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Does a High Ratio of Dietary Omega-6/Omega-3 Fatty Acids Increase the Risk of *Helicobacter pylori* Infection? A Case-Control Study

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ABSTRACT

Helicobacter pylori infection is the cause of 90% of non-cardia gastric cancer. Several dietary elements have been identified as possible contributors to *H. pylori* infection and its advancement through various pathways. Based on the anti-inflammatory and anti-microbial effects of a diet low in omega-6 and high in omega-3 polyunsaturated fatty acids (PUFAs), this study aimed to assess the ratio of dietary omega-6 to omega-3 PUFAs and the risk of developing *H. pylori*. The present case-control study was conducted on 150 cases with *H. pylori* infection and 302 controls. The omega-6 to omega-3 ratio was calculated using food intake information sourced from a validated food frequency questionnaire. Physical activity and demographic data were collected through a related questionnaire. The association between the odds of *H. pylori* infection and the omega-6 to omega-3 ratio was evaluated using logistic regression models. A p value < 0.05 was considered statistically significant. The findings revealed that individuals in the third tertile had significantly higher odds of *H. pylori* (odds ratio [OR], 2.10; 95% confidence interval [CI], 1.30–3.40) in the crude model. Furthermore, even after adjusting the potential confounders including sex, age, body mass index, physical activity, energy intake, alcohol, and smoking status, this association remained significant (fully adjusted model: OR, 2.00; 95% CI, 1.17–3.34). Our study revealed a higher ratio of omega-6 to omega-3 was related to a higher likelihood of *H. pylori* infection. Therefore, it is advisable to maintain a balanced intake of PUFAs in the diet.

Keywords: *Helicobacter pylori*; Unsaturated fatty acids; Omega-6; Omega-3; Inflammation

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Conflict of Interest
The authors declare that they have no competing interests.

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INTRODUCTION

Gastric cancer ranks fifth in common malignancies worldwide and is the fourth most prevalent cause of cancer-related mortality, primarily affecting older adults [1]. *Helicobacter pylori* infection is attributed to 90% of non-cardiac cancers [2]. According to the International Agency for Research on Cancer, *H. pylori* is a type I carcinogenic agent and is believed to be responsible for 80% of all stomach cancers due to its effects on inflammation, peptic ulcer, chronic gastritis, and primary gastric lymphoma [3]. Research conducted in Latin America, Canada, Iran, China, Russia, and Jordan has revealed a high outbreak of *H. pylori* infection [4]. Bacterial adhesion to stomach epithelial cells leads to the generation of nitrogen and reactive oxygen species (ROS), triggering inflammation and promoting carcinogenesis development [5].

Studies have demonstrated that nutrition can alter the growth or change of the gastrointestinal microbiome, which can influence chronic disease [6]. Dietary fatty acids are essential nutrients that impact a variety of disorders throughout life. Polyunsaturated fatty acids (PUFAs) are found in cell membranes and can regulate inflammatory processes and antioxidant signaling pathways [7]. Omega-3 PUFAs, such as docosahexaenoic acid (DHA), eicosapentaenoic acid (EPA), and α-linolenic acid (ALA), are known for their antioxidant, anti-inflammatory, and anticancer properties, whereas omega-6 PUFAs, like linoleic acid (LA) and arachidonic acid (AA), are associated with inflammation [8]. An optimal ratio of omega-6/omega-3 (less than 4 to 1) is necessary for effective regulation and response to external agents, as well as management of inflammation in the body [7,9]. However, the Western dietary pattern has a high ratio of omega-6 to 3 PUFAs, which has been associated with an increased risk of inflammation-related disorders [7].

