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Dietary Acid Load and Risk of Gastric Cancer: A Case-Control Study in Iran

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ABSTRACT

Background: Dietary Acid Load (DAL) is the balance between acid-producing and base-producing food. Previous studies have assessed the association between DAL and the risk of several cancers. However, few studies have investigated the association between DAL and Gastric Cancer (GC) risk. The current study was carried out to evaluate the association between DAL and GC risk in Iran. **Methods:** The current case-control study was conducted on 184 patients newly diagnosed with GC and 276 healthy controls. A validated diet history questionnaire (DHQ) was applied to assess dietary intake. DAL was calculated by computing amounts of protein intake into potassium contents through net endogenous acid production (NEAP) method. Multi-adjusted logistic regression was used to define the association between DAL and GC risk. **Results:** The mean age of participants was 56.26 years. Intakes of energy, dietary fiber, zinc, selenium, grain, fruits, and vegetables were significantly lower, and protein intake was significantly higher in the case group compared to the control group. A direct association was observed between DAL and GC risk (OR=4.59; 95% CI:2.61-8.07; *P-trend*<0.001, for T2 versus T3). In the fully adjusted model, DAL was positively associated with the risk of GC (OR=3.55; 95% CI:1.89-6.99; *P-trend*<0.001). **Conclusion:** Higher DAL scores were directly associated with greater GC odds which supports the current recommendations for decreasing the risk of cancer incidence.

Introduction

Gastric cancer (GC) is known as the fifth most prevalent cancer (Smyth *et al.*, 2020) and the third cause of cancer mortality in the world (Bray *et al.*, 2018). This illustrates the poor prognosis of this cancer type and clarifies the importance of applying strategies for its prevention and early diagnosis. Smoking, H. *pylori* infection, alcohol consumption, and industrial chemical exposures are recognized as the most critical risk factors for GC (Cheng *et al.*, 2016). Nutritional factors are

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also considered one of the most important risk factors for GC (Tsugane and Sasazuki, 2007). However, there is no strong evidence for this association except for body fatness (Liu *et al.*, 2021) and ultra-processed food with added salt (Lin *et al.*, 2014).

Although a decrease in the risk of GC has been observed in developed countries in recent years, developing countries including Iran are still encountering a large incidence of GC (Torre *et al.*, 2016). In Iran, GC has been known as the first cause of cancer mortality, the leading common cancer among men, and the second most common cancer among women in Iran (Kalan Farmanfarma *et al.*, 2020). Considering the increasing prevalence of GC in Iran and different dietary habits of the Iranian population, it is essential to study the association between dietary habits and GC risk in this region. This hospital-based case-control study was conducted to investigate the association between Iranian dietary patterns and the risk of GC. The association between each food item solely and the risk of GC has been evaluated previously in various studies (Ferro *et al.*, 2020, Han *et al.*, 2015, Zhao *et al.*, 2017). For instance, a case-control study in China reported an increase in GC risk in higher intakes of fresh and processed meat, dairy products, and fish (Wang *et al.*, 2022). However, higher intakes of vegetables were associated with a reduction in the risk of GC in the mentioned study (Wang *et al.*, 2022). Another case-control investigation in Korea suggested an inverse association between flavonoid intake and GC risk in women and not men (Woo *et al.*, 2014). Higher consumption of citrus fruits and allium vegetables, and lower intakes of smoked and barbecue meat, potatoes, and desert were also correlated with reduced risk of GC in a hospital-based case-control study (Lazarevic *et al.*, 2010). However, several food items are consumed together, and the nutrient or chemical contents of each item might affect another or their relationship with the risk of chronic diseases. Studies on food items are barely able to assess the synergistic or inhibitory effects. Moreover, diets might include several unknown compounds that might affect our bodies and health in unrecognized ways. Therefore, evaluating the association between various dietary patterns and the risk of GC can be more valuable. The protective roles of some primary dietary patterns, such as Mediterranean or DASH patterns on the risk of GC have been proven previously (Kim *et al.*, 2021, Schwingshackl *et al.*, 2017). However, limited studies have examined the association between DAL and the risk of GC (Ronco *et al.*, 2022) .

