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ORIGINAL RESEARCH

The Role of Psychological Distress and Unhealthy Lifestyle in Angina with Nonobstructive Coronary Arteries: A Cross-Sectional Study

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Purpose: This study aimed to investigate the impact of mental health and lifestyle factors on women with angina with nonobstructive coronary arteries (ANOCA), and to identify potential risk factors associated with ANOCA.

Methods: In this cross-sectional study, 84 female patients diagnosed with ANOCA and 42 age-matched healthy women served as controls. All participants underwent endothelial function testing and laboratory assessments. Demographic data, psychological status, and lifestyle behaviors were evaluated using self-administered questionnaires, Hospital Anxiety and Depression Scale (HADS), Perceived Stress Scale (PSS), and Post-Traumatic Stress Disorder Checklist—Civilian Version (PCL-C). Group differences in key variables were analyzed, and logistic regression was performed to identify independent risk factors and examine potential mediation effects.

Results: Compared with controls, women with ANOCA exhibited significantly higher scores on HADS-depression, HADS-anxiety, PCL-C, and PSS, along with lower exercise frequency, elevated serum hs-C-reactive protein (hs-CRP), and higher white blood cell (WBC) counts (all $P < 0.05$). They were also more likely to report anxiety, depression, post-traumatic stress symptoms, poor sleep quality, and short sleep duration (all $P < 0.05$). Hypertension was more prevalent in ANOCA group, while no difference was found in peripheral vascular function. After multivariable adjustment, depressive symptoms, higher PSS scores, elevated WBC counts, and hs-CRP levels were identified as independent risk factors. Mediation analysis revealed that anxiety fully mediated the associations of exercise frequency ($\beta = -0.07$, $P > 0.05$) and poor sleep quality ($\beta = 0.48$, $P > 0.05$) with ANOCA, and partially mediated the link between short sleep duration and ANOCA ($\beta = 1.86$, $P < 0.01$).

Conclusion: Women with ANOCA are more likely to experience psychological distress, unhealthy lifestyle habits, and systemic inflammation. Depression, perceived stress, elevated WBC counts, and hs-CRP levels are independent risk factors, and unhealthy lifestyle may affect ANOCA by exacerbating anxiety.

Keywords: angina with nonobstructive coronary arteries, psychological distress, lifestyle behavior, inflammation

Introduction

Currently, approximately 112 million individuals worldwide suffer from angina, with prevailing diagnostic approaches primarily focused on identifying stenosis in large epicardial coronary arteries.[1,2] Among patients with stable angina who undergo coronary angiography, nearly half are found to have no obstructive coronary artery disease, with about two-thirds of these patients being women.[3] Patients presenting with anginal symptoms who undergo evaluation by

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cardiologists and are confirmed to have <50% luminal stenosis on coronary angiography (CAG) or coronary computed tomography angiography (CTA) are classified as having angina with nonobstructive coronary arteries (ANOCA).[4,5]

Evidence indicates that patients with ANOCA are at increased risk of major adverse cardiovascular events (MACE) and all-cause mortality.[6–8] Among women with ANOCA, the prevalence of mental stress–induced myocardial ischemia (MSIMI) is significantly higher compared to healthy controls.[9] Coronary microvascular dysfunction (CMD), including microvascular spasm, endothelial dysfunction, epicardial coronary spasm, and/or myocardial bridging, is considered a cause of angina in these patients.[10–13] Due to persistent anginal symptoms, patients with ANOCA frequently seek medical attention or require hospitalization, resulting in a considerable healthcare burden, reduced quality of life, and an increased risk for psychological distress such as anxiety and depression.[11,14–16]

An increasing number of studies indicate that negative emotional states, such as depression and anxiety, as well as psychological stress, are strongly associated with elevated cardiovascular risk, particularly among women.[17–20] Such psychological distress may contribute to atherosclerosis and microvascular dysfunction through various mechanisms, including heightened inflammatory responses, endothelial dysfunction, activation of the hypothalamic-pituitary-adrenal (HPA) axis and autonomic nervous system (ANS).[17,21] Geng et al demonstrated a correlation between worsening psychological status and mild anginal symptoms in female ANOCA patients, underscoring the importance of managing symptoms in the context of mental health.[22] Furthermore, adverse lifestyle behaviors such as insufficient sleep and physical inactivity have been shown to significantly increase cardiovascular risk.[23,24] Notably, patients with ANOCA are typically younger and have fewer traditional cardiovascular risk factors.[25] However, studies specifically examining risk factors for ANOCA remain limited.

Therefore, identifying non-traditional cardiovascular risk factors, including psychological and lifestyle-related components, is crucial for a more comprehensive understanding of the etiology of ANOCA in women and for optimizing management strategies. This study aims to identify the risk factors associated with ANOCA in women and to explore the influence of psychological distress and unhealthy lifestyle on its development.

