

## Research Paper

# Preventable lifestyle and eating habits associated with gastric adenocarcinoma: A case-control study

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## Abstract

**Background:** Besides the well-established risk factors for gastric adenocarcinoma (GaC), many other etiological factors remain largely unexplored. This large comprehensive case-control study aimed to investigate the preventable lifestyle and eating habits associated with GaC.

**Methods:** Consecutive patients with primary microscopically-confirmed GaC diagnosed in 2016-2018 were matched by sex, age, height, and socioeconomic status at a 1:1 ratio with healthy controls. Association of GaC versus control with investigated factors was assessed using the multivariable-adjusted conditional logistic regression for paired samples.

**Results:** Together 302 GaC patients and 302 healthy controls were investigated. Participants receiving higher education and those eating majorly vegetables had less frequently GaC. The majorly frying cooking habit was associated with a higher incidence of GaC. People complaining about poor sleep quality had more often GaC. The more often one smoked, the more often he/she had GaC. A higher frequency for having pickled food was associated with more frequent GaC, while having more frequently vegetables/fruit, beans, or kelps was associated with less often GaC. A greater preference for sour or bitter taste was associated with less frequent GaC. The frequencies of thin liquid intake after meal, swallowing hot food without adequate cooling, doing other things while eating, eating overnight food, and eating midnight snack were all positively associated with GaC, while going to bed regularly was associated with less often GaC.

**Conclusions:** Education level, sleep quality, smoking, the frequencies of use of several foods and seasonings, the preference for specific tastes, and various eating and living habits were associated with GaC. The findings offer important hints for further prospective investigations and for easy effective GaC-preventative strategy-making.

Key words: Gastric adenocarcinoma; lifestyle; eating habits; etiology; case-control study.

## Introduction

Gastric cancer, the majority of which is gastric adenocarcinoma (GaC), is the 5<sup>th</sup> most commonly diagnosed malignancy and the 3<sup>rd</sup> leading cause of cancer mortality in both sexes combined worldwide, with ~1,034,000 new cases and ~783,000 deaths in 2018 [1]. Its incidence is highest in Eastern Asia [2]. In China, gastric cancer was estimated to affect ~679,000

patients and to cause 498,000 deaths in 2015, and was both the 2<sup>nd</sup> most commonly diagnosed cancer and the 2<sup>nd</sup> leading cause of cancer death in both sexes combined [3].

*Helicobacter pylori* (*Hp*) is the major risk factor for GaC, contributing to ~90% of new cases of non-cardia GaC [4, 5]. Some unhealthy dietary habits (*e.g.*, food

preservation by salting and low fruit/vegetable intake), alcohol consumption, and tobacco smoking have also been shown to be associated with a higher risk of GaC [1, 6-13]. Notably, results on the associations of GaC with some factors (*e.g.*, drinking, smoking, and red meat intake) remain controversial [1, 6-16], and many other preventable risk factors have not yet been well established.

This study aimed to comprehensively investigate the easily-modifiable lifestyle and eating habits associated with GaC and to offer evidence for disease prevention. Our findings can potentially aid to identify people at high risk of GaC and be used for risk-adapted screening.

## Methods

### Participants

Consecutive patients with first primary microscopically-confirmed GaC diagnosed in the First Affiliated Hospital of Anhui Medical University (FAHAMU) between July 2016 and August 2018 were included in this case-control study. Patients with previous malignancies, with cancers other than GaC, with other benign gastric diseases, with diseases impairing memory (*e.g.*, dementia), with severe dysfunction of important organs, or with severe systematic unfitness were excluded. They were matched by sex, age, height, and socioeconomic status at a 1:1 ratio with healthy controls confirmed not to have any gastric disorders except superficial gastritis. Since many patients with GaC are diagnosed at an advanced stage and are usually significantly thinner compared to the healthy controls and their pre-disease conditions, weight was not included as a matching factor. All participants did not have previous symptomatic reflux, and had fridges for food preservation. Individuals with any first-degree relative having GaC were excluded. Informed consents were obtained from all participants. This study was approved by the Internal Review Board of FAHAMU.

### Collected information

Participants were requested to carefully respond to a valid, uniform, and standardized questionnaire and to report their regular, habitual, customary, long-lasting conditions (before having obvious digestive symptoms in GaC patients). To ensure the validity and completeness of the responses, the completion of each questionnaire was supervised by one of the trained authors, who only explained items neutrally when necessary but did not offer any directive or indicative clues.

Information on participant characteristics (sex, age, height, weight, education level, marital status,

alcohol drinking, smoking, and passive smoking) and comorbidities (hepatitis, diabetes, hypertension, and allergy) were first collected. Tumor location and differentiation were retrieved for patients. All participants were further requested to report the following: Number of people living and eating together with; eating and cooking habits; drinking water source; frequency score (FS) for intake of pork, chicken, beef, fish, processed meat, pickled food, dried food, smoked/baked food, vegetables/fruit, beans, stewed food, fried food, cereals, tuber crops, kelps, and dairy products; FS for use of yellow rice wine, soy sauce, vinegar, monosodium glutamate, chicken essence, onion/garlic, pepper, and ginger; FS for intake of thick (*e.g.*, thick soup and milk) and thin liquid (*e.g.*, water and juice) before, during, and after meal; FS for several eating habits (swallowing hot food without adequate cooling, not sufficiently chewing, overeating, doing other things while eating, eating deteriorated food, eating overnight food, eating within 0.5 hours after sports, eating midnight snack, and having milk before sleep); FS for eating at home, eating at canteen, and eating box lunch; FS for several sleeping habits (going to bed regularly, dreaming, and afternoon nap); FS for and time of housework and exercise per day; preference score (PS) for sour, sweet, bitter, spicy, and salty tastes; regularity score (RS) for having breakfast, lunch, and supper; degree of satiety and food intake per meal; rest hours after meal; nighttime and noontime sleeping hours; and quality of sleep.