Dietary acid load (DAL) is defined as the acidity potential of a diet and is considered to be associated with the risk of several diseases. Food groups such as meat, cereal, and eggs could increase the DAL score, while fruit and vegetables might have the opposite role (Adeva and Souto, 2011, Cosgrove and Johnston, 2017, Kahleova *et al.*, 2021, Osuna-Padilla *et al.*, 2019). DAL is demarcated as the balance of acid-producing food like meat, eggs, and refined grains, and base-producing food items including fruits and vegetables (Scialla and Anderson, 2013). It is claimed that having a dietary pattern rich in potassium can reduce the risk of GC and other mortality-related conditions (Harrison *et al.*, 1997).

Earlier studies have investigated the association between DAL and the risk of different types of cancers. However, these results were conflicting and inconsistent (Ronco *et al.*, 2021, Safabakhsh *et al.*, 2020, Shi *et al.*, 2021, Wu *et al.*, 2020). According to the current information, no studies have investigated the association between DAL and GC risk in Middle-East countries. This study was carried out to assess the association between DAL and GC odds in Iran.

Materials and Methods

Study population

The present case-control investigation was conducted between May 2010 and June 2012 at the Cancer Research Institute, Imam Khomeini Complex, Tehran University of Medical Sciences, Tehran, Iran. Patients diagnosed with GC from all provinces of the country who visited Imam Khomeini Hospital were invited to participate. Patients without a pathologic approval of GC

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during the last six months and those with a previous history of any type of cancer were excluded. To employ the case and control groups, two methods of convenience sampling and a non-random sample method were applied, respectively. The control group was selected among the relatives of patients hospitalized in non-oncology wards of the hospital. The response rate was 95% in cases and 70% in controls. Patients for whom GC was a secondary diagnosis, those diagnosed over six months ago, or those unable to recall their dietary habits were excluded from the study. Additionally, control subjects with any cancer diagnosis or those adhering to a specific diet due to illness were also excluded.

Dietary assessment

A dish-based, 146-item, semi-quantitative diet history questionnaire (DHQ) was utilized to ascertain the dietary patterns of the study participants. The DHQ, originally developed by researchers at the US National Cancer Institute (NCI), serves to investigate the link between diet and cancer risk (Csizmadi *et al.*, 2007). Given that food items vary across countries; numerous researchers have adapted the DHQ to reflect local dietary practices. These region-specific modifications of the DHQ generally maintain high validity in different areas (Okubo *et al.*, 2008, Shahar *et al.*, 2000, Subar *et al.*, 2001). This study translated and tailored the DHQ to align with Iranian dietary customs. A comprehensive report on the modification process and the validation study was reported previously (Toorang *et al.*, 2020a, Toorang *et al.*, 2019). The validity of the DHQ for evaluating the amounts of energy, protein, carbohydrate, protein, fiber, vitamin A, carotene, niacin, folate, vitamin B12, biotin, vitamin C, sodium, magnesium, iron, zinc, and selenium was confirmed by finding a high correlation coefficient between nutrient assessments by DHQ and those derived by using multiple 24-h recalls (r>0.5 for all) (Toorang *et al.*, 2020a, Toorang *et al.*, 2019) .

A face-to-face interview was performed by trained specialists to complete the questionnaire. The dietary intakes of the participants were asked during the last six months for the control group and the year before cancer diagnosis for the patients. They could report their intake in the form of a spoon, plate, bowl, and scoop, which are recognized as Iranian home scales. Then, the reported amounts were converted to Grams/day by applying household measurements. Finally, the food consumption tables provided by the United States Department of Agriculture (USDA) were used for calculating total daily energy and macro and micronutrients. The USDA food composition table was applied due to the absence of an updated and comprehensive Iranian food composition database. The inclusion of a wide variety of food items in USDA table makes it appropriate for international studies, and it is frequently employed in research across various nations (Ahuja *et al.*, 2013, Haytowitz *et al.*, 2011, Larrick *et al.*, 2022, Van Puyvelde *et al.*, 2020).

