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ORIGINAL ARTICLE

Psychological health mediates the association between diet and upper gastrointestinal cancer: a cross-sectional analysis from a large-scale population-based screening project

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ABSTRACT

Objective: Upper gastrointestinal (UGI) cancer, including esophageal and gastric cancers, poses a significant health burden. While unhealthy dietary patterns are a recognized risk factor for UGI cancer, the complex interplay with psychological health that influences UGI cancer risk remains underexplored. The current study aimed to determine the association between dietary quality and UGI cancer, and the link with depression and anxiety symptoms.

Methods: Cross-sectional data were drawn from the baseline survey of the National Cohort of Esophageal Cancer study that was conducted between 2017 and 2019 in five high-risk regions of China. Dietary quality was evaluated using the Diet Balance Index (DBI)-16. Psychological symptoms were measured with the Generalized Anxiety Disorder 7-item Scale (GAD-7) and the Patient Health Questionnaire (PHQ)-9. Eligible participants underwent endoscopy screening and suspicious cases were confirmed *via* pathologic biopsies.

Results: A total of 434 UGI cancer cases were confirmed among 29,068 participants. Logistic regression models indicated that poor diet quality, reflected by an inadequate intake [low bound score (LBS)] and unbalanced diet [dietary quality distance (DQD)], was associated with psychological distress (e.g., LBS and anxiety: OR = 1.36, 95% CI: 1.19–1.56). UGI cancer participants had more severe psychological symptoms (e.g., anxiety and UGI cancer: OR = 1.20, 95% CI: 1.14–1.26). Path analysis further revealed that psychological symptoms significantly mediate the relationship between poor dietary quality and UGI cancer risk; specifically, anxiety symptoms mediated 27.78% of the LBS-UGI cancer link.

Conclusions: The current study revealed a significant association between dietary quality and UGI cancer risk, suggesting that psychological symptoms may have a mediating role. Incorporating dietary and psychological health management into public health strategies is crucial for comprehensive cancer prevention.

KEYWORDS Upper gastrointestinal cancer; dietary quality; anxiety symptoms; depression symptoms; mediate role

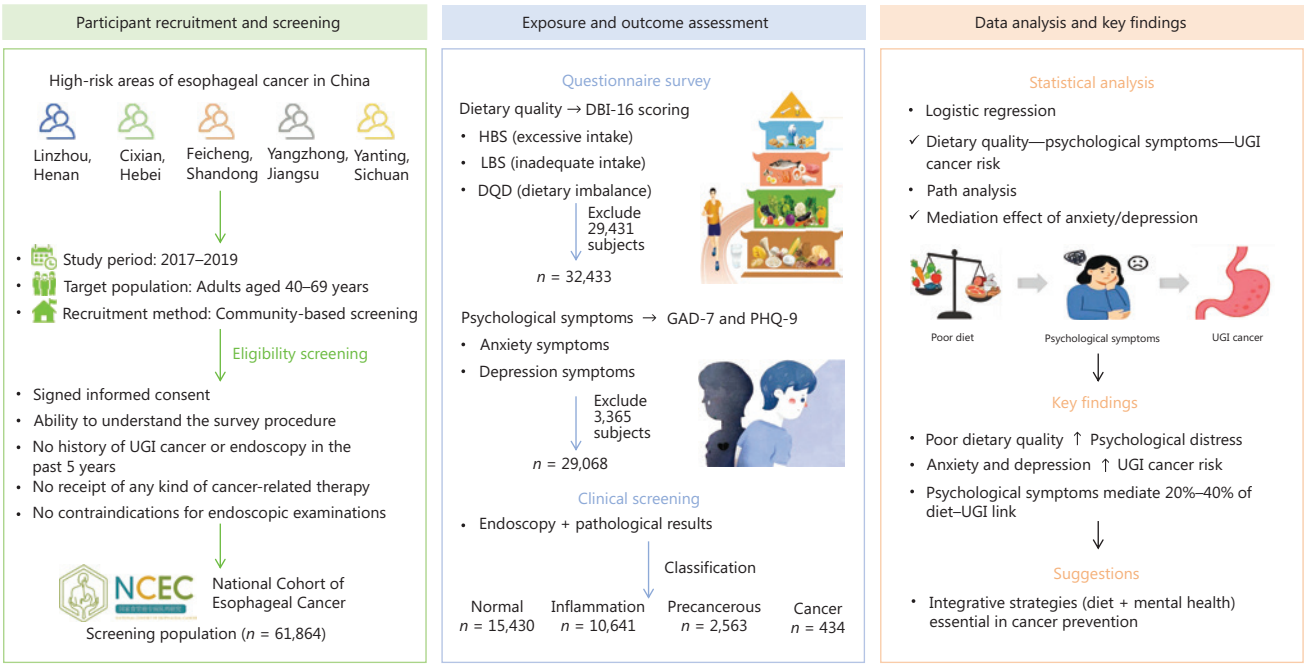
Introduction

Upper gastrointestinal (UGI) cancer, including esophageal and gastric cancers, accounted for 1.4 million new cancer cases and 1.1 million deaths globally in 2022, contributing to substantial financial burdens on individuals and healthcare systems[1]. In China, the largest developing country with a transitioning cancer profile, UGI cancers represent approximately 40% of the global incidence and mortality[2], highlighting the need for effective prevention and intervention strategies.

Dietary factors have been identified as crucial modifiable contributors to UGI cancer risk[3,4]. It is estimated that 5.1%–5.9% of cancer cases are attributable to poor diet quality annually[5]. It has been shown that adherence to healthy dietary patterns, characterized by high intake of fruits, vegetables, and whole grains, may protect against digestive cancers[6,7]. A recent large-scale prospective study involving high-risk Chinese populations further demonstrated that unbalanced diets are associated with increased UGI cancer risk[8].

In addition to dietary factors, psychological disorders have drawn increasing attention due to the rising prevalence and association with various diseases, including cancer. A

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Study flowchart The flowchart illustrates the recruitment and screening process for the baseline survey of the National Cohort of Esophageal Cancer (2017–2019). A total of 61,864 individuals (40–69 years of age) from high-risk regions were initially screened. The exposure assessment flowchart shows that dietary quality was evaluated using the Diet Balance Index (DBI)-16 with three derived indicators: high bound score (HBS); low bound score (LBS); and dietary quality distance (DQD). A total of 29,431 individuals were excluded based on dietary questionnaire responses due to incomplete dietary data. Psychological symptoms were assessed *via* the GAD-7 and PHQ-9 scales, and an additional 3,365 subjects were excluded for incomplete responses, resulting in a final analytic cohort of 29,068 participants. All included participants underwent clinical endoscopy and pathologic examination. Participants were classified into four groups based on pathologic results: normal (n = 15,430); inflammation (n = 10,641); pre-cancer (n = 2,563); and cancer (n = 434). The statistical analysis involved logistic regression models to examine the associations between dietary quality, psychological symptoms, and UGI lesions. Path analysis was performed to test the mediating role of anxiety and depression symptoms in the association between poor diet and UGI cancer risk. The associative mediation effect of psychological symptoms accounted for 20%–40% of the total association. The current study provides evidence in support of the need for integrated cancer prevention strategies targeting both dietary and mental health factors.

meta-analysis revealed that depression and anxiety disorders increased cancer risk by 13%[9]. Research on the brain-gut axis further provides a biological basis for the high co-morbidity of psychological disorders and gastrointestinal diseases[10]. In addition, previous studies have demonstrated a close link between diet and mental health[11,12]. Dietary imbalance and low dietary diversity elevate the risks of anxiety and depressive disorders[13], and low intake of fresh fruits and vegetables is associated with a higher prevalence of these psychological symptoms[14].