Methods

Patients and Study Design

This study was conducted at Guangdong Provincial People's Hospital between June 2019 and April 2021. A total of 84 female patients aged between 18 and 75 years who were diagnosed with ANOCA were enrolled. ANOCA was defined as angina with <50% luminal stenosis in major epicardial coronary arteries as assessed by coronary angiography. Additionally, 42 age-matched healthy female volunteers without chest pain and without evidence of obstructive coronary artery disease were recruited as the control group. Major exclusion criteria included chest pain attributable to non-cardiac circulatory disorders and the use of antidepressants or antipsychotics within the past month. The enrollment process for the participants is shown in Figure 1.

All participants underwent early morning fasting venous blood collection to evaluate routine hematological parameters, lipid profiles, cardiac enzyme levels, D-dimer concentrations, and inflammatory biomarkers, including high-sensitivity C-reactive protein (hs-CRP) and interleukin-6 (IL-6). Endothelial function was assessed using the EndoPAT2000 device. Demographic and clinical data were collected systematically, and participants completed a battery of psychological questionnaires. All evaluations were conducted on separate days within a one-week period to ensure consistency and accuracy in data collection.

Basic Information Collection

Clinical and sociodemographic information was collected through a questionnaire, including age, occupation, marital status, education level, monthly income, menopausal status, family history, and chronic disease history.

Education level was categorized into four groups: (1) Primary school or below, (2) Middle school, (3) High school, and (4) University or above. Participants with less than high school education were classified as having a low educational level. Occupation was categorized into: (1) manual labor, (2) mental labor, and (3) household work. Monthly income was divided into seven categories: (1) <3,000 RMB; (2) 3,000–5,000 RMB; (3) 5,000–7,000 RMB; (4) 7,000–9,000 RMB;

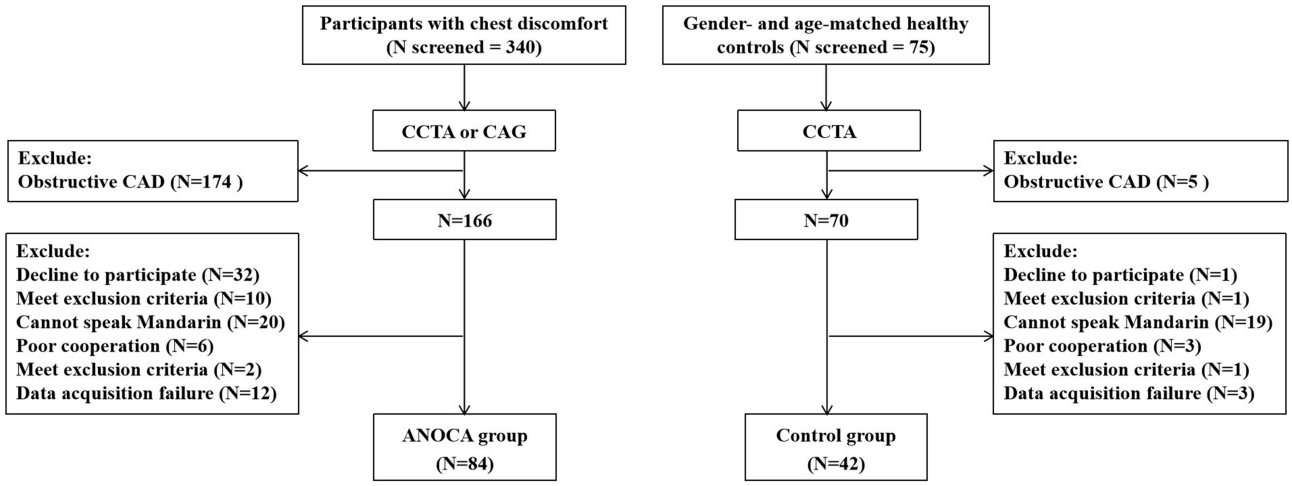

Figure 1 Flowchart of participant enrollment.
Abbreviations: CCTA, Coronary computed tomography angiography; CAG, Coronary angiography; ANOCA, Angina with nonobstructive coronary arteries; CAD, Coronary artery disease.

(5) 9,000–10,000 RMB; (6) 10,000–20,000 RMB; and (7) >20,000 RMB. A monthly income <3,000 RMB was defined as low income. Assessment of coronary artery lesions was based on coronary angiography (CAG) or coronary computed tomography angiography (CTA). Coronary stenosis of <20% was defined as Grade 1 stenosis. Stenosis between 20% and <50% was defined as Grade 2 stenosis.