Assessment of DAL

Net Endogenous Acid Production (NEAP) method was conducted to estimate the DAL. The protein and potassium contents of the diet are considered to calculate the DAL in this method. The NEAP was calculated through the following formula:

NEAP = (54.5*g Protein/Potassium meq)-10.

Since potential changes might be observed in the patients' dietary intakes, tertile cut-off points of these dietary scores were determined based on scores in control subjects.

Assessment of GC

The diagnosis of GC was confirmed by performing a gastroscopic or surgical biopsy by an expert pathologist. Patients who met the definition of GC explained by the second edition of the International Classification of Diseases for Oncology (ICDO code c16), and those diagnosed with stomach cancer histologically during the last year to the day of the interview, were considered eligible to participate as the case group.

Assessment of covariates

The demographic and general characteristics of the participants, including gender, marital status,

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education level, residential status, and smoking and drinking habits, were derived through an interview conducted by a bachelor student of health sciences. The weight and height of patients before cancer diagnosis were considered in this study due to the potential effect of GC on body weight. The height and weight of the control group were measured at the time of the interview. To calculate body mass index (BMI), we divided weight (kg) by height (meters) squared. Patients were categorized as current smokers and non-smokers based on their reported smoking habits during the last year. Ten milliliters of venous blood samples were taken from all attendants at both fasting and non-fasting status to examine for H. *pylori* infection. IGF antibodies in serum samples were measured using ELISA kits. Serologic examinations were carried out by experienced technicians who were not aware of either the study setting or the participants' case/control status. The H. *pylori* antibody test was repeated in a random collection of serums to prove validity. The existence of antibodies and seropositivity of more than 0.87 was considered positive.

Ethical considerations

This study was conducted according to the guidelines laid down in the Declaration of Helsinki and all procedures involving human subjects/patients were approved by the Ethics Committee of Cancer Research Center, Tehran University of Medical Sciences (no.17198). Written informed consent was obtained from all participants.

Data analysis

The dietary intakes of participants across tertiles of DAL were evaluated by conducting one-way ANOVA. The chi-square test and one-way ANOVA were carried out to estimate the categorical and continuous characteristics of the participants, respectively. The association between DAL and the risk of GC was investigated in a multi-adjusted Logistic regression. Age (continuous), gender (male/female), and energy intake (continuous) were adjusted in the first partial model. Further controls for educational level (illiterate/literate), marital status (married/single), H. *pylori* infection (positive/negative), alcohol consumption (continuous), and smoking status (smoker/nonsmoker) were applied in the second model. This association was then adjusted for BMI in the final model. The estimated power of this analysis was 0.99, calculated using the power analysis method by STAT. The parameters considered were significance level (alpha)=0.05, number of cases (N)=184, baseline probability (*P0*) = 0.33, and odds ratio (OR) = 2.87.

Results

This case-control study enrolled 184 patients with newly diagnosed GC and 273 healthy controls. The mean age of study participants was 56.6 (men: 58.5 and women: 52.6). Almost 32% of study participants were women. The general properties of the population are shown in **Table 1.** The case group was older (61.7 versus 53.2, $P<0.01$), had a higher alcohol consumption (7.2 g/d versus 1.7 g/d, $P<0.01$), and were more smokers (86% versus 82%, $P<0.01$). BMI of the participants in the case group was slightly higher than the control group (26.1 vs. 25.6, $P<0.01$) and the proportion of married participants (66.9% vs. 26%, $P<0.01$) and men (75.5% vs. 63.6%, $P=0.01$) were higher in the case group. The control group had a higher percentage of literates (74.4% vs. 36.9%) and helicobacter infection (55.7% vs. 39.1%, $P=0.01$). Age was significantly different across tertiles of DAL in control group (57.3±11.6 versus 49.0±11.8, $P<0.001$). Other characteristics of participants were not significantly different in the tertile of DAL in either cases or controls.

