥70	482 (11.5)	173 (14.6)	309 (10.3)	
Sex				
Men	2,580	823 (69.6)	1,757 (58.7)	<0.001
Women	1,597	359 (30.4)	1,238 (41.3)	
Highest level of education				
Primary school	650	208 (17.6)	442 (14.8)	<0.001
Secondary school	1,890	568 (48.1)	1,322 (44.1)	
High school or higher	1,637	406 (34.3)	1,231 (41.1)	
Fridge use [a]				
Yes	3,130	764 (68.0)	2,366 (82.5)	<0.001
No	1,047	359 (32.0)	503 (17.5)	
BMI, mean (SD)[a]	21.3 (3.05)	19.4 (2.8)	21.3 (3)	
<18.5	960	469 (41.5)	491 (16.8)	<0.001
18.5-22.9	2,171	541 (47.8)	1,630 (55.7)	
≥23.0-24.9	595	86 (7.6)	509 (17.4)	
≥25	334	35 (3.1)	299 (10.2)	
Family history of cancer				
No	3,830	1,066 (90.2)	2,764 (92.3)	0.03
Yes	347	116 (9.8)	231 (7.7)	
Smoking status				
Never smoker	2,423	601 (50.8)	1,822 (60.8)	<0.001
Ever smoker	1,754	581 (49.2)	1,173 (39.2)	
Alcohol consumption				
Never drinkers	2,318	612 (51.8)	1,706 (57.0)	<0.001
Ever drinkers	1,859	570 (48.2)	1,289 (43.0)	
Coffee drinking status				
Never drinker	3,211	922 (78.0)	2,289 (76.4)	<0.001
Ever drinker	966	260 (22.0)	706 (23.6)	
History of diabetes				
Yes	200	29 (2.9)	171 (6.5)	<0.001
No	3,457	878 (97.1)	2,479 (93.5)	
Total energy intake (Kcal/day), mean (SD)	1688.63 (445.86)	1,650.6 (455)	1703.6 (441.4)	0.07
Blood group [a]				
A	735	258 (26.6)	477 (20.8)	0.001
AB	166	55 (5.7)	111 (4.8)	
B	949	278 (28.5)	671 (29.2)	
O	1,417	380 (39.1)	1,037 (45.2)	
H. Pylori infection [a]				
Negative	827	265 (39.8)	562 (40.2)	0.88
Positive	1,236	400 (60.2)	836 (59.8)	
Food groups, Mean (SD)				
Bean (g/week)	60.6 (78.6)	51.1 (62.1)	64.0 (83.5)	<0.001
Vegetables (g/week)	1034.5 (724.6)	1004.9 (729.4)	1043.4 (723.2)	<0.001

Fruits (g/week)	721.6 (701.7)	537.9 (531.4)	772.2 (733.8)	<0.001
Meat (g/week)	1275.4 (784.4)	1052.7 (828.7)	1333.6 (762)	<0.001
Fish (g/week)	392.3 (334.6)	348.7 (332.8)	404 (334.2)	<0.001
Selected micronutrient intakes				
Protein (g/day)	72.0 (23.7)	66.8 (22.6)	74.1 (23.8)	<0.001
Fat (g/day)	35.7 (17.3)	30.7 (15.7)	37.6 (17.5)	<0.001
Carbohydrates (g/day)	272 (85.7)	278.4 (87.6)	269.5 (84.9)	<0.001
Iron intake, mg/day mean (SD)	11.5 (4.0)	11.0 (3.9)	11.7 (4.0)	<0.001
Median (Range)	11.5 (3.6-40.4)	10.7 (3.6-36.6)	11.1 (3.7-40.4)	
Category 1	702 (16.8)	257 (21.7)	445 (14.9)	<0.001
Category 2	693 (16.6)	181 (15.3)	512 (17.1)	
Category 3	699 (16.7)	192 (16.2)	507 (16.9)	
Category 4	691 (16.5)	189 (16.0)	502 (16.8)	
Category 5	698 (16.7)	185 (15.7)	513 (17.1)	
Category 6	694 (16.6)	178 (15.1)	516 (17.2)	

[a] Based on available data, SD is standard Deviation, and BMI is body Mass Index (Asian category, kg/m^2)

Table 2. Characteristics of Study Participants by Iron Intake among Controls in the Current Case-Control Study