Assessment of Lifestyle Factors

Lifestyle-related information, including smoking history, physical activity, and sleep habits, was obtained using a self-reported questionnaire. Smoking status was categorized as: 1. Yes, 2. Quit smoking, 3. No. Participants who selected "Yes" or "Quit smoking" were considered to have a smoking history. Physical activity was assessed by exercise frequency and duration. Exercise frequency was classified into five levels: 0. Never; 1. Less than once per week; 2. 1–2 times per week; 3. 3–5 times per week; 4. More than 6 times per week. Exercise duration was categorized as: 1. <30 minutes; 2. 30–60 minutes; 3. >1 hour. An exercise score was calculated as the product of frequency and duration levels; higher scores indicated greater physical activity. Participants who never exercised were classified as physically inactive.

Sleep assessment included average daily sleep duration and subjective sleep quality over the past month. Sleep duration was categorized as: 1. <3 hours; 2. 4–6 hours; 3. 6–8 hours; 4. >8 hours. A sleep duration of less than 6 hours per day was defined as short sleep. Subjective sleep quality was rated as: 1. Satisfactory; 2. Fair; 3. Unsatisfactory. Participants who selected "Fair" or "Unsatisfactory" were considered to have poor sleep quality.

Psychological Assessment

Three validated self-report scales were used to assess psychological status: (1) Hospital Anxiety and Depression Scale (HADS): HADS was used to screen for anxiety and depression. It includes two subscales: HADS-Anxiety (HADS-A) and HADS-Depression (HADS-D), with a total of 14 items. A score >7 on HADS-A indicates anxiety, and a score >7 on HADS-D suggests depression;[26] (2) Perceived Stress Scale (PSS): The 14-item version (PSS-14) was employed to assess perceived stress over the past month. Negative items reflect perceived distress, while positive items represent coping ability. The total score ranges from 0 to 56, with higher scores indicating higher levels of perceived stress. Positive items were reverse-scored before summation;[27,28] (3) Post-Traumatic Stress Disorder Checklist—Civilian Version (PCL-C): The PCL-C was used to assess symptoms of post-traumatic stress disorder (PTSD). It includes 17 items. A total score of 17–37 indicates the absence of significant PTSD symptoms, while a score of 38–85 suggests the presence of PTSD symptoms; higher scores indicate greater severity.[29] All participants in this study were native Chinese speakers. The

Chinese versions of the HADS, PSS-14, and PCL-C have been previously validated and have demonstrated good reliability and validity in Chinese populations.[30–32]

Assessment of Peripheral Endothelial Function

Peripheral endothelial function was evaluated using the EndoPAT2000 device (Itamar Medical Ltd) based on peripheral arterial tonometry (PAT).[33] This noninvasive method provides a simple and reliable measure of endothelial function through the calculation of the reactive hyperemia index (RHI). The procedure involved inflating a blood pressure cuff on the upper arm to supra-systolic levels for 5 minutes to induce ischemia, followed by cuff deflation to elicit reactive hyperemia. The device automatically recorded changes in digital pulse amplitude and calculated the RHI. The RHI was calculated as the ratio of post- to pre-occlusion pulse amplitude in the occluded finger, normalized to the control finger. Higher RHI values indicated better endothelial function; RHI <1.67 was considered indicative of endothelial dysfunction. Participants were instructed to abstain from caffeine- or theophylline-containing substances for at least 12 hours and to avoid nitrate medications for at least 48 hours prior to testing. The test was conducted in the early morning in a quiet, dimly lit room after participants had rested for at least 30 minutes.

Statistical Analysis

Statistical analysis was performed using SPSS version 26.0. Categorical variables were expressed as frequencies and percentages, and continuous variables as mean ± standard deviation. The Student's *t*-test was used for comparisons of normally distributed continuous variables; non-parametric tests were applied when normality was not met. Pearson chi-square test or Fisher's exact test was used to compare categorical variables. Ordinal variables were analyzed using the Wilcoxon rank-sum test.

Multivariable logistic regression analysis was conducted to identify independent risk factors associated with ANOCA. Variables that showed statistical significance in the univariable analysis, along with additional covariates to control for potential confounding effects, were entered into the multivariable model. The model included the following variables: history of hypertension, poor sleep quality, short sleep duration, anxiety, depression, PTSD status, PSS score, exercise score, hs-CRP, IL-6, D-dimer, and white blood cell (WBC) count, age, and the degree of coronary artery stenosis. Mediation analysis was conducted using the causal steps approach. To improve the robustness of the logistic regression estimates, bootstrapping was applied. Categorical variables were coded as follows: history of hypertension = 1, no history of hypertension = 0; Grade 1 coronary stenosis = 0, Grade 2 stenosis = 1; presence of depression, anxiety, PTSD, short sleep duration, or poor sleep quality = 1, absence of these conditions = 0. The dependent variable was coded as follows: control group = 0, ANOCA group = 1. A p-value < 0.05 was considered statistically significant.

