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Anxiety disorders and risk of self-reported ulcer: a 10-year longitudinal study among US adults☆,☆☆

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ABSTRACT

Objective: Previous epidemiologic studies have documented a link between anxiety disorders and ulcer among adults. Few studies have examined these associations over time and little is understood about the pathways underlying these relationships.
Method: Data were drawn from $n=2101$ adult participants in the Midlife Development in the United States I and II. Data on ulcer diagnoses were collected through self-report: among participants in the current sample, 38 reported ulcer at Waves 1 and 2 (prevalent ulcer), and 18 reported ulcer at Wave 2 but not at Wave 1 (incident ulcer). Panic attacks and generalized anxiety disorder at Wave 1 (1994) were examined in relation to prevalent (past 12 months) and incident ulcer approximately 10 years later at Wave 2 (2005).
Results: Anxiety disorders at Wave 1 were associated with increased prevalence of ulcer [odds ratio (OR)=4.1, 95% confidence interval (CI)=2.0–8.4], increased risk of incident ulcer at Wave 2 (OR=4.1, 95% CI=1.4–11.7) and increased risk of treated ulcer at Wave 2 (OR=4.7, 95% CI=2.3–9.9) compared with those without anxiety.
Conclusions: In this large population sample of adults, anxiety disorders were associated with an increased risk of ulcer over a 10-year period. These relationships do not appear to be explained by confounding or mediation by a wide range of factors. Future studies should address potential mechanisms underlying the relationship between anxiety and ulcer.

1. Introduction

In the United States, peptic ulcer is associated with major morbidity [1]; an estimated 500,000 new cases of ulcer occur each year in the United States, and nearly 5 million people are affected by the disease at any given time [2]. Although the prevalence of ulcer has been decreasing in recent years according to epidemiological studies [3,4], it remains a substantial public health problem [5]. Moreover, ulcers can result in serious complications including bleeding, perforation and, in some cases, even death [5].

The etiology of peptic ulcer disease is complex and not well understood. Following the discovery of the bacterium *Helicobacter (H.) pylori*, which is believed to be responsible for the onset of the disease, alternate and perhaps more complicated causal theories of ulcer have fallen out of favor [6]. Specifically, theories that centered on the diathesis-stress model were deemed outdated and misguided [7]. However, *H. pylori* does not explain all incident cases of ulcer [8], as the bacterium is present in many individuals who do not develop ulcer and is not present in all who do develop the disease. Furthermore, although the prevalence of *H. pylori* is decreasing and eradication therapies for the bacterium are more common, the population prevalence of ulcer complications has remained unaffected [9]. These findings suggest that a multifactorial model of the causation of ulcer may be more useful than a singular causal pathway in understanding the development of the disease [6].

In an earlier report, Goodwin and Stein [10] found that neuroticism, but not anxiety disorders, was associated with ulcer. However, this study relied on cross-sectional data, which may account for the lack of significant findings between anxiety and ulcer. Thus, investigating the associations between anxiety and incident ulcer over time may provide a different perspective of the anxiety–ulcer link than that reported by Goodwin and Stein [10].

Previous studies have documented a link between anxiety and ulcer [11-14]. Specifically, numerous studies have found associations between panic attack (PA) [14-15] and generalized anxiety disorder (GAD) with ulcer [11-14]. Two main pathways may account for these associations. First, these anxiety disorders could be causally related to an increased risk for development of ulcer. Evidence in support of

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such a causal relationship requires longitudinal data documenting this sequence, although this is necessary but not sufficient to suggest a causal link (and plausibility of an underlying biological mechanism for this pathway). To our knowledge, no previous study has examined this possibility. Second, there are a number of variables that appear to be common risk factors for both ulcer and anxiety disorders. These include stressful life events (e.g., child abuse) [7,16-20], smoking [21-23], exposure to secondhand smoke [24] and personality factors (e.g., neuroticism) [10,25]. Previous studies have not comprehensively investigated the potential confounding role of these factors in the relationship between anxiety disorders and ulcer among adults over prolonged periods. Studies to date have relied primarily on cross-sectional data [10,14,26,27]. Most recently, Scott et al. (2013) conducted a study using data from the World Health Organization World Mental Health Surveys initiative to explore the associations between a wide variety of mental disorders and ulcer. After adjusting for a variety of factors, the results showed that individuals with temporally prior social phobia, specific phobia and posttraumatic stress disorder were more likely to develop ulcer [14]. Nonetheless, understanding whether and to what degree mental health and ulcer are related over time — in addition to when they co-occur contemporaneously — can shed new light on causal pathways and the possible mechanisms of these relationships. In sum, the underlying pathways explaining the relationship between mental health and ulcer has remained unclear due partly to methodological limitations of previous studies — namely, (a) uncontrolled confounders, (b) untested mediators and (c) lack of long-term follow up.