Although these findings provide important insights into the individual roles of diet and psychological health, the potential interaction as co-contributors to UGI cancer and the complex pathways remain underexplored. In addition to the direct biological effects of diet, emerging evidence suggests that psychological health may mediate the relationship between dietary quality and chronic disease outcomes. Poor diet quality can promote systemic inflammation and oxidative stress, impair gut microbiota composition, and disrupt neuroendocrine signaling, all of which are implicated in the development of depressive and anxiety symptoms[15]. These psychological disturbances may contribute to carcinogenesis by altering immune function, hormonal balance, and health behaviors, such as appetite regulation and physical activity[16,17]. Therefore, understanding psychological health as a potential mediator provides a novel biopsychosocial perspective for elucidating the complex mechanisms linking diet to UGI cancer. The current study determined the association between dietary quality and UGI cancer with a focus on whether psychological symptoms may mediate this relationship. We aimed to provide a new comprehensive prevention and control strategy that integrates biopsychosocial healthcare by examining the interplay between these factors to reduce the burden of UGI cancer.

Materials and methods

Study population

The National Cohort of Esophageal Cancer (NCEC) is a prospective cohort study with comprehensive exposure data collection and long-term follow-up to study UGI cancer and other diseases including hypertension, diabetes, etc. Detailed descriptions of the NCEC have been previously provided by Chen et al[18]. The current study utilized cross-sectional data from the baseline phase of the NCEC. Residents in 5 high-risk regions in China (Linzhou, Cixian, Feicheng, Yangzhong, and Yanting) were invited to participate in the survey between 2017 and 2019. The inclusion criteria were as follows: (1) aged 40–69 years; (2) signed informed consent; (3) ability to understand the survey procedure clearly; (4) no severe visual or auditory impairments. The exclusion criteria were as follows: (1) previous diagnosis of UGI cancer or other cancers; (2) receipt of any type of cancer-related therapy; (3) prior UGI tract examination within 5 years; and (4) contraindications to an endoscopic examination (e.g., acute perforation of the upper digestive tract; severe heart, lung, kidney, and brain dysfunction; and multi-organ failure).

A standardized laptop-based questionnaire was used to collect demographic characteristics, dietary information, and psychological conditions through face-to-face interviews with trained staff. Eligible participants subsequently underwent an UGI endoscopy examination. UGI pathologic diagnosis was used to confirm the suspicious lesions detected by endoscopic examination. Participants were classified into four groups based on the pathologic results: (1) normal (no pathologic findings); (2) inflammation (esophagitis, gastric carditis, or gastritis); (3) pre-cancerous lesions [low-grade intraepithelial neoplasia (LGIN) for esophageal cancer, and atrophic gastritis, intestinal metaplasia (IM), and intraepithelial neoplasia (IN) for gastric and cardia cancers]; (4) cancer [high-grade intraepithelial neoplasia (HGIN) in esophagus; and esophageal, gastric, and cardiac cancers].

Formal ethics approval was granted by the Ethics Committee of the National Cancer Center/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College (No. 16-171/1250). All participants were informed of the purpose of the study and provided written informed consent. All procedures were in accordance with the Helsinki Declaration.

Data collection

Diet and diet quality

Dietary intake of food subgroups at the individual level was assessed using an 18-item semi-quantitative food frequency questionnaire (FFQ)[19], which captured participants' dietary habits over the past 1 year. Salt and cooking oil consumption were recorded at the household level during the same period. Each food item had a frequency option (never or rarely, monthly, 1–3 d/week, 4–6 d/week, or daily). The frequency of consumption for each food item was converted into the average daily intake (g/d) by multiplying the reported frequency by the standard portion size for each food group. The resulting individual-level daily intakes were then used to evaluate dietary quality according to the Diet Balance Index (DBI)-16.

The DBI-16 is a comprehensive tool that is used to assess overall dietary quality in Chinese populations. The DBI-16 incorporates energy distribution and food group intake based on the latest *The Chinese Dietary Guidelines* and *Chinese Food Guide Pagoda*, capturing both insufficient and excessive dietary consumption[13,20]. *Chinese Food Guide Pagoda* includes the following 13 food subgroups (points): cereals (−12 to 12); vegetables (−6 to 0); fruits; dairy products; soybean products; meat products; fish/shrimps; eggs; cooking oils; alcoholic beverage; addible sugar; salt; and water. Water and sugar consumption was not included in the current study due to the lack of data. The detailed categories and scoring methods are shown in **Table S1**.

A score of 0 for any food item indicates that the intake meets dietary recommendations, while positive scores reflect excessive intake and negative scores indicate inadequate intake. The dietary quality was then comprehensively assessed using three indicators derived from the DBI-16 score (range value): (a) the high bound score (HBS) is the sum of all positive scores and represents excessive intake across food groups (0–38); (b) the low bound score (LBS) is the sum of absolute values of negative scores and represents insufficient intake (0–60); and (c) the dietary quality distance (DQD) is the sum of the LBS and HBS and represents the overall dietary balance (0–78). Each DBI-16 indicator was categorized to reflect the overall level of dietary imbalance as follows: (a) good or acceptable diet intake (score ≤40%), indicating almost no issues with diet or a low level of dietary problems; (b) poor diet intake (score = 40%–60%), indicating a moderate level of dietary problems; and (c) worst diet intake (score >60%), indicating a high level of dietary problems[13,17].

Anxiety symptoms

The Generalized Anxiety Disorder 7-item Scale (GAD-7) was used to evaluate the severity of a general anxiety disorder. The items encompass a feeling of nervousness, an inability to stop worrying, difficulty relaxing, feeling restless, being easily annoyed or irritable, and feeling afraid. Response scores represent the frequency of each item over the past 2 weeks (0 = not at all, 1 = several days, 2 = more than 50% of the days, and 3 = nearly every day). The GAD-7 score is the sum of each item score with higher scores reflecting worse anxiety. A binary variable can also be used for GAD-7 in which scores ≥5 indicate anxiety[21]. The GAD-7 showed good psychometric properties in the Chinese population with a Cronbach's α coefficient of 0.88 in this study.

Depression symptoms

The Patient Health Questionnaire-9 (PHQ-9) was used to assess the presence and severity of depression with proven test-retest reliability and validity in both primary medical care and clinical practice[22]. The PHQ-9 consists of 9 items based on the *DSM-V* criteria for major depression: anhedonia; depressed mood; sleep problems; fatigue; weight/appetite change; feelings of worthlessness/guilt; poor concentration; psychomotor retardation/agitation; and thoughts of self-harm/suicidal ideation. Response scores reflect the frequency of symptoms over the past 2 weeks (0 = not at all, 1 = several days, 2 = more than 50% the days, and 3 = nearly every day). The PHQ-9 score is the sum of each item score; a higher score indicates more severe depression with a minimum clinically significant difference of 7[23]. The PHQ-9 also demonstrated good psychometric properties in the Chinese population with a Cronbach's α coefficient of 0.90 in this study.