H. pylori alters the metabolism of omega-6 PUFAs in the gastric mucosal cells of rats, resulting in elevated AA compounds and prostaglandin E2 concentrations [10]. Omega-3 PUFAs, on the other hand, demonstrate anti-*H. pylori* effects. An in vivo study indicated that DHA prevents bacterial colonization and growth in the gastric mucosa of mice by disrupting the bacterial cell membrane [11]. Furthermore, research on rats found that omega-3 PUFAs reduce gastritis by lowering inflammatory variables such as nitric oxide, malondialdehyde, and gastrin and regulating mucosal glutathione levels [12]. Moreover, A review study proposed that walnut consumption, as a dietary source of omega-3 PUFAs, might contribute to *H. pylori* eradication via regulating inflammation-associated cytokine [13]. However, Despite the clinical improvement, a trial study found that fish oil supplementation, in combination with pantoprazole and clarithromycin, was ineffective in eliminating *H. pylori* [14].

While the positive effects of omega-3 PUFAs are widely acknowledged, their precise role in *H. pylori* infection remains incompletely understood. This current study hypothesized that diets with a low ratio of omega-6 to 3 PUFAs might influence the likelihood of *H. pylori* infection due to the anti-inflammatory signaling cascade and ROS purification effects of omega-3 [13]. To our knowledge, this study is the first to examine the connection between the dietary ratio of omega-6 to omega-3 PUFAs and the probability of *H. pylori* infection.

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MATERIALS AND METHODS

Study design and participants

The present case-control study was conducted on patients aged 18 to 65 with *H. pylori* infection referred to the gastroenterology clinic of Rasoul Akram Hospital, Tehran, Iran from June to November 2021. Participants in the case group were selected from patients who were in the active stage of infection and had not been treated before participating in this study. In the control group, people were selected who were confirmed not to be infected with *H. pylori* through diagnostic methods. Those who had previously been diagnosed with *H. pylori* and were resistant to treatment or had been treated were excluded from the research. Additionally, individuals with a body mass index (BMI) < 18.5 or > 35, those with malignant or inflammatory disease, a medical history of psychosis, or memory disturbances, individuals following a special diet (vegan, ketogenic, fasting, and etc.), pregnant, lactating, and those who were illiterate to fill out the questionnaire were excluded from the study. Furthermore, after analysis, participants who under-or over-estimated their energy intake (< 800 kcal or > 4,200 /day) were excluded [15]. All methods were carried out in accordance with relevant guidelines and regulations. The current study was evaluated and approved by the Iran University of Medical Sciences Ethics Committee (IR.IUMS.REC 1396.32632). All patients signed an informed consent form to conduct the study and receive their information.

Data collection

Demographic data and anthropometric indexes

Data regarding participants' sex (male/female), age, alcohol consumption (yes/no), and smoking (yes/no) of the participants were gathered through a face-to-face interview. The physical activity of the participants was evaluated by the International Physical Activity Questionnaire [16]. Anthropometric indexes were assessed by a trained dietitian. Height and weight were measured with a digital scale (Seca 807) with a precision of 100 g and a stadiometer (Seca 206) with a precision of 0.5 cm, respectively. BMI was then calculated for each patient with formula. Waist circumference was measured using a flexible tape with a precision of 0.5 cm.

Diagnosis tools

H. pylori infection was diagnosed through different methods, including serological antibody testing (immunoglobulin [Ig] G and IgA) in blood samples, stool antigen testing in fecal matter samples, gastric biopsy, endoscopy, and urea breath test (UBT).

Dietary evaluation

The 168-item food frequency questionnaire (FFQ) was utilized as a validated block format for assessing dietary intakes in the preceding year [17]. Expert interviewers (MKS and ZE) elicited participants' dietary intake by inquiring about the serving size of each food item, whether consumed yearly, monthly, weekly, or daily. To increase the accuracy of estimations, interviewers presented serving size or household measurements of each food item to participants. Subsequently, the daily consumption of each food item was calculated in grams, considering both the frequency of consumption and the serving size of each food item. Based on the nutrient contents of foods, participants' daily intake of nutrients (micro- and macro-nutrients) was obtained. The gram of omega-3 and omega-6 fatty acids were obtained from food analysis. The omega-3 group includes ALA, EPA, and DHA. The omega-6 group includes LA and AA. Their ratio was then calculated by dividing the values of omega-6 and omega-3.