Characteristics	Total (N=2,995)	Category 1 (n=445)	Category 2 (n=512)	Category 3 (n=507)	Category 4 (n=502	Category 5 (n=513)	Category 6 (n=516)	*P-value*
Iron intake, mg/day, mean (SD)	11.7 (4.1)	7 (0.9)	8.9 (0.5)	10.3 (0.4)	11.6 (0.4)	13.2 (0.6)	18.3 (4.4)	
Age, mean (SD)	55.4 (12.1)	58.4 (11.5)	56.8 (11.7)	55.5 (12.3)	54.4 (12)	53.3 (12.1)	53.8 (12.4)	
10-39	367 (12.3)	35 (7.9)	51 (10.0)	67 (13.2)	61 (12.2)	76 (14.8)	77 (14.9)	<0.001
40-49	622 (20.8)	62 (13.9)	101 (19.7)	104 (20.5)	120 (23.9)	125 (24.4)	110 (29.8)	
50-59	916 (30.6)	144 (32.4)	154 (30.1)	145 (28.6)	160 (31.9)	159 (31.0)	154 (25.2)	
60-69	781 (26.1)	129 (29.0)	151 (29.5)	130 (25.6)	129 (25.7)	112 (21.8)	130 (8.7)	
≥70	309 (10.3)	75 (16.9)	55 (10.7)	61 (12.0)	32 (6.4)	41 (8.0)	45	
Sex								
Men	1,757 (58.7)	233 (52.4)	295 (57.6)	288 (56.8)	305 (60.8)	324 (63.2)	312 (60.5)	0.02
Women	1,238 (41.3)	212 (47.6)	217 (42.4)	219 (43.2)	197 (39.2)	189 (36.8)	204 (39.5)	
Highest level of education								
Primary school	442 (14.8)	96 (21.6)	98 (19.1)	83 (16.4)	60 (12.0)	57 (11.1)	48 (9.3)	<0.001
Secondary school	1,322 (44.1)	195 (43.8)	224 (43.8)	217 (42.8)	229 (45.6)	221 (43.1)	236 (45.7)	
High school or higher	1,231 (41.1)	154 (34.6)	190 (37.1)	207 (40.8)	213 (42.4)	235 (45.8)	232 (45.0)	
Fridge use								
Yes	2,366 (79.0)	382 (85.8)	419 (81.8)	389 (786.7)	381 (75.9)	390 (76.0)	405 (78.5)	<0.001
No	629 (21.0)	63 (14.2)	93 (18.2)	118 (23.3)	121 (24.1)	123 (24.0)	111 (21.5)	
BMI, mean (SD)[a]	20.8 (3.1)	20.7 (3.1)	20.9 (3.1)	20.5 (3)	20.7 (2.9)	21 (3.2)	20.9 (2.9)	0.41
<18.5	491 (16.8)	79 (18.5)	84 (16.6)	93 (18.8)	88 (17.8)	71 (14.2)	76 (15.0)	
18.5-22.9	1,630 (55.7)	230 (53.7)	286 (56.6)	267 (53.9)	276 (55.8)	284 (56.7)	287 (56.8)	
≥23.0	808 (27.6)	119 (27.8)	135 (26.8)	135 (27.3)	131 (26.4)	146 (29.1)	142 (28.2)	
Family history of cancer								
No	2,764 (92.3)	419 (94.2)	463 (90.4)	472 (93.1)	471 (93.8)	476 (92.8)	463 (89.7)	0.04
Yes	231 (7.7)	26 (5.8)	49 (9.6)	35 (6.9)	31 (6.2)	37 (7.2)	53 (10.3)	
Smoking status								
Never smoker	1,822 (60.8)	281 (63.1)	323 (63.1)	307 (60.6)	297 (59.2)	299 (58.3)	315 (61.0)	0.54
Ever smoker	1,173 (39.2)	164 (36.9)	189 (36.9)	200 (39.4)	205 (40.8)	214 (41.7)	201 (39.0)	
Alcohol consumption								
Never drinkers	1,706 (57.0)	287 (64.5)	307 (60.0)	282 (55.6)	271 (54.0)	267 (52.0)	292 (56.6)	<0.001
Ever drinkers	1,289 (43.0)	158 (35.5)	205 (40.0)	225 (44.4)	231 (46.0)	246 (48.0)	224 (43.4)	
Coffee drinking status								
Never drinker	2,289 (76.4)	383 (86.1)	432 (84.4)	392 (77.3)	361 (71.9)	369 (71.9)	352 (68.2)	<0.001
Ever drinker	706 (23.6)	62 (13.9)	80 (15.6)	115 (22.7)	141 (28.1)	144 (28.1)	164 (31.8)	
History of diabetes [a]								
Yes	171 (6.5)	41 (9.4)	34 (7.0)	27 (5.9)	21 (4.6)	26 (6.3)	22 (5.4)	<0.001
No	2,479 (93.5)	393 (90.6)	449 (93.0)	428 (94.1)	434 (95.4)	388 (93.7)	387 (94.6)	
Total energy intake (Kcal/day), mean (SD)	1688.6 (445.9)	1134.6 (196.7)	1439.6 (230.8)	1616.9 (249.7)	1773.7 (262.5)	1938.2 (280.1)	2234.2 (386.1)	

