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ORIGINAL RESEARCH

A Study on the Association Between Risk Factors and Psychosocial Factors of Non-Cardiac Chest Pain (NCCP) in Adults Aged 40 and Above Based on 2013-2018 US NHANES Data

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Background: Non-cardiac chest pain (NCCP) is a prevalent clinical symptom frequently associated with psychosocial factors. This study aimed to investigate the relationship between anxiety, depression, fatigue, and NCCP, with a particular focus on how these psychosocial factors influence the risk of NCCP occurrence.

Methods: Based on data from the NHANES database, we analyzed the clinical characteristics, psychosocial status, and the occurrence of non-cardiogenic chest pain in 4557 participants. After weighting, the sample size was 64,650,723.91. Spearman correlation analysis and weighted multivariable logistic regression models were used to explore the associations between anxiety, depression, fatigue, and non-cardiogenic chest pain and to assess the independent impact of these factors on the risk of non-cardiogenic chest pain.

Results: The results of the weighted logistic regression indicate that anxiety and depression are significantly associated with non-cardiac chest pain, and the severity of anxiety is positively correlated with the risk of non-cardiac chest pain (OR = 2.778, 95% CI = [2.772, 2.784]). Furthermore, compared with participants who reported "no fatigue at all", those who reported feeling fatigued "almost every day" had a 1.927-fold higher risk of non-cardiac chest pain. Multivariate regression analysis identified depressive and anxious symptoms as important predictors of non-cardiac chest pain.

Conclusion: This study highlights the important role of psychosocial factors in the occurrence of Non-cardiac chest Pain, particularly the significant influence of anxiety, depression, and fatigue on Non-cardiac chest Pain risk. The findings underscore the need to incorporate psychosocial assessments into the clinical diagnosis and management of Non-cardiac chest Pain, offering new perspectives and strategies for pain management.

Keywords: non-cardiac chest pain, anxiety, depression, fatigue, psychosocial factors

Introduction

Chest pain is oneof the most common chief complaints in clinical practice, accounting for a substantial number of emergency department visits and consuming considerable healthcare resources each year.[1,2] Despite continuous improvements in diagnostic and treatment protocols, current pathways remain inefficient due to their heavy reliance on the biomedical model.[3,4] A study involving over 60,000 emergency transport cases revealed that approximately 16% of emergencies were triggered by chest pain, yet more than half of these patients were not diagnosed with any organic disease.[5] Notably, over 60% of patients presenting to the emergency department with chest pain are diagnosed with non-cardiac chest pain (NCCP). Though NCCP is not due to immediate life-threatening cardiac issues, it brings big challenges in emergencies. Patients suffer severe discomfort and anxiety, leading to repeated ED visits. This strains emergency services and incurs high medical costs. In developed nations, annual costs for NCCP evaluation and management in EDs can reach millions, covering direct diagnostic expenses and indirect costs from long stays and

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follow-up. In LMICs, with limited resources, overusing emergency services for NCCP diverts resources from critical cases. Lack of proper psychological care leads to higher reconsultation rates and lower quality of life. For instance, in an LMIC, long travel distances, long waits, and poor psychological support worsen patients' conditions and increase medical burdens.

Although NCCP generally has a favorable prognosis, it is associated with a significant increase in reconsultation rates and secondary healthcare resource utilization.[6–8] Traditional diagnostic pathways often interpret chest pain as an early warning sign of cardiovascular events, leading to a large number of unnecessary examinations[9] The longstanding neglect of psychosocial assessments may further exacerbate long-term impairments in patients' quality of life.

Studies have shown that patients with NCCP frequently suffer from psychological distress such as anxiety and depression, and the impact on their quality of life is comparable to that of patients with cardiac chest pain.[10,11] A survey conducted in Japan reported that approximately 70% of chest pain patients were diagnosed with NCCP, with psychological distress significantly associated with diminished quality of life.[12,13] However, systematic research on the role of psychosocial factors in chest pain remains limited. For example, the quality of life in NCCP patients is influenced not only by depression but also by cardiac anxiety and somatization symptoms.[14] Additionally, depression and anxiety levels are significantly higher in NCCP patients than in those with cardiac chest pain, and psychological distress shows a dose-dependent negative correlation with quality of life.[15,16] It is worth noting that even among patients with angina pectoris, comorbid depression and anxiety significantly increase the risk of non-cardiac readmissions and adverse events.[17] These findings suggest that emotional disorders may broadly affect the long-term prognosis of patients with chest pain. The above evidence highlights that the detrimental impact of psychosocial factors on the quality of life in NCCP patients should not be underestimated, underscoring the urgent need to explore the mechanisms linking psychosocial factors to chest pain to optimize clinical management.

In recent years, research has gradually revealed the critical role of psychosocial factors in the onset, perception, and chronification of chest pain. Beyond anxiety and depression, psychological abnormalities such as chronic fatigue and attention disorders have also been shown to be significantly associated with chronic pain syndromes.[18] More notably, recent studies have proposed that psychological distress in patients with NCCP may exhibit bidirectional interactions with chronic somatic diseases, such as alcoholic liver disease and fatty liver disease, suggesting that some psychological symptoms may be driven by underlying physiological and pathological mechanisms, thereby exacerbating the experience of chest pain.[19] This finding offers a new perspective for understanding the complexity of mind-body interactions.

Although existing studies have made certain advances, most remain limited by focusing on a single psychosocial factor and are often constrained by small sample sizes and single-center designs.[20] The National Health and Nutrition Examination Survey (NHANES), as a nationwide, stratified sampling cross-sectional study, integrates demographic, health behavior, psychological, and clinical data, providing an ideal platform for systematically analyzing the association between multidimensional factors and chest pain. Based on NHANES data from 2013–2018, this study employed multivariate logistic regression models to control for confounders such as age, BMI, and chronic diseases, and utilized neural network algorithms to quantify the independent predictive value of psychological factors including anxiety, depression, and fatigue. Through cross-methodological validation, this study aims to elucidate the mechanisms by which psychological factors contribute to chest pain, thereby providing a theoretical basis for integrating psychological screening and intervention strategies into clinical practice.

Materials and Methods

Clinical Data

The data used in this study were obtained from the NHANES database (https://www.cdc.gov/nchs/nhanes/index.htm). NHANES is a cross-sectional survey conducted by the National Center for Health Statistics (NCHS) and the Centers for Disease Control and Prevention (CDC) in the United States. It aims to provide nationally representative data on the civilian, non-institutionalized US population. The data collection protocols were approved by the NCHS Ethics Review Board, and all participants provided informed consent prior to interviews and examinations.

