Am J Transl Res 2024;16(2):617-624
www.ajtr.org /ISSN:1943-8141/AJTR0154759

Original Article

Pepsinogen II and a no-pickled food diet are risk factors for female patients with anxiety: a cross-sectional study

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Received December 4, 2023; Accepted February 10, 2024; Epub February 15, 2024; Published February 28, 2024

Abstract: Objectives: No studies have evaluated the relationship between lifestyle and Pepsinogen (PG)I, PGII and Gastrin (G)17 in patients with anxiety. Using data from the Affiliated Hospital of Xuzhou Medical University study, we aimed to identify factors associated with anxiety. Methods: We conducted a retrospective cross-sectional observational study involving 779 Chinese healthy checkup participants (301 males; mean age, 47.60±16.17 years) who underwent stomach-related health examinations. Results: Anxiety was defined as a Hamilton Anxiety Scale (HAM-A) Scale score ≥14. The odds ratios, with 95% confidence intervals, were calculated using binary logistic analysis to assess the risk of anxiety and healthy checkup participants while adjusting for several covariates. In the HAM-A≥14 group (anxiety group), sex, PGII and pickled dishes were independent influencing factors. Binary logistic regression analysis revealed a significant difference in anxiety risk between the high PGII group and the low PGII group for females (P=0.005). There was also a significant difference in anxiety risk between the groups consuming pickled and non-pickled food for females (P=0.010). Logistic regression analysis indicated a higher risk of anxiety in females aged ≤50 years who belonged to the high PGII + no pickled foods group. Conclusions: Our study revealed that in females aged ≤50 years, high levels of PGII and no pickled foods were associated with a higher risk of anxiety.

Keywords: Healthy checkup participants, anxiety, PG, gastrin 17, screening

Introduction

Anxiety and depression, the most common mental health disorders, have a significant impact on a large portion of the global population though the gut-brain axis [1]. Previous studies have demonstrated a strong association between anxiety and depression with irritable bowel syndrome (IBS) [2]. Furthermore, transcutaneous auricular vagal nerve stimulation has been shown to alleviate symptoms of dyspepsia as well as depression/anxiety, while also improving gastric functions such as accommodation and slow waves [3]. Additionally, it has been found that emotional stress like anxiety and depression can lead to changes in both gastric acid secretion and gastric motility [4, 5].

In recent years, there has been increasing attention on stomach health. However, approximately 67.5% of people in China have never undergone stomach-related tests, such as Helicobacter pylori (Hp) test [6]. The most common reasons for not undergoing these tests were "no symptoms" (55.7%) and "lack of knowledge about the benefits of this test" (21.1%). Therefore, many healthy individuals do not understand their own stomachs. Furthermore, healthy individuals with anxiety often experience upset stomachs, and combining acid suppressants with anti-anxiety medication can improve clinical symptoms [7, 8]. Additionally, a study involving 1001 participants who underwent endoscopy showed that anxiety was significantly associated with the prevalence of dyspepsia and postprandial discomfort syndrome [9]. Serum pepsinogen (PG)I, PGII and gastrin (G)17 can reflect the secretory function of the gastric mucosa, which has been used in large-scale screening for early gastric cancer in China and has achieved notable results [10]. Currently, there is no literature report on the relationship between anxiety, depression and PGI, PGII and G17 in healthy individuals. The literature has demonstrated that the consumption of pickles/pickled food can lead to atrophic changes in the gastric mucosa, resulting in a gradual decrease

https://doi.org/10.62347/TZRM6783

Table 1. Characteristics of the study participants

	Anxiety	Non-anxiety	P
Number	224	555	
Age, y	50 (37, 58)	50 (34, 59)	0.596
Under 50 y	104 (46.43%)	276 (49.73%)	0.429
Gender, male	60 (26.78%)	241 (43.42%)	<0.001
PGI, μg/L	122.07 (95.75, 169.21)	128.61 (99.77, 169.31)	0.501
PGII, μg/L	9.98 (6.12, 16.71)	8.45 (5.45, 13.88)	0.003
PGR	12.73 (8.94, 18.06)	14.76 (10.60, 20.83)	<0.001
G17, pmol/L	4.88 (2.38, 18.80)	6.27 (2.3, 15.63)	0.281
Salty food	46 (20.54%)	103 (18.56%)	0.546
Spicy food	59 (26.34%)	(30.81%)	0.226
Pickles	46 (20.54%)	158 (28.47%)	0.024
Smoking	15 (6.70%)	76 (15.87%)	0.006
Drinking	19 (8.48%)	81 (14.59%)	0.024
H. pylori	132 (58.93%)	359 (64.64%)	0.140