Blood group [a]								
A	477 (20.8)	74 (20.7)	100 (22.5)	85 (21.8)	81 (20.5)	75 (21.4)	62 (17.3)	0.61
AB	111 (4.8)	24 (6.7)	15 (3.4)	13 (3.4)	16 (4.1)	21 (6.0)	22 (6.1)	
B	671 (29.2)	101 (28.3)	127 (28.5)	114 (29.2)	119 (30.1)	102 (29.0)	108 (30.2)	
O	1,037 (45.2)	158 (44.3)	203 (45.6)	178 (45.6)	179 (46.3)	153 (43.6)	166 (46.4)	
H. Pylori infection [a]								
Negative	562 (40.2)	90 (43.3)	91 (39.6)	99 (39.0)	113 (39.5)	93 (40.6)	76 (39.8)	0.95
Positive	836 (59.8)	118 (56.7)	139 (60.4)	155 (61.0)	173 (60.5)	136 (59.4)	115 (60.2)	
Food groups, Mean (SD)								
Bean (g/week)	64.0 (83.5)	40.1 (36.5)	45.7 (46.4)	54.7 (56.1)	65.1 (70)	70.7 (86.1)	103.7 (138.5)	<0.001
Vegetables (g/week)	1,043.4 (723.2)	654.8 (306.5)	801.5 (315.7)	901.3 (462.6)	951.8 (482)	1,258.1 (771.7)	1,680.1 (1,080.0)	<0.001
Fruits (g/week)	772.2 (733.8)	436.7 (274.6)	546.9 (266.5)	646.9 (353.9)	738.1 (361.3)	916.8 (674.8)	1,380.8 (1,344.9)	<0.001
Meat (g/week)	1333.6 (762)	892.6 (439.4)	1156.2 (530.6)	1295.7 (610.1)	1479.8 (685.8)	1,592.6 (850.0)	1,722.6 (1,047.6)	<0.001
Fish (g/week)	404 (334.2)	246 (173.4)	318.8 (190.1)	390.7 (247)	421.7 (284.8)	475.8 (343.3)	617.3 (535.5)	<0.001
Selected micronutrient intakes								
Protein (g/day)	74.1 (23.8)	47.7 (9)	60 (9)	67.6 (10.1)	74.8 (11.6)	83.7 (13.3)	107.0 (27.1)	<0.001
Fat (g/day)	37.6 (17.5)	24.7 (9.7)	31.5 (12.2)	34.1 (13.4)	38.3 (15.6)	42.5 (16.1)	52.6 (20.9)	<0.001
Carbohydrates (g/day)	269.5 (84.9)	185.1 (45.7)	229.6 (64.6)	260.1 (67.4)	285.2 (73.4)	306.7 (76.1)	339 (78.8)	<0.001

[a] Based on available data, SD is standard Deviation, and BMI is body Mass Index (Asian category, kg/m^2)

Bold numbers: Statistically significant (P<0.05)

Table 3. Association Between Iron Intake and Risk of Gastric Cancer, Overal and Stratified Analysis by Sex, Types of Iron and Histologic Types in the Current Case-Control Study