According to Article 32 of the "Measures for the Ethical Review of Life Sciences and Medical Research Involving Humans" issued by the National Health Commission of China in 2023, when conducting life sciences and medical research involving humans, ethical review may be exempted if any of the following conditions are met: - Research uses publicly available data obtained legally, or data collected through observation without interfering with public behavior (Item 1 of Article 32);- The purpose of the research is public health or health services research of social populations, and the research does not intervene in the natural state or social behaviors of the populations during the study (Item 2 of Article 32). In this study, the NHANES database data we used is nationally representative survey data legally released by the US CDC and NCHS. Its collection process has been approved by the NCHS Ethics Review Board, and the study only conducts secondary analysis on de-identified public data without any intervention on participants or social populations. Therefore, this study meets the exemption conditions of both Item 1 and Item 2 of Article 32 and does not require additional approval from our institutional ethics review board.

In this study, publicly available data files from NHANES 2013–2018 were utilized to construct the dataset. The study population included all respondents of the NHANES survey.

Study Population

NHANES collects data from the civilian, non-institutionalized US population using a multistage probability sampling design to ensure national representativeness. The survey targets individuals across all age groups, covering different categories such as gender, age, and education level to accurately reflect the diversity of the US population.

Original Sample Size

A total of 29,400 participants were included from the 2013–2018 NHANES cycles.

Screening Process

Exclusion Criteria

(1) Participants with missing Non-cardiac chest Pain data were excluded (n = 17,949).
(2) Participants with missing psychosocial factor data were excluded (n = 4850).
(3) Participants with missing data for other covariates and those under 40 years old (eg, health status, chronic diseases) were excluded (n = 2044).
(4) Finally, a total of 4557 valid participants were included in the analysis (Figure 1).

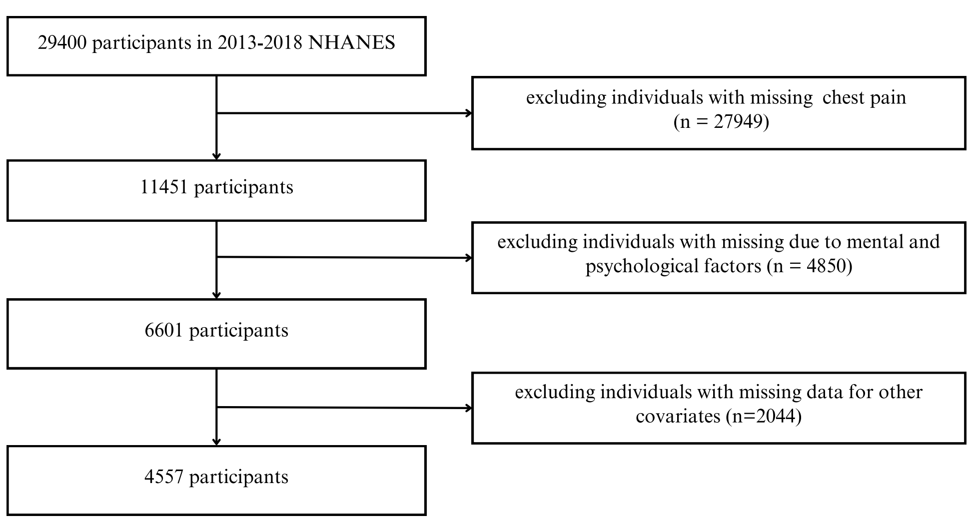

Figure 1 Original Sample Size. This flowchart illustrates how, during the research process, participants with missing data are gradually excluded, ultimately determining the number of participants who meet the study requirements.

Data Collection

In this study, the dependent variable was the state of non-cardiac chest pain, with data collected through specific questionnaire items. Participants were divided into two groups: those with and without non-cardiac chest pain. Psychosocial factors were treated as independent variables and collected via structured questionnaires. For anxiety assessment, apart from two basic questions, the Generalized Anxiety Disorder Scale (GAD-7) was used, which contains seven items and classifies anxiety into four levels—none, mild, moderate, and severe—based on the total score. This scale has good reliability and validity. Depression was assessed using the Patient Health Questionnaire (PHQ-9), which contains nine items and classifies depression into three levels—none, borderline, and depressive—based on the total score, and its accuracy is widely recognized. Fatigue was assessed using the PROMIS (Patient-Reported Outcomes Measurement Information System) Fatigue Scale, which can accurately measure fatigue from multiple dimensions and categorize it into levels, and is professionally authoritative. In addition, feelings such as sadness, poor self-perception, and attention difficulties were assessed via questionnaire and divided into four categories. For the PHQ-9, GAD-7, and PROMIS Fatigue Scale, if an individual item was missing, the mean or median of the non-missing items was used for estimation; if multiple items were missing, the corresponding scale data were excluded from analysis. All questions were administered by trained interviewers during home visits using the CAPI system.

Numerous covariates were included in the analysis. Demographic information was obtained from the demographics questionnaire and included variables such as age, sex, educational level, marital status, and household income. Clinical data were collected from examination or questionnaire responses and covered a range of lifestyle and health-related covariates, including BMI, smoking status, alcohol consumption, hypertension, and diabetes.

Smoking status was determined based on responses to the following questions: "{Have you/Has SP} smoked at least 100 cigarettes in {your/his/her} entire life?", "{Do you/Does SP} now smoke cigarettes?", and "How long has it been since {you/SP} quit smoking cigarettes?" Participants were classified into three groups: never smokers (those who had not smoked at least 100 cigarettes and were not currently smoking), current smokers (those who had smoked at least 100 cigarettes and were currently smoking), and former smokers (those who had smoked at least 100 cigarettes but had since quit, with a recorded quit date).

Alcohol consumption was assessed using the questions: "In the past 12 months, how often did {you/SP} drink any type of alcoholic beverage? PROBE: How many days per week, per month, or per year did {you/SP} drink?" and "During the past 12 months, about how often did {you/SP} drink any type of alcoholic beverage? PROBE: How many days per week, per month, or per year did {you/SP} drink?" Based on monthly drinking frequency, participants were classified as never drinkers, occasional drinkers (less than 4 drinking days per month), frequent drinkers (4–15 drinking days per month), and heavy drinkers (more than 15 drinking days per month).

Diabetes and hypertension status were determined through interviews conducted by trained personnel using the CAPI system at participants' homes.