Results

Characteristics of Participants

Table 1 presents the sociodemographic and clinical characteristics of participants in the ANOCA group and the control group. A total of 84 female patients with ANOCA and 42 age-matched healthy controls were included. The two groups had comparable mean ages (53.5 ± 8.6 years vs 53.4 ± 8.5 years), with no significant differences in menopausal status, marital status, income level, educational attainment, or manual labor occupation (all P > 0.05). Similarly, body mass index (BMI), blood pressure, heart rate, and lipid profiles, including total cholesterol and low-density lipoprotein cholesterol (LDL-C), were generally similar between groups. In terms of cardiac biomarkers, including creatine kinase-MB isoenzyme (CKMB), creatine kinase (CK), and lactate dehydrogenase (LDH), no significant group differences were observed (all P > 0.05), suggesting no acute myocardial injury at baseline. The prevalence of traditional cardiovascular risk factors, including diabetes, smoking history, family history of coronary artery disease, and degree of coronary stenosis, was generally similar between the groups. However, the prevalence of hypertension was significantly higher in the ANOCA group (23.8%) than in controls (2.4%), P = 0.002.

Table 1 Baseline Characteristics of the Participants

Variable	Control Group (n = 42)	ANOCA Group (n = 84)	P value
Age (years)	53.4 ± 8.5	53.5 ± 8.6	0.935
Postmenopausal [n (%)]	28 (66.7%)	54 (55.9%)	0.792
Smoking history [n (%)]	1 (2.4%)	3 (3.6%)	0.593
BMI (kg/m²)	23.5 ± 2.6	23.5 ± 2.8	0.966
Unmarried [n (%)]	6 (14.3%)	7 (8.3%)	0.300
Low income level [n (%)]	12 (28.6%)	28 (33.3%)	0.588
Low education level [n (%)]	13 (31.0%)	33 (39.3%)	0.360
Manual labor [n (%)]	7 (16.7%)	20 (23.8%)	0.357
Systolic blood pressure (mmHg)	115.7 ± 17.4	115.2 ± 12.2	0.749
Diastolic blood pressure (mmHg)	71.4 ± 9.3	71.2 ± 9.0	0.905
Heart rate (bpm)	68.5 ± 9.1	69.6 ± 10.4	0.580
Total cholesterol (mmol/L)	5.4 ± 0.9	5.1 ± 1.1	0.094
LDL-C (mmol/L)	3.4 ± 0.7	3.2 ± 0.8	0.149
CKMB (U/L)	11.6± 2.1	13.0± 2.9	0.104
CK (U/L)	102.3± 53.8	86.2± 49.0	0.100
LDH (U/L)	174.3± 61.4	172.3± 30.0	0.806
Hypertension history [n (%)]	1 (2.4%)	20 (23.8%)	0.002
Diabetes history [n (%)]	1 (2.4%)	7 (8.3%)	0.267
Hyperlipidemia history [n (%)]	6 (14.3%)	23 (27.4%)	0.100
Family history of CAD [n (%)]	4 (9.5%)	16 (19.0%)	0.168
Grade 1 coronary stenosis [n (%)]	40 (95.2%)	74 (88.1%)	0.168

Abbreviations: BMI, Body Mass Index; LDL-C, Low-Density Lipoprotein Cholesterol; CAD, Coronary Artery Disease; CKMB, Creatine Kinase-MB Isoenzyme; CK, Creatine Kinase; LDH, Lactate Dehydrogenase.

Sleep and Exercise Behavior in ANOCA and Control Groups

We examined differences in lifestyle patterns between the ANOCA group and the control group. As shown in Table 2, the ANOCA group had a significantly higher proportion of participants with short sleep duration (48.8% vs 11.9%, $P < 0.001$) and poor sleep quality (70.2% vs 38.1%, $P < 0.05$) compared to controls. The average exercise score was also lower in the ANOCA group (5.57 ± 3.63 vs 6.71 ± 3.37, $P < 0.05$), indicating reduced physical activity. Although a higher percentage of physical inactivity was observed in the ANOCA group (19.0% vs 7.1%), the difference did not reach statistical significance ($P = 0.078$). These findings suggest that ANOCA patients tend to have poorer sleep and lower physical activity levels than healthy individuals.

Table 2 Comparison of Sleep and Exercise Behavior Between the Control and ANOCA Groups

Lifestyle Factor	Control Group (n = 42)	ANOCA Group (n = 84)	P value
Short sleep duration [n (%)]	5 (11.9%)	41 (48.8%)	<0.001
Poor sleep quality [n (%)]	16 (38.1%)	59 (70.2%)	0.001
Physically inactive [n (%)]	3 (7.1%)	16 (19.0%)	0.078
Exercise score (mean ± SD)	6.71 ± 3.37	5.57 ± 3.63	0.026

Notes: Short sleep duration was defined as <6 hours per day. Poor sleep quality was defined as a subjective rating of "Fair" or "Unsatisfactory." Physically inactive participants were those who reported never exercising.