The current study prospectively investigates the relationship between anxiety disorders and (a) prevalence of ulcer, (b) incidence of ulcer and (c) treatment of ulcer 10 years later among adults in the United States. In addition, this study examines cigarette smoking and substance use disorders as potential mediators in the relationship between anxiety and development of ulcer. Finally, we also investigate the potential confounding role of child abuse, secondhand smoke exposure, neuroticism, and demographic characteristics (e.g., age, marital status, gender, education and income) in these relationships.

2. Methods

2.1. Participants

Data were drawn from the two waves of the Midlife Development in the United States Survey (MIDUS) — a national survey of Americans in adulthood that investigated behavioral, psychological and social factors related to physical and mental health [28,29]. The MacArthur Midlife Research Network collected Wave 1 data from 1994 to 1995 and Wave 2 data from 2004 to 2006. Wave 1 consisted of a nationally representative multistage probability sample (main sample) of community-dwelling English speakers in the continental United States (n=3032). Participants who completed the telephone interview were mailed a self-administered questionnaire. The response rate from the mailed questionnaire was 86.6%, yielding an overall response rate of 61% (.70*.87=.61). Approximately 70% of Wave 1 participants took part in the Wave 2 survey collected by the Institute on Aging at the University of Wisconsin-Madison and supported by the National Institute on Aging (2004–2006). Wave 2 participants completed a 30-min telephone interview and a self-administered questionnaire was mailed to them. Of the 3032 participants from Wave 1, 2101 completed the Wave 2 telephone surveys (response rate of 69.5%). For this study, we analyzed only data from those who participated in the Wave 1 main sample who completed both the phone and mail-in surveys, participated in the Wave 2 survey, and had complete information for Wave 2 outcome variables.

2.2. Measures

2.2.1. Ulcer

The MIDUS included questions regarding the presence of 27 health problems or medical conditions over the preceding 12 months in both Wave 1 and Wave 2. All these began with the same stem ("In the past 12 months, have you experienced or been treated for…?"). Accordingly, the question regarding ulcer was phrased as follows: "In the past 12 months, have you experienced or been treated for any of the following — ulcer?" Variables representing the presence or absence of ulcer in the past 12 months at each wave were created (presence=1, absence=0).

2.2.2. Ulcer treatment

The MIDUS queried participants about treatment for a variety of health problems or medical conditions over the past 30 days in Wave 2. All these began with the same stem ("During the past 30 days have you taken prescription medicine for any of the following conditions…?"). Thus, to assess whether or not participants had been treated for ulcer, participants were asked: "During the past 30 days have you taken prescription medicine for any of the following conditions — ulcers?" Variables representing the presence or absence of ulcer treatment during the past 30 days at Wave 2 were created (presence=1, absence=0).

2.2.3. Cigarette smoking and substance use problems

All participants were asked whether they were currently regular cigarette smokers at Wave 1 and Wave 2. At Wave 1, participants were also asked whether they had experienced or been treated for any alcohol or drug problems within the past 12 months.

2.2.4. Anxiety disorders

The MIDUS psychiatric diagnoses were based on the Composite International Diagnostic Interview Short Form (CIDI-SF) scales, a series of diagnostic-specific scales that were developed from item-level analyses of the Composite International Diagnostic Interview questions in the National Comorbidity Survey [30]. The CIDI-SF scales were designed to reproduce the full Composite International Diagnoses as exactly as possible, with only a small subset of the original questions. CIDI-SF syndromes at 12 months included in the MIDUS were PAs and GAD. For mood and anxiety disorders, the kappa for CIDI-SF, compared with the Structured Clinical Interview for DSM Disorders (SCID), is 0.46 and 0.44, respectively, suggesting fair–good agreement [31]. Some evidence suggests that CIDI-SF may produce slightly higher estimates or be more reflective of "any affective disorder" than major depressive disorder, for instance, because it is a screening tool and casts a wider net [32]. Validity data have been presented suggesting that there is a strong relationship between diagnoses based on the CIDI-SF and the full CIDI [33,34]. These measures were used in Wave 1 and Wave 2 for past-12-month disorders.