Statistical Analysis

This study used SPSS version 25.0 and Python (Pycharm 2024.3.2) for statistical analysis. First, the baseline characteristics of 4557 participants were described, dividing them into the non-cardiac chest pain group (n = 1343) and the non-non-cardiac chest pain group (n = 3214). Continuous variables were presented as mean ± standard deviation (SD), and categorical variables were presented as frequencies and percentages. Independent samples *t*-tests were used to assess differences in continuous variables between groups, and chi-square tests were used to analyze differences in categorical variables. During the exploratory analysis phase, Spearman correlation analysis was initially used to evaluate the associations between demographic variables, lifestyle factors, health status, psychosocial factors, and non-cardiac chest pain. However, we recognized that Spearman correlation analysis has certain limitations for primary analyses involving binary outcomes and ordinal exposures. Therefore, in the main analysis, considering factors such as the complex sampling design of the study, we employed weighted survey logistic regression models (adjusting for age, sex, educational level, income, marital status, BMI, chronic diseases, and lifestyle factors) to more accurately investigate the independent effects of psychosocial factors on non-cardiac chest pain. Additionally, a Sankey diagram was plotted to illustrate the strength of associations between different categories of psychosocial factors and non-cardiac chest pain. A neural network model was also used to analyze the importance of predictor variables, and the receiver operating characteristic (ROC) curve was employed to assess the model's discriminative ability, with the area under the curve (AUC) quantifying model performance. In all statistical analyses, a two-sided P value < 0.05 was considered statistically significant.

Results

Baseline Characteristics

A total of 4557 participants were included in this study. Weighted sample size (n=64,650,723.91). Participants were divided into two groups based on the presence or absence of Non-cardiac chest Pain (Non-cardiac chest Pain group: 19202915.04 participants; no Non-cardiac chest Pain group: 45447808.87 participants) for baseline characteristic analysis.

The results showed that Non-cardiac chest Pain was significantly associated with several variables. The results showed that non-cardiac chest pain was significantly associated with multiple variables. In the non-cardiac chest pain group, it was more common among individuals with lower household income, higher BMI, and higher prevalence of hypertension.

Psychosocial factors such as feelings of sadness, fatigue, poor self-perception, difficulty concentrating, anxiety, and depression were closely associated with Non-cardiac chest Pain, all showing significant differences ($P < 0.001$).

Additionally, smoking status ($P < 0.001$) and alcohol consumption ($P < 0.001$) were also significantly associated with the presence of Non-cardiac chest Pain.

Age, gender, education, and diabetes were not significantly associated with the occurrence of non-cardiac chest pain (Table 1).

Spearman Correlation Analysis

Spearman correlation analysis was performed to assess the relationships between various variables and Non-cardiac chest Pain (Table 2).

From a demographic perspective, age ($r = 0.018$, $P = 0.233$), sex ($r = 0.006$, $P = 0.695$), and education level ($r = -0.026$, $P = 0.076$) were not significantly associated with Non-cardiac chest Pain, suggesting that these factors had a relatively minor impact on the occurrence of Non-cardiac chest Pain.

Household income ($r = -0.110$, $P < 0.001$) was significantly negatively correlated with Non-cardiac chest Pain, indicating that lower household income may increase the risk of Non-cardiac chest Pain.

In terms of lifestyle and health status, marital status ($r = 0.099$, $P < 0.001$), BMI ($r = 0.071$, $P < 0.001$), hypertension ($r = 0.137$, $P < 0.001$), and diabetes ($r = 0.069$, $P < 0.001$) were all significantly positively correlated with Non-cardiac chest Pain, suggesting that these factors may elevate the risk of experiencing Non-cardiac chest Pain.

Smoking ($r = 0.114$, $P < 0.001$) was significantly positively correlated with Non-cardiac chest Pain, while alcohol consumption ($r = -0.006$, $P = 0.674$) showed no significant association with Non-cardiac chest Pain.

Regarding psychosocial factors, sadness ($r = 0.203$, $P < 0.001$), fatigue ($r = 0.235$, $P < 0.001$), poor self-perception ($r = 0.168$, $P < 0.001$), difficulty concentrating ($r = 0.167$, $P < 0.001$), anxiety ($r = 0.236$, $P < 0.001$), and depression ($r = 0.238$, $P < 0.001$) were all significantly positively correlated with Non-cardiac chest Pain, with relatively strong correlation coefficients, indicating a substantial impact of psychosocial factors on Non-cardiac chest Pain.

Multivariate Logistic Regression Analysis

Using weighted multivariable logistic regression analysis, we examined the independent association between psychosocial factors and non-cardiac chest pain after adjusting for potential confounders such as age, sex, education level, income, marital status, body mass index (BMI), chronic diseases (hypertension and diabetes), and lifestyle factors (smoking and alcohol consumption) (Table 3). The results showed a clear dose-response relationship between anxiety and depression and the risk of non-cardiac chest pain: participants with mild (OR = 1.767), moderate (OR = 1.881), and severe anxiety

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Table 1 Baseline Characteristics and Outcomes