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Statistical analysis

Qualitative and quantitative variables are presented as frequency (percentage) and mean ± standard deviation, respectively. The comparison of categorical and quantitative variables between two groups was conducted using the chi-square and independent samples t test, respectively. Data normality was evaluated using the Kolmogorov-Smirnov test and histogram chart. Binary logistic regression analysis was utilized to assess the odds ratios (ORs) and 95% confidence intervals (CIs), adjusted for covariates in various models. Additionally, statistical analysis was performed using SPSS software (version 21; SPSS Inc., Chicago, IL, USA). A p value < 0.05 was considered statistically significant.

RESULTS

Among the 500 participants, 150 individuals with confirmed *H. pylori* infection were categorized as the case group. Meanwhile, 302 volunteers were designated as the control group to evaluate the impact of dietary omega-6 to omega-3 ratios on the likelihood of *H. pylori* occurrence. This analysis excluded participants who provided inaccurate estimates of their energy intake. Women comprised 59.5% of the participants with a mean age of 39.5 years, and a mean BMI of 26.5 kg/m^2. Compared to controls, participants with *H. pylori* infection smoked significantly more, had a higher BMI, and were older; however, most participants were non-smokers and non-alcohol users. Additionally, there was no significant difference in physical activity between the two groups, with approximately 74% of participants reporting low physical activity levels. Regarding diagnosis methods, 27.8%, 24.5%, 25.8%, and 21.6% of endoscopic biopsy, UBT, serum Ig, and stool antigen were used, respectively.

Patient characteristics are shown in **Table 1**. It reveals significant differences in energy, protein, carbohydrate, and monounsaturated fatty acid intake (p < 0.001).

Table 2 shows the food group intake based on energy distribution. Significant differences were observed in legumes, starchy vegetables, green leafy vegetables, dairy products, chickens, red meats, nuts (p < 0.001, for all), fruits (p = 0.030), whole grains (p = 0.007), vegetable oils (p = 0.002), organ meats (p = 0.035), fishes (p = 0.019), and added sugars (p = 0.010) between the case and control groups.

The crude and multivariable-adjusted OR and 95% CI for *H. pylori* across tertiles of omega-6 to omega-3 ratio are displayed in **Table 3**. In the crude model, participants in the last tertile were significantly more likely to be infected with *H. pylori* than those in the first tertile (OR, 2.10; 95% CI, 1.30–3.40). Furthermore, the association remained significant even after adjusting for potential confounders in models 2 and 3 (model 2: OR, 2.12; 95% CI, 1.26–3.55 and model 3: OR, 2.00; 95% CI, 1.17–3.34).

DISCUSSION

The current case-control study revealed that higher omega-6 to 3 ratios were associated with a 2-fold odds of *H. pylori* infection. Additionally, the findings indicated an increase in developing *H. pylori* with increasing age and BMI.

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Table 1. The features of case and control participants