Covariate variables

A uniform questionnaire was utilized to assess covariates, including gender, age, marital status, education, occupation, household income, lifestyle factors (smoking, alcohol consumption habits, and physical exercise), health conditions (digestive system diseases, hypertension, and diabetes), and body mass index (BMI). Marital status was classified into two categories ("unmarried/living alone/divorced/widowed" and "married"). Education level was divided into three groups ("primary school or below," "junior/senior high school," and "undergraduate or above"). Occupation was divided into two groups ("manual labor" and "non-manual labor/other work"). Household income was stratified into four levels (<30,000 RMB per year, 30,000–70,000 RMB per year, 70,000–110,000 RMB per year, and >110,000 RMB per year). Smoking and alcohol consumption habits were classified as "no" and "yes." Participants were defined as "current drinkers" if they consumed alcohol ≥1 time/month. Digestive system diseases, hypertension, and diabetes conditions were classified as "no" and "yes." BMI was divided into four groups ("<18.5 kg/m^2," "18.5–23.9 kg/m^2," "24.0–27.9 kg/m^2," and ">28.0 kg/m^2"). Physical activity levels were estimated using self-reported data.

Statistical analysis

Continuous variables are presented as means and standard deviations or medians and quantiles. Differences in baseline characteristics among participants with different diagnoses of UGI lesions were assessed using the Mann-Whitney U test for continuous variables and the chi-squared test for categorical variables.

Multivariable logistic regression models were used to estimate associations given the cross-sectional nature of the data in which both exposures (diet and psychological symptoms) and outcome (UGI lesions) were assessed at the same time point and presented as odds ratios (ORs) with 95% confidence intervals (CIs). Specially, the pathologic diagnoses were modeled as a multinomial outcome with the "normal" group as the reference category. Multicollinearity was evaluated using variance inflation factors (VIFs) to ensure the logistic regression assumptions were met with all VIF values <10, indicating no significant multicollinearity among the covariates. Residual diagnostics were also performed to examine the goodness-of-fit and ensure no major deviations from model assumptions. All logistic regression models were adjusted for covariates, including gender, age, household income, smoking, alcohol consumption habits, digestive system diseases, hypertension, diabetes, and BMI. The selection of these covariates was based on a combination of statistical evidence and theoretical reasoning. First, variables were considered that demonstrated significant differences ($P < 0.001$) across the UGI lesion groups in baseline characteristics (**Table 1**), indicating the potential association with the outcome. Second, variables were incorporated that are established or postulated confounders in the literature on UGI cancer, diet, and mental health[24,25]. This dual approach ensured that the models accounted for key demographic, socioeconomic, lifestyle, and health-related factors that could confound the relationships under investigation.

A path analysis was performed within a structural equation modeling (SEM) framework to determine the mediating role of psychological symptoms in the associative pathway between dietary quality and the risk of UGI cancers. The outcome variable, UGI lesions, was treated as an ordinal categorical variable with four levels ("normal," "inflammation," "pre-cancer," and "cancer"). Dietary quality indicators (HBS, LBS, and DQD) and psychological symptoms (anxiety and depression) were modeled as continuous variables. A weighted least squares mean and variance adjusted (WLSMV) estimator with a probit link function was used to appropriately handle the categorical outcome. The mediation model was specified based on the following established prerequisites: (1) a significant association between dietary quality and psychological symptoms; and (2) a significant association between psychological symptoms and UGI lesions[26]. The aforementioned covariates, including demographic and health-related factors, were controlled in the analysis to mitigate potential confounding effects. A bootstrapping procedure was utilized with 5,000 resamples to ensure the precision and reliability of the parameter estimates. This approach enabled the calculation of standard errors and the computation of bias-corrected bootstrapped CIs for all parameter estimates, enhancing the robustness of the findings. The model fit was assessed using a range of inferential goodness-of-fit indices, including the chi-square statistic ($\chi 2$), the comparative fit index (CFI), the root mean square error of approximation (RMSEA), and the standardized root mean square residual (SRMR). A CFI value >0.95 with RMSEA and SRMR values <0.06 indicated an acceptable model fit, as recommended in the literature[27]. These criteria were used to evaluate whether the mediation model provided

an adequate representation of the data and to ensure the validity of the inferences drawn from the analysis. All mediation models were adjusted for the same covariates included in the logistic regression analyses.

The false discovery rate (FDR) correction was applied separately using the Benjamini-Hochberg procedure for different analytical frameworks to address potential type I error inflation from multiple comparisons. All 11 exposure-outcome pairs were corrected for logistic regression analyses assessing direct associations. The 6 mediation pathways were separately corrected for mediation analyses testing indirect effects. This stratified approach maintains statistical rigor while acknowledging the distinct nature of direct association tests versus mediation pathway tests. All analyses with FDR-adjusted q-values <0.05 were considered statistically significant after multiple testing correction.

All data analyses were performed using R software (version 4.2.3). A two-sided $P < 0.05$ was considered statistically significant.

Results

Baseline characteristics of participants across different UGI lesion groups

A total of 29,068 eligible participants were recruited from 5 high-risk regions. Participants were categorized based on endoscopic findings and pathologic diagnosis, as follows: 15,430 (53.08%) were classified as normal; 10,641 (36.61%) had inflammation; 2,563 (8.82%) had pre-cancerous conditions; and 434 (1.49%) were diagnosed with UGI cancer. The baseline characteristics of these participants are presented in **Table 1**. The mean age of participants was 55.95 years (SD: 7.70 years) and 40.86% were male. Significant differences in baseline characteristics were detected across the groups (all $P < 0.01$), except for BMI ($P = 0.20$).

Approximately 40% of participants reported moderate and high levels of excessive food intake problems (HBS),