FS was defined as: 0, never; 1,  $\leq 1$  time per month; 2, 2-3 times per month; 3, 1-2 times per week; 4, 3-4 times per week; 5, 5-6 times per week; 6, 1 time per day; 7, 2 times per day; 8, 3 times per day; 9,  $\geq 4$  times per day. The frequency was modified from the Food Frequency Questionnaire [17]. PS ranged from 1 (extremely dislike) to 7 (extremely like) with an increment of 1. RS ranged from 1 (very regular) to 5 (very irregular) with an increment of 1.

### Statistical analyses

The paired *t* and  $\chi^2$  tests were used for comparing continuous and categorical variables between groups, respectively. Associations of GaC versus control with the investigated factors were first computed in basic models using the multivariable conditional logistic regression for paired samples adjusting for sex, age, and height, and the significant factors were then all incorporated into a final multivariable logistic model also adjusting for sex, age, and height. Subgroup analyses were further performed for cardia and non-cardia cancers, respectively. Statistical significance was defined by 2-sided  $P < 0.05$ . Data analyses were performed using

R 3.5.1 (<https://www.r-project.org/>).

## Results

### Participant characteristics

Initially 628 questionnaires were collected. After excluding the unqualified ones and their pairs, finally 604 cases ( $n_{\text{Patients}}=302$ ;  $n_{\text{Controls}}=302$ ) were analyzed. Male proportions in both groups were 69%. The mean ages in the patient and control groups were  $60 \pm 11$  and  $59 \pm 11$  years, respectively. Mean heights were  $165 \pm 7$  and  $164 \pm 7$  cm for patients and controls, respectively. For patients, the proportions of tumors located at the gastric cardia, fundus/body, antrum/pylorus, and whole stomach were 46%, 23%, 29%, and 2%, respectively, and the proportions of well-differentiated, moderately-differentiated, and poorly-differentiated/undifferentiated cancers were 5%, 25%, and 70%, respectively.

### Basic models

Compared to uneducated patients, patients going to primary school (OR=0.55), middle school (OR=0.41), high school (OR=0.45), and college/university (OR=0.25) were significantly associated with less often GaC (Table 1). Alcohol drinking was significantly associated with more frequent GaC (OR=2.46), and per 1 higher FS the odds for GaC increased by 0.10. Smoking was associated with more often GaC (OR=2.26), and the odds for GaC increased by 0.17 per 1 higher FS. The FS for passive

smoking was also significantly associated with GaC (OR=1.21). No significant associations of GaC with marital status, or histories of hepatitis, diabetes, hypertension, or allergy were observed.

Regarding food and liquid intake (Table 2), the FS for intake of pork (OR=0.89), beef (OR=0.84), fish (OR=0.82), and egg (OR=0.84) was significantly inversely associated with GaC. Particularly, the number of eggs eaten per day was significantly negatively associated with GaC (OR=0.74), and not eating any eggs per day was associated with a higher proportion of GaC compared to eating 1 egg per day (OR=2.17). The FS for having processed meat (OR=1.23), pickled food (OR=1.21), dried food (OR=1.26), and smoked/baked food (OR=1.19) was significantly positively associated with GaC. Having vegetables/fruit, beans, cereals, tuber crops, and kelps decreased the odds for GaC by 0.34, 0.25, 0.18, 0.17, and 0.24 per every additional PS, respectively. The FS for use of yellow rice wine (OR=0.81), soy sauce (OR=0.89), vinegar (OR=0.84), onion/garlic (OR=0.81), pepper (OR=0.85), and ginger (OR=0.79) was significantly inversely associated with GaC, while the FS for use of monosodium glutamate (OR=1.09) and chicken essence (OR=1.07) was positively associated with GaC. The PS for sour (OR=0.86), bitter (OR=0.70), and spicy tastes (OR=0.82) was significantly less frequently associated with GaC.

**Table 1.** Basic participant characteristics

| Variable                | Value/comment <sup>1</sup> | Controls       | Patients       | OR (95% CI) <sup>2</sup> | <i>P</i> <sub>trend</sub> |
|-------------------------|----------------------------|----------------|----------------|--------------------------|---------------------------|
| Education               | Uneducated                 | 64 (21)        | 91 (32)        | 1.00 (ref.)              | 0.001                     |
|                         | Primary school             | 84 (28)        | 82 (29)        | 0.55 (0.34-0.88)         |                           |
|                         | Middle school              | 85 (29)        | 69 (24)        | 0.41 (0.25-0.67)         |                           |
|                         | High school                | 32 (11)        | 28 (10)        | 0.45 (0.24-0.85)         |                           |
|                         | College/university         | 33 (11)        | 17 (6)         | 0.25 (0.12-0.52)         |                           |
| Marital status          | Married                    | 269 (89)       | 259 (87)       | 1.00 (ref.)              | 0.322                     |
|                         | Single                     | 33 (11)        | 38 (13)        | 1.29 (0.78-2.15)         |                           |
| Migrant                 | No                         | 258 (85)       | 167 (62)       | 1.00 (ref.)              | <0.001                    |
|                         | Yes                        | 44 (15)        | 102 (38)       | 3.66 (2.37-5.66)         |                           |
| History of hepatitis    | No                         | 296 (98)       | 260 (96)       | 1.00 (ref.)              | 0.310                     |
|                         | Yes                        | 6 (2)          | 10 (4)         | 1.72 (0.60-4.90)         |                           |
| History of diabetes     | No                         | 273 (90)       | 247 (94)       | 1.00 (ref.)              | 0.164                     |
|                         | Yes                        | 29 (10)        | 16 (6)         | 0.63 (0.33-1.21)         |                           |
| History of hypertension | No                         | 224 (74)       | 212 (79)       | 1.00 (ref.)              | 0.112                     |
|                         | Yes                        | 78 (26)        | 55 (21)        | 0.72 (0.48-1.08)         |                           |
| History of allergy      | No                         | 293 (97)       | 258 (96)       | 1.00 (ref.)              | 0.260                     |
|                         | Yes                        | 9 (3)          | 12 (4)         | 1.68 (0.68-4.15)         |                           |
| Alcohol drinking        | No                         | 172 (57)       | 94 (32)        | 1.00 (ref.)              | <0.001                    |
|                         | Yes                        | 129 (43)       | 199 (68)       | 2.46 (1.70-3.57)         |                           |
| Smoking                 | Frequency score            | 2 ± 3; 0 (0-3) | 3 ± 3; 2 (0-5) | 1.10 (1.03-1.19)         | 0.008                     |
|                         | No                         | 106 (35)       | 49 (17)        | 1.00 (ref.)              | <0.001                    |
|                         | Yes                        | 195 (65)       | 242 (83)       | 2.26 (1.51-3.39)         |                           |
| Passive smoking         | Frequency score            | 2 ± 3; 0 (0-1) | 4 ± 4; 3 (0-9) | 1.17 (1.10-1.23)         | <0.001                    |
|                         | Frequency score            | 1 ± 2; 0 (0-2) | 3 ± 3; 2 (0-5) | 1.21 (1.13-1.30)         | <0.001                    |