Variables	Cases (n = 150)	Controls (n = 302)	p value
Sex*			**0.011**
Male	48 (32.0)	135 (44.7)	
Female	102 (68.0)	167 (55.3)	
Helicobacter pylori diagnosis*			0.167
Endoscopic biopsy	51 (34.0)	75 (24.8)	
Urea breath test	30 (20.0)	81 (26.8)	
Serum immunoglobulin	37 (24.7)	80 (26.5)	
Stool antibody	32 (21.3)	66 (21.9)	
Smoke status*			**0.025**
Yes	11 (7.3)	8 (2.6)	
No	139 (92.7)	294 (97.4)	
Alcohol status*			0.203
Yes	16 (10.7)	21 (7.0)	
No	134 (89.3)	281 (93.0)	
Physical activity*			0.484
Low	114 (76.0)	220 (72.8)	
Moderate	29 (19.3)	59 (19.5)	
High	7 (4.7)	23 (7.6)	
Age (yr)†	42.0 ± 13.5	37.1 ± 8.4	< **0.001**
BMI (kg/m^2)†	28.1 ± 6.6	24.8 ± 3.2	< **0.001**
Waist circumference (cm)†	108.8 ± 13.6	96.5 ± 6.3	< **0.001**
Energy (kcal/day)‡	2,590.7 (932.8)	2,246.9 (854.9)	< **0.001**
Protein (g/day)‡	91.6 (39.4)	72.5 (29.1)	< **0.001**
Carbohydrate (g/day)‡	380.1 (149.0)	317.3 (129.6)	< **0.001**
Total fat (g/day)‡	76.9 (42.7)	75.4 (36.9)	0.429
SFA (g/day)‡	23.4 (11.3)	25.6 (14.1)	0.778
MUFA (g/day)‡	24.7 (13.8)	25.6 (14.6)	**0.004**
PUFA (g/day)‡	16.7 (9.4)	15.5 (9.8)	0.652

Values are mean ± standard deviation or median (interquartile range) for continuous and percentage for categorical variables.
Significant values are shown in bold.
BMI, body mass index; SFA, saturated fatty acid; MUFA, monounsaturated fatty acid; PUFA, polyunsaturated fatty acid.
*Using chi-square test for categorical.
†Using independent samples t test for normal continuous variables.
‡Using Mann-Whitney for abnormal continuous variables.

Table 2. Food group intake between the case and control participants (% of total energy)

Variables	Cases (n = 150)	Controls (n = 302)	p value
Refined grains	28.4 ± 12.8	27.7 ± 12.2	0.578
Whole grains	17.4 ± 13.5	13.9 ± 12.3	**0.007**
Nuts	3.5 ± 3.3	2.0 ± 2.6	< **0.001**
Legumes	3.4 ± 2.7	1.3 ± 1.8	< **0.001**
Fruits	8.8 ± 4.6	10.1 ± 6.7	**0.030**
Green leafy vegetables	1.0 ± 0.8	0.7 ± 0.5	< **0.001**
Yellowy vegetables	0.2 ± 0.3	0.3 ± 0.3	0.468
Starchy vegetables	0.8 ± 0.7	1.4 ± 1.2	< **0.001**
Other vegetables	3.6 ± 1.8	3.5 ± 1.4	0.556
Vegetable oils	5.8 ± 4.5	4.4 ± 4.1	**0.002**
Animal fats	2.1 ± 3.3	2.2 ± 2.7	0.826
Red meats	0.9 ± 0.8	2.7 ± 2.6	< **0.001**
Organ meats	0.1 ± 0.2	0.1 ± 0.2	**0.035**
Processed meats	0.4 ± 0.7	0.5 ± 0.8	0.154
Chickens	3.8 ± 3.1	2.6 ± 2.6	< **0.001**
Eggs	1.3 ± 1.1	1.2 ± 1.1	0.298
Fishes	0.6 ± 0.6	0.8 ± 0.7	**0.019**
Dairy products	10.9 ± 5.3	16.9 ± 7.5	< **0.001**
Sweetened beverages	1.0 ± 1.2	0.8 ± 1.1	0.160
Added sugars	5.5 ± 3.5	6.4 ± 4.0	**0.010**

Significant values are shown in bold.
Using independent samples t test for normal continuous variables.

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Table 3. Association between tertiles of omega-6/omega-3 ratio and *Helicobacter pylori* infection

Tertiles of omega 6 to 3 ratio	Case/control, No.	Model 1*	Model 2†	Model 3‡
Omega 6 to 3 ratio				
T_1 (≤ 10.10)	42/108	1.00 (Ref.)	1.00 (Ref.)	1.00 (Ref.)
T_2 (10.11–10.82)	40/111	0.92 (0.55–1.53)	1.02 (0.59–1.75)	1.04 (0.59–1.82)
T_3 (≥ 10.83)	68/83	**2.10 (1.30–3.40)**	**2.12 (1.26–3.55)**	**2.00 (1.17–3.41)**
p_{trend}		**0.002**	**0.004**	**0.011**

Obtained from logistic regression. Values are presented as odds ratio (95% confidence interval). Significant values are shown in bold.
BMI, body mass index.
*Model 1: crude model.
†Model 2: adjusted for sex, age, and BMI.
‡Model 3: adjusted for sex, age, BMI, physical activity, energy intake, alcohol, and smoking status.