Psychological Profile Differences Between ANOCA and Control Groups

As shown in Table 3, there were significant differences in psychological status between female patients with ANOCA and healthy controls. The ANOCA group had higher rates of anxiety (50.0% vs 9.5%) and depression (36.9% vs 2.4%) (both $P < 0.001$), with significantly elevated HADS-A (7.94 ± 3.8 vs 3.4 ± 2.5) and HADS-D scores (6.25 ± 3.5 vs 3.07 ± 2.2) (both $P < 0.001$). PTSD status was observed in 35.7% of ANOCA patients but was absent in controls ($P < 0.001$), with a significantly higher mean PCL-C score in the ANOCA group (35.3 ± 9.3 vs 25.5 ± 5.9, $P < 0.001$). Perceived stress levels were also significantly higher in the ANOCA group, as reflected by PSS scores (26.9 ± 7.9 vs 18.6 ± 6.3, $P < 0.001$). These findings indicate that female patients with ANOCA have significant psychological distress compared to healthy individuals. They are more likely to experience anxiety, depression, and PTSD, and to exhibit higher levels of perceived stress.

Assessment of Endothelial Function and Inflammatory Biomarkers

As shown in Table 4, no significant differences in endothelial function were observed between the two groups. The mean RHI values were comparable (1.76 ± 0.50 vs 1.81 ± 0.62, $P > 0.05$), and the prevalence of endothelial dysfunction was similar (46.4% vs 47.6%, $P > 0.05$), indicating that both groups had comparable endothelial function profiles. This may be largely attributed to the similarity in traditional cardiovascular risk factors between the groups. However, significant differences were noted in inflammatory biomarkers. Compared with the control group, patients with ANOCA exhibited significantly elevated serum levels of hs-CRP (1.2 ± 1.5 mg/L vs 0.8 ± 0.7 mg/L, $P < 0.05$) and higher white blood cell counts (6.1 ± 1.6 $\times 10^9$/L vs 5.5 ± 1.0 $\times 10^9$/L, $P < 0.05$), suggesting a heightened inflammatory state among ANOCA patients.

Table 3 Comparison of Psychological Profiles Between Between the Control and ANOCA Groups

Psychological Variable	Control Group (n = 42)	ANOCA Group (n = 84)	P value
HADS-D score (mean ± SD)	3.1 ± 2.2	6.3 ± 3.5	<0.001
Depression status [n (%)]	1 (2.4%)	31 (36.9%)	<0.001
HADS-A score (mean ± SD)	3.4 ± 2.5	7.9 ± 3.8	<0.001
Anxiety status [n (%)]	4 (9.5%)	42 (50.0%)	<0.001
PTSD status [n (%)]	0 (0.0%)	30 (35.7%)	<0.001
PCL-C score (mean ± SD)	25.5 ± 5.9	35.3 ± 9.3	<0.001
PSS score (mean ± SD)	18.6 ± 6.3	26.9 ± 7.9	<0.001

Table 4 Endothelial Function and Inflammatory Biomarkers Between the Control and ANOCA Groups

Variable	Control Group (n = 42)	ANOCA Group (n = 84)	P value
Endothelial dysfunction (%)	20 (47.6%)	39 (46.4%)	0.900
RHI	1.81 ± 0.62	1.76 ± 0.50	0.566
hs-CRP (mg/L)	0.8 ± 0.7	1.2 ± 1.5	0.022
IL-6 (pg/mL)	15.9 ± 32.0	5.9 ± 11.1	0.011
White blood cell count ($\times 10^9$/L)	5.5 ± 1.0	6.1 ± 1.6	0.039
D-dimer (ng/mL)	516.0 ± 797.7	303.0 ± 108.2	0.018

Abbreviations: RHI, Reactive Hyperemia Index; hs-CRP, high-sensitivity C-reactive protein; IL-6, interleukin-6.

Logistic Regression to Identify Risk Factors for ANOCA

As shown in Table 5, multivariable logistic regression analysis revealed that depression status was strongly associated with the occurrence of ANOCA (OR = 57.82, 95% CI: 2.59–80.39; P = 0.001), identifying it as the most significant independent predictor. In addition, higher Perceived Stress Scale (PSS) scores were independently associated with ANOCA. For each one-point increase in PSS score, the risk of ANOCA increased by 17% (OR = 1.17, 95% CI: 1.04–1.32; P = 0.011), suggesting that psychological stress contributes to disease risk. These results highlight that psychological distress, particularly depression status and elevated PSS scores, are independent risk factors for the development of ANOCA.

Elevated inflammatory biomarkers also emerged as independent predictors. The results showed that hs-CRP was associated with an increased risk of ANOCA (OR = 2.57, 95% CI: 1.01–6.55; P = 0.048), as was an elevated white blood cell count (OR = 2.19, 95% CI: 1.27–3.78; P = 0.005). These findings underscore the importance of incorporating both psychological evaluation and inflammatory biomarker assessment into the clinical management of women presenting with ANOCA.