Categorical variables are shown as count (percentage [%]), and continuous variables as mean ± standard deviation.

<sup>1</sup>Frequency score assignment was as follows: 0, never; 1, ≤1 time per month; 2, 2-3 times per month; 3, 1-2 times per week; 4, 3-4 times per week; 5, 5-6 times per week; 6, 1 time per day; 7, 2 times per day; 8, 3 times per day; 9, ≥4 times per day.

<sup>2</sup>Odds ratio (OR) with 95% confidence interval (CI) for the association of each variable with gastric cancer versus control was calculated using multivariable logistic regression with adjustment for sex and age. Significant ORs are marked in bold. ref., reference.

**Table 2.** Food and liquid intake

| Variable             | Value/comment <sup>1</sup> | Controls       | Patients       | OR (95% CI) <sup>2</sup> | P <sub>trend</sub> |
|----------------------|----------------------------|----------------|----------------|--------------------------|--------------------|
| Pork                 | Frequency score            | 4 ± 2; 4 (3-6) | 4 ± 2; 4 (3-6) | 0.89 (0.81-0.98)         | 0.019              |
| Chicken              | Frequency score            | 3 ± 1; 3 (2-3) | 2 ± 2; 2 (1-3) | 0.95 (0.85-1.07)         | 0.401              |
| Beef                 | Frequency score            | 2 ± 1; 1 (1-2) | 1 ± 1; 1 (1-2) | 0.84 (0.72-0.97)         | 0.021              |
| Fish                 | Frequency score            | 3 ± 1; 3 (2-3) | 2 ± 1; 2 (1-3) | 0.82 (0.72-0.92)         | 0.001              |
| Egg                  | Frequency score            | 4 ± 2; 5 (3-6) | 4 ± 2; 4 (2-5) | 0.84 (0.76-0.92)         | <0.001             |
| Eggs per day         | As continuous              | 1 ± 1; 1 (1-1) | 1 ± 1; 1 (1-1) | 0.74 (0.55-0.98)         | 0.037              |
|                      | 0                          | 40 (13)        | 65 (23)        | 2.17 (1.38-3.40)         | 0.003              |
|                      | 1                          | 229 (76)       | 181 (63)       | 1.00 (ref.)              |                    |
|                      | ≥2                         | 33 (11)        | 41 (14)        | 1.35 (0.81-2.25)         |                    |
| Processed meat       | Frequency score            | 1 ± 1; 0 (0-1) | 1 ± 1; 1 (0-2) | 1.23 (1.08-1.40)         | 0.002              |
| Pickled food         | Frequency score            | 3 ± 2; 2 (1-5) | 4 ± 2; 4 (2-6) | 1.21 (1.12-1.31)         | <0.001             |
| Dried food           | Frequency score            | 1 ± 1; 1 (0-2) | 2 ± 2; 2 (1-3) | 1.26 (1.12-1.41)         | <0.001             |
| Smoked/baked food    | Frequency score            | 1 ± 1; 0 (0-1) | 1 ± 1; 0 (0-1) | 1.19 (1.02-1.38)         | 0.028              |
| Vegetables and fruit | Frequency score            | 6 ± 1; 6 (6-7) | 5 ± 2; 6 (4-7) | 0.66 (0.59-0.73)         | <0.001             |
| Beans                | Frequency score            | 4 ± 2; 4 (3-5) | 3 ± 2; 3 (2-4) | 0.75 (0.67-0.84)         | <0.001             |
| Stewed food          | Frequency score            | 2 ± 1; 1 (1-2) | 2 ± 1; 1 (1-2) | 1.03 (0.91-1.18)         | 0.638              |
| Fried food           | Frequency score            | 1 ± 1; 1 (1-2) | 2 ± 1; 1 (1-2) | 1.07 (0.95-1.21)         | 0.265              |
| Cereals              | Frequency score            | 3 ± 2; 3 (2-4) | 2 ± 2; 2 (1-3) | 0.82 (0.75-0.91)         | <0.001             |
| Tuber crops          | Frequency score            | 3 ± 2; 3 (2-4) | 3 ± 2; 3 (2-3) | 0.83 (0.75-0.93)         | 0.001              |
| Kelps                | Frequency score            | 2 ± 1; 2 (1-3) | 2 ± 1; 2 (1-2) | 0.76 (0.67-0.86)         | <0.001             |
| Yellow rice wine     | Frequency score            | 4 ± 2; 4 (2-6) | 3 ± 2; 2 (0-4) | 0.81 (0.75-0.87)         | <0.001             |
| Soy sauce            | Frequency score            | 5 ± 2; 6 (4-6) | 5 ± 2; 5 (4-6) | 0.89 (0.81-0.97)         | 0.009              |
| Vinegar              | Frequency score            | 4 ± 2; 5 (3-6) | 3 ± 2; 3 (2-6) | 0.84 (0.78-0.91)         | <0.001             |
| Monosodium glutamate | Frequency score            | 3 ± 3; 1 (0-6) | 3 ± 3; 3 (0-6) | 1.09 (1.02-1.16)         | 0.006              |
| Chicken essence      | Frequency score            | 3 ± 3; 2 (0-6) | 3 ± 3; 4 (0-6) | 1.07 (1.01-1.14)         | 0.033              |
| Onion and garlic     | Frequency score            | 6 ± 2; 6 (5-6) | 5 ± 2; 5 (3-7) | 0.81 (0.74-0.89)         | <0.001             |
| Pepper               | Frequency score            | 5 ± 2; 5 (3-6) | 4 ± 2; 4 (2-6) | 0.85 (0.79-0.92)         | <0.001             |
| Ginger               | Frequency score            | 5 ± 2; 6 (5-6) | 5 ± 2; 5 (3-6) | 0.79 (0.72-0.86)         | <0.001             |
| Dairy product        | Frequency score            | 1 ± 2; 0 (0-3) | 1 ± 2; 1 (0-2) | 1.01 (0.92-1.09)         | 0.999              |
| Sour taste           | Preference score           | 3 ± 2; 2 (2-4) | 3 ± 1; 2 (2-4) | 0.86 (0.77-0.97)         | 0.010              |
| Sweet taste          | Preference score           | 4 ± 2; 4 (2-5) | 4 ± 2; 4 (2-5) | 0.91 (0.82-1.01)         | 0.077              |
| Bitter taste         | Preference score           | 3 ± 1; 2 (2-4) | 2 ± 1; 2 (1-3) | 0.70 (0.61-0.80)         | <0.001             |
| Spicy taste          | Preference score           | 4 ± 2; 4 (3-5) | 4 ± 2; 4 (2-5) | 0.82 (0.74-0.91)         | <0.001             |
| Salty taste          | Preference score           | 4 ± 1; 4 (4-5) | 4 ± 2; 4 (3-5) | 0.98 (0.88-1.10)         | 0.747              |