Variable		Non-Cardiac Chest Pain		P-value
		No (n=45447808.87)	Yes (n=19202915.04)	
Age		58.50±11.58	69.0±11.75	0.254
Gender	Male	21663040.67 (47.7%)	9643410.74 (50.2%)	0.300
	Female	23784768.2 (52.3%)	9559504.3 (49.8%)	
Educational level	Less than 9th grade	2254224.6 (5.0%)	976214.9 (5.1%)	0.308
	9-11th grade	3505560.4 (7.7%)	1721062.2 (9.0%)	
	High school graduate/GED or equivalent	10069247.7 (22.2%)	4835962.5 (25.2%)	
	Some college or AA degree	14372101.8 (31.6%)	5707335.2 (29.7%)	
	College graduate or above	15246674.4 (33.5%)	5962340.3 (31.0%)	
Household_income	Under $20,000	5217571.0 (11.5%)	3610758.1 (18.8%)	<0.001
	$20,000 to $74,999	20897165.8 (46.0%)	8753182.9 (45.6%)	
	Over $75,000	19333072.0 (42.5%)	6838974.1 (35.6%)	
Marital status	Married	29877620.8 (65.7%)	10917713.1 (56.9%)	0.002
	Widowed	3564998.4 (7.8%)	1737672.6 (9.0%)	
	Divorced	5550084.9 (12.2%)	2856180.9 (14.9%)	
	Separated	1062771.3 (2.3%)	749894.6 (3.9%)	
	Never married	3015193.6 (6.6%)	1652605.5 (8.6%)	
	Living with partner	2377139.8 (5.2%)	1288848.3 (6.7%)	
BMI		29.30±6.39	30.29±7.27	0.003
Hypertension	Yes	17878916.0 (39.3%)	10121254.2 (52.7%)	<0.001
	No	27568892.87 (60.7%)	9081660.84 (47.3%)	
Diabetes	Yes	37351695.7 (82.2%)	15023675.1 (78.2%)	0.099
	No	6711935.0 (14.8%)	3537591.1 (18.4%)	
	Borderline	1384178.1 (3.0%)	641648.9 (3.3%)	
Low Mood	Not at all	37794847.8 (83.2%)	12512519.5 (65.2%)	<0.001
	Several days	5899094.5 (13.0%)	4320114.9 (22.5%)	
	More than half the days	1120739.5 (2.5%)	1340599.1 (7.0%)	
	Nearly every day	633127.0 (1.4%)	1029681.6 (5.4%)	
Fatigue	Not at all	25022972.3 (55.1%)	5919674.4 (30.8%)	<0.001
	Several days	15013399.0 (33.0%)	8067984.4 (42.0%)	
	More than half the days	2899680.3 (6.4%)	1959723.9 (10.2%)	
	Nearly every day	2511757.2 (5.5%)	3255532.4 (17.0%)	
Negative Self-Perception	Not at all	40385375.9 (88.9%)	14501783.3 (75.5%)	<0.001
	Several days	3859427.4 (8.5%)	3020520.6 (15.7%)	
	More than half the days	546697.7 (1.2%)	808632.1 (4.2%)	
	Nearly every day	656307.9 (1.4%)	871979.1 (4.5%)	
Inattention	Not at all	40310959.6 (88.7%)	1448913.8 (75.3%)	<0.001
	Several days	3685630.2 (8.1%)	2453251.6 (12.8%)	
	More than half the days	765580.3 (1.7%)	1132146.7 (5.9%)	
	Nearly every day	685638.8 (1.5%)	1148602.9 (6.0%)	
Anxiety	No anxiety	11187778.3 (24.6%)	2221473.4 (11.6%)	<0.001
	Mild anxiety	16694755.4 (36.7%)	5830515.2 (30.4%)	
	Moderate anxiety	5414224.4 (11.9%)	2722456.3 (14.2%)	
	Severe anxiety	12151050.7 (26.7%)	8428470.2 (43.9%)	
Depression	No depression	23690012.6 (52.1%)	5697780.9 (29.7%)	<0.001
	Borderline depression	15368081.7 (33.8%)	7418072.3 (38.6%)	
	Depression	6389714.5 (14.1%)	6087061.9 (31.7%)	

(*Continued*)

Table 1 (Continued).

Variable		Non-Cardiac Chest Pain		P-value
		No (n=45447808.87)	Yes (n=19202915.04)	
Smoking	Never smoked	25347274.5 (55.8%)	8343933.8 (43.5%)	<0.001
	Former smoker	13289469.3 (29.2%)	6802586.1 (35.4%)	
	Current smoker	6811065.0 (15.0%)	4056395.1 (21.1%)	
Drinking	Never drank	10216690.9 (22.5%)	5176706.6 (27.0%)	0.035
	Light drinking	21119069.3 (46.5%)	9627674.3 (50.1%)	
	Moderate drinking	9910571.4 (21.8%)	2763410.9 (14.4%)	
	Heavy drinking	4201477.3 (9.2%)	1635123.2 (8.5%)	

Table 2 Spearman Correlation Analysis

Variable	Correlation Coefficient	P-value
Age	0.018	0.233
Gender	0.006	0.695
Educational level	−0.026	0.076
Household_income	−0.110**	<0.001
Marital status	0.099**	<0.001
BMI	0.071**	<0.001
Hypertension	0.137**	<0.001
Diabetes	0.069**	<0.001
Low Mood	0.203**	<0.001
Fatigue	0.235**	<0.001
Negative Self-Perception	0.168**	<0.001
Inattention	0.167**	<0.001
Anxiety	0.236**	<0.001
Depression	0.238**	<0.001
Smoking	0.114**	<0.001
Drinking	−0.006	0.674

Note: **indicates that the data has a statistically significant difference ($p < 0.001$).

(OR = 2.778) had progressively higher risks of non-cardiac chest pain (all P values < 0.001). Similarly, individuals with borderline depression (OR = 1.692) and diagnosed depression (OR = 2.070) also had significantly increased risks of non-cardiac chest pain (P < 0.001). The impact of fatigue was particularly notable As the frequency of fatigue increased, the risk of non-cardiac chest pain rose stepwise, from "a few days" (OR = 1.407) to "more than half the days" (OR = 1.615), and to "nearly every day" (OR = 1.927) (P < 0.001). Furthermore, individuals who had difficulty concentrating almost every day had an increased risk of non-cardiac chest pain (OR = 1.849, P < 0.001). Those who felt sad nearly every day also had a higher risk of non-cardiac chest pain (OR = 1.341, P < 0.001), as did individuals with poor self-perception (OR = 1.632, P < 0.001).

Association Analysis Between Psychosocial Factors and Non-Cardiac Chest Pain: Based on Sankey Diagram

Based on the independent influencing factors identified through logistic regression analysis (ie, anxiety, depression, and fatigue), we constructed a Sankey diagram that visually presents the association patterns between these three variables and Non-cardiac chest Pain. Analysis of the Sankey diagram shows significant interrelationships and feedback effects among anxiety, depression, fatigue, and Non-cardiac chest Pain. The diagram displays variable relationships across four layered columns of nodes: the first column represents anxiety, the second column represents depression, the third column

Table 3 Weighted Multinomial Logistic Regression

Variable code	Variable		OR	95% CI	P-value
LM	Low Mood	Not at all	Ref		
		Several days	1.061	(1.059,1.063)	<0.001
		More than half the days	1.269	(1.265,1.273)	<0.001
		Nearly every day	1.341	(1.335,1.346)	<0.001
FTG	Fatigue	Not at all	Ref		
		Several days	1.407	(1.405, 1.410)	<0.001
		More than half the days	1.615	(1.611,1.618)	<0.001
		Nearly every day	1.927	(1.924,1.931)	<0.001
NSP	Negative Self-Perception	Not at all	Ref		
		Several days	1.048	(1.046, 1.050)	<0.001
		More than half the days	1.434	(1.432,1.436)	<0.001
		Nearly every day	1.632	(1.629,1.635)	<0.001
INA	Inattention	Not at all	Ref		
		Several days	1.096	(1.094, 1.099)	<0.001
		More than half the days	1.466	(1.460, 1.472)	<0.001
		Nearly every day	1.849	(1.846, 1.853)	<0.001
ANX	Anxiety	No anxiety	Ref		
		Mild anxiety	1.767	(1.764, 1.769)	<0.001
		Moderate anxiety	1.881	(1.877,1.885)	<0.001
		Severe anxiety	2.778	(2.772,2.784)	<0.001
DEP	Depression	No depression	Ref		
		Borderline depression	1.692	(1.687, 1.698)	<0.001
		Depression	2.070	(2.063, 2.077)	<0.001

represents fatigue, and the fourth column represents Non-cardiac chest Pain status (present/absent). The direction and thickness of the connecting streams indicate that psychological states such as anxiety and depression interact bidirectionally with physical symptoms like fatigue and Non-cardiac chest Pain.