Anxiety means HAM-A≥14; non-anxiety means HAM-A<14.

in pepsinogen levels over time [11]. It has been hypothesized that the intake of pickled foods may contribute to the pathogenesis of gastric cancer [10]. In general, prolonged consumption of pickled food exerts detrimental effects on the gastric mucosa. Therefore, we conducted this retrospective observational study to determine whether anxiety contribute to changes in PGI, PGII and G17 levels and whether they are affected by the pickled diet among healthy individuals.

The aim of this study was to evaluate the associations between anxiety [as determined by the Hamilton Anxiety Scale (HAM-A) scales] and PGI, PGII, G17 levels and a pickled diet among healthy individuals.

Materials and methods

Study population

This retrospective cross-sectional observational study was approved by the ethics committee of the Affiliated Hospital of Xuzhou Medical University (Approval no. XYFY2020-KL045-01), and written informed consent was obtained from all participants. The study was conducted between April 2020 and April 2022 at the Affiliated Hospital of Xuzhou Medical University, China. The subjects were healthy individuals who underwent stomach examinations in the outpatient department and physical examination center of the Affiliated Hospital of Xuzhou Medical University. The socioeconomic status and education level of the patients were similar to that of the average residents in Xuzhou residents, with slight variations from low to high levels. Inclusion criteria: participants had to be between 18 and 80 years old; a proportion of the study participants completed a checkup assessment, which included a general questionnaire survey, anthropometric measurements, serum PGI, PGII, G17, 13 carbon breath test; participants underwent standard gastroscopy to rule out moderate to severe gastritis, gastric ulcers, gastric atrophy and intestinal metaplasia, as well as stomach cancer; and the participants were evaluated for anxiety levels using the HAM-A scale. Exclusion criteria: the participants who presented with neoplastic diseases; previous use of histamine H2-blockers or proton-pump inhibitors within the past 2 months; history of psychiatric disorders, thyroid disorders, or inflammatory disorders; severe liver or kidney dysfunction; presence of tumors; history of stroke or cardiovascular disease. Out of 1656 individuals who underwent all relevant evaluations for this study's purpose(s), a total number of 857 participants were excluded due to various reasons: 757 individuals taking acid-suppressing drugs; 51 individuals who did not provide consent to participate or had incomplete data; 26 individuals with a history of Hp eradication treatment; and 23 individuals with relevant medical histories unrelated to our research objectives. Ultimately, the final sample size consisted of 779 participants (301 males and 478 females) (**Table 1**).

Data collection

Participants completed questionnaires regarding high salt diet (defined as an average salt intake greater than 20 g/day), spicy diet (defined as consuming spicy food more than 3 times/week), pickled foods (defined as consumption greater than 3 times/week), drinking habits (defined as alcohol intake greater than 50 g/day), smoking habits (defined as smoking more than one cigarette/day). Blood analysis included determination of serum PGI, PGII, and G17 levels, as well as recording of 13-carbon breath test. Anxiety was assessed based on the HAM-A Scale [12].

HAM-A Scale

The anxiety levels of patients were assessed using the HAM-A Scale in this study, with the results serving as the indicators of anxiety. The HAM-A Scale consists of 14 items that measure the severity of a patient's anxiety, including the general factor such as anxiety, nervousness, fear, insomnia, physical complaints, and behavior, as well as somatic symptoms like gastro-intestinal, genito-urinary, respiratory, cardiovascular, somatic general and autonomic symptoms [13]. Each item is rated on a five-point Likert scale ranging from 0 (never) to 4 (extremely often), with higher scores indicating greater levels of anxiety [14]. Two trained assessors evaluated the HAM-A Scale through conversation and observation before scoring independently. A total score between 0-30 is possible on the HAM-A Scale; scores ≥14 are generally considered indicative of an anxious state [15].

H. pylori (Hp) infection was defined based on a positive 13-carbon breath test (DOB≥4)

All participants underwent 13C-UBT examination using the Shenzhen Hedway device [16]. The specific examination process involved the patient exhaling into the first bag of air on an empty stomach. Then, they took 75 mg 13-carbon carbon and waited for 30 minutes before exhaling into the second bag. The results of both bags of exhaled air were analyzed using the HCBT-01 breath test instrument. A value of DOB≥4 indicated a positive result for Hp.