Categorical variables are shown as count (percentage [%]), and continuous variables as mean ± standard deviation.

<sup>1</sup>Frequency score assignment was as follows: 0, never; 1, <1 time per month; 2, 2-3 times per month; 3, 1-2 times per week; 4, 3-4 times per week; 5, 5-6 times per week; 6, 1 time per day; 7, 2 times per day; 8, 3 times per day; 9, ≥4 times per day. Preference score ranged from 1 (extremely dislike) to 7 (extremely like).

<sup>2</sup>Odds ratio (OR) with 95% confidence interval (CI) for the association of each variable with gastric cancer versus control was calculated using multivariable logistic regression with adjustment for sex and age. Significant ORs are marked in bold. ref., reference.

Concerning eating and living habits (Table 3), the number of people living or eating together with was not significantly associated with GaC. Compared to people having majorly vegetables for food, those keeping a balanced diet (OR=2.17) and having majorly meat (OR=3.77) were significantly more likely to have GaC. The majorly frying cooking habit was significantly associated with a higher possibility of GaC compared to majorly steaming/boiling (OR=2.67). Drinking well water was significantly associated with GaC compared to tap water (OR=2.36). The RS for breakfast (OR=1.54), lunch (OR=1.77), and supper (OR=1.78) was significantly positively associated with GaC, while no significant association was shown for degree of satiety. Higher FS for thin liquid intake before meal (OR=1.13), both thick (OR=1.13) and thin liquid intake during meal (OR=1.12), and thin liquid intake after meal (OR=1.19) was associated with increased odds for GaC, while higher FS for thick liquid intake after meal was associated with less frequent GaC (OR=0.89). The FS for overeating (OR=1.47), not sufficiently chewing

(OR=1.16), doing other things while eating (OR=1.13), swallowing hot food without adequate cooling (OR=1.25), eating deteriorated food (OR=1.87), eating overnight food (OR=1.16), eating within 0.5 hours after sports (OR=1.13), and eating midnight snack (OR=1.54) was all significantly positively associated with GaC, while there was no significant association between GaC and having milk before sleep. While eating at home was significantly associated with less frequent GaC (OR=0.88 per 1 FS), eating at canteen was significantly associated with more often GaC (OR=1.12 per 1 FS). The FS for eating box lunch was not significantly associated with GaC. No significant associations were observed for rest hours after meal, or nighttime or noontime sleep hours. Compared to good sleep quality, moderate (OR=1.88) and poor quality (OR=2.81) were associated with increased odds for GaC. The more often one goes to bed regularly and has afternoon nap, the decreased odds for GaC (OR=0.80 and 0.93 per 1 FS, respectively). No significant associations of GaC with housework or exercise were observed.