2.2.5. Neuroticism

Assessment of personality traits in the Midlife Development Inventory Personality Scales (MIDI), based on the "big five" factor model [35] was grounded on the results of a pilot study conducted in 1994 with a probability sample of 1000 men and women, aged 30–70 (574 valid cases were usable for item analysis). Items with the highest item to total scale correlations and factor loadings were selected for the MIDI [30,36-40]. Forward regressions were also run to determine the smallest number of items needed to account for over 90% of the total scale variance. Many of the negatively worded items (unemotional, unreliable, unsophisticated, unsympathetic, shy, unsociable) were dropped due to low variance. New items were added to increase reliabilities on some scales. Participants were instructed to rate how much of the time a particular word described them on a Likert-scale ranging from 1 "a lot," 2 "some," 3 "a little" to 4 "not at all." The neuroticism scale is comprised of four words that include "moody," "worrying," "nervous" and "calm," (α=0.74). The items were recoded

Table 1
Demographics and univariate correlates of prevalent ulcer (past 12 months) at Wave 2

Demographics, history of anxiety disorders, & behavioral characteristics	No Ulcer W2	Ulcer W2	*p* value
	n=1715	*n*=38	
Age (M, S.D.)	45.5 (12.7)	50.5 (14.3)	.013
Gender			.14
Male	762 (44.4%)	12 (31.6%)	
Female	953 (55.6%)	26 (68.4%)	
Race			.002
White	1480 (86.3%)	28 (73.7%)	
Black/African–American	95 (5.5%)	4 (10.5%)	
Native American/Alaskan	8 (0.5%)	2 (5.3%)	
Asian	14 (0.8%)	0 (0%)	
Native Hawaiian/Pacific Islander	24 (1.4%)	1 (2.6%)	
Other	9 (0.5%)	0 (0%)	
Marital status			*P*<.001
Married	1177 (68.6%)	17 (44.7%)	
Separated	27 (1.6%)	1 (2.6%)	
Divorced	257 (15.0%)	5 (13.2%)	
Widowed	124 (7.2%)	9 (23.7%)	
Never married	128 (7.5%)	6 (15.8%)	
Education			*P*<.001
Grade school up to GED	231(13.5%)	18 (48.6%)	
High school graduate	562 (32.8%)	8 (21.6%)	
Some college	454 (26.5%)	9 (24.3%)	
Bachelors degree	262 (15.3%)	0 (0%)	
Any graduate school	206 (12.0%)	2 (5.4%)	
Annual household income (M, S.D.)	67,685 (57,399)	35,570 (34,969)	*P*<.001
Ulcer treatment (past 30 days), W2	13 (0.76%)	21 (55.3%)	*P*<.001
PA, W1	115 (6.7%)	8 (21.1%)	.022
GAD, W1	57 (3.3%)	6 (15.8%)	*P*<.001
Any physical or severe abuse in childhood	479 (27.9%)	10 (26.3%)	.967
Adulthood SHS exposure	995 (58.0%)	25 (65.8%)	.087
Smoke regularly, W2	304 (17.7%)	12 (31.6%)	.097
Substance use disorder, W1	41 (2.4%)	5 (13.2%)	.001
Neuroticism, W1 (M, S.D.)	2.29 (.68)	2.67 (.79)	.002

GED=General Educational Development; W1=Wave 1 (past 12 months); SHS=secondhand smoke; W2=Wave 2 (past 12 months); *M*=mean; S.D.=standard deviation.

(except for "calm") such that higher scores reflected greater levels of neuroticism. Once the appropriate items were recoded, the scale score was then computed by calculating the sum of the all the values of the items. The alphas are based on the MIDUS national sample. Scores on the neuroticism scale measured at Wave 1 were used in the current analyses.

2.2.6. Child maltreatment

Physical abuse categories were modeled after the Conflict Tactics Scale using 15 different item measures from the MIDUS self-administered questionnaire [41]. Participants were asked how frequently their mother, father, sister, brother or someone else smashed or kicked something in anger; pushed, grabbed or shoved them; slapped them; threw something at them; kicked, bit or hit them with a fist; hit or tried to hit them with something; beat them up; choked them; or burned or scalded them. Participants who reported experiencing any physical or severe physical abuse were coded as 1, and those who reported experiencing no physical or severe physical abuse were coded as 0.