Endoscopic examination [17]

All participants underwent gastroscopy and then received the results. Healthy individuals are defined as those without gastric ulcers, erosive gastritis, atrophic gastritis, gastric cancer, and other stomach diseases.

Statistical analysis

An independent statistician conducted all analyses using SPSS version 23.0 for Windows software (IBM Corp., Armonk, NY, USA), and a significance level of $P<0.05$ was considered in all tests. The data presented in this article include information up until December 2022. Categorical variables were reported as frequencies and proportions, while continuous variables were described by their median and interquartile range. These variables were compared using the Chi-square test, Fisher's exact test, or Wilcoxon rank-sum test. A logistic regression model was employed to assess the risk for anxiety. To investigate factors associated with the prevalence of anxiety, all significant variables from the univariate analysis were included in the binary model. An interaction test was conducted to examine whether the odds ratios (ORs) remained consistent across the stratified groups.

Results

Basic characteristics

In the HAM-A≥14 group, which represents the anxious group, the proportion of males was significantly lower ($P<0.001$), PGII levels were increased ($P=0.003$), while PGR levels were decreased ($P<0.001$). Additionally, the proportion of individuals who enjoyed eating pickled diets ($P=0.024$), smoking ($P=0.006$) and drinking ($P=0.024$) were significantly reduced. However, there were no differences in age, PGI levels, G17 levels, consumption of high-salt food or overly spicy diet or Hp infection status (**Table 1**).

The binary logistic analysis revealed that gender (OR, 0.518; 95% CI, 0.349-0.768), PGII (OR, 1.026; 95% CI, 1.004-1.047) and pickled diets (OR, 0.610; 95% CI, 0.416-0.895) were independent influencing factors in the HAM-A≥14 group (**Table 2**).

The risk of anxiety was associated with the expression of PGII and pickled food

All participants were divided into a high PGII group and a low PGII group using the median method. It was shown that there was a signifi-

Table 2. Binary regression analysis of characteristics of all patients

Variable	Univariate logistic			Binary logistic		
	OR	95% CI	P	OR	95% CI	P
Gender	0.477	0.339-0.670	<0.001	0.518	0.349-0.768	0.001
PGII	1.029	1.011-1.046	0.001	1.026	1.004-1.047	0.018
PGR	0.974	0.957-0.991	0.003	0.987	0.969-1.006	0.168
Pickles	0.649	0.447-0.943	0.023	0.610	0.416-0.895	0.012
Smoking	0.452	0.254-0.806	0.007	0.626	0.319-1.228	0.173
Drinking	0.542	0.321-0.918	0.023	1.014	0.544-1.888	0.965

Table 3. Characteristics of the study participants with the level of PGII

	Low PGII	High PGII	P
Number	388	391	
Age, y	53.00 (20.00, 61.00)	62.00 (55.00, 67.00)	<0.001
Under 50 y	232 (59.79%)	221 (56.52%)	0.355
Gender, male	141 (36.34%)	160 (40.92%)	0.190
PGI, μg/L	95.89 (75.97, 127.38)	122.48 (114.11, 134.56)	<0.001
PGII, μg/L	5.37 (4.27, 5.45)	9.39 (8.99, 12.58)	<0.001
PGR	17.59 (14.15, 29.83)	12.69 (12.59, 13.04)	<0.001
G17, pmol/L	3.72 (1.07, 7.01)	6.27 (3.88, 21.47)	<0.001
Salty food	68 (33.33%)	81 (16.40%)	0.886
Spicy food	99 (48.53%)	131 (22.78%)	0.133
Pickles	76 (25.25%)	128 (26.78%)	0.580
Smoking	25 (12.25%)	66 (11.48%)	0.235
Drinking	36 (17.65%)	64 (11.13%)	0.548
Hp	217 (55.93%)	274 (70.08%)	<0.001
Anxiety	46 (22.55%)	178 (30.96%)	0.032

cant difference in anxiety risk between the high PGII group and the low PGII group (P=0.032) (**Table 3**).