**Table 3.** Eating and living habits

| Variable                                     | Value/comment <sup>1</sup> | Controls       | Patients       | OR (95% CI) <sup>2</sup> | P <sub>trend</sub> |
|--|----------------------------|----------------|----------------|--------------------------|--------------------|
| No. of people living together with           | As continuous              | 3 ± 2; 2 (1-4) | 3 ± 2; 2 (1-4) | 1.10 (1.00-1.21)         | 0.060              |
| No. of people eating together with           | As continuous              | 2 ± 2; 2 (1-4) | 3 ± 2; 2 (1-4) | 1.05 (0.96-1.15)         | 0.295              |
| Eating habit                                 | Majorly vegetables         | 139 (46)       | 70 (25)        | 1.00 (ref.)              | <0.001             |
|  | Balanced                   | 142 (47)       | 165 (59)       | 2.17 (1.49-3.15)         |                    |
|  | Majorly meat               | 19 (6)         | 43 (15)        | 3.77 (2.00-7.10)         |                    |
| Cooking habit                                | Majorly steaming/boiling   | 280 (93)       | 241 (83)       | 1.00 (ref.)              | <0.001             |
|  | Majorly frying             | 22 (7)         | 51 (17)        | 2.67 (1.55-4.59)         |                    |
| Drinking water                               | Well water                 | 47 (16)        | 88 (30)        | 2.36 (1.57-3.55)         | <0.001             |
|  | Tap water                  | 253 (84)       | 201 (70)       | 1.00 (ref.)              |                    |
| Breakfast                                    | Regularity score           | 2 ± 1; 1 (1-1) | 2 ± 1; 2 (1-3) | 1.54 (1.33-1.79)         | <0.001             |
| Lunch  | Regularity score           | 1 ± 1; 1 (1-1) | 2 ± 1; 2 (1-3) | 1.77 (1.48-2.11)         | <0.001             |
| Supper                                       | Regularity score           | 1 ± 1; 1 (1-1) | 2 ± 1; 2 (1-3) | 1.78 (1.50-2.12)         | <0.001             |
| Degree of satiety                            | As continuous              | 8 ± 4          | 8 ± 2          | 0.99 (0.93-1.06)         | 0.800              |
| Food intake                                  | On diet                    | 42 (14)        | 30 (11)        | 0.78 (0.46-1.32)         | 0.593              |
|  | Normal                     | 195 (66)       | 182 (68)       | 1.00 (ref.)              |                    |
|  | Overeating                 | 59 (20)        | 56 (21)        | 1.05 (0.69-1.61)         |                    |
| Overeating                                   | Frequency score            | 0 ± 1; 0 (0-1) | 1 ± 2; 0 (0-2) | 1.47 (1.28-1.68)         | <0.001             |
| Thick liquid intake before meal              | Frequency score            | 1 ± 2; 0 (0-1) | 1 ± 2; 0 (0-2) | 1.05 (0.95-1.15)         | 0.342              |
| Thin liquid intake before meal               | Frequency score            | 1 ± 2; 0 (0-1) | 2 ± 3; 1 (0-3) | 1.13 (1.05-1.21)         | 0.001              |
| Thick liquid intake during meal              | Frequency score            | 1 ± 2; 0 (0-1) | 2 ± 2; 1 (0-3) | 1.13 (1.03-1.22)         | 0.006              |
| Thin liquid intake during meal               | Frequency score            | 1 ± 2; 0 (0-1) | 2 ± 2; 1 (0-3) | 1.12 (1.04-1.21)         | 0.004              |
| Thick liquid intake after meal               | Frequency score            | 2 ± 3; 1 (0-5) | 2 ± 2; 1 (0-3) | 0.89 (0.83-0.96)         | 0.002              |
| Thin liquid intake after meal                | Frequency score            | 1 ± 3; 0 (0-2) | 3 ± 3; 2 (0-5) | 1.19 (1.11-1.27)         | <0.001             |
| Not sufficiently chewing                     | Frequency score            | 2 ± 2; 1 (0-4) | 3 ± 3; 2 (0-5) | 1.16 (1.08-1.23)         | <0.001             |
| Doing other things while eating              | Frequency score            | 1 ± 2; 0 (0-1) | 2 ± 2; 0 (0-2) | 1.13 (1.04-1.22)         | 0.005              |
| Swallowing hot food without adequate cooling | Frequency score            | 1 ± 2; 0 (0-2) | 3 ± 3; 2 (0-5) | 1.25 (1.16-1.35)         | <0.001             |
| Eating deteriorated food                     | Frequency score            | 0 ± 1; 0 (0-0) | 1 ± 1; 0 (0-1) | 1.87 (1.48-2.35)         | <0.001             |
| Eating overnight food                        | Frequency score            | 2 ± 2; 2 (0-4) | 3 ± 3; 3 (1-5) | 1.16 (1.06-1.26)         | 0.001              |
| Eating within 0.5 h after sports             | Frequency score            | 1 ± 2; 0 (0-2) | 2 ± 2; 1 (0-3) | 1.13 (1.03-1.23)         | 0.008              |
| Rest hours after meal                        | As continuous              | 1 ± 1; 1 (0-1) | 1 ± 1; 1 (1-1) | 1.05 (0.82-1.34)         | 0.723              |
| Eating midnight snack                        | Frequency score            | 0 ± 1; 0 (0-0) | 1 ± 2; 0 (0-1) | 1.54 (1.29-1.83)         | <0.001             |
| Eating at home                               | Frequency score            | 7 ± 2; 8 (7-8) | 7 ± 2; 8 (6-8) | 0.88 (0.81-0.96)         | 0.004              |
| Eating at canteen                            | Frequency score            | 1 ± 2; 0 (0-0) | 1 ± 2; 0 (0-1) | 1.12 (1.02-1.22)         | 0.017              |
| Eating box lunch                             | Frequency score            | 1 ± 2; 0 (0-1) | 1 ± 2; 1 (0-2) | 1.06 (0.96-1.17)         | 0.256              |
| Milk before sleep                            | Frequency score            | 1 ± 2; 0 (0-1) | 1 ± 1; 0 (0-1) | 0.93 (0.84-1.03)         | 0.183              |
| Nighttime sleep hours                        | As continuous              | 8 ± 1; 8 (7-8) | 8 ± 1; 8 (7-8) | 0.94 (0.84-1.06)         | 0.341              |
| Noontime sleep hours                         | As continuous              | 1 ± 1; 1 (1-2) | 1 ± 1; 1 (0-2) | 0.99 (0.81-1.23)         | 0.957              |
| Sleep quality                                | Good                       | 94 (31)        | 46 (17)        | 1.00 (ref.)              | <0.001             |
|  | Moderate                   | 90 (30)        | 82 (31)        | 1.88 (1.17-3.02)         |                    |
|  | Poor                       | 115 (38)       | 140 (52)       | 2.81 (1.80-4.39)         |                    |
| Going to bed regularly                       | Frequency score            | 5 ± 2; 6 (4-6) | 4 ± 2; 4 (1-6) | 0.80 (0.74-0.87)         | <0.001             |
| Dreaming                                     | Frequency score            | 3 ± 2; 3 (1-5) | 3 ± 2; 3 (2-5) | 1.02 (0.94-1.11)         | 0.608              |
| Afternoon nap                                | Frequency score            | 4 ± 2; 4 (1-6) | 3 ± 2; 4 (1-6) | 0.93 (0.87-1.00)         | 0.048              |
| Heavy housework                              | Frequency score            | 3 ± 3; 3 (1-6) | 3 ± 3; 2 (1-6) | 1.00 (0.94-1.07)         | 0.925              |
| Light housework                              | Frequency score            | 5 ± 2; 5 (3-6) | 4 ± 3; 5 (2-6) | 1.01 (0.94-1.09)         | 0.724              |
| Housework hours per day                      | As continuous              | 2 ± 2; 2 (1-4) | 3 ± 2; 2 (1-3) | 1.06 (0.98-1.15)         | 0.158              |
| Exercise                                     | Frequency score            | 3 ± 3; 3 (0-6) | 3 ± 3; 3 (0-5) | 0.95 (0.89-1.01)         | 0.081              |
| Exercise hours per day                       | As continuous              | 2 ± 3; 1 (0-3) | 2 ± 3; 1 (0-3) | 1.02 (0.96-1.09)         | 0.491              |

Categorical variables are shown as count (percentage [%]), and continuous variables as mean ± standard deviation.

