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Association of Mental Health Scores with Biomarkers of Cardiovascular Disease Among Overweight Adults: Findings from the PREDIMED-PLUS Trial

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Master of Public Health

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By

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Bachelor of Medicine, Bachelor of Surgery

NRI Institute of Medical Sciences, 2018

Faculty Thesis Advisor: Alvaro Alonso, MD, PhD

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Abstract

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By Niharika Ikkurthy

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Methods: Cross-sectional data from 536 participants in the PREDIMED-Plus trial, a Spanish lifestyle intervention study aimed at preventing cardiovascular disease, were analyzed. Participants aged 55–75 years with BMI ≥27 and <40 kg/m² and no history of cardiovascular disease were included. The primary exposure was depressive scores, measured by the Beck Depression Inventory. The outcomes included the cardiovascular biomarkers: high-sensitivity Troponin T (hsTnT), N-terminal pro-B-type natriuretic peptide (NT-proBNP), high-sensitivity C-reactive protein (hsCRP), 3-nitrotyrosine, and serum carboxy-terminal propeptide of type I procollagen (PICP). Multivariate linear regression models were used to assess associations while adjusting for sociodemographic, clinical, and lifestyle factors.

Results: The mean (SD) age of participants was 65.13 (4.86) years, with females comprising 39.7% of the sample. The mean (SD) BDI score was 8.12 (7.11). In crude analyses, for every one-unit increase in BDI score, hsTnT decreased by 0.0069 units on the log-transformed scale (95% CI: –0.0116 to –0.0022, p = 0.0037). This association became not significant in multivariate analyses. In crude sex-stratified analyses, for every one-unit increase in BDI score, NT-proBNP increased by 0.0168 units among females (95% CI: 0.0016 to 0.0321, p = 0.03), while no significant associations were observed in males. After adjustment for covariates, no significant relationships were identified between BDI scores and 3-nitrotyrosine, hsCRP, or PICP.

Conclusions: Depressive symptoms were independently associated with elevated levels of biomarkers specific to myocardial damage and cardiac overload in a population without known cardiovascular disease, in unadjusted and sex-stratified analyses, thought the associations disappear after covariate adjustment. The findings highlight potential sex-specific patterns, particularly with NT-proBNP in females, suggesting a need for further research into the role of depressive symptoms in early cardiac stress among at-risk populations. These findings also support the inclusion of depression screening in cardiovascular risk assessment and suggest a potential for improved cardiovascular outcomes through integrated mental health interventions.

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INTRODUCTION

Background

It is estimated that depression has a lifetime prevalence of around 17%, while cardiovascular diseases collectively are the leading cause of death worldwide(1,2). While the public health burden of infectious diseases has decreased over the past three decades, the burden due to chronic conditions such as ischemic heart disease and mental health disorders has increased significantly, with rates rising as nations develop(3). Worldwide, approximately 160 million people are reported to be affected by major depressive disorder (MDD), making it one of the most common mental health disorders(4).

Depression is also linked to an increased risk of diseases related to other systems, and an increase in the severity of diseases of other organ systems, cancer, cerebrovascular disease, etc (5). Significant associations were found between depression and CNS disorders such as Alzheimer's disease, dementia, and cognitive decline. It was found that those with depression had 1.96 times the risk of developing dementia compared to those who did not. Similarly, significant associations were found between depression and metabolic conditions such as diabetes and obesity(4). Similarly, cardiovascular disease and depression often coexist, both diseases influencing the other to cause worse psychological and clinical outcomes(6).

On a biological basis, several theories aim to explain the link between depression and cardiovascular disease. The theories range from socio-behavioral to genetic to physiological(7). Depression and cardiovascular disease may have shared mechanisms of development. Low-grade systemic inflammation is commonly present in both diseases. This may be due to the effects that systemic inflammation has on the cardiovascular system, including atherosclerotic lesions, changes in endothelial reactivity, and myocardial function. In the case of depression, systemic inflammation is associated with peripheral immune activation, which in turn affects mood and behavior through increased serotonin release, increased oxidative stress, and activation of the hypothalamic-pituitary-adrenal axis (HPA Axis) (8). A link may also exist between stress and cardiovascular disease, where high-stress situations such as financial stress, natural disasters, episodes of post-traumatic stress disorder, and similar conditions lead to the activation of a sympathetic nervous outflow. The activation of cardiac sympathetic nervous outflow leads to irregular cardiac rhythm, decreased blood flow, left ventricular hypertrophy, and myocardial infarction. These symptoms all lead to an increased risk of acute coronary events. A well-known

example of this theory in action is the phenomenon of white-coat hypertension, where the stress of a doctor's presence leads to a transitory elevation of blood pressure(2).