2.3. Statistical analyses

First, bivariate analyses were used to investigate differences in age, gender, education, race and marital status between adults with and without ulcer. Statistical significance was set at $p<.05$. Logistic regression analyses were then used to calculate odds ratios (ORs) [with 95% confidence intervals (CIs)] estimating the associations between GAD or PA at Wave 1 and odds of prevalent ulcer at Wave 2. Analyses were then adjusted for race, marital status, gender, education, substance use disorder at Wave 1, neuroticism at Wave 1, cigarette smoking at Waves 1 and 2 and history of childhood physical abuse. In a second model, logistic regression analyses were used to determine the strength of the association between GAD or PA at Wave 1 and incident ulcer at Wave 2 (present at Wave 2, not present at Wave 1). Logistic regression was also used in a third model to estimate the association between GAD or PA at Wave 1 and ulcer treatment at Wave 2 (no treatment at Wave 1). Formal mediation analyses were conducted using recently published SAS macros [42] to determine whether either smoking or substance use disorder was a mediator of observed associations between anxiety and ulcer. The natural indirect effect was calculated which expresses how much the log odds of ulcer would change on average if anxiety were present but the mediator (smoking or substance abuse) were changed from the level it would take if anxiety were not present to the level it would take if anxiety were present.

3. Results

3.1. Sociodemographic characteristics and ulcer

There were 38 self-reported prevalent ulcers and 18 self-reported incident ulcers at Wave 2. Sociodemographic characteristics associated with ulcer at Wave 2 are presented in Table 1. Ulcer was significantly more common among Native Americans, individuals who had completed fewer years of formal education, older persons and those who had lower income and were widowed (Table 1). There were no statistically significant differences in gender between individuals with and without ulcer.

Results of univariate analyses indicated that individuals diagnosed with ulcer were more likely to have substance use disorder and higher levels of neuroticism (Table 1). GAD and PAs were more common among those with, compared to without, ulcer at Wave 1.

3.2. Anxiety disorders and prevalent ulcer

Ulcer was common among 6.6% (n=11/166) of participants with past 12-month GAD or PA at Wave 1 compared with 1.7% (n=27/1586) who did not have GAD or PA (OR=4.1, 95% CI=2.0–8.4; see Table 2).

3.3. Anxiety disorders and incident ulcer

Anxiety disorder was associated with increased odds of incident ulcer 10 years later (Table 3). Participants with past-12-month GAD or

Table 2
Anxiety disorders at Wave 1 and prevalent ulcer at Wave 2

	No GAD or PA @ W1	GAD or PA @ W1	OR (95% CI)	AOR[a] (95% CI)	AOR[b] (95% CI)	AOR[c] (95% CI)	AOR[d] (95% CI)	AOR[e] (95% CI)
	n=1586	*n*=166						
Ulcer @ W2	27 (1.7%)	11 (6.6%)	**4.1 (2.0, 8.4)**	**2.8 (1.2, 6.4)**	**3.8 (1.7, 8.4)**	**2.7 (1.1, 6.6)**	**5.9 (2.3, 15.3)**	**5.5 (2.2, 13.7)**

Bold=*P*<.05.
[a] Adjusted odds ratio for age, race, marital status, gender, education and income.
[b] Adjusted odds ratio for substance use disorder, W1.
[c] Adjusted odds ratio for neuroticism, W1.
[d] Adjusted odds ratio for current regular smoking, W2.
[e] Adjusted odds ratio for any physical or severe abuse in childhood.

Table 3
Anxiety disorders at Wave 1 and incident ulcer at Wave 2 (no ulcer at Wave 1)

	No GAD or PA @ W1	GAD or PA @ W1	OR (95% CI)	AOR[a] (95% CI)	AOR[b] (95% CI)	AOR[c] (95% CI)	AOR[d] (95% CI)	AOR[e] (95% CI)
	n=1469	*n*=141						
Ulcer @ W2 (not W1)	13 (0.9%)	5 (3.5%)	**4.2 (1.4, 13.2)**	**3.6 (1.1, 11.5)**	**3.1 (1.0, 10.3)**	**3.9 (1.2, 12.4)**	**5.4 (1.6, 18.1)**	**4.2 (1.1, 15.3)**

Bold = $P<.05$.
[a] Adjusted for age, race, marital status, gender, education and income.
[b] Adjusted for substance use disorder, W1.
[c] Adjusted for neuroticism, W1.
[d] Adjusted for current regular smoking, W2.
[e] Adjusted for any physical or severe abuse in childhood.