<sup>1</sup>Regularity score ranged from 1 (very regular) to 5 (very irregular). Frequency score assignment was as follows: 0, never; 1, ≤1 time per month; 2, 2-3 times per month; 3, 1-2 times per week; 4, 3-4 times per week; 5, 5-6 times per week; 6, 1 time per day; 7, 2 times per day; 8, 3 times per day; 9, ≥4 times per day.

<sup>2</sup>Odds ratio (OR) with 95% confidence interval (CI) for the association of each variable with gastric cancer versus control was calculated using multivariable logistic regression with adjustment for sex and age. Significant ORs are marked in bold. ref., reference.

### Final multivariable model

In the final multivariable model (Table 4), participants receiving primary school (OR=0.27) or middle school education (OR=0.21) had significantly less often GaC compared to those uneducated. Compared to people keeping a balanced diet, those having majorly vegetables had significantly less frequently GaC (OR=0.23). The majorly frying cooking habit was significantly associated with a higher incidence of GaC compared to the majorly steaming/boiling habit (OR=10.23). Compared to people having good sleep quality, those complaining

about poor sleep quality had significantly more often GaC (OR=3.18). The more often one smoked, the more often he/she had GaC (OR=1.28 per 1 FS). Higher FS for having pickled food was significantly associated with more frequent GaC (OR=1.41), while having more frequently vegetables/fruit (OR=0.60), beans (OR=0.73), or kelps (OR=0.72) was significantly associated with less often GaC. A greater PS for sour (OR=0.77) or bitter taste (OR=0.50) was significantly associated with less frequent GaC. The FS for thin liquid intake after meal (OR=1.27), swallowing hot food without adequate cooling (OR=1.21), doing other

things while eating (OR=1.23), eating overnight food (OR=1.25), and eating midnight snack (OR=1.49) was all significantly positively associated with GaC, while going to bed regularly was significantly associated with less often GaC (OR=0.81 per 1 FS).

The association patterns for cardia and non-cardia cancers were mostly similar with the whole cases, only with few exceptions. For cardia cancers, The FS for having eggs was significantly associated with less often GaC (OR=0.32). The FS for eating vegetables/fruit was more strongly associated with reduced cardia carcinoma frequency (OR=0.16) compared to overall and non-cardia carcinomas. The FS for vinegar use (OR=0.65) and the PS for spicy taste (OR=0.57) were only significantly negatively associated with non-cardia cancers. More frequent pepper use was only significantly associated with less often cardia cancers (OR=0.47), and more often thin liquid intake during meal (OR=2.27), more often chewing insufficiently (OR=2.69), more frequently eating deteriorated food (OR=7.84), and more

irregular supper intake (OR=6.37) were only significantly associated with more frequent cardia cancers.

## Discussion

This study comprehensively reported eating and living habits associated with GaC in a large Chinese population, offering further insights into potentially modifiable factors and providing important evidence for making GaC-preventive strategies. Furthermore, some differences in association patterns and/or strengths between cardia and non-cardia cancers were found for some factors.

We found that people receiving primary or middle school education had significantly less often GaC compared to uneducated people, which is consistent with some previous studies showing that better education was associated with reduced GaC risk [18, 19].