The relationship between depression and cardiovascular disease has been investigated over the last few decades, and a complex and consistent association between the two has been found (5,6,9). Although an association has been established, much remains to be understood about its nature. However, the two diseases appear to have a bidirectional relationship (10).

Inflammatory biomarkers are often considered early, reliable predictors of future cardiovascular disease. This study examined how participants' mental health, specifically their burden of depressive symptoms, could influence cardiac biomarkers by looking at their Beck Depression Inventory (BDI) Score, a widely accepted tool for screening for major depressive disorder.

Depression and Cardiac Markers

High-sensitivity C-reactive Protein

High-sensitivity C-reactive protein (hsCRP), a biomarker of inflammation, has been linked to possible cardiovascular events in adults, those at high risk, and the elderly(11). Elevated levels of hs-CRP are associated with a significantly higher risk of cardiovascular death, recurrence of heart disease, and a higher risk of adverse outcomes occurring within 90 days of discharge from a major cardiovascular event(11,12).

NT-proBNP

NT-proBNP is considered a gold standard biomarker for heart failure, released from cardiac ventricular myocytes in response to myocardial wall stress(13). The biomarker is highly sensitive for both diagnosing and prognosticating heart failure across its spectrum, including in asymptomatic individuals(14). Elevated NT-proBNP levels reflect the severity of heart failure

and can predict adverse cardiovascular events and mortality, making it invaluable for risk stratification and guiding therapy in clinical practice(15).

High-sensitivity Troponin T

High-sensitivity troponin T (hsTnT) can detect myocardial injury, providing strong diagnostic and prognostic information in acute coronary syndromes, stable coronary artery disease, and heart failure(16). Additionally, its high level of sensitivity allows for early detection of cardiac events and risk assessment for mortality and hospitalization(17).

Serum carboxy-terminal peptide of procollagen type I

Serum carboxy-terminal peptide of procollagen type I (PICP) is associated with myocardial fibrosis, especially in people with hypertension. In hypertensives, PICP could be as useful as echocardiographic findings in estimating myocardial fibrosis(18). Myocardial fibrosis is histologically defined as cardiac remodeling, which occurs in one of two pathways. The first is where a fibrotic scar develops on the myocardium following a cardiovascular event such as myocardial infarction. The second is called diffuse myocardial fibrosis, which occurs due to chronic stress on the heart due to conditions such as pressure overload, areas of ischemia, valvular diseases, and cardiomyopathies(19). Myocardial fibrosis is linked with a host of heart diseases, such as ischemic heart diseases, heart failure, hypertensive cardiomyopathy, congenital heart diseases, as well as aging(20). In the elderly, PICP may be useful in determining mortality risk in heart failure with reduced ejection fraction(21).

3-Nitrotyrosine

Like oxidative stress, there is a parallel and similar process in humans called nitrosative stress, caused by a higher level of nitrosants than antioxidants. A higher concentration of nitrating species leads to the generation of 3-nitrotyrosine, which is associated with a number of

pathological conditions, including cardiovascular diseases such as coronary artery disease, myocardial infarction, and atherosclerosis(22).

Beck Depression Inventory

The Beck Depression Inventory (BDI) is a 21-question self-reported questionnaire intended to measure the severity of depression in people ≥ 13 years old. The original BDI was designed in 1961. Over the years, the original BDI and subsequent updated versions have been widely accepted and utilized for assessing mental health and the severity of depression(23). The BDI has become so widely used as a result of its ease of use and efficiency, as well as the many versions available for different populations and in different languages(24).

Rationale

Despite the consistent association between depression and cardiovascular disease, most existing studies examine this relationship in populations with established cardiovascular disease or approach the association from the opposite direction, looking at how cardiovascular disease causes depression. There is limited evidence examining this association through subclinical biomarkers in asymptomatic, at-risk individuals. Our study addresses this gap by evaluating inflammatory biomarkers in a relatively healthy yet high-risk group— overweight older adults.

Statement of Problem

Heart disease is the leading cause of death, disease, and disability in the modern world. In the last three decades, the percentage of disability-adjusted life years caused by ischemic heart disease has increased by 50%(3). It is estimated that cardiovascular disease prevalence in the United States is approximately 9.9%, affecting 28.6 million in the year 2020(25). This includes conditions such as coronary heart disease, heart failure, and stroke. Those with both cardiovascular disease and depression are likely to have poorer outcomes in terms of morbidity

and mortality, as well as psychological health(6). With such a large number of people affected and such severe effects, it is essential to understand the possible risk factors and early predictors of cardiovascular disease and what role depressive disorders play in the pathway.