Mediating Role of Anxiety Between Lifestyle Factors and ANOCA

To investigate whether psychological distress, particularly anxiety, mediates the association between lifestyle factors and ANOCA, this study employed the causal steps approach. As detailed in Supplemental Tables S1–S3, ANOCA served as the dependent variable, lifestyle factors as independent variables, and anxiety status as the mediating variable.

As illustrated in Figure 2A, poor sleep quality initially predicted a higher risk of ANOCA ($\beta = 1.34$, $P < 0.01$) and was also strongly associated with elevated anxiety levels, as measured by HADS-A scores ($\beta = 3.45$, $P < 0.001$). However, after adjusting for anxiety, the direct relationship between poor sleep quality and ANOCA became non-significant ($\beta = 0.48$, $P > 0.05$), indicating that anxiety fully mediated this association. Similarly, Figure 2B shows that short sleep duration significantly predicted both ANOCA ($\beta = 1.95$, $P < 0.001$) and HADS-A scores ($\beta = 1.79$, $P < 0.05$). After controlling for HADS-A scores, short sleep duration ($\beta = 1.86$, $P < 0.01$) remained a significant predictor of ANOCA, suggesting a partial mediation effect. In contrast, the exercise score was negatively associated with both ANOCA occurrence ($\beta = –0.12$, $P < 0.05$) and anxiety levels ($\beta = –0.16$, $P < 0.01$). When anxiety was included in the regression model, the association between exercise score and ANOCA occurrence became non-significant ($\beta = –0.07$, $P > 0.05$), suggesting that anxiety may have mediated the relationship between reduced physical activity and ANOCA (Figure 2C).

In summary, these findings demonstrate that anxiety plays a pivotal mediating role in the association between unhealthy lifestyle behaviors—including insufficient exercise, poor sleep quality, and short sleep duration—and the development of ANOCA in women.

Table 5 Logistic Regression Analyses of Risk Factors in Patients with ANOCA

Variable	Regression Coefficient (β)	OR (95% CI)	P value
Depression status	4.06	57.82 (2.59–80.39)	0.001
PSS score	0.16	1.17 (1.04–1.32)	0.011
hs-CRP	0.94	2.57 (1.01–6.55)	0.048
White blood cell count	0.78	2.19 (1.27–3.78)	0.005

Notes: The model included the following covariates: history of hypertension, poor sleep quality, short sleep duration, anxiety status, depression status, PTSD status, Perceived Stress Scale (PSS) score, exercise score, high-sensitivity C-reactive protein (hs-CRP), interleukin-6 (IL-6), D-dimer, white blood cell count, age, and degree of coronary artery stenosis.