**Table 4.** Factors associated with gastric cancer using full multivariable-adjusted model, overall and by location

| Variable                                     | Value/comment <sup>1</sup> | Overall gastric cancer   |                           | Cardia cancer            |                           | Non-cardia cancer        |                           |
|--|----------------------------|--------------------------|---------------------------|--------------------------|---------------------------|--------------------------|---------------------------|
|  |                            | OR (95% CI) <sup>2</sup> | <i>P</i> <sub>trend</sub> | OR (95% CI) <sup>2</sup> | <i>P</i> <sub>trend</sub> | OR (95% CI) <sup>2</sup> | <i>P</i> <sub>trend</sub> |
| Education                                    | Uneducated                 | 1.00 (ref.)              | <b>0.014</b>              | 1.00 (ref.)              | <b>0.079</b>              | 1.00 (ref.)              | <b>0.012</b>              |
|  | Primary school             | 0.27 (0.09-0.78)         |                           | 0.03 (<0.01-0.83)        |                           | 0.11 (0.02-0.64)         |                           |
|  | Middle school              | 0.21 (0.06-0.72)         |                           | <0.01 (<0.01-0.12)       |                           | 0.21 (0.03-1.34)         |                           |
|  | High school                | 1.51 (0.38-6.03)         |                           | 0.09 (<0.01-4.27)        |                           | 1.81 (0.24-14.00)        |                           |
| Eating habit                                 | College/university         | 0.46 (0.10-2.12)         |                           | 0.20 (<0.01-15.73)       |                           | 0.05 (<0.01-0.66)        |                           |
|  | Majorly vegetables         | 0.23 (0.09-0.56)         | <b>0.003</b>              | 0.03 (<0.01-0.44)        | <b>0.037</b>              | 0.11 (0.02-0.46)         | <b>0.011</b>              |
|  | Balanced                   | 1.00 (ref.)              |                           | 1.00 (ref.)              |                           | 1.00 (ref.)              |                           |
| Cooking habit                                | Majorly meat               | 0.34 (0.10-1.19)         |                           | 0.32 (0.01-9.57)         |                           | 0.43 (0.07-2.62)         |                           |
|  | Majorly steaming/boiling   | 1.00 (ref.)              | <b>0.001</b>              |                          |                           |                          |                           |
| Sleep quality                                | Majorly frying             | 10.23 (2.70-38.80)       |                           |                          |                           |                          |                           |
|  | Good                       | 1.00 (ref.)              | <b>0.015</b>              |                          |                           |                          |                           |
|  | Moderate                   | 1.01 (0.38-2.70)         |                           |                          |                           |                          |                           |
|  | Poor                       | 3.18 (1.23-8.23)         |                           |                          |                           |                          |                           |
| Smoking                                      | Frequency score            | 1.28 (1.12-1.46)         | <b>&lt;0.001</b>          | 1.64 (1.12-2.41)         | <b>0.012</b>              | 1.32 (1.07-1.61)         | <b>0.009</b>              |
| Egg  | Frequency score            |                          |                           | 0.32 (0.12-0.83)         | <b>0.019</b>              |                          |                           |
| Pickled food                                 | Frequency score            | 1.41 (1.16-1.71)         | <b>&lt;0.001</b>          | 2.00 (1.10-3.63)         | <b>0.023</b>              | 1.55 (1.12-2.14)         | <b>0.008</b>              |
| Vegetables and fruit                         | Frequency score            | 0.60 (0.46-0.79)         | <b>&lt;0.001</b>          | 0.16 (0.06-0.45)         | <b>0.001</b>              | 0.73 (0.51-1.05)         | <b>0.094</b>              |
| Beans  | Frequency score            | 0.73 (0.55-0.97)         | <b>0.032</b>              |                          |                           | 0.54 (0.35-0.86)         | <b>0.009</b>              |
| Kelps  | Frequency score            | 0.72 (0.54-0.96)         | <b>0.026</b>              | 0.24 (0.09-0.61)         | <b>0.003</b>              |                          |                           |
| Vinegar                                      | Frequency score            |                          |                           |                          |                           | 0.65 (0.46-0.92)         | <b>0.015</b>              |
| Pepper                                       | Frequency score            | 0.84 (0.68-1.03)         | <b>0.090</b>              | 0.47 (0.26-0.83)         | <b>0.010</b>              |                          |                           |
| Sour taste                                   | Preference score           | 0.77 (0.59-1.00)         | <b>0.047</b>              |                          |                           |                          |                           |
| Bitter taste                                 | Preference score           | 0.50 (0.36-0.69)         | <b>&lt;0.001</b>          | 0.14 (0.05-0.41)         | <b>&lt;0.001</b>          | 0.38 (0.22-0.65)         | <b>0.001</b>              |
| Spicy taste                                  | Preference score           |                          |                           |                          |                           | 0.57 (0.38-0.86)         | <b>0.008</b>              |
| Thin liquid intake during meal               | Frequency score            |                          |                           | 2.27 (1.12-4.61)         | <b>0.024</b>              |                          |                           |
| Thin liquid intake after meal                | Frequency score            | 1.27 (1.06-1.52)         | <b>0.008</b>              |                          |                           | 1.45 (1.12-1.87)         | <b>0.005</b>              |
| Swallowing hot food without adequate cooling | Frequency score            | 1.21 (1.00-1.47)         | <b>0.045</b>              |                          |                           | 1.44 (1.07-1.95)         | <b>0.017</b>              |
| Supper                                       | Regularity score           |                          |                           | 6.37 (1.20-33.88)        | <b>0.030</b>              |                          |                           |
| Not sufficiently chewing                     | Frequency score            | 1.18 (1.00-1.40)         | <b>0.058</b>              | 2.69 (1.48-4.86)         | <b>0.001</b>              |                          |                           |
| Doing other things while eating              | Frequency score            | 1.23 (1.01-1.50)         | <b>0.041</b>              |                          |                           | 1.50 (1.10-2.05)         | <b>0.011</b>              |
| Eating deteriorated food                     | Frequency score            | 1.37 (0.95-1.96)         | <b>0.093</b>              | 7.84 (2.32-26.49)        | <b>0.001</b>              |                          |                           |
| Eating overnight food                        | Frequency score            | 1.25 (1.03-1.52)         | <b>0.025</b>              |                          |                           | 1.57 (1.13-2.18)         | <b>0.007</b>              |
| Eating midnight snack                        | Frequency score            | 1.49 (1.09-2.03)         | <b>0.013</b>              | 3.57 (1.04-12.30)        | <b>0.044</b>              | 2.04 (1.22-3.41)         | <b>0.007</b>              |
| Going to bed regularly                       | Frequency score            | 0.81 (0.68-0.96)         | <b>0.018</b>              |                          |                           | 0.74 (0.56-0.96)         | <b>0.025</b>              |

<sup>1</sup>Frequency score assignment was as follows: 0, never; 1,  $\leq 1$  time per month; 2, 2-3 times per month; 3, 1-2 times per week; 4, 3-4 times per week; 5, 5-6 times per week; 6, 1 time per day; 7, 2 times per day; 8, 3 times per day; 9,  $\geq 4$  times per day. Preference score ranged from 1 (extremely dislike) to 7 (extremely like). Regularity score ranged from 1 (very regular) to 5 (very irregular).

<sup>2</sup>Odds ratio (OR) with 95% confidence interval (CI) for the association of each variable with cancer (overall, cardia, and non-cardia) versus control was calculated using multivariable logistic regression with adjustment for sex, age, and all significant variables identified in the preliminary models adjusting for sex and age only. Results with  $P < 0.10$  are shown, and significant ORs with  $P < 0.05$  are marked in bold. ref., reference.