Binary logistic regression analysis revealed a significant difference in anxiety risk between the high PGII group and the low PGII group among females (OR, 1.032; 95% CI, 1.010-1.055), but no difference was observed in males. Furthermore, there was a significant difference in anxiety risk between females consuming pickled food and those not consuming pickled food (OR, 0.551; 95% CI, 0.349-0.867), while no difference was found in males (**Table 4**).

The risk of anxiety was higher in the high PGII group and the no pickled foods group in females ≤50 years old

Females were divided into a group aged ≤50 years old and a group aged >50 years old using the median method. Binary logistic regression analysis showed that the risk of anxiety in the group aged ≤50 years old was significantly higher than in the low PGII group (OR, 1.804; 95% CI, 1.045-3.115). However, there was no difference in the group aged >50. Additionally, the risk of anxiety in the pickled foods group aged ≤50 years old was significantly lower than that in the no pickles group (OR, 0.297; 95% CI, 0.132-0.667), but there was no difference in the pickles group aged >50 years old (**Table 5**).

The highest risk of anxiety was found in the high PGII group of females under 50

We classified females aged ≤50 years into 4 groups (low PGII + no pickles, low PGII + pickled foods, high PGII + no pickled foods, and high PGII + pickled foods) and conducted additional risk analysis. Logistic regression analysis revealed that the risk of anxiety in the high PGII + no pickled foods group was higher than that in the low PGII + no pickled foods, low PGII + pickled foods, and high PGII + pickled foods groups

Table 4. Association of anxiety with the expression level of PGII and Pickles food

All	OR	95% CI	P
Males			
HAM-A≥14			
High PGII/low PGII	1.299	0.733-2.302	0.370
Pickles/no Pickles	0.879	0.452-1.707	0.703
Females			
HAM-A≥14			
High PGII/low PGII	1.032	1.010-1.055	0.005
Pickles/no Pickles	0.551	0.349-0.867	0.010

Table 5. Relationship of anxiety with the expression level of PGII and Pickles food in females

All	OR	95% CI	P
HAM-A≥14			
Age ≤50 years			
High PGII/low PGII	1.804	1.045-3.115	0.034
Pickles/no Pickles	0.297	0.132-0.667	0.003
Age >50 years			
High PGII/low PGII	1.317	0.770-2.254	0.315
Pickles/no Pickles	0.772	0.433-1.376	0.380

Table 6. Relationship of anxiety with the expression level of PGII and Pickles food in females under 50

All	OR	95% CI	P
HAM-A≥14			
Low PGII + no Pickled food	1		
Low PGII + Pickled food	0.560	0.210-1.492	0.246
High PGII + Pickled food	0.626	0.378-1.037	0.069
High PGII + no Pickled food	1.508	1.114-2.040	0.008
Low PGII + Pickled food	1		
High PGII + Pickled food	0.662	0.282-1.556	0.344
High PGII + no Pickled food	4.060	1.498-11	0.006
High PGII + Pickled food	1		
High PGII + no Pickled food	9.256	2.016-42.491	0.004

(OR, 1.508, 4.060, 9.256, respectively; 95% CI, 1.114-2.040, 1.498-11, 2.016-42.491, respectively). However, there was no difference in anxiety risk among the low PGII + no pickled foods, low PGII + pickled foods, and high PGII + pickled foods groups (**Table 6**).

Discussion

Currently, gastroscopy is considered the gold standard for diagnosing stomach diseases [18]. However, utilizing serum gastric function tests such as PG and G17 can help identify individuals at higher risk of gastric disease, thereby increasing the positivity rate of gastroscopy. Anxiety is closely associated with various stomach conditions. For instance, anxiety and depression have been linked to the development of Gastroesophageal reflux disease [19]. Moreover, excessive secretion of gastric hydrochloric acid (HCl) can lead to gastrointestinal (GI) disorders and anxiety. Ranitidine, which blocks histamine-2 receptors in parietal cells, inhibits HCl secretion in gastric mucosa and improves symptoms related to anxiety in humans [20]. Currently, serum gastric function test serves as an important screening tool for early detection of gastric cancer. Understanding the relationship between anxiety and serum gastric function will contribute to better data analysis and more accurate screening.