LITERATURE REVIEW

Over the years, the link between inflammatory biomarkers, depression, and cardiovascular events has been studied. However, most existing studies have only conducted two part of the three-part association that is the aim of this analysis. Multiple studies have been conducted on the relationship between high-sensitivity C-reactive protein, which has both pro-inflammatory and anti-inflammatory properties, and its relation to either mental illness or cardiovascular events. Studies overwhelmingly looked at the relationship between inflammatory biomarkers, depression, and cardiovascular disease in subjects who had existing cardiovascular disease(26–29).

Carney et al. conducted a clinical trial in which patients who were post-myocardial infarction, with depression or low levels of social support, were assigned to either usual care or an intervention of cognitive behavioral therapy and/or sertraline (for those with serious depression). The study measured survival following the myocardial infarction. Overall, no difference was found between the intervention and control groups. Still, among those with serious depression who responded to the intervention, there was a strong association between survival and depression scores(30).

Lesperance et al. found significant and proportional risks between the BDI score and long-term cardiovascular mortality. Those with mild baseline scores of BDI (10-18) had a 3.17 (1.79-5.60) increased risk of cardiac mortality compared to those with a BDI score of <5. The study

additionally found that when depression scores decreased in such people with baseline depression, their prognosis improved as well. The paper suggests that the pathways causing cardiac disease and depression may be more closely linked than is apparent or that they might follow the same pathways(31). The study also showed that depression has an effect on mortality outcomes but does not seem to have similar effects on surviving myocardial infarction, angioplasty outcomes, or bypass outcomes.

Sherwood et al. studied the effects of depression and clinical biomarkers on heart failure with reduced ejection fraction outcomes. They assessed depression by using the BDI and the biomarker activity by measuring B-type natriuretic peptide in patients attending heart failure clinics and followed up. Throughout the follow-up of roughly 4 years, it was found that a 10-point higher BDI score was associated with a 35% higher hazard of death or cardiovascular hospitalization. The study found that heart failure patients with reduced ejection fraction are at higher risk for mortality during the study period.

Abdelmoneim et al. conducted a study looking at the possible use of stress testing and cardiac biomarkers as prognostic tools for identifying women at risk for coronary artery disease. They used the biomarkers NT-proBNP, ANP, ET-1, and hsCRP as the markers of interest and conducted stress echocardiography. They found that stress echocardiography was a good predictor of future coronary artery disease and that among the biomarkers, only NT-proBNP differed significantly between those who developed coronary artery disease and those who did not(32).

In a recent study by Macchi et al., the researchers studied the link between BDI scores, obesity, PCSK9 (proprotein convertase subtilisin/kexin type 9), and cardiovascular disease. Among obese patients, it was found that increased PCSK9 is associated with a raised cardiovascular risk.

Conversely, a genetic reduction of PCSK9 levels was associated with a proportional decrease in coronary artery disease(33).

Celano et al. explored the relation between inflammatory marker levels among participants recovering from acute coronary syndrome and found that among the recovering participants, those with depression had elevated inflammatory markers, indications of endothelial damage, and higher NT-proBNP. They also found that positive psychological constructs were associated with lower levels of inflammation and improved cardiac function(34).

Madva et al., in 2021, looked at the association between cardiac biomarkers and depression scores among post-acute coronary stroke patients. Using multiple models, they found that there was an association between depressive symptoms and elevated endothelin-1 (ET-1). The association still became stronger among patients with an established MDD history. However, this study was hindered by the fact that patients often developed depressive symptoms following acute coronary stroke, again drawing doubt to the directionality of the association(35).

The consistent and increasing literature over the years suggests a definite relationship between depressive symptoms and cardiac outcomes, and that those with depression or depressive symptoms form a more at-risk population. Thus, inspecting this association further and understanding its mechanism of action and where that mechanism begins may play a crucial role in reducing the impact of cardiovascular disease.

AIMS AND OBJECTIVES

This thesis aimed to assess the effect of depression on cardiac biomarkers to understand better the pathophysiology and mechanisms behind the interaction between depression and cardiac

health. By doing so, the thesis aimed to better identify individuals at risk for cardiovascular disease based on their mental health status.