The dietary intakes of participants in the case and control groups and across tertiles of DAL are demonstrated in **Table 2**. Significant higher intakes of energy (2821.6±1098.6 kcal/d versus 2384.7±1165.3 kcal/d, $P<0.01$), dietary fiber (21.7±9.0 g/d versus 17.6±9.3 g/d, $P<0.01$), zinc (12.9±5.4 mg/d versus 11.8±4.9 mg/d, $P=0.03$), selenium (95.6±52.7 µg/d versus 74.1±52.5 µg/d, $P<0.01$), grains (216.1±171.9 versus 140.4±169.7, $P<0.01$), fruits (507.9±348.1 g/d versus 356.2±268.9 g/d, $P<0.01$), and vegetables

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(367.5±214.6 g/d versus 239.5±169.7 g/d, *P*<0.01) were observed in the control group compared to the case group. The consumption of protein was significantly greater in the case group than in the control group (18.5±4.2% of energy vs. 15.4±4.1% of energy, *P*<0.01). No significant difference in other dietary intakes was observed between the case and control groups. Higher tertiles of DAL were associated with higher intakes of energy (2880.3±1135.2 vs. 2540.1±961.3, *P*=0.006), proteins (16.5±3.6% of energy vs. 13.3±4.4% of energy, *P*<0.001), fats (30.6±9.7% of energy vs. 25.5±10.4% of energy, *P*<0.001), zinc (12.9±4.9 mg/d vs. 11.5±5.5 mg/d, *P*=0.002), selenium (111.4±67.7 µg/d vs. 78.4±39.9 µg/d, *P*<0.001), red meat (19.9±24.4 g/d vs. 15.6±20.6 g/d, *P*=0.009), grains (271.6±222.8 g/d vs 152.8±101.4 g/d, *P*<0.001), dairy (960.5±611.2 g/d vs. 852.2±652.5 g/d, *P*=0.001), and fish (11.2±10.4 g/d vs. 7.3±3.5 g/d, *P*<0.001) in the control group. However, intakes of dietary fiber (18.9±7.9 g/d vs. 23.5±8.9 g/d, *P*<0.001), fruits (349.9±262.2 g/d vs. 589.4±368.1 g/d, *P*<0.001), and vegetables (267.7±176.0 g/d vs. 457.2±213.9 g/d, *P*<0.001) were lower in the third tertile compared to the first tertile of DAL in control group. Intakes of selenium (87.8±61.2 µg/d vs. 59.2±43.8 µg/d, *P*=0.002) and grains (188.6±213.2 g/d vs. 75.3±80.7, *P*<0.001) were higher in the third tertile compared to the first tertile of DAL in the case group. However, patients in the highest tertile of DAL consumed less fruit (280.3±187.1 g/d vs. 483.3±407.2 g/d, *P*<0.001) and vegetables (195.1±110.3 g/d vs. 320.3±260.4, *P*<0.001) compared to the first tertile.

Crude and adjusted odds ratios of GC across tertile of DAL are shown in **Table 3**. An increased risk of GC was observed in the third tertile compared to the first tertile of the DAL in the crude model (OR=2.87, 95% CI:1.74-4.74; *P-trend*<0.001). The association strengthened after adjusting for age, sex, and energy intake (OR=4.59; 95% CI:2.61-8.07; *P-trend*<0.001) in the second model. Further adjustments for education, marriage status, H. *pylori* infection, alcohol consumption, smoking, and BMI did not affect this association in the third (OR = 3.56, 95% CI: 1.89-6.69; *P-trend*<0.001) and the fully adjusted model (OR=3.55, 95% CI:1.89-6.96; *P-trend*<0.001). Linear analysis of the association between DAL and the risk of GC also showed a significant increase in the GC risk by following a high DAL score dietary pattern in both crude (1.01(1.01-1.02)) and fully adjusted models (1.02(1.01-1.03)).

Discussion

A significant direct association was observed between DAL and the risk of GC in the current case-control study. This association was even stronger after adjusting for several potential confounders.