Better education could help to form and keep healthy eating and living habits, while well-educated people might face greater pressure in this competitive modern era. The associations for those receiving high school and college/university education were insignificant in overall patients and most subgroups, which could be partly explained by the small case numbers in these groups. People having majorly vegetables for food had significantly less frequent GaC, which is also supported by previous studies [20, 21]. Furthermore, we found that more frequent vegetable/fruit intake was significantly associated with a reduced frequency of cardia cancer but not of non-cardia cancer. Previous evidence remains controversial regarding the association between red meat intake and GaC risk [16], and The Netherlands Cohort Study did not show a significant association [15]. The insignificance for the habit of majorly meat intake in our study might be partly explained by the paucity of participants in that group. The majorly frying cooking habit, which could generate various carcinogenic substances in a temperature-dependent manner, was associated with a higher overall GaC incidence compared to majorly steaming/boiling. We found that poor sleep quality was significantly associated with a higher GaC incidence compared to good quality. Notably, sleep quality could be influenced by various factors like time to go to bed and psychiatric status. We further found that the frequency of going to bed regularly was significantly associated with a reduced risk of GaC especially non-cardia cancer. Our finding that smoking was associated with GaC in a dose-dependent manner was well supported by previous literature [22]; however, we did not observe a significant association for alcohol drinking frequency, on which previous evidence remains controversial [14].

The frequency of pickled food intake, a well-recognized risk factor for GaC [23], was associated with increased risks of both cardia and non-cardia cancers. Interestingly, more frequent egg intake was significantly associated with a reduced risk of cardia cancer but not of non-cardia cancer. While higher frequencies of intake of beans and kelps were both significantly associated with a decreased overall GaC risk, beans intake was significantly associated with non-cardia cancer and kelps intake with cardia cancer. More often vinegar use was significantly associated with a reduced non-cardia cancer risk, and a greater preference for sour taste was significantly associated with a lower overall GaC risk. We previously reported that distal GaC was mostly associated with hypoacidity [24], and adequate acidification of inner-stomach environment might be protective against malignancy, possibly by inhibiting

growth and proliferation of organisms. More frequent pepper use was associated with a lower incidence of cardia cancer, and a greater preference of spicy taste was significantly associated with a lower cardia cancer risk. However, an early study [25] reported that Chili pepper consumption was positively associated with GaC risk. The discrepancies from our findings could be possibly due to the different strains between Asia and South America. Notably, a greater preference for bitter taste was significantly associated with reduced incidences of both cardia and non-cardia cancers. The associations with various food and seasoning intake and flavor preference offer important clues for easy GaC-preventative strategy making, which should be further validated by prospective studies.

Some specific eating habits were further found to be associated with GaC risk through multivariable analysis. The more often one had thin liquid during meal, the more probably he/she had cardia adenocarcinoma, while more frequent thin liquid intake after meal was significantly associated with an increased risk of non-cardia cancer. Thin liquid intake during/after meal could dilute the gastric liquid, thus increasing the burden of stomach. Notably, we did not observe a significant association for thick liquid intake. Swallowing hot food without adequate cooling was associated with an increased GaC risk, which might be due to the damaging effect of heat to gastric mucosa. Insufficiently chewing was associated with an increased GaC risk, which could be attributed to the increased digestive burden for the stomach. Doing other things while eating could reduce the blood flow to the stomach, potentially causing the organ to be more vulnerable. The frequencies of eating deteriorated and overnight food, which might contain increased carcinogenic microorganisms and chemical compounds, were both associated with an increased GaC risk. Among 3 meals in a day, only the irregularity degree of supper was significantly associated with cardia cancer. A short interval between having supper and going to bed could induce and accelerate reflux, a risk factor for cardia cancer. Accordingly, eating midnight snack was significantly associated with an increased GaC risk. Nearly all of these potential GaC risk factors could be modifiable. If prospectively validated, GaC-preventative strategies could be accordingly made.

This case-control study was limited by its retrospective observational nature. The associations observed do not suggest causality, and should be validated in prospective cohorts. Recall bias could affect the accuracy of the results. There could be other risk factors that have not been accounted for in this study (*e.g.*, depression). *Hp* infection status was not

adjusted for in this study, considering that the measure for cancer patients might not reflect the real pre-cancer status. Some originally *Hp*-infected patients may have the infection status turn negative during the development of cancer. Furthermore, it would be difficult to know the exact duration of infection which might differ largely between the patient and control groups. The case numbers in some subgroups were not large enough to obtain statistical significance, and larger relevant studies are encouraged. Notably, the risk factors for GaC in Western people could be different from those in Asian people. Molecular and genetic risk factors could potentially further help to identify people at risk.

Our study is a large comprehensive investigation on various easily modifiable factors potentially causing GaC in Asian people. Further subgroup analyses according to tumor location were conducted. While some identified GaC-associated factors have been reported previously, there are various newly detected modifiable and preventable eating and living habits, which provide important informative clues for future investigations and which will contribute greatly to GaC prevention if validated prospectively. Once validated, the findings can serve as references for making effective population-based strategies to prevent GaC. Through health education campaigns to raise the public awareness of the modifiable and preventable factors associated with GaC, it can be expected that a significant proportion of GaC cases can be avoided in a cost-effective manner, especially for individuals without *Hp* infection who may have poorer prognosis if developing GaC [26]. Our evidence-based findings provide novel clues to help to identify people at a high risk of GaC which can be potentially used for risk-adapted screening and which may contribute to early diagnosis. Modifying the validated factors may even help to prolong survival and improve quality of life for patients with GaC, and further studies in these aspects are needed.

In conclusion, education level, sleep quality, smoking, the frequencies of use of several foods and seasonings, the preference for specific tastes, and various eating and living habits were significantly associated with GaC, with some location-specific differences. Our findings offer important hints for further prospective investigations and for easy effective GaC-preventative strategy making.

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## Authors' contributions

Huang L, Chen L, Gui ZX, Liu S, Wei ZJ, and Xu AM designed the research; Huang L, Chen L, Gui ZX, Liu S, and Wei ZJ performed the research; Huang L analyzed and interpreted the data, and wrote the manuscript; Chen L, Gui ZX, Liu S, Wei ZJ, and Xu AM critically reviewed the paper.

## Ethics approval and consent to participate

This study was approved by the Institutional Review Board of First Affiliated Hospital of Anhui Medical University. Written informed consent was obtained from each investigated individual. No individual patient data were reported.

## Availability of data and materials

The data that support the findings of this study are available from our center but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available.

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## Competing Interests

The authors have declared that no competing interest exists.

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