Dietary Iron Intake, by Category (mean, SD)	Controls	Cases	Multivariable Model OR (95% CI)
Overall			
Category 1, 6.8 (1.0)	445	257	**1.64 (1.27, 2.12)**
Category 2, 8.9 (0.5)	512	181	1.00
Category 3, 10.3 (0.4)	507	192	1.17 (0.90, 1.53)
Category 4, 11.6 (0.4)	502	189	**1.35 (1.01, 1.82)**
Category 5, 13.2 (0.6)	513	185	**1.65 (1.18, 2.31)**
Category 6, 18.1 (4.3)	516	178	**2.00 (1.36, 2.95)**
Continuous scale (per SD increment)			**1.18 (1.07, 1.30)**
P_{trend}			<0.001
By Sex			
Men			
Category 1, 6.8 (1)	233	165	**1.65 (1.19, 2.3)**
Category 2, 8.9 (0.5)	295	123	1.00
Categolry 3, 10.3 (0.4)	288	140	1.22 (0.88, 1.69)
Category 4, 11.6 (0.4)	305	135	1.29 (0.90, 1.86)
Category 5, 13.2 (0.6)	324	129	**1.53 (1.00, 2.33)**
Category 6, 17.9 (4.1)	312	131	**1.95 (1.21, 3.15)**
Continuous scale (per SD increment)			**1.16 (1.03, 1.31)**
P_{trend}			**0.01**
Women			
Category 1, 6.8 (1)	212	92	**1.71 (1.12, 2.62)**
Category 2, 8.9 (0.5)	217	58	1.00
Category 3, 10.3 (0.4)	219	52	1.09 (0.69, 1.73)
Category 4, 11.6 (0.4)	197	54	1.39 (0.83, 2.31)
Category 5, 13.2 (0.6)	189	56	**1.96 (1.12, 3.44)**
Category 6, 18.5 (4.5)	204	47	**2.26 (1.15, 4.46)**
Continuous scale (per SD increment)			**1.25 (1.06, 1.48)**
P_{trend}			**0.01**
$P_{heterogeneity}$			0.14
By types of Iron			
Heme Iron Intake			
Category 1, 0.2 (0.1)	445	276	1.18 (0.93, 1.50)
Category 2, 0.3 (0.1)	502	211	1.00
Category 4, 0.3 (0.1)	525	205	1.13 (0.89, 1.44)
Category 4, 0.4 (0.2)	482	174	1.25 (0.96, 1.62)
Category 5, 0.4 (0.2)	518	162	**1.35 (1.03, 1.78)**
Category 6, 0.5 (0.3)	523	154	**1.43 (1.06, 1.93)**
Continuous scale (per SD increment)			**1.11 (1.03, 1.19)**
P_{trend}			**0.01**
Non-heme Iron Intake			
Category 1, 2.2 (0.4)	447	259	**1.78 (1.38, 2.30)**
Category 2., 2.8 (0.3)	510	177	1.00
Category 3, 3.3 (0.4)	523	188	1.06 (0.81, 1.37)
Category 4, 3.7 (0.5)	499	182	1.14 (0.86, 1.52)
Category 5, 4.3 (0.6)	499	202	**1.48 (1.09, 2.01)**
Category 6, 5.7 (1.4)	517	174	**1.52 (1.08, 2.13)**
Continuous scale (per SD increment)			**1.10 (1.01, 1.20)**
P_{trend}			0.02
By Histologic Types			
Non-cardia			
Category 1, 7 (0.9)	445	246	**1.59 (1.22, 2.06)**
Category 2, 8.9 (0.5)	512	176	1.00
Category 3, 10.3 (0.4)	507	186	1.17 (0.90, 1.53)
Category 4, 11.6 (0.4)	502	182	**1.36 (1.01, 1.83)**
Category 5, 13.2 (0.6)	513	183	**1.69 (1.21, 2.38)**
Category 6, 18.3 (4.4)	516	172	**2.02 (1.37, 3.00)**

Continuous scale (per SD increment)			**1.19 (1.08, 1.31)**
P_{trend}			<0.001
Cardia			
Category 1, 6.8 (1)	445	11	**3.42 (1.18, 9.90)**
Categoy 2, 9.6 (0.8)	1,019	11	1.00
Category 3, 11.6 (0.4)	502	7	1.21 (0.41, 3.62)
Category 4, 15.6 (3.9)	1,029	8	0.84 (0.22, 3.30)
Continuous scale (per SD increment)			0.82 (0.40, 1.71)
P_{trend}			0.60

[a] Model adjusted for age groups (10-39, 40-49, 50-59, 60-60, ≥70), sex (if applicable), highest education level (primary, secondary, high school or higher), BMI (kg/m^2, <18.5, 18.5-<23, ≥23), alcohol consumption (yes/no), family history of cancer (yes/no), smoking status (ever/never), history of diabetes (yes/no), coffee drinking (yes/no), total energy intake (kcal/day, tertile), protein intake (g/day, tertile), fat intake (g/day, tertile), carbohydrates intake (g/day, tertile), fridge at home, blood group (A, AB, B, O), four periods of data collection, and *H. Pylori* status;