Table 1 Characteristics of study participants

Characteristics	Overall n = 29,068	Normal n = 15,430	Inflammation n = 10,641	Pre-cancer n = 2,563	Cancer n = 434	P
Sex						<0.001
Men	11,878 (40.86%)	6,004 (38.91%)	4,314 (40.54%)	1,301 (50.76%)	259 (59.68%)	
Women	17,190 (59.14%)	9,426 (61.09%)	6,327 (59.46%)	1,262 (49.24%)	175 (40.32%)	
Age (years)	55.95 (7.70)	55.52 (7.85)	55.66 (7.44)	58.99 (7.00)	60.48 (6.94)	<0.001
Marital status						0.001
Unmarried/living alone/ divorced/widowed	1,948 (6.70%)	981 (6.36%)	719 (6.76%)	208 (8.12%)	40 (9.22%)	
Married	27,120 (93.30%)	14,449 (93.64%)	9,922 (93.24%)	2,355 (91.88%)	394 (90.78%)	
Education						<0.001
Primary school or below	13,414 (46.15%)	7,122 (46.16%)	4,783 (44.95%)	1,303 (50.84%)	206 (47.47%)	
Junior or senior high school	15,396 (52.97%)	8,210 (53.21%)	5,722 (53.77%)	1,241 (48.42%)	223 (51.38%)	
Undergraduate or above	258 (0.88%)	98 (0.64%)	136 (1.28%)	19 (0.74%)	5 (1.15%)	
Occupation						<0.001
Manual labor occupations	22,386 (77.01%)	12,367 (80.15%)	7,819 (73.48%)	1,874 (73.12%)	326 (75.16%)	
Non-manual labor occupations & others	6,682 (22.99%)	3,063 (19.85%)	2,822 (26.52%)	689 (26.88%)	108 (24.88%)	
Household income (10,000 RMB[a])						<0.001
<3.0	6,448 (22.18%)	4,145 (26.86%)	1,657 (15.57%)	547 (21.34%)	99 (22.81%)	
3.0–7.0	15,386 (52.93%)	9,331 (60.47%)	4,713 (44.29%)	1,164 (45.42%)	178 (41.01%)	
7.0–11.0	5,246 (18.05%)	1,656 (10.73%)	2,927 (27.51%)	553 (21.58%)	110 (25.35%)	
≥11	1,988 (6.84%)	298 (1.93%)	1,344 (12.63%)	299 (11.67%)	47 (10.83%)	

Table 1 Continued

Characteristics	Overall *n* = 29,068	Normal *n* = 15,430	Inflammation *n* = 10,641	Pre-cancer *n* = 2,563	Cancer *n* = 434	*P*
Smoking						<0.001
No	22,155 (76.22%)	11,604 (75.20%)	8,305 (78.05%)	1,932 (75.38%)	314 (72.35%)	
Yes	6,913 (23.78%)	3,826 (24.80%)	2,336 (21.95%)	631 (24.62%)	120 (27.65%)	
Alcohol consumption						<0.001
No	25,325 (87.12%)	13,317 (86.31%)	9,407 (88.40%)	2,218 (86.54%)	383 (88.25%)	
Yes	3,743 (12.88%)	2,113 (13.69%)	1,234 (11.60%)	345 (13.46%)	51 (11.75%)	
Digestive system diseases						<0.001
No	23,370 (80.40%)	12,963 (84.01%)	8,144 (76.53%)	1,944 (75.85%)	319 (73.50%)	
Yes	5,698 (19.60%)	2,467 (15.99%)	2,497 (23.47%)	619 (24.15%)	115 (26.50%)	
Hypertension						<0.001
No	25,688 (88.37%)	14,088 (91.30%)	9,099 (85.51%)	2,152 (83.96%)	349 (80.41%)	
Yes	3,380 (11.63%)	1,342 (8.70%)	1,542 (14.49%)	411 (16.04%)	85 (19.59%)	
Diabetes						<0.001
No	28,202 (97.02%)	15,051 (97.54%)	10,281 (96.62%)	2,455 (95.79%)	415 (95.62%)	
Yes	866 (2.98%)	379 (2.46%)	360 (3.38%)	108 (4.21%)	19 (4.38%)	
BMI[b] (kg/m^2)						0.200
<18.5	560 (1.93%)	292 (1.89%)	198 (1.86%)	61 (2.38%)	9 (2.07%)	
18.5–23.9	12,827 (44.13%)	6,829 (44.26%)	4,628 (43.49%)	1,175 (45.84%)	195 (44.93%)	
24.0–27.9	11,713 (40.30%)	6,161 (39.93%)	4,365 (41.02%)	1,013 (39.52%)	174 (40.09%)	
≥28.0	3,968 (13.65%)	2,148 (13.92%)	1,450 (13.63%)	314 (12.25%)	56 (12.90%)	
Physical activity						<0.001
Less 1–3 times/month	24,619 (84.69%)	13,493 (87.44%)	9,177 (86.24%)	2,197 (85.72%)	382 (88.02%)	
1–2 times/week	676 (2.33%)	292 (1.89%)	306 (2.88%)	70 (2.73%)	8 (1.84%)	
3–5 times/week	591 (2.03%)	210 (1.36%)	292 (2.74%)	74 (2.89%)	15 (3.46%)	
Daily or almost every day	2,552 (8.78%)	1,435 (9.30%)	866 (8.14%)	222 (8.66%)	29 (6.68%)	
HBS[c] score	13.95 (6.20)	14.38 (6.26)	13.34 (6.05)	13.85 (6.23)	13.86 (6.11)	<0.001
HBS group						<0.001
Low level	17,603 (60.56%)	8,886 (57.59%)	6,881 (64.66%)	1,563 (60.98%)	273 (62.90%)	
Moderate level	9,308 (32.02%)	5,234 (33.92%)	3,136 (29.47%)	804 (31.37%)	134 (30.88%)	
High level	2,157 (7.42%)	1,310 (8.49%)	624 (5.86%)	196 (7.65%)	27 (6.22%)	
LBS[d] score	36.88 (6.76)	37.28 (6.63)	36.45 (6.90)	36.30 (6.75)	36.77 (6.90)	<0.001
LBS group						<0.001
Low level	994 (3.42%)	403 (2.61%)	467 (4.39%)	105 (4.10%)	19 (4.38%)	
Moderate level	12,576 (43.26%)	6,494 (42.09%)	4,706 (44.23%)	1,183 (46.16%)	193 (44.47%)	

Table 1 Continued

Characteristics	Overall *n* = 29,068	Normal *n* = 15,430	Inflammation *n* = 10,641	Pre-cancer *n* = 2,563	Cancer *n* = 434	*P*
High level	15,498 (53.32%)	8,533 (55.30%)	5,468 (51.39%)	1,275 (49.75%)	222 (51.15%)	
DQD[e] score	40.53 (7.66)	41.02 (7.58)	39.88 (7.72)	40.17 (7.67)	40.73 (7.78)	<0.001
DQD group						<0.001
Low level	3,159 (10.87%)	1,446 (9.37%)	1,359 (12.77%)	303 (11.82%)	51 (11.75%)	
Moderate level	21,008 (72.27%)	11,165 (72.36%)	7,695 (72.31%)	1,836 (71.63%)	312 (71.89%)	
High level	4,901 (16.86%)	2,819 (18.27%)	1,587 (14.91%)	424 (16.54%)	71 (16.36%)	
GAD score	1.65 (2.30)	1.65 (2.28)	1.64 (2.35)	1.66 (2.20)	1.71 (2.03)	<0.001
Anxiety symptoms						0.001
No	26,117 (89.85%)	13,956 (90.45%)	9,468 (88.98%)	2,306 (89.97%)	387 (89.17%)	
Yes[f]	2,951 (10.15%)	1,474 (9.55%)	1,173 (11.02%)	257 (10.03%)	47 (10.83%)	
PHQ score	1.85 (2.67)	1.83 (2.60)	1.84 (2.79)	1.86 (2.60)	1.87 (2.53)	<0.001
Depression symptoms						<0.001
No	27,591 (94.92%)	14,762 (95.67%)	10,001 (93.99%)	2,421 (94.46%)	407(93.78%)	
Yes[g]	1,477 (5.08%)	668 (4.33%)	640 (6.01%)	142 (5.54%)	27 (6.22%)	

[a]RMB = Chinese Yuan (Renminbi); [b]BMI = body mass index; [c]HBS, excessive intake; score range of HBS, 0–38 (low level: 0–15; moderate level: 16–23; high level: ≥24); [d]LBS, inadequate intake; score range, LBS is 0–60 (low level: 0–24; moderate level: 25–36; high level: ≥37); [e]DQD, overall unbalance; score range, DQD is 0–78 (low level: 0–31; moderate level: 32–47; high level: ≥48); [f]Anxiety symptoms (Yes): GAD-7 score ≥5; [g]Depression symptoms (Yes): PHQ-9 score ≥7. *P*-values from Chi-square (categorical variables) or Mann-Whitney U tests (continuous variables), comparing across the four groups.

while 97% reported moderate and high levels of inadequate intake problems (LBS). Overall dietary imbalance (DQD) was reported by 90% of participants. Anxiety symptoms (GAD-7 ≥5) were present in 10.15% of the participants (2,951/29,068), while 5.08% (1,477/29,068) of the participants were affected by depression (PHQ-9 ≥7).