From a causal perspective, anxiety and depression can serve as initiating factors, triggering fatigue through psychological mechanisms such as excessive worry. Long-term psychological distress disrupts sleep and alters hormonal balance, leading to physical and mental exhaustion and resulting in fatigue. Fatigue may also cause non-cardiac chest pain due to muscle tension and changes in pain perception. Conversely, non-cardiac chest pain can exacerbate anxiety by inducing health-related fears, while persistent or severe pain may lead to depression and interfere with activities and social interactions, worsening the psychological state.

In addition, fatigue can directly cause feelings of loss of control, triggering anxiety and depressive emotions, which in turn can further intensify fatigue, creating a cyclical pattern. The diagram intuitively quantifies the strength of associations and causal pathways among symptoms through the visualization of flows, confirming that psychological health issues and physical symptoms are not isolated but exhibit complex interactions. These findings suggest that interventions for such symptoms need to integrate both psychological and physiological dimensions, using systematic health management strategies to achieve symptom relief and overall health improvement (Figure 2).

Construction of the Neural Network Model

In the part of this study where a neural network model is used to analyze and predict variable importance, we adopt a multilayer perceptron architecture. The number of neurons in the input layer is determined by the number of predictor variables, and we set two hidden layers with 64 and 32 neurons respectively, both using ReLU activation functions to enhance nonlinear representation capabilities. For the output layer, we set 1 neuron with a Sigmoid activation function for the binary classification problem. Regarding hyperparameters, the batch size is 32, the learning rate is 0.001, it is trained for 100 iterations, and L2 regularization with a coefficient of 0.01 is applied to prevent overfitting. Model

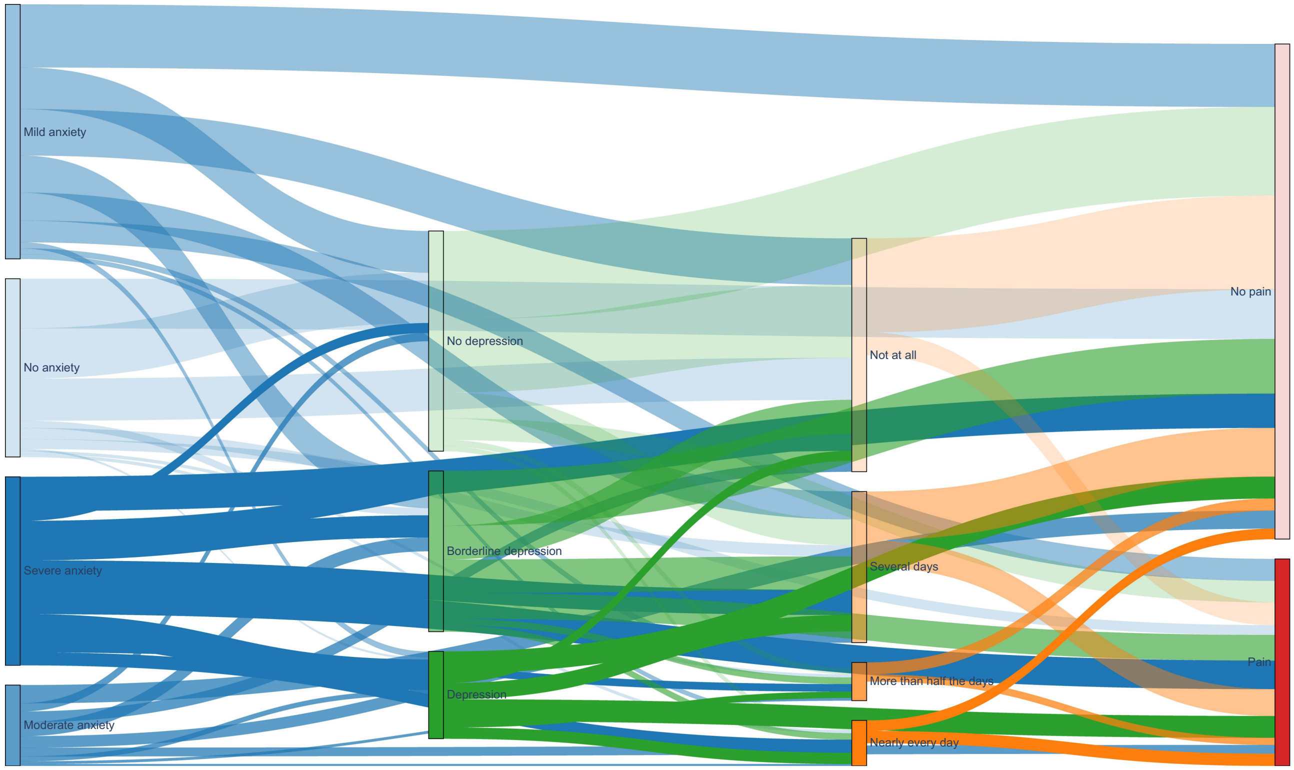

Figure 2 Sankey diagram. This Sankey diagram uses anxiety, depression, fatigue, and Non-cardiac chest Pain (with/without) as nodes, connected by colored streams to show the relationships between variables. The width of each node reflects the number or proportion of cases, the direction of the stream indicates the direction of the relationship, and the width represents the strength of the relationship. Different colors distinguish categories of relationship paths. Overall, it provides an intuitive visualization of the complex relationships between psychological states such as anxiety, fatigue, and Non-cardiac chest Pain, as well as the direction and magnitude of their interactions.

performance and stability are evaluated using five-fold cross-validation, and the model is also calibrated to ensure prediction reliability.

Based on the evaluation requirements for the predictive performance of neural network models, we plotted the Receiver Operating Characteristic (ROC) curve to demonstrate its performance in the task of determining the presence of non-cardiac chest pain (Figure 3). This curve visually presents the relationship between sensitivity and 1 - specificity, used to quantify the model's ability to distinguish between two outcomes (presence/absence of non-cardiac chest pain). The two curves in the figure correspond to the predictions for "presence of non-cardiac chest pain" and "absence of non-cardiac chest pain", respectively, with both achieving an area under the curve (AUC) of 0.711, 95% CI: (0.682,0.763). This value lies between 0.5 (random classification) and 1.0 (perfect classification), indicating that the model has a certain discriminative capability, but there is still room for improvement. Notably, the two curves show a similar upward trend; as specificity decreases, sensitivity correspondingly increases. The small difference between the curves suggests that the model maintains relatively high stability across different classification scenarios.