Abbreviations: CI: confidence interval; OR, 95%CI: odds ratio; SD: standard deviation

Bold numbers: Statistically significant (P<0.05)

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Figure 1. Restricted cubical splines of the association between iron intake and gastric cancer risk

Figure 1 provided the cubical splines, showing the association between total iron intake and risk of gastric cancer in (A) Overall population, (B) Among men, and (C) Among women

Figure 2. Restricted cubical splines of the association between iron-heme intake and gastric cancer risk

Figure 2 provided the cubical splines, showing the association between iron-heme intake and risk of gastric cancer in (A) Overall population, (B) Among men, and (C) Among women

Figure 3. Restricted cubical splines of the association between iron non-heme intake and gastric cancer risk

Figure 3 provided the cubical splines, showing the association between total non-iron intake and risk of gastric cancer in (A) Overall population, (B) Among men, and (C) Among women

Figure 1

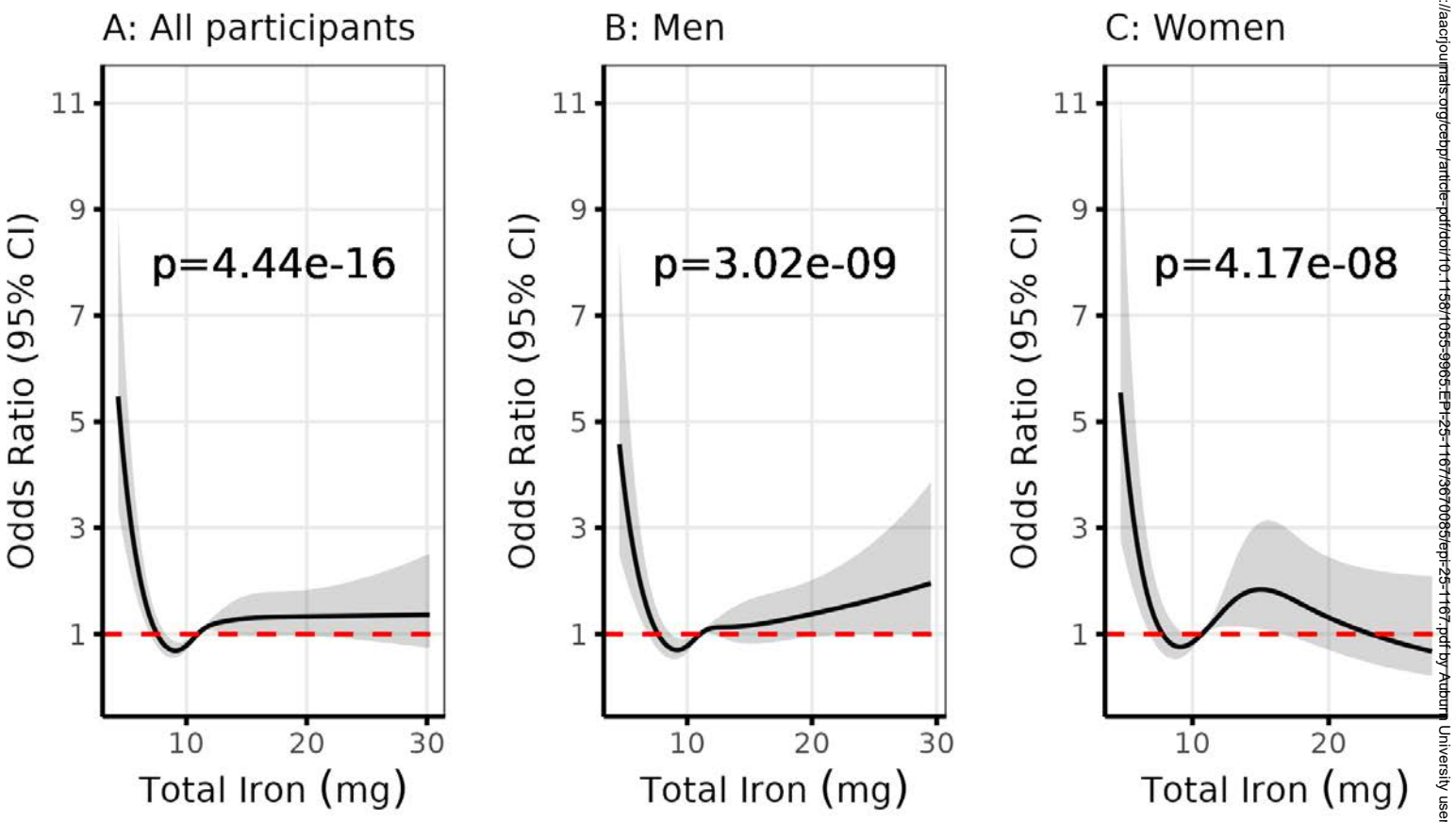

Figure 2

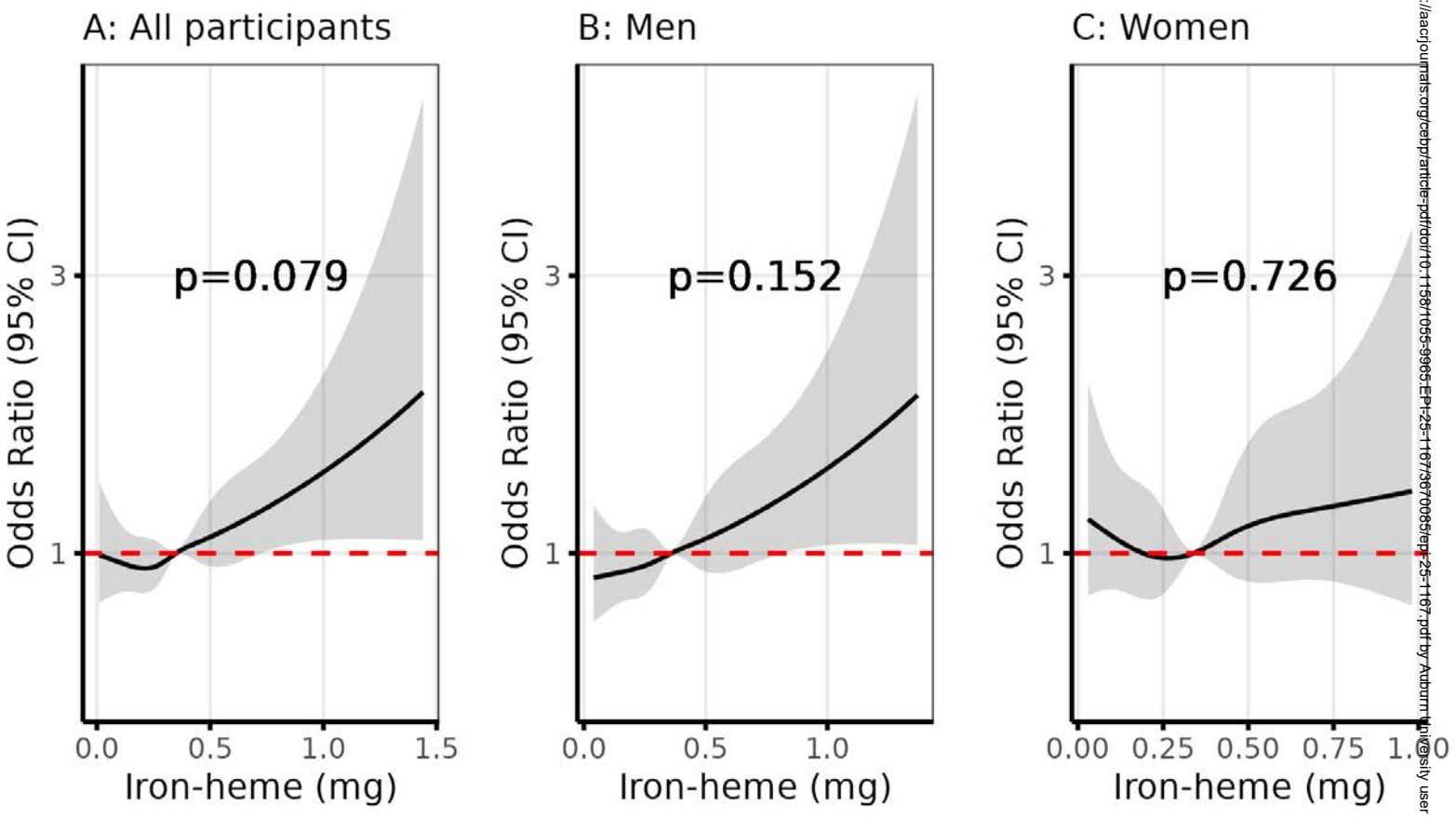

Figure 3