Association between dietary quality, psychological symptoms, and pathologic outcomes

Figure 1 demonstrates the association between DBI-16 components and anxiety and depression symptoms. Inverse associations were noted between HBS and anxiety and depression symptoms after adjusting for potential confounders, whereas LBS and DQD had positive correlations. Participants with high LBS and DQD levels were more strongly associated with anxiety (LBS: OR = 1.36, 95% CI: 1.19–1.56; DQD: OR = 1.10, 95% CI: 1.02–1.20) and depressive symptoms (LBS: OR = 1.36, 95% CI: 1.16–1.58; DQD: OR = 1.14, 95% CI: 1.05–1.25) when DBI-16 was treated as a categorial variable. **Figure 2** shows the association between anxiety and depression symptoms and UGI lesions. Participants with higher-grade lesions exhibited more severe psychological symptoms. Participants diagnosed with UGI cancer exhibited significantly higher levels of distressing symptoms compared to the normal group (anxiety symptoms: OR = 1.20, 95% CI: 1.14–1.26; depression symptoms: OR = 1.14, 95% CI: 1.10–1.19). **Figure 3** illustrates the association between DBI-16 components and UGI lesions. Participants with moderate or high LBS had significantly higher odds of being diagnosed with UGI cancer compared to participants with low LBS (moderate LBS: OR = 1.68, 95% CI: 1.02–2.78; high LBS: OR = 1.92, 95% CI: 1.15–3.19).

The associations between dietary quality (HBS, LBS, and DQD) and psychological symptoms, as well as UGI lesions, were further analyzed by treating dietary quality variables as continuous variables. The results showed consistent trends with the categorical variable results. Specifically, higher LBS and DQD scores were positively associated with a greater probability of anxiety and depressive symptoms, while HBS exhibited an inverse association. Similarly, higher LBS and DQD scores were linked to increased severity of UGI lesions, whereas higher HBS scores showed a protective effect. Detailed results are presented in **Tables S2 and S3**.

In summary, the analyses of direct associations revealed that poor dietary quality and adverse psychological symptoms

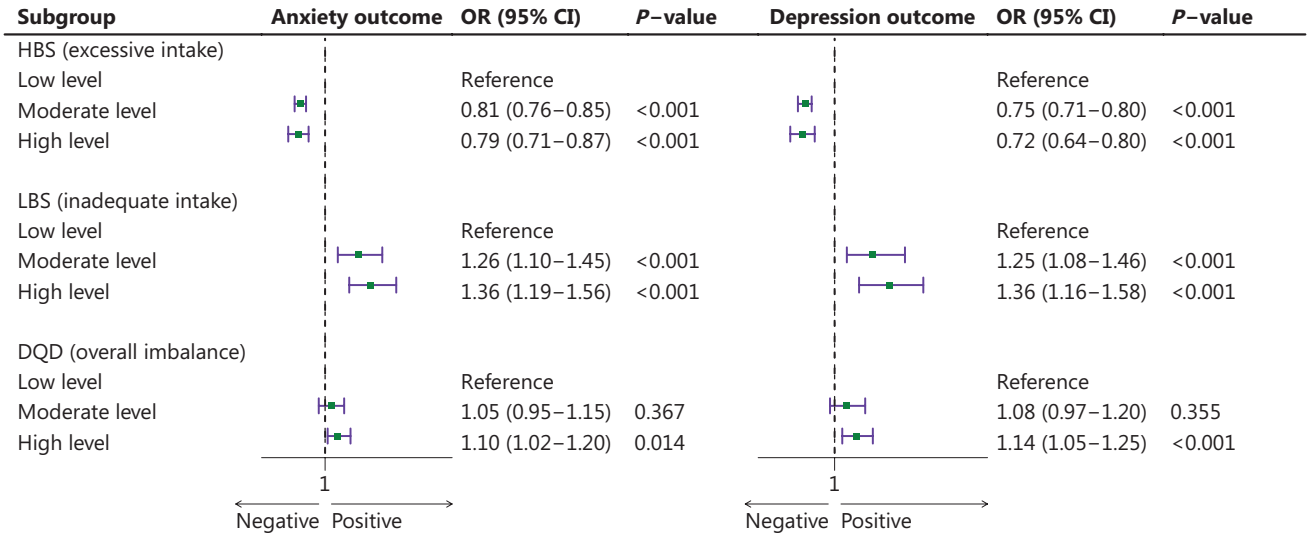


Figure 1 Adjusted odds ratios (ORs) and 95% confidence intervals (95% CIs) for the relationship between dietary quality and anxiety and depression symptoms, adjusted for sex, age, household income, smoking, alcohol consumption habits, digestive system diseases, hypertension, diabetes, and BMI. HBS, excessive intake; score range of HBS, 0–38 (low level, 0–15; moderate level, 16–23; high level, ≥24); LBS, inadequate intake; score range of LBS, 0–60 (low level, 0–24; moderate level, 25–36; high level, ≥37); DQD, overall imbalance; score range of DQD, 0–78 (low level, 0–31; moderate level, 32–47; high level, ≥48).

are associated with an increased risk of UGI lesions. The ORs, despite modest values, indicated a stable and dose-dependent increase in risk. Even modest effect sizes can be highly meaningful for a high-burden disease, like UGI cancer, from a public health perspective, particularly when the risk factors involved (diet and mental health) are highly prevalent and amenable to population-level intervention.

Path analysis

Path analysis was used to examine the indirect relationship between dietary quality and UGI cancer risks mediated by psychological symptoms. Six models were constructed based on different components of the independent variable and mediator, as illustrated in **Figure 4**. Furthermore, standardized coefficients and 95% CIs are reported for the path estimates in the mediation models. For clarity, all estimates are presented as standardized coefficients (denoted as '*b*') in **Figure 4** and the corresponding figure legends provide further detail on these standardizations. Model fit results are demonstrated in **Table S4**, indicating satisfactory model performance.