Previous studies have assessed the association between acid-producing food items and the risk of several cancer types. For example, no significant association was found between higher levels of DAL and the risk of breast cancer in a case-control study conducted by Safabakhsh *et al*. (Safabakhsh *et al.*, 2020). Using the NEAP score, Alvaro *et al*. demonstrated a positive association between DAL and the risk of lung cancer (Ronco *et al.*, 2021). However, when the same investigators assessed DAL using the Potential Renal Acid Load (PRAL) score, they failed to find any association (Ronco *et al.*, 2021). In a longitudinal study, Shi *et al.* examined the association of DAL with the risk of pancreatic cancer. They found a significant positive association between DAL and the risk of pancreatic cancer, either by PRAL or NEAP score (Shi *et al.*, 2021). Only one study has evaluated the relationship between DAL and the risk of GC (Ronco *et al.*, 2022) . However, the mentioned study was carried out in Uruguay with dietary intakes which are significantly different from Middle-east countries (Ronco *et al.*, 2022) . Although the assessment of DAL with the risk of GC is interesting, investigating this association is of high importance, particularly in an area where GC is highly prevalent and several dietary factors, including DAL, may significantly contribute to this risk.

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Table 1. General characteristics of participants across tertile of dietary acid load.

Variable	Total population			Tertile							
				Control				Case			
	Control	Case	P-value	T1(n=91)	T2(n=91)	T3(n=91)	P-value[b]	T1(n=31)	T2(n=64)	T3(n=89)	P-value[b]
Age (years)	53.2±11.8[a]	61.7±12.7	<0.01	57.3±11.6	53.3±10.7	49.0±11.8	<0.001	61.3±13.1	60.6±13.1	62.6±12.4	0.62
Alcohol intake (g/day)	1.7±12.0	7.2±88.7	<0.01	57.3±11.6	0.31±1.8	1.8±9.4	0.28	0.13±0.73	0.8±0.52	1.2±10.9	0.09
Body mass index (kg/m^2)	25.6±5.1	26.1±5.0	<0.01	57.3±11.6	25.7±5.7	25.7±5.3	0.93	27.1±4.6	26.8±4.6	25.3±5.4	0.10
Gender (male)	174(63.7)[c]	138(75.5)	0.01	67(73.6)	53(58.2)	54(59.3)	0.06	22(70.9)	48(75.0)	68(76.4)	0.83
Marital status (married)	71(26.0)	123(66.9)	<0.01	20 (21.9(	28(30.8)	23(25.3)	0.39	21(67.7)	36(56.3)	66(74.2)	0.07
Education (literate)	203(74.4)	68(36.9)	<0.01	71(78.0)	61(67.0)	71(78.0)	0.15	14(45.2)	28(43.8)	26(29.2)	0.11
Smoking (yes)	82(30.0)	86(46.7)	<0.01	57.3±11.6	31(34.1)	27(29.7)	0.53	12(38.7)	29(45.3)	45(50.6)	0.5
H. *pylori* infection(positive)	152(55.7)	72(39.1)	0.01	44(48.4)	49(53.9)	59(64.8)	0.07	15(48.4)	24(37.5)	33(37.1)	0.51

[a:]Means ± SD; [b] Obtained from chi-square test for categorical and one-way ANOVA for continuous variables; [c]: n(%).

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Table 2. Dietary intakes (Mean±SD) of participants across tertile of dietary acid load.