PA at Wave 1 were significantly more likely than those without GAD or PA at Wave 1 to report having an ulcer at Wave 2 (OR=4.2, 95% CI=1.4–13.2) (among those who did not have an ulcer at Wave 1).

3.4. Anxiety disorders and treated ulcer

The results suggest that those with an anxiety disorder have increased odds of being treated for ulcer at Wave 2 (Table 4). Participants with past-12-month GAD or PA at Wave 1 were significantly more likely than those without GAD or PA at Wave 1 to report being treated for ulcer at Wave 2 (OR=4.7, 95% CI=2.3–9.9) (among those who were not treated for ulcer at Wave 1).

3.5. Anxiety and ulcer adjusted for confounders

To examine potential confounding factors, we adjusted for socio-demographic characteristics (age, race, marital status, gender, education and income) in a multivariable model, neuroticism at Wave 1 in a separate univariate model, and history of frequent abuse in childhood in another. The association between anxiety and ulcer (prevalent, incident, and treated) persisted even after controlling for those factors (Tables 2, 3, and 4).

3.6. Anxiety and ulcer tested for mediators

To evaluate the potentially mediating role of substance use disorders and cigarette smoking in the relationship between anxiety and ulcer (prevalent, incident and treated), we adjusted for differences in substance use disorder at Wave 1 in one model and current regular smoking at Wave 2 in another model. Neither smoking behavior nor substance use disorder significantly impacted the relationship between anxiety disorders and ulcer (Tables 2, 3 and 4). Formal mediation analyses did not support the role of mediation by smoking or substance abuse disorder. The respective natural indirect effects for smoking and substance abuse disorder were 1.14 [0.98, 1.34], $P=.09$ and 1.14 [0.92,1 .41], $P=.23$.

4. Discussion

Findings from this study are consistent with and extend previous knowledge in two ways. First, anxiety disorders are associated with increased ulcer risk both concurrently and on follow-up (prevalent, incident, and treated). Second, these relations are not due to confounding or mediation by a wide range of factors including demographics, substance use disorder, neuroticism, smoking or child abuse.

To our knowledge, this is the first study to prospectively examine the relation between anxiety and ulcer in a nationally representative sample. Using prospective longitudinal data over a 10-year period, results of this study suggest that anxiety disorders are associated with increased prevalence of ulcer 10 years later among adults in the community. It is not possible to determine the pathway of these associations from these data alone. In order to examine whether the relationship between anxiety and ulcer is due to third variables, we examined a range of potentially confounding and mediating factors. As expected, none of these variables affected these relationships in a substantive way. Our results suggest a strong relationship between anxiety and ulcer that persists over a long period and does not appear to be explained by many of the common confounders or mediators that we tested, as might be suspected. Several, but not all (i.e., neuroticism), of these factors have been examined in previous cross-sectional studies [10,26,27]. There may be other variables that were not accounted for in the models of the present study, such as elevated cortisol [43], that may mediate the association between anxiety disorders and ulcer. Future research should work to identify other factors that could influence this relationship.

Although the pathway of the associations between GAD and PA with ulcer cannot be known from these data alone, the results suggest that the anxiety disorders under investigation may be risk factors for developing ulcer. Anxiety can potentially increase gastric acid secretion, predisposing one to develop ulcer [44]. Thus, efforts at treating anxiety disorders and/or reducing stress levels may play a role in reducing the risk of developing ulcer. In particular, non-pharmacological treatments including meditation, deep breathing, progressive muscle breathing and other relaxation techniques are cost-effective and easily applied interventions to incorporate into

Table 4
Anxiety disorders at Wave 1 and treatment of ulcer at Wave 2

	No GAD or PA @ W1	GAD or PA @ W1	OR (95% CI)	AOR[a] (95% CI)	AOR[b] (95% CI)	AOR[c] (95% CI)	AOR[d] (95% CI)	AOR[e] (95% CI)
	n=1219	*n*=132						
Ulcer treatment @ W2 (not W1)	23 (1.9%)	11 (8.3%)	**4.7 (2.3, 9.9)**	**4.1 (1.8, 9.25)**	**3.9 (1.8, 8.5)**	**2.9 (1.2, 6.8)**	**4.3 (1.7, 11.1)**	**4.9 (1.8, 13.2)**

Bold = $P<.05$.
[a] Adjusted for age, race, marital status, gender, education and income.
[b] Adjusted for substance use disorder, W1.
[c] Adjusted for neuroticism, W1.
[d] Adjusted for current regular smoking, W2.
[e] Adjusted for any physical or severe abuse in childhood.

one's lifestyle in order to reduce levels of anxiety and, potentially, to lower risk of developing ulcer.