Notably, psychological symptoms, particularly anxiety and depression, were shown to mediate the relationship between dietary quality and risk of UGI cancers. Specifically, depression symptoms accounted for 40.91% of the relationship between LBS and UGI lesions with the model estimating an indirect effect of 0.09 ($P < 0.001$) and a direct effect of 0.13 ($P < 0.001$). In addition, the depression mediation effect was 38.24% (indirect effect = 0.13, $P < 0.001$; direct effect = 0.21, $P < 0.001$) for the relationship between DQD and UGI lesions. Similarly, anxiety symptoms were shown to mediate the effect of dietary quality on UGI lesions, albeit to a lesser degree. Anxiety symptoms mediated 27.78% of the total association between LBS and UGI lesions (indirect effect = 0.05, $P < 0.001$; direct effect = 0.13, $P < 0.001$) and 20.69% of the association between DQD and UGI lesions (indirect effect = 0.06, $P < 0.001$; direct effect = 0.23, $P < 0.001$).

In contrast, the mediation effects for HBS revealed a different pattern. Specifically, excessive intake was negatively associated with psychological symptoms and UGI lesions. Depression symptoms mediated 23.08% of the relationship between HBS and UGI lesions (indirect effect = −0.03, $P < 0.001$; direct effect = −0.10, $P < 0.001$) and anxiety symptoms mediated 8.33% of the relationship (indirect effect = −0.01, $P < 0.001$; direct effect = −0.11, $P < 0.001$).

The path analysis collectively demonstrated that anxiety and depression symptoms serve as significant associative mediators in the relationship between dietary quality and UGI cancer risk. The estimated mediation proportions, accounting for 20%–40% of the total associations for inadequate intake (LBS) and overall dietary imbalance (DQD), provided quantitative insight into the interplay between these factors. Although this cross-sectional design precluded a causal inference regarding the mediation pathway, the findings substantiated that the link between diet and UGI cancer is partially explained through psychological health. This reinforces the notion that future preventive strategies could be more effective by concurrently addressing dietary patterns

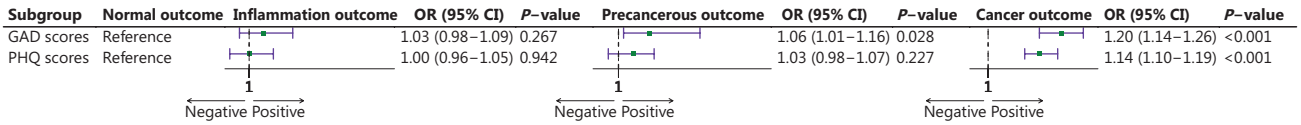


Figure 2 Adjusted odds ratios (ORs) and 95% confidence intervals (95% CIs) for the relationship between anxiety and depression symptoms and pathologic results, adjusted for sex, age, household income, smoking, alcohol consumption habits, digestive system diseases, hypertension, diabetes, and BMI.

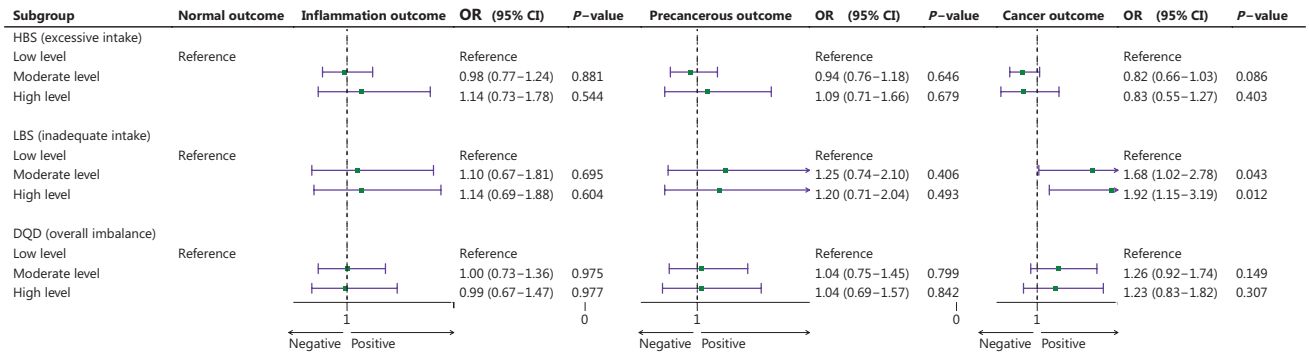


Figure 3 Adjusted odds ratios (ORs) and 95% confidence intervals (95% CIs) for the relationship between dietary quality and pathologic results, adjusted for sex, age, household income, smoking, alcohol consumption habits, digestive system diseases, hypertension, diabetes, and BMI.

and psychological well-being, potentially yielding synergistic benefits in risk reduction.

Sensitivity analysis

Sensitivity analyses were performed to determine the potential impact of BMI due to the complex relationship between BMI and UGI cancer and ensure the robustness of the findings. The sample was stratified into three BMI categories: normal (≤23.9 kg/m^2); overweight (24.0–27.9 kg/m^2); and obese (≥28.0 kg/m^2). Separate path analyses were performed for each BMI category in each model. The results demonstrated consistent associations across all BMI categories in each model, confirming the stability of the main findings under different conditions. The model fits, path coefficients (b), P-values, and 95% CIs for these sensitivity analyses are summarized in **Tables S5–S10**.

Sensitivity analyses using the FDR correction confirmed the robustness of the primary findings. All key mediation pathways remained highly significant after FDR correction (all $q < 0.001$), providing strong evidence for the psychological mediation hypothesis. Similarly, most direct associations between dietary quality and psychological symptoms, and between psychological symptoms and UGI cancer, survived FDR correction. However, the direct association between excessive intake (HBS) and UGI cancer, and between overall dietary imbalance (DQD) and UGI cancer, did not reach significance after FDR correction, suggesting that these relationships primarily have an impact through psychological pathways rather than through direct effects (**Tables S11 and S12**).

Sensitivity analyses were also performed using proportional odds ordinal logistic regression to examine the overall trend of associations across the ordered UGI lesion spectrum (normal, inflammation, pre-cancer, and cancer). However, formal testing using the Brant test indicated significant violations of the proportional odds assumption for all key predictors (all $P < 0.05$), suggesting that the effects of these variables were not uniform across different stages of disease progression. Therefore, while these ordinal regression results are presented for comparative purposes in **Table S13**, the multinomial logistic regression models remained the primary analytical approach because the multinomial logistic regression models more accurately captured the stage-specific nature of the associations.

Discussion

The evolving paradigm from a purely biological to a biopsychosocial model of cancer etiology underscores the need to investigate pathways involving modifiable risk factors. The current large-scale, cross-sectional study provides evidence consistent with such a pathway for UGI cancer. Poor dietary quality, characterized by both inadequate intake of essential foods (high LBS) and overall dietary imbalance (high DQD),

was not only directly associated with UGI cancer risk but also linked indirectly through symptoms of anxiety and depression, which statistically mediated a substantial portion (20%–40%) of the association. This integrative finding suggested that psychological health may serve as a modifiable element in the diet-cancer relationship, highlighting a potential target for comprehensive prevention strategies.