Variable	Total study population			Tertiles							
	Control	Case	P-value[a]	Control				Case			
				T1(n=91)	T2(n=91)	T3(n=91)	P-value[b]	T1(n=31)	T2(n=64)	T3(n=89)	P-value[b]
Energy (kcal/day)	2821.6±1098.6	2384.7±1165.3	<0.01	2540.1±961.3	3044.3±1140.6	2880.3±1135.2	0.006	2246.7±1394.6	2271.3±1016.2	2541.4±1178.3	0.34
Protein (% of energy)	15.4±4.1	18.5±4.2	<0.01	13.3±4.4	16.3±3.5	16.5±3.6	<0.001	17.4±4.4	18.7±3.6	18.7±4.5	0.30
Fats (%of energy)	29.5±9.8	30.7±7.3	0.14	25.5±10.4	32.4±7.9	30.6±9.7	<0.001	29.7±7.3	31.2±7.5	30.8±7.3	0.66
Carbohydrates (% of energy)	54.2±8.9	53.1±7.5	0.16	55.3±9.9	53.1±7.4	54.3±9.2	0.24	54.4±7.8	52.8±6.8	52.9±7.9	0.57
Dietary fiber (g/day)	21.7±9.0	17.6±9.3	<0.01	23.5±8.9	22.8±9.5	18.9±7.9	0.001	19.8±13.9	17.9±7.8	16.6±8.3	0.24
Zink (mg/day)	12.9±5.4	11.8±4.9	0.03	11.5±5.5	14.3±5.6	12.9±4.9	0.002	10.4±5.2	11.9±4.7	12.3±5.1	0.17
Selenium (µg/day)	95.6±52.7	74.1±52.5	<0.01	78.4±39.9	96.9±40.9	111.4±67.7	<0.001	59.2±43.8	62.3±36.7	87.8±61.2	0.002
Red meat (g/day)	17.1±21.1	16.2±17.5	0.64	15.6±20.6	15.8±17.8	19.9±24.4	0.009	12.2±12.7	16.1±17.4	17.7±18.9	0.33
grains (g/day)	216.1±171.9	140.4±169.7	<0.01	152.8±101.4	199.4±126.6	271.6±222.8	<0.001	75.3±80.7	104.9±102.1	188.6±213.2	<0.001
Fruits (g/day)	507.9±348.1	356.2±268.9	<0.01	589.4±368.1	584.4±352.3	349.9±262.2	<0.001	483.3±407.2	399.7±253.8	280.3±187.1	<0.001
Vegetables (g/day)	367.5±214.6	239.5±169.7	<0.01	457.2±213.9	377.4±210.1	267.7±176.0	<0.001	320.3±260.4	262.2±166.8	195.1±110.3	<0.001
Dairy (g/day)	1009.1±691.2	1048.9±558.4	0.52	852.2±652.5	1214.6±758.1	960.5±611.2	0.001	919.7±580.4	1150.9±537.5	1020.6±619.7	0.16
Low-fat dairy	570.7±651.3	596.9±580.3	0.66	525.9±600.3	630.0±738.2	556.3±609.1	0.524	556.1±519.4	734.7±602.3	512.0±571.8	0.06
Fish (g/day)	8.9±7.3	10.0±7.4	0.11	7.3±3.5	8.3±5.5	11.2±10.4	<0.001	10.8±9.8	9.3±6.5	10.3±7.0	0.62
Nuts (g/day)	6.7±17.4	4.3±9.2	0.08	7.7±19.8	8.6±21.6	3.8±6.6	0.14	5.9±18.6	4.7±7.4	3.4±3.9	0.38
legume (g/day)	34.8±27.5	33.6±25.1	0.65	32.4±25.4	35.6±30.4	36.3±26.6	0.59	32.7±29.1	32.0±21.9	35.1±25.8	0.73

[a]: Independent t—test; [b]: One-way ANOVA test

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Table 3. Odds Ratio and 95% Confidence Interval (CIs) for gastric cancer across tertile of dietary acid load.

	T1	T2	T3	Ptrend[a]	Continuous
Cases/control (273/184)	91/31	91/64	91/89	-	-
Crude	1	2.06 (1.23-3.47)	2.87(1.74-4.74)	<0.001	1.01(1.01-1.02)
Model A[b]	1	3.05(1.72-5.39)	4.59(2.61-8.07)	<0.001	1.02(1.01-1.03)
Model B [c]	1	2.52(1.34-4.79)	3.56(1.89-6.69)	<0.001	1.02(1.01-1.03)
Model C[d]	1	2.49(1.32-4.72)	3.55(1.89-6.96)	<0.001	1.02(1.01-1.03)

[a]: Trend based on the median values of each tertile; [b]: Adjusted for age (continuous), sex (male/female), and energy intake (continuous); [c:] Further adjusted for education (illiterate/literate), marital status (married/single), alcohol intake (continuous), H. pylori infection (positive/negative), and smoking status (smoker/nonsmoker); [d]: Additionally, controlling forbody mass index (continuous).