This study has several central limitations that should be considered when interpreting the results. First, the number of respondents with prevalent ulcer at Wave 2 was quite low ($n=38$) relative to the large sample size ($n=1753$). However, the estimated 1-year prevalence rate of physician-diagnosed peptic ulcer in the population is approximately 1.1%–1.5% [45-47], yielding a similar prevalence rate to that of our data (2.2%), however our results need to be replicated with a larger sample. Additionally, the assessment of ulcer was restricted to the past 12 months at Waves 1 and 2; thus, a lifetime history of ulcer was not possible to obtain. Another concern is that medical history data were gathered using self-report; thus, we relied on the accuracy of the participants' recall in evaluating the presence of ulcer. There is a high risk of false-positive ulcer reports from patients who have not undergone proper diagnostic evaluations and it is possible that people with anxiety disorders could be more prone to report an ulcer without diagnostic verification. However, 21 out of the 38 participants who reported that they had ulcer at Wave 2 also reported having been treated for ulcer at Wave 2, corroborating nearly 60% of the respondents' self-report of ulcer. In addition, this limitation is somewhat diminished by evidence that suggests that patients' self-reported medical diagnoses are fairly accurate and generally congruent with physician or medical record confirmation of those conditions [48,49]. Nevertheless, the self-reported nature of ulcer is a matter of concern, and thus, our findings should be interpreted with caution. Another potential factor vulnerable to misreport is child abuse, which was reported retrospectively and likely occurred years prior. Furthermore, participants were asked if, within the past 12 months, they had experienced ulcer, but type of ulcer was not specified; thus, it was not possible to discriminate duodenal from gastric ulcers, which are located in the duodenum and in the stomach, respectively. It seems unlikely that participants confused foot ulcers with gastric/duodenal ulcers, but since the development of foot ulcer is most commonly associated with sequelae of diabetes mellitus including neuropathy and peripheral vascular disease [50,51], we reanalyzed the data excluding participants who were being treated for diabetes at both Waves 1 or 2, and the results all remained the same. Additionally, information on additional anxiety disorders including social anxiety disorder, posttraumatic stress disorder, specific phobia, and obsessive–compulsive disorder, as well as on symptoms of anxiety that do not meet diagnostic criteria for an anxiety disorder, were unavailable. As a result, the findings of this study are not intended to generalize to all anxiety disorders. Future studies should examine the relationship between additional anxiety disorders as well as subclinical anxiety disorders and ulcer. Another issue is that anxiety and neuroticism are complex and partially overlapping constructs that are difficult to disentangle from one another [52,53]. Thus, descriptions of anxiety including "worrying" and "nervousness" may overlap with neuroticism. As such, our efforts to control statistically for neuroticism may lead to a curtailment of the effect of anxiety disorders or may be insufficient to control for the role of neuroticism. Finally, other risk factors of ulcer were unable to be examined in the current investigation. First, information regarding how many participants may have been infected with *H. pylori* was not available. However, it is unlikely that *H. pylori* would be a confounder or mediator of anxiety. Nevertheless, future studies that can include *H. pylori* status in investigating the relationship between mental health, personality factors and ulcer are needed. Second, data on the use of nonsteroidal anti-inflammatory drugs (NSAIDs), which has been consistently found to increase the risk of gastrointestinal bleeding and ulcer [54-56], were very limited and therefore not included in the current study. Future investigations that can include the use of NSAIDs are needed to limit any potential bias in risk ratios between anxiety and ulcer.

5. Conclusions

Findings from this study suggest a strong association between anxiety disorders and ulcer over time. Although the mechanisms of this relationship are not yet understood, several potential confounding factors and mediators were examined that do not appear to explain this relationship over a 10-year period. Although the results of this study must be interpreted with caution, the findings merit increased and sustained efforts into investigating how these diseases are linked. While *H. pylori* has been widely accepted as the primary causal influence on the genesis of ulcers, the current findings are consistent with other reviews [43,57,58] and epidemiologic [6,12,59-61] findings which suggest that factors including anxiety disorders may contribute to the pathogenesis of ulcer and warrant consideration.

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