LBS assesses insufficient intake of key food groups, such as fruits, vegetables, legumes and dairy products[28]. Similarly, DQD provides a comprehensive measure of diet balance. Diets deficient in these key food groups may contribute to chronic inflammation, oxidative stress, and impaired immune function, all of which are mechanisms known to promote cancer development[29]. For example, fruit and non-starchy vegetables

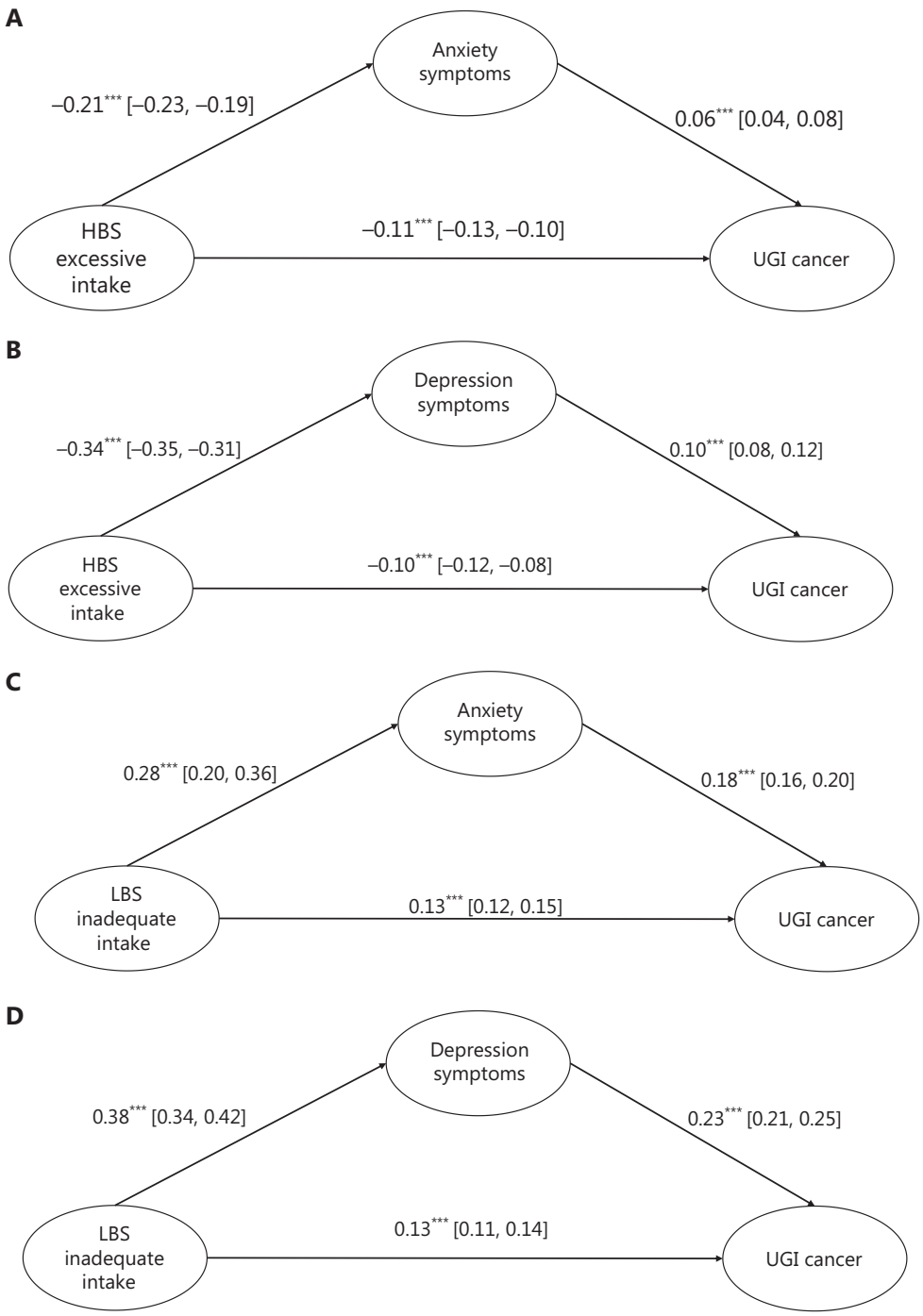


Figure 4 Continued

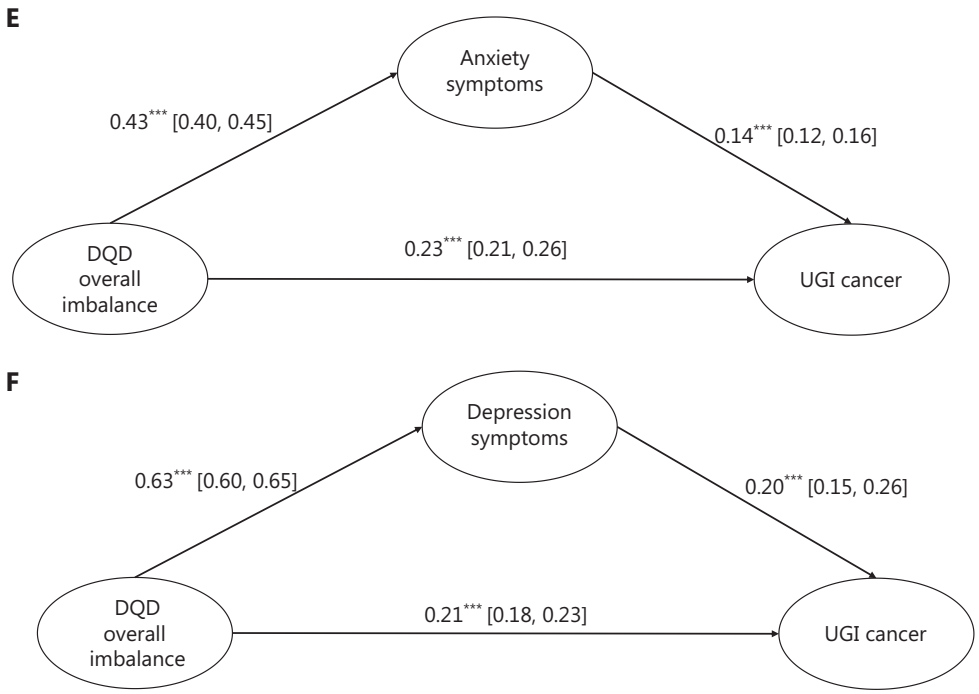


Figure 4 Mediation model between DBI-16 and UGI with anxiety or depression symptoms as mediator. (A) HBS and UGI with anxiety symptoms; all estimates are standardized. The indirect effect was statistically significant, b = −0.01 (95% CI: −0.01, −0.02), as was the total effect, b = −0.12 (95% CI: −0.13, −0.11), ***P < 0.001; (B) HBS and UGI with depression symptoms; the indirect effect was statistically significant, b = −0.03 (95% CI: −0.02, −0.04), as was the total effect, b = −0.13 (95% CI: −0.15, −0.11), ***P < 0.001; (C) LBS and UGI with anxiety symptoms; the indirect effect was statistically significant, b = 0.05 (95% CI: 0.03, 0.07), ***P < 0.001, as was the total effect, b = 0.18 (95% CI: 0.15, 0.22), ***P < .001; (D) LBS and UGI with depression symptoms; the indirect effect was statistically significant, b = 0.09 (95% CI: 0.07, 0.11), as was the total effect, b = 0.22 (95% CI: 0.18, 0.25), ***P < 0.001; (E) DQD and UGI with anxiety symptoms; the indirect effect was statistically significant, b = 0.06 (95% CI: 0.05, 0.07), as was the total effect, b = 0.29 (95% CI: 0.25, 0.33), ***P < 0.001; (F) DQD and UGI with depression symptoms; the indirect effect was statistically significant, b = 0.13 (95% CI: 0.09, 0.17), as was the total effect, b = 0.34 (95% CI: 0.27, 0.40), ***P < 0.001.