Although there is no well-known mechanism through which DAL might affect the risk of GC, there are some clues in this regard. Acidogenic diets may lead to a rise in cortisol levels, which can take part in carcinogenesis by increasing insulin resistance (Rizza *et al.*, 1982) and insulin-like growth factor 1 (IGF-1) (Jafari Nasab *et al.*, 2021, Robey, 2012). Other factors, rather than hormones, might also be able to explain this observation. Some studies have suggested that metabolic acidosis caused by acidogenic diets stimulates cancer metastasis (Böhme and Bosserhoff, 2016, Huang *et al.*, 2016, Justus *et al.*, 2013, Rofstad *et al.*, 2006). Metabolic acidosis might reduce circulating levels of adiponectin (Disthabanchong *et al.*, 2011), a substance claimed to be protective against cancer risk (Jiang *et al.*, 2019). Metabolic acidosis might also lead to hyperinsulinemia in long term, which can provoke tumorigenesis (Chiefari *et al.*, 2021) and the production of reactive oxygen species (ROS) (Arcidiacono *et al.*, 2012). The inflammatory effects of DAL have been also investigated in various studies. Circulating levels of C-reactive protein (CRP) have increased after consuming an acidogenic diet in a randomized clinical trial (Wu *et al.*, 2019). In addition, an increase in oxidative stress by diets full of red meat and processed food may also explain the association between DAL and the risk of GC (Toorang *et al.*, 2020b). Moreover, diets with high acid load scores are usually rich in protein (Müller *et al.*, 2021), which might increase IGF-1 levels, leading to an enhancement in growth-factor-dependent cell proliferation (Levine *et al.*, 2014, Shanmugalingam *et al.*, 2016). Stimulation in the secretion of glucocorticoids and reducing their degradation due to the consumption of high DAL dietary patterns (Esche *et al.*, 2016) might also increase the risk of hyperinsulinemia (Janssen, 2022) and tumor development (Khadka *et al.*, 2023).

This is the first study evaluating the association between DAL and risk of GC in multi-adjusted models in the Middle Eastern area. Validated questionnaires have been applied to assess each participant's main characteristics and dietary intake. However, some limitations might be observed in the study. Although various probable confounders were considered in the present study, residual confounders cannot be ignored. In case-control studies, we may face selection and recall biases. However, trained specialists have performed face-to-face interviews to reduce potential biases. In addition, the use of FFQ for dietary assessment might result in some sort of misclassification. The present study used nutrient composition tables of food items of USDA, instead of local Iranian food, which can be considered a further limitation.

Conclusion

A positive association was found between DAL and GC odds using a case-control design. This finding supports the current recommendation for healthy eating to lower the risk of cancer incidence. However, longitudinal studies are required to examine this issue, particularly in other regions of the world where GC is prevalent. Assessment of the hypothesis in gastric precancerous lesions, including intestinal

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metaplasia and atrophic gastritis may also help understand the mechanism behind this association. Based on the study results, DAL increases the risk of GC, indicating that adherence to a healthy diet with an appropriate acid-base balance might help prevent cancer-related conditions. Further studies, especially cohort studies, are required to confirm this finding. It is also essential to study the role of dietary load in cardia and non-cardia stomach cancer.

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Authors' Contribution

F Dehghani and K Zendehdel designed and developed the original study. S Narmcheshm, M Hadji, and B Sasanfar supervised sampling and the interviews. F Toorang conducted the primary analysis of data. A Esmaillzadeh led the analyzing process and drafting of this paper. F Dehghani developed the draft. All authors approved the final version of the manuscript.

Conflict of interests

None of the authors declare conflicts of interest.

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