H. pylori is a significant factor in stomach and duodenal ulcers, chronic active gastritis, and gastric cancer [3]. While most people with *H. pylori* do not show clinical symptoms, the infection causes inflammation of the stomach epithelium, with approximately1%–3% of individuals getting stomach cancer and 10% suffering from peptic ulcers [18]. Eradicating *H. pylori* bacteria is a severe problem due to the presence of treatment-resistant strains, making the discovery of novel medications or solutions critical in determining the rate of eradication [19]. Many dietary components can have considerable antibacterial activity against *H. pylori*. Dietary changes can limit the colonization process of this bacterium, and thus the occurrence of gastritis [20].

Inflammatory substances secreted by *H. pylori* are advantageous to the bacteria but detrimental to the host. The inflammation disrupts the secretory function of the stomach and damages its tissue [21]. Dietary components, notably PUFAs, have the ability to regulate antioxidant signaling pathways and modulate inflammatory processes [22]. Clinical research indicates a positive association between the occurrence of bacterial infections and inflammation [23]. It has been proposed that consuming omega-3 fatty acids, such as DHA and EPA, within the range of 3 to 5 g, may reduce the risk of chronic diseases, particularly cardiovascular diseases, and exhibit anti-inflammatory properties [22,24]. Furthermore, omega-3 PUFAs appear to protect the stomach from gastric mucosa damage caused by stress, medications, and *H. pylori* infection [25]. Additionally, omega-3 PUFAs can reduce stomach inflammation produced by *H. pylori* by reducing the expression of interleukin (IL)-8, which has pro-inflammatory features [26]. Yamamoto et al. [27] showed that omega-3 fatty acids (100 μM of EPA and DHA each) effectively block *H. pylori* infection in mouse stomachs by inhibiting bacterial colonization through futalosine pathway blockade, with EPA showing greater efficacy than DHA.

Regions with high EPA + DHA blood levels (> 8%) were the Sea of Japan, Scandinavia, and areas with indigenous populations or populations not fully adapted to Westernized food habits. Conversely, very low blood levels (≤ 4%) were observed in North America, Central and South America, Europe, the Middle East, Southeast Asia, and Africa [28]. Several research have investigated the impact of dietary or supplemental PUFAs (including both omega-3 and omega-6 PUFAs, or omega-3 fatty acids alone) on the growth and elimination of *H. pylori*. In a double-blind, randomized clinical trial (RCT), Meier et al. [14] found that in patients with dyspepsia without an ulcer, adding fish oil (1,500 mg/3 times/day for one week) was less effective than metronidazole in the treatment of *H. pylori* when combined with pantoprazole and clarithromycin. Their study showed that omega-3 consumption could not eradicate *H. pylori* [14]. Similarly, there was no significant difference in the rates of eradication in a double-blind RCT with 97 *H. pylori* patients who took 2 g of EPA and DHA every day for 12

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weeks along with four common *H. pylori*-eradication drugs. However, there was a statistically significant decrease in IL-8 and high sensitivity C-reactive protein levels [29].

It is evident that DHA and EPA inhibit bacterial growth [30]. Moreover, according to reports, omega-3 fatty acid consumption has been associated with antibacterial effects at concentrations exceeding 500 mg per day [31]. Furthermore, Thompson et al. [32] demonstrated that the growth of *H. pylori* was moderately inhibited by the addition of PUFAs, including omega-6 and omega-3. Additionally, Correia et al. [11] found that DHA altered the shape of *H. pylori* bacteria, inhibiting their development and colonization in mice's stomachs.