contain numerous potential anti-tumorigenic agents, such as carotenoids, vitamins C and E, and selenium, which are likely responsible for lowering the risk of UGI cancer[7]. Furthermore, in agreement with previous studies[30,31], the current study illustrated that psychological symptoms were associated with inadequate intake (LBS) and dietary imbalance (DQD). As mentioned earlier, high levels of LBS and DQD often indicate a lack of necessary nutrients and bioactive compounds, which are linked to increased risks of depression and anxiety[32]. Among these nutrients and bioactive compounds, vitamin C, which is abundant in fruits and vegetables, modulates the neurotransmitter system, thereby acting as an antidepressant and anxiolytic[33]. Vitamin D, which is primarily found in fish and eggs, has a role in supporting mood regulation[34].

The current study also identified a positive association between distressed mood and UGI cancer risk, which is consistent with previous studies[35,36]. Possible explanations include that depression and anxiety symptoms may lead to prolonged secretion of stress hormones, like cortisol[37,38]. This prolonged secretion can suppress the immune system and foster an inflammatory environment conducive to cancer development[39], particularly in the gastrointestinal tract[40]. Another explanation is that psychological stress exerts long-ranging effects throughout the microbiota-gut-brain axis[41,42], leading to dysregulation of the gastrointestinal nervous system and impaired gut motility[43]. This effect could contribute to gastrointestinal pathologies, including cancer[44]. However, existing epidemiologic studies involving the association between psychological symptoms and cancers have yielded conflicting results. Some studies have found no relationship between psychological symptoms and cancer outcomes[45,46], which differs from the findings herein. These inconsistencies could be attributed to several factors. For example, combining different site-specific cancers may further confound the relationship between depression, anxiety, and cancer due to the distinct biological and behavioral mechanisms in various tumor types. In addition, studies with shorter follow-up periods may fail to detect underlying subclinical tumors because most cancers have a long latency period. These factors highlight the need for further research, particularly studies that account for the

specific biological foundations and differential impacts of psychological stress across various cancer types.

A distinct pattern was noted in which high scores on the HBS, indicating excessive intake, were negatively associated with psychological symptoms and UGI lesions. The HBS is characterized by high consumption of cereals, salt, and cooking oils. While elevated salt and oil intake may contribute to increased risk, the dietary fiber present in cereals may exert potential protective effects against UGI lesions, which could partially explain the observed associations[47,48]. Moreover, a high-fiber diet may alter neurotransmitter concentrations, reducing the risk of depression[49], which could contribute to the negative association between excessive intake and psychological symptoms. Some studies have suggested that higher caloric intake may be associated with reduced immediate psychological distress due to the short-term pleasurable effects of consuming high-energy foods[50]. However, this relationship is likely complex and mediated by numerous factors, including metabolic health, body image, and long-term health concerns, introducing biases in self-reported psychological symptoms[51].

Despite these findings, several limitations in the current study need to be addressed in future research. First, given the cross-sectional nature of the current study, we were unable to establish causal directionality between dietary quality, psychological symptoms, and UGI lesions. Poor dietary quality may be associated with psychological distress, which in turn could contribute to an increased risk of UGI cancer. It is also plausible that a feedback loop exists, in which early-stage or subclinical UGI disease may contribute to changes in psychological status or dietary behaviors. For example, physical discomfort or anxiety about health could influence food intake or emotional responses[9,52]. Furthermore, while there was an adjustment for the range of important covariates, the potential for unmeasured or residual confounding persists. Factors, such as detailed socioeconomic status, genetic predisposition, or early-life exposures, which might influence diet, mental health, and cancer risk simultaneously, were not fully captured. Therefore, the mediation analysis demonstrated associative mediation rather than causal mediation. The identified pathways should be interpreted as evidence of a complex interplay that is consistent with, but not proof of, a mediating mechanism. To better understand these causal pathways and temporal relationships, future studies should adopt a prospective cohort design with repeated measures of exposure and a mediator. By recruiting participants who are cancer-free at baseline and assessing the dietary habits and psychological health prior to a cancer diagnosis, researchers can track the onset of UGI cancer and better isolate the temporal relationship between diet, psychological health, and cancer risk. Second, our sample was drawn from regions with a high incidence of UGI cancer, which may limit the generalizability of our findings to other populations. The dietary habits, environmental factors, and genetic predispositions in these high-risk areas could differ from those in regions with a lower incidence, potentially influencing the observed associations. Therefore, caution is warranted when applying these results to different geographic contexts. Future studies should aim to replicate these findings in regions with diverse dietary practices and varying cancer incidence rates to assess the robustness and applicability of the results across different populations. Third, while the DBI-16 is a culturally tailored tool for assessing dietary quality in the Chinese population, the exclusion of water and sugar consumption from the index may have narrowed the scope of dietary quality assessment. Both water and added sugar intake are important contributors to dietary patterns, the omission of these variables may introduce bias and limit the comprehensiveness of the DBI-16 in capturing the full spectrum of dietary behaviors. Future research should consider incorporating water and sugar consumption into dietary quality indices to enhance the validity and reliability, providing a more accurate assessment of the interplay between dietary patterns, psychological health, and disease outcomes.

Conclusions

In conclusion, this large cross-sectional study provided evidence that psychological symptoms are significantly associated with and may partially mediate the link between dietary quality and UGI cancer risk. Although the effect sizes were modest, the widespread prevalence of suboptimal diet and psychological distress underscored the potential population-level impact of interventions targeting this pathway. Therefore, the findings herein advocate for a holistic cancer prevention model that integrates psychological health support into dietary and lifestyle guidance. In high-risk regions, brief and feasible tools targeting diet quality and psychological distress could enhance risk stratification. Furthermore, combining dietary guidance with psychological interventions, such as cognitive-behavioral therapy or other evidence-based psychological treatments, could enhance the effectiveness of dietary recommendations and improve overall health outcomes[53]. The hypotheses generated herein regarding this complex interplay now require rigorous testing in prospective cohort studies, which are needed to establish causality, assess the impact of long-term exposure, and inform the design of targeted intervention trials.

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Conflict of interest statement

No potential conflicts of interest are disclosed.

Author contributions

Conceived and designed the analysis: Yueying Zhang, Shanrui Ma, Wenqiang Wei.
Collected the data: Xinqing Li, Ru Chen, Shaoming Wang.
Contributed data or analysis tools: Shanrui Ma, Shaoming Wang.
Performed the analysis: Yueying Zhang.
Wrote the paper: Yueying Zhang, Shanrui Ma.

Data availability statement

The data generated in this study are available upon request from the corresponding authors.

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