From the calibration plot, it can be seen that the curve of the neural network model is close to the dashed line (ideal calibration line), indicating that the model's predicted probabilities generally correspond to the actual outcomes, though it is not perfectly calibrated (Figure 4). In regions with relatively low and high average predicted probabilities, the model's performance slightly deviates from the ideal calibration line, suggesting that the predicted probabilities may have some errors in these ranges. Overall, the model demonstrates a reasonable level of calibration.

By constructing a neural network model, we analyzed the importance of each independent variable in predicting Non-cardiac chest Pain (Figure 5).

Among all predictive variables, anxiety had the greatest impact on the Non-cardiac chest Pain outcome variable, with an importance value close to 0.12; self-perception bias and fatigue followed closely, each with an importance value of

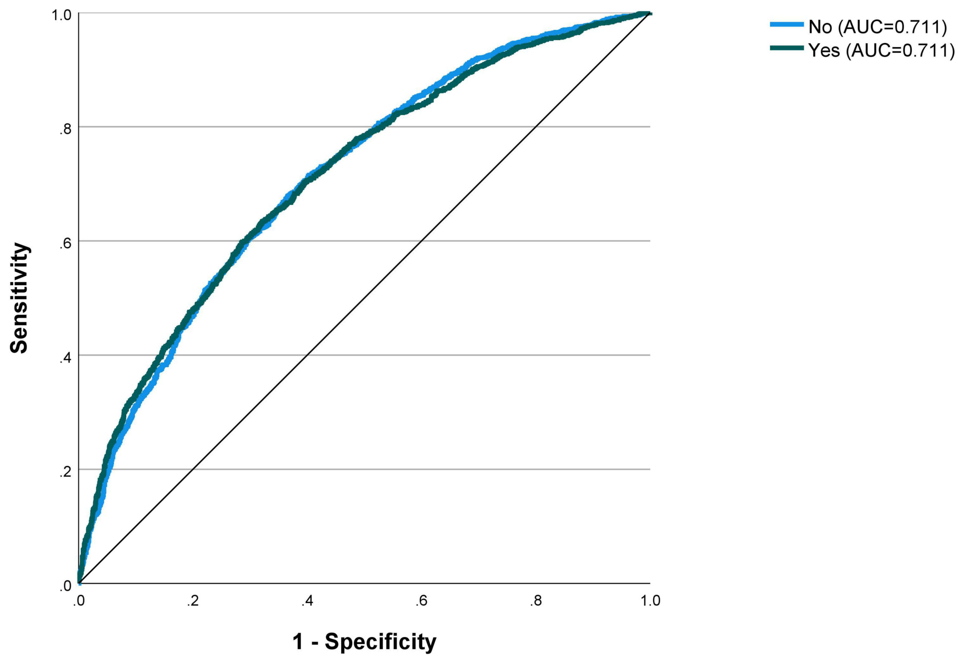

Figure 3 Receiver Operating Characteristic Curve. This ROC curve evaluates the binary classification performance of the neural network model in predicting Non-cardiac chest Pain (presence/absence). The horizontal axis represents the false positive rate (1 - specificity), and the vertical axis represents the true positive rate (sensitivity). There are two curves representing "no Non-cardiac chest Pain" and "Non-cardiac chest Pain", both with an AUC of 0.711.

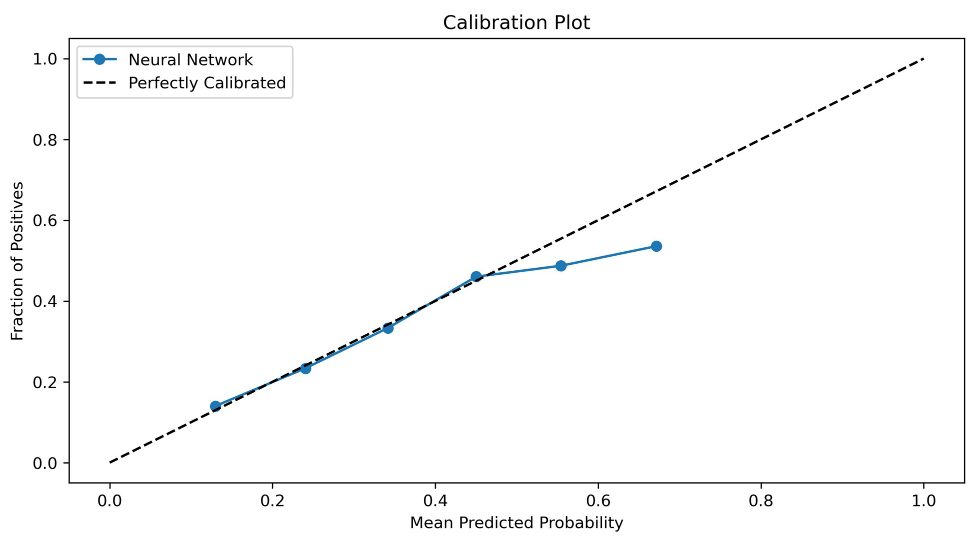

Figure 4 Calibration curve. Neural Network (solid line, blue dot markers): represents the calibration curve of the neural network model. This curve shows the relationship between the average predicted probability by the neural network model and the actual proportion of positive cases. Each blue dot on the curve corresponds to the observed proportion of positive cases at different average predicted probability values.Perfectly Calibrated (dashed line): represents the ideal calibration curve. When the model's predicted probabilities perfectly match the actual occurrence probabilities, its calibration curve coincides with this dashed line. That is, if the model is perfectly calibrated, the observed proportion of positive cases at any given average predicted probability value should equal that predicted probability.

approximately 0.11; attention difficulties and BMI also showed relatively high importance, around 0.09. The importance of depression and hypertension was at a moderate level, about 0.065; the importance of age and diabetes was slightly lower, around 0.057. The importance of other variables was relatively low, with sadness having the lowest importance, approximately 0.022. These results suggest that in this neural network model, psychological and behavioral factors (such as anxiety, self-perception bias, and fatigue) contribute more significantly to the prediction of Non-cardiac chest Pain, whereas some socioeconomic factors (such as household income and education level) have relatively weaker effects.