The objective of this analysis was to characterize the association between depression and the biomarkers of cardiovascular disease risk. The association was assessed using five biomarkers related to cardiovascular disease risk: NT-proBNP, hsCRP, PICP, 3-nitrotyrosine, and hsTnT. These biomarkers were taken as proxy indicators of cardiovascular disease risk. BDI scores were considered as proxy indicators of depression. Through finding whether a relationship exists between BDI scores and each of the biomarkers mentioned above, it can be ascertained if BDI scores can help predict cardiovascular disease far before its onset. Furthermore, the analysis may help in identifying the mechanisms through which depression may increase the risk of cardiovascular disease.

METHODS

Study Population and Data

The data analyzed came from adults between the ages of 55-75 who were participants of the PREDIMED-Plus trial at the baseline visit(36). The PREDIMED-Plus trial is a multi-site intensive lifestyle intervention program aimed at preventing cardiovascular disease, especially among those who are overweight and obese. Therefore, the study included those with a BMI of ≥ 27 and < 40 kg/m^2. For this analysis, baseline data from participants from three centers were used (University of Navarra, Araba University Hospital, and Son Espases University Hospital). The study population included participants who had not enrolled in the previous PREDIMED trial and were living independently (outside a long-term care home).

Only those without a history of previous cardiovascular disease (angina, myocardial infarction, any history of coronary revascularization procedures, ventricular arrhythmia, congestive heart failure, aortic aneurysm, etc.) were eligible to be included in the study. The study excluded those with a recent history of malignancy or currently affected by any malignant condition, those who were unlikely to follow the recommended diet, those enrolled in any other weight loss program before the study, and those who had undergone any form of weight loss surgery or had the intention to do so. Data related to their weekly physical activity was also collected.

The study participants were assigned to either the intervention or control groups from 2013-2017. The intervention group received intensive lifestyle interventions with dietary changes (adopting an energy-restricted Mediterranean diet), cognitive-behavioral weight management, and increased physical activity recommendations. The survey contained information of their consumption of different food groups, their adherence to the Mediterranean diet, and socio-demographic factors.

During the baseline visit, data related to their demographic variables such as age, sex, education, marital status, and employment status was taken. Basic laboratory tests were conducted measuring cholesterol levels, blood pressure was measured, and they were questioned regarding their smoking habits and alcohol consumption. The survey also contains a self-administered SF-36 questionnaire and details regarding their medication usage for mental health issues, hypertension, and cholesterol.

Dataset

A subset of the PREDIMED-Plus trial dataset was used, which contained information from 566 participants at the baseline visit. The data contained 106 variables, including the cardiac biomarkers of interest to this analysis, BDI questionnaire results, demographic variables,

laboratory tests, medication usage, the SF-36 questionnaire, and participants' adherence to the energy-restricted Mediterranean diet of the PREDIMED-Plus trial.

Variables

For the analysis, general demographic variables related to the trial participants—such as age, sex, marital status, level of education, and employment status—were examined. Indicators of health were assessed using data from the SF-36 questionnaire. Data related to general health factors, including smoking status, rate of alcohol consumption, presence of comorbidities (diabetes, hypertension, kidney disease), and physical activity levels, were also included.

The 17-point questionnaire from the PREDIMED-Plus trial was also examined. This questionnaire assessed participants' adherence to the diet and lifestyle interventions proposed by the trial, which focused on the Mediterranean diet. Information on dietary practices such as vegetable and fruit consumption, frequency of red meat consumption, and sugary drink consumption was collected.

Clinical metrics, including serum cholesterol levels (total, HDL, and LDL), blood pressure (measured as the mean of three readings), BMI (body mass index), and triglycerides, were recorded. Medication history was documented for drugs related to mental health conditions (such as sedatives, anxiety medication, or sleeping pills). Medications taken for the treatment of comorbidities and pre-existing mental health conditions were also considered. Details from the 17-point questionnaire were reviewed to evaluate dietary practices in relation to the energy-restricted Mediterranean diet, the primary intervention of the PREDIMED-Plus trial.

The main exposure of interest of depression was assessed using BDI scores. The outcomes of interest were the levels of inflammatory biomarkers measured in the study, including hsTnT, 3-

nitrotyrosine, C-reactive protein, NT-proBNP, and serum carboxy-terminal propeptide of procollagen type I (PICP).

Data Analysis

Data analysis was conducted using RStudio (version 4.3). The R packages “tidyverse”, “tableone”, “readxl”, “haven”, “epiR”, “ggpubr”, “aod”, “sandwich,” “broom”, “kableExtra”, “tibble”, “patchwork”, and “ggplot2” were utilized for data manipulation and statistical procedures. The process of data analysis has been summarized in Figure 1.

Data Cleaning and Variable Transformation

Univariate analyses were performed to describe demographic and social characteristics of the