Omega-3 fatty acid antimicrobial mechanisms may include interruption of adenosine triphosphate generation, cell-to-cell communication, the electron transport system, fatty acid synthesis, alterations in membrane hydrophobicity, and cellular leakage [33]. In line with these findings, our study confirmed that higher dietary omega-3 consumption might protect against *H. pylori* overgrowth.

In addition, it has been discovered that omega-3 fatty acids exhibit antioxidant properties [7,34], which directly correlates with their antimicrobial effect [35]. Further studies have shown that antioxidant compounds suppress microbial growth through various mechanisms, including the leakage of intracellular proteins, modification of essential fatty acids in organisms, and binding to electron donors inside the cell [36].

LA, an essential omega-6 fatty acid in the human diet, is converted by the body into other omega-6 PUFAs such as dihomo-gamma-linolenic acid, gamma-linolenic acid, and AA [37]. One of the important PUFAs found in the cell membrane is AA, which leads to inflammation by producing eicosanoids [38]. It has been demonstrated that a lower in the omega-6 to omega-3 fatty acid ratio is associated with reduced inflammation. Conversely, an increase in the ratio of omega-6 to omega-3 PUFAs has been linked to increased pro-inflammatory cytokines and eicosanoids [39]. Therefore, not only is consuming of omega-3 fatty acids important for reducing inflammation, but also maintaining a balanced omega-6 to omega-3 ratio (lower than 4 to 1), is recommended [40]. In addition, an increase in the ratio of omega-6 to omega-3 PUFAs is related to reduced immune system function [41]. Consequently, the high ratio of omega-6 to omega-3 PUFAs provides a susceptible environment for the growth of *H. pylori* by causing inflammation and changing the function of the immune system. In the present study, the findings indicated if the omega-6 to omega-3 ratio is more than 10.83, the chance of developing *H. pylori* is higher. This relationship remained positive and significant after adjusting for confounding factors.

Furthermore, Wang et al. [42] found that some alterations in gut microbial species and functions are associated with *H. pylori* infection. Additionally, a study by Ghosh et al. [43] illustrated that omega-6 causes dysbiosis, while omega-3 can eliminate this effect. Therefore, increasing the omega-6 to omega-3 ratio may increase the chance of developing *H. pylori* infection.

The present study's findings also showed that in individuals infected with *H. pylori*, BMI is significantly higher than in the control group. Xu et al. [44] similarly showed a positive association between BMI and *H. pylori* infection. In addition, it was shown in research by Satoh et al. [45] that *H. pylori* was higher in obese people than in the control group. Obesity is recognized to be associated with an increased risk of infection by various pathogens [46]. Moreover, an increased degree of obesity is also linked to impaired immune function [47].

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Therefore, the increase in the chance of developing *H. pylori* with an increase in BMI can be justified by the abovementioned reasons.

The present study has several strengths. To the best of our knowledge, this study represents the first attempt to assess the association between ratio of omega-6 to omega-3 PUFAs and odds of *H. pylori* infection. Moreover, it included the use of valid and reliable questionnaires, face-to-face interviews for data collection, and the full participation of almost all identified people in the control and case groups.

However, there are several limitations in our study. Firstly, misclassification and recall bias may occur when using FFQ for dietary assessment, especially among patients infected by *H. pylori* who have altered their lifestyle due to symptoms. Secondly, there was a lack of details regarding cooking methods, which may alter the configuration of PUFAs through high heating. Lastly, as a general concern with case-control studies, causal relationships cannot be inferred from these types of studies.

CONCLUSION

The study showed that a higher intake ratio of omega-6 to omega-3 PUFAs was linked to an increased risk of *H. pylori* infection, suggesting that dietary changes could be beneficial in preventing and managing this condition. However, more research is required to validate these findings and explore how omega-3 and omega-6 fatty acids impact *H. pylori* survival, potentially deepening our comprehension of these connections.

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