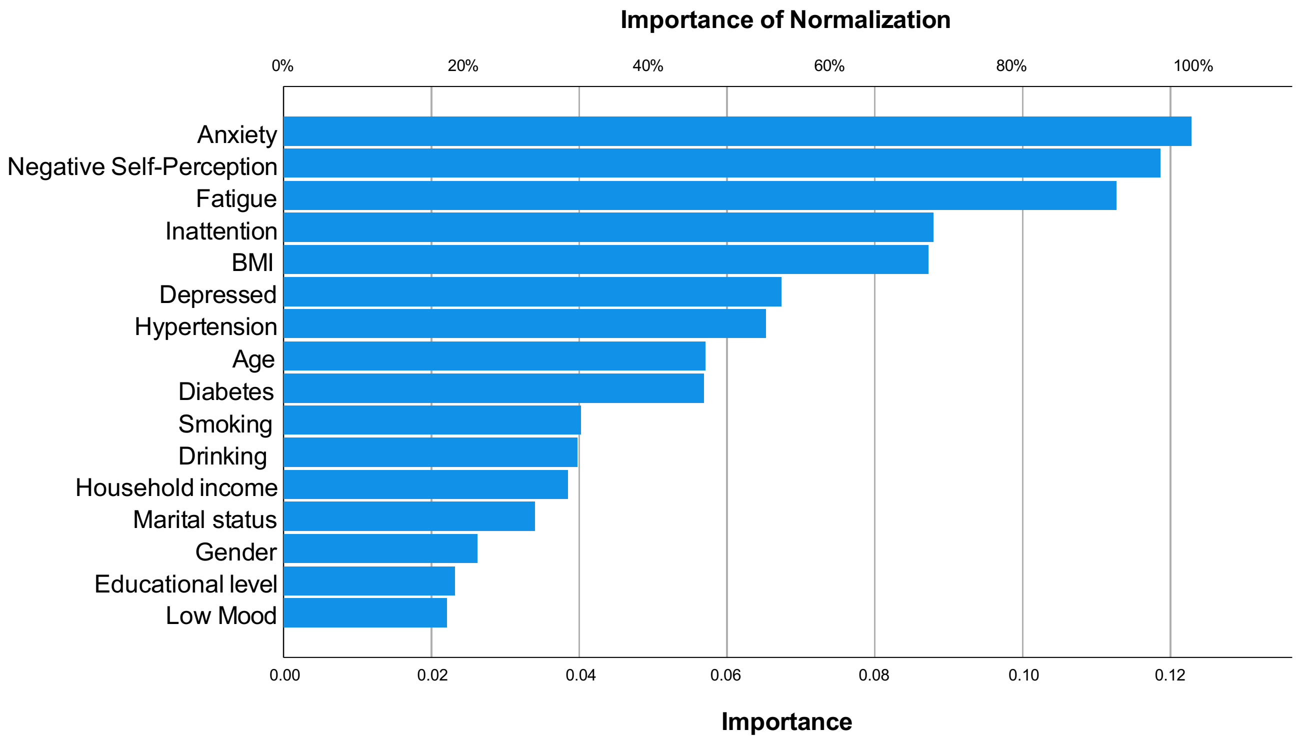

Figure 5 Importance analysis of independent variables. This chart illustrates the importance of various independent variables in predicting Non-cardiac chest Pain outcomes within a neural network model. Using a horizontal bar chart format, it visually compares the relative significance of different variables. X-axis: Represents the importance of the variables, ranging from 0.00 to 0.12. A higher value indicates a more critical role of the variable in predicting Non-cardiac chest Pain. Y-axis: Lists the names of the independent variables, from top to bottom: Anxiety, Negative Self-Perception, Fatigue, Frustration, BMI, Depressed, Hypertension, Age, Diabetes, Smoking, Drinking, Household Income, Marital Status, Gender, Educational Level, Low Mood.

Discussion

Based on NHANES data from 2013 to 2018, this study analyzed the relationships between psychosocial factors—such as anxiety, depression, fatigue, sadness, and difficulty concentrating—and the occurrence of Non-cardiac chest Pain. We found that psychosocial factors, particularly anxiety, depression, and fatigue, were significantly associated with the incidence of Non-cardiac chest Pain. Moreover, the severity of anxiety and depression exhibited a dose-response relationship with the risk of Non-cardiac chest Pain. Through multivariate logistic regression and neural network model analyses, we further identified the independent associations of these psychological factors with the occurrence of Non-cardiac chest Pain.

Compared to cardiac chest pain, psychosocial factors play a more prominent role in non-cardiac chest pain (NCCP). In patients with cardiac chest pain, although some studies indicate that comorbid depression and anxiety significantly increase the risk of non-cardiac readmissions and adverse events, the pathogenesis of cardiac chest pain primarily revolves around organic lesions of the cardiovascular system, with psychosocial factors mainly serving as auxiliary factors affecting prognosis and recurrence. In contrast, for NCCP patients, psychosocial factors such as anxiety, depression, and fatigue are not only important predictors of chest pain occurrence but are also closely associated with the chronicity of pain and a decline in quality of life. Anxiety was found to be significantly associated with Non-cardiac chest Pain. In our study, the likelihood of experiencing Non-cardiac chest Pain increased significantly with higher severity levels of anxiety.

We fully recognize the value of integrating the 2021 American College of Cardiology/American Heart Association (ACC/AHA) guidelines. In the revised version, we combined these guidelines to discuss our study in depth. From the guidelines, it is clear that in the well-known aspects, for cardiac chest pain, the pathogenesis centered on structural lesions of the cardiovascular system has been relatively well established, and psychosocial factors as auxiliary factors affecting prognosis and recurrence are also discussed to some extent. However, in the field of non-cardiac chest pain, the guidelines do not delve deeply into the core role of psychosocial factors or their specific mechanisms, leaving many questions unanswered. This allows us to clearly highlight the innovation and value of the current study. Our research focuses on exploring the role of psychosocial factors in the previously unknown area of non-cardiac chest pain, and through rigorous analysis and investigation, it provides a unique contribution to this field.

Patients with anxiety often experience discomfort, increased heart rate, and shortness of breath—physiological reactions that are closely linked to the onset of Non-cardiac chest Pain. Anxiety may trigger stress responses in the cardiovascular system by activating the sympathetic nervous system, thereby enhancing the perception of pain[21] In this study, patients with severe anxiety had a 2.778-fold increased risk of Non-cardiac chest Pain, suggesting a substantial impact of the psychophysiological effects of anxiety on Non-cardiac chest Pain.