Our study confirmed the findings of a retrospective cross-sectional questionnaire study involving 779 participants (aged 18-79 years), which indicated significant differences in the incidence of anxiety [21]. Additionally, we observed that females had a significantly higher risk of anxiety compared to males. These results suggest that sex may play an important role in influencing the risk of anxiety among individuals undergoing regular checkup population. It was also found that the anxiety levels of the females increased significantly in the COVID-19 post-pandemic period [22]. This could be attributed to women's tendency towards sedentary and inactive lifestyles, highlighting the potential benefits of promoting physical activity for overall mental well-being among women [23]. Second, in this study, compared with the nonanxiety group, patients in the anxiety group had significantly higher PGII values and significantly lower PGR. Binary regression analysis also indicated that PGII was an independent risk factor for anxiety. These findings suggest that increased levels of PGII in a healthy checkup population may enhance the risk of anxiety. The elevation of

PGII indicated hyperemia and edema of the gastric mucosa, which could be attributed to gastric hypersensitivity induced by anxiety [24]. Thirdly, in this study, the anxious group was associated with significantly lower levels of consumption of pickled food, smoking and alcohol compared to the non-anxious group. Binary regression analysis revealed that pickled food independently contributed as an independent risk factor for anxiety. This suggests an inverse association between pickled foods and the risk of anxiety. It had been documented that pickled products have a certain effect on stimulating appetite and relieving anxiety [25].

In an animal study, it was found that gastritis induced by high doses of methamphetamine worsen anxiety-like behavior in female rats [26]. Additionally, gastritis induced by iodoacetamide was found to mimic anxiety and depression in female rats, but no such psychological response was observed in male rats [27]. Our study also revealed a higher risk of anxiety in females compared to males.

The stomach is not only a digestive organ but also a secretory organ [28]. PGII reflects the secretion function of gastric mucosa [29]. Recent animal and human studies have shown that ghrelin regulates the hypothalamic-pituitary-adrenal axis and influences anxiety and mood disorders [30]. Ghrelin, produced by secretory cells in the gastric mucosa, plays a central role in neurohormonal regulation of food intake and energy homeostasis [31]. Although the exact mechanism is unknown, some animal studies suggest that ghrelin regulates stress response and fear memory. It is known that the decreased plasma ghrelin concentration is associated with the PGI/II ratio [32], indicating that serum gastric function can reflect changes in human mood regulation to a certain extent.

In our study, sex, PGII and pickles were independent influencing factors that influenced anxiety risk. In other words, a female aged ≤50 years old with high levels of PGII and not consuming pickles was associated with a significantly higher risk of anxiety. High levels of PGII indicate a more severe inflammatory state of the gastric mucosa, leading to more severe gastric symptoms. Recurrent gastric symptoms may increase the risk of anxiety through the brain-gut axis [33]. Additionally, pickled foods are characterized by high nitrite. Nitrite has a beneficial effect on neuronal anti-hypoxic stress in vivo, which can protect neurons in animals from hypoxia-induced anxiety induced by chronic hypoxia injury [34]. Therefore, females aged ≤50 years old with high levels of PGII, and no consumption of pickled foods represent the group at highest risk of anxiety among healthy individuals undergoing checkups.

This study has several advantages. Firstly, it was proposed at the beginning that being female, having high PGII levels, and not consuming pickled foods is correlated with increased the risk of anxiety in individuals. Secondly, the HAM-A scale was used for screening anxiety, which has been well validated in the Chinese population. Thirdly, our conclusions are based on a model. The results of our current study demonstrate that changing the model did not alter the final results.

This study has some limitations. Firstly, there was no direct investigation into the effects of sex hormones, such as estrogen, on anxiety/depression and serum gastric function. However, our findings regarding sex differences suggest that sex hormones do play a role to some extent. Secondly, while the results were statistically reliable, the study design did not establish causality. As this is a cross-sectional study, no causal relationship can be inferred. Finally, this study was conducted at a single center and it is necessary to involve a larger number of centers in order to validate our results.

Conclusion

Our study found that in females aged ≤50 years, high levels of PGII and the absence of pickled food consumption were associated with a higher risk of anxiety. Further research is needed to uncover the mechanisms underlying these findings.

Acknowledgements

This work was supported by the Key Development Project of Science and Technology Bureau in Xuzhou (Social development) [grant number KC22233]; the Key Laboratory of Jiangsu Province Open project [grant number XZSYSKF2021029] and the Project supported by the Affiliated Hospital of Xuzhou Medical University [grant number 2020KA003; 2023-ZL19].

Disclosure of conflict of interest

None.

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