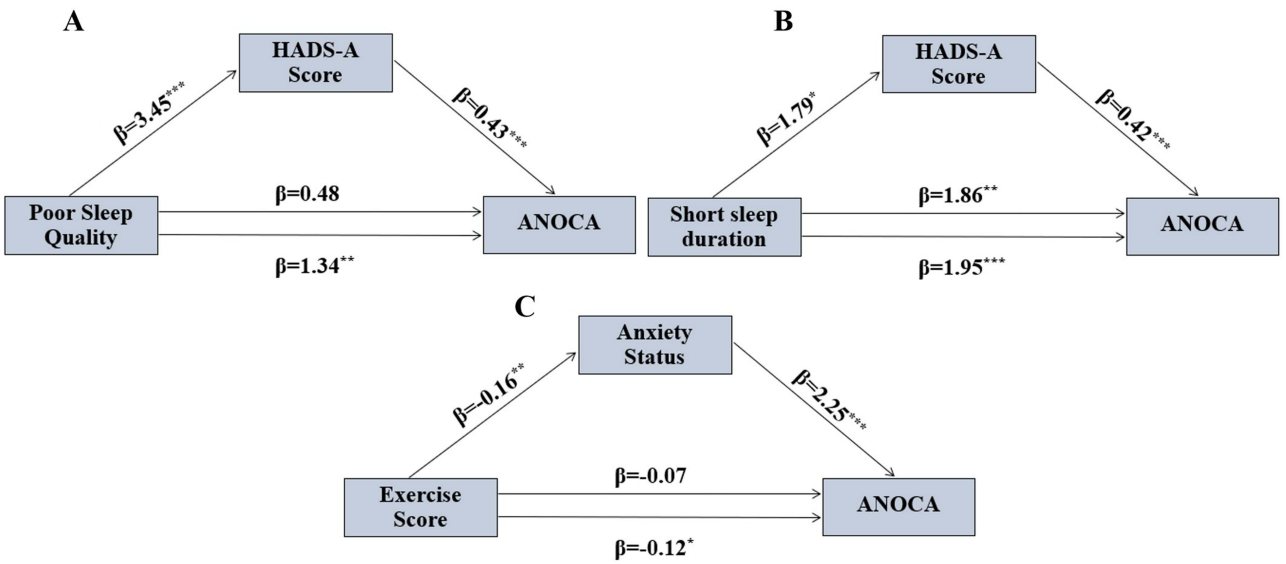

Figure 2 Anxiety as a Mediator Between Lifestyle Factors and ANOCA. (**A**) Mediation model illustrating the role of HADS-A score in the association between poor sleep quality and ANOCA; (**B**) Mediation model illustrating the role of HADS-A score in the association between short sleep duration and ANOCA; (**C**) Mediation model illustrating the role of anxiety scores in the association between exercise scores and ANOCA. *p < 0.05, **p < 0.01, and ***p < 0.001.

Discussion

This study employs a cross-sectional case-control design to reveal that female patients with ANOCA generally exhibit psychological distress and unhealthy lifestyles. Further analysis identifies depression, higher perceived stress levels, and elevated white blood cell count as independent risk factors for ANOCA. Additionally, anxiety serves as a mediator between unhealthy lifestyles and ANOCA.

A previous meta-analysis showed that anxiety significantly increases the risk of cardiovascular events, including cardiovascular death (41%), coronary heart disease (41%), stroke (71%), and heart failure (35%).[20] Furthermore, depressive symptoms and their history are closely associated with the occurrence and mortality risk of cardiovascular diseases.[34] This study observes that patients with ANOCA experience significant deterioration in mental health, being more likely to suffer from anxiety, depression, post-traumatic stress symptoms, and elevated perceived stress (Table 3). These findings further emphasize the potential role of mental health in the development of cardiovascular diseases. Social psychological stress, such as work-related stress and economic difficulties, has been proven to be closely related to an increased risk of acute myocardial infarction.[18] Women are more likely than men to report high-pressure events, which may be linked to gender differences in comorbidities, mental and physical health, family relations, and economic conditions. Changes in modern society, such as increased female employment rates, higher divorce rates, and a rise in single-person households, have profoundly altered women's social roles, potentially creating new sources of psychological stress. Post-traumatic stress disorder (PTSD) is a highly disabling mental illness that occurs frequently after trauma events such as intimate partner violence or natural disasters, and it is not uncommon in the general population.[35] Women are more likely to become victims of intimate partner violence, and this social phenomenon poses a significant threat to their mental health.[36] Therefore, mental health in women's social relationships, especially in the ANOCA population, should be of particular concern.

Furthermore, this study identifies high perceived stress levels and depressive symptoms as independent risk factors for ANOCA (Table 5). Depression can lead to chronic dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis, resulting in hormonal and neuroendocrine abnormalities, such as elevated cortisol levels, increased glucocorticoid secretion, and ultimately, hypertension, insulin resistance, visceral fat accumulation, coagulation dysfunction, and dyslipidemia—all of which further impair vascular endothelial function.[21] Additionally, depression is closely associated with dysfunction of central and peripheral serotonin, and chronic stress can alter serotonin levels, potentially accelerating the progression of atherosclerosis through this mechanism. Previous studies have shown that 75–90% of ANOCA

patients undergoing coronary function tests (CFT) exhibit coronary microvascular dysfunction (CMD), microvascular spasm, or endothelial dysfunction.[4] Endothelial dysfunction caused by negative emotions may play an important role in the pathogenesis of ANOCA. Similarly, chronic stress, such as prolonged work-related stress, can lead to an increased incidence of hypertension, which may explain the higher prevalence of hypertension observed in ANOCA patients (Table 1).

Psychological factors may also indirectly influence the occurrence of cardiovascular diseases by affecting health behaviors. Individuals with anxiety, depression, and high stress levels often exhibit more unhealthy lifestyle behaviors, including increased smoking rates, reduced physical activity, prolonged sedentary time, excessive alcohol consumption, and poor treatment adherence.[37,38] This study found that, compared to healthy controls, patients with ANOCA showed poorer sleep quality and physical activity, with a significant reduction in weekly exercise frequency (Table 2). To further explore the mechanisms underlying the role of psychological distress and lifestyle behaviors in ANOCA, a mediation effect analysis was conducted. The results suggested a close relationship between psychological states and behavioral patterns (Figure 2). Anxiety was found to play a full mediating role between exercise scores and ANOCA. On one hand, exercise scores directly predicted anxiety status; on the other hand, exercise scores indirectly affected the occurrence of ANOCA by influencing anxiety. Individuals with low physical activity levels are more likely to experience anxiety, which may contribute to the onset of ANOCA via several biological mechanisms. Although the precise pathways linking anxiety and ANOCA remain unclear, several plausible mechanisms have been proposed in the literature, largely extrapolated from related cardiovascular and psychosomatic research. These mechanisms mainly involve activation of the hypothalamic–pituitary–adrenal (HPA) axis, autonomic nervous system (ANS) dysfunction, abnormalities in serotonin function, and inflammatory responses.[21]

Additionally, this study found that HADS-A scores also fully mediated the relationship between sleep quality and ANOCA. Poor sleep quality was associated with higher HADS-A scores, which in turn indirectly increased the risk of ANOCA. Anxiety and sleep quality are often mutually influencing: anxiety can lead to sleep disturbances, while poor sleep can induce anxiety, and persistent anxiety may also affect coronary function by promoting the formation of atherosclerosis. Moreover, we observed that HADS-A scores partially mediated the relationship between short sleep duration and ANOCA. Individuals with shorter sleep durations tended to have higher HADS-A scores, thereby indirectly increasing the risk of ANOCA. The adverse effects of short sleep on the cardiovascular system include enhanced sympathetic nervous activity, increased cortisol secretion, and disruptions in growth hormone metabolism. Short sleep duration is also closely linked to elevated blood glucose, blood pressure, and lipid levels, as well as socioeconomic factors such as low socioeconomic status (SES).[39]

This study also found significantly elevated inflammatory markers in patients with ANOCA, including WBC count and hs-CRP (Table 4), among which WBC count was identified as an independent risk factor for ANOCA (Table 5). Consistent with this finding, previous meta-analyses have shown that leukocytosis is an independent predictor of cardiovascular mortality, reflecting the chronic inflammatory response associated with atherosclerosis progression.[40,41] hs-CRP is likewise recognized as a key inflammatory biomarker associated with cardiovascular events.[42] The initial stage of atherosclerosis is characterized by leukocyte accumulation in the arterial intima, where they interact with retained lipoproteins and their oxidative derivatives. The oxidation of lipids within the vascular wall generates pro-inflammatory mediators such as tumor necrosis factor-α (TNF-α) and hs-CRP, which in turn promote further leukocyte recruitment, inflammatory responses, foam cell formation, and endothelial dysfunction, thereby facilitating the development of atherosclerotic plaques.[43] Notably, psychological distress and short sleep duration have been shown to adversely influence inflammatory processes.[21,39,42] Acute psychological stress (eg, anger or frustration) can also trigger the mobilization of inflammatory leukocytes, such as monocytes, from the bloodstream to the aortic wall through stress hormone signaling, thereby promoting the rupture of atherosclerotic plaques.[44] In this study, peripheral vascular function was assessed non-invasively, and no overt peripheral vascular dysfunction was observed in either the control or ANOCA groups. This may be attributed to the relatively mild degree of atherosclerosis in both groups.

In summary, this study highlights the interplay between psychological distress and unhealthy lifestyle behaviors in relation to the development of ANOCA. The integration of psychological assessment, behavioral lifestyle evaluation, and inflammatory marker monitoring may facilitate early identification of high-risk female patients with ANOCA. In clinical

practice, greater emphasis should be placed on these non-traditional risk factors, and comprehensive management strategies incorporating psychological interventions and lifestyle modifications may play a beneficial role in symptom alleviation and prognostic improvement.

Despite certain strengths, this study has several limitations. First, the generalizability of our findings is limited by the relatively small sample size and the exclusive inclusion of female participants. Although bootstrapping was applied during analysis to enhance the robustness of our results, future research with larger and more diverse cohorts is necessary to validate and extend these findings. Second, psychological and lifestyle data were collected through self-reported questionnaires, which may introduce reporting bias. Third, given the cross-sectional design, causal relationships between ANOCA and psychological distress cannot be established. Future large-scale, multicenter prospective cohort studies are warranted to clarify the directionality of these associations and to further explore the long-term impact of psychological and lifestyle factors on the development and prognosis of ANOCA.

Conclusion

In conclusion, women with ANOCA are more prone to psychological distress and unhealthy lifestyle behaviors, accompanied by more pronounced inflammatory responses. Depression, elevated perceived stress, and increased WBC count are independent risk factors for the development of ANOCA. Unhealthy lifestyle behaviors may affect women with ANOCA either directly or indirectly through anxiety. Therefore, clinicians should pay close attention to the potential psychological and lifestyle problems in patients with ANOCA, and proactively conduct psychological screenings and lifestyle assessments to identify and intervene in these risk factors among female patients at an early stage.

Data Sharing Statement

The data underlying this article will be shared on reasonable request to the corresponding author.

Ethics Approval and Informed Consent to Participate

The research protocol was approved by the Ethics Committee of Guangdong Provincial People's Hospital (Approval No. GDREC2019298H(R3)). Written informed consent was obtained from all participants in accordance with the principles outlined in the Declaration of Helsinki.

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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 agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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