Similarly, depressive symptoms were also significantly associated with Non-cardiac chest Pain. Our results showed that individuals with depression had a notably higher likelihood of experiencing Non-cardiac chest Pain, and this likelihood increased with the severity of depressive symptoms. Several mechanisms may explain how depression exacerbates Non-cardiac chest Pain: first, individuals with depression often suffer from emotional distress and physical exhaustion, leading to heightened pain sensitivity; second, endogenous analgesic mechanisms may be impaired under depressive states, reducing pain tolerance.[22]

Our multivariate regression analysis revealed that individuals in a borderline depressive state (OR = 1.692) as well as those with confirmed depression (OR = 2.070) had significantly increased likelihoods of experiencing Non-cardiac chest Pain, suggesting that the presence of depressive symptoms is significantly associated with Non-cardiac chest Pain.

Fatigue was identified as another important psychosocial factor in this study and was found to be significantly associated with Non-cardiac chest Pain. Notably, the risk of Non-cardiac chest Pain increased progressively with the frequency of fatigue symptoms. This finding supports existing literature suggesting that fatigue not only reflects poor emotional regulation but may also amplify pain perception through physiological mechanisms. Fatigue may contribute to the onset or exacerbation of Non-cardiac chest Pain by impairing autonomic nervous function and enhancing inflammatory responses.[23,24] In our study, participants who reported feeling fatigued "almost every day" had a 1.927-fold higher risk of experiencing Non-cardiac chest Pain compared to those who reported "no fatigue at all", highlighting the crucial role of fatigue in the development of Non-cardiac chest Pain.

Although difficulty concentrating and poor self-perception showed relatively weaker associations with Non-cardiac chest Pain in our study, a certain degree of correlation was still observed. Difficulty concentrating may often accompany anxiety and depression and is closely related to an individual's pain tolerance and perception levels. Poor self-perception (eg, negative self-evaluation) may, in certain circumstances, intensify the experience of pain by increasing attention to bodily symptoms. However, compared to anxiety and depression, their impact on Non-cardiac chest Pain was relatively minor.

Beyond the influence of individual psychosocial factors, our study also revealed significant interactions among anxiety, depression, and fatigue. Through the Sankey diagram analysis, we clearly observed that anxiety and depression often led to increased feelings of fatigue, which in turn intensified the subjective experience of Non-cardiac chest Pain. This finding suggests that psychosocial factors may not only influence Non-cardiac chest Pain through independent pathways but also exert compounded effects through mutual interactions. Therefore, when clinically assessing Non-cardiac chest Pain, it is essential to comprehensively consider the multidimensional impact of psychological factors rather than focusing solely on isolated symptoms, in order to achieve a more holistic understanding of pain mechanisms.

The results of this study highlight the significant associations of psychosocial factors, particularly anxiety, depression, and fatigue, with the occurrence of Non-cardiac chest Pain. In clinical practice, healthcare providers should pay close attention to these psychological aspects, especially when managing patients with non-cardiac Non-cardiac chest Pain. We suggest considering the integration of psychological assessments into clinical evaluations for patients with chronic non-cardiac chest Pain, and exploring the use of specific psychosocial interventions such as cognitive behavioral therapy (CBT) and mindfulness-based therapy to alleviate pain symptoms and improve patients' quality of life. Such a comprehensive management strategy could not only relieve Non-cardiac chest Pain but also enhance overall patient health outcomes.

Comorbidity plays a complex role in the occurrence and development of chest pain. In this study, chronic diseases such as hypertension and diabetes were significantly positively correlated with chest pain (hypertension $r = 0.137$, $P < 0.001$; diabetes $r = 0.069$, $P < 0.001$). These chronic diseases may affect chest pain through various mechanisms. On one hand, the chronic diseases themselves may cause physical discomfort and functional impairments, which can trigger or worsen chest pain. For example, patients with hypertension may experience chest pain symptoms due to increased cardiac workload. On the other hand, there is an interaction between chronic diseases and psychological factors, jointly influencing chest pain. Patients with chronic diseases may develop anxiety and depression due to the long-term illness, and these emotions may further exacerbate the subjective experience of chest pain. For instance, patients with diabetes may need to manage their diet and monitor their blood glucose levels over a long period, and such lifestyle changes may induce anxiety, which in turn may make patients more sensitive to symptoms like chest pain. Additionally, unhealthy lifestyle habits such as smoking and drinking are also more common among patients with comorbidities, and these factors are similarly associated with chest pain. This study found that smoking was significantly positively correlated with chest pain ($r = 0.114$, $P < 0.001$). Smoking may affect the cardiovascular system through mechanisms such as damaging vascular endothelial cells and promoting atherosclerosis, thereby inducing chest pain. The relationship between alcohol consumption and chest pain is more complex: moderate drinking may have certain protective effects on the cardiovascular system, but excessive drinking can lead to liver damage, blood pressure fluctuations, and increase the risk of chest pain. In patients with comorbidities, the interactions among these factors may be even more complex and warrant further in-depth study.

Furthermore, future research should investigate the potential integration of psychosocial factors into multidimensional predictive models for Non-cardiac chest Pain, aiming to develop more personalized interventions and treatment strategies. Given the significant associations of psychological factors with Non-cardiac chest Pain, greater attention should be paid to psychological interventions, especially cognitive behavioral therapy (CBT) and mindfulness-based therapy, for patients with chronic non-cardiac chest Pain, as psychological support may serve as a crucial strategy for enhancing long-term health outcomes.

Although this study reveals a significant association between psychological factors and chest pain, there are limitations: it uses a cross-sectional design, making it difficult to determine causality; the data comes from self-reported questionnaires, which may involve information bias; the study population mainly consists of US civilians, so the sample's representativeness is limited, and the applicability of the results to other populations remains to be verified; moreover, there may be uncontrolled confounding factors. Future research should improve study design, enhance data accuracy, expand sample representativeness, and broaden the scope of confounding factor control.

Conclusion

This study identified significant associations between psychosocial factors—specifically anxiety, depression, and fatigue—and Non-cardiac chest Pain. Our analyses showed a dose-response relationship between the severity of anxiety and depression and the likelihood of experiencing Non-cardiac chest Pain, and indicated the significant association of fatigue with an increased likelihood of Non-cardiac chest Pain occurrence. Moreover, the interactions among psychological factors jointly influenced the perception of Non-cardiac chest Pain.

These findings highlight the significance of considering psychosocial factors in the management of Non-cardiac chest Pain, especially for patients with chronic non-cardiac chest Pain. Future studies should further investigate the application of specific psychological interventions, such as cognitive behavioral therapy (CBT) and mindfulness-based therapy, in the management of Non-cardiac chest Pain to enhance patients' health outcomes.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agreed to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no conflicts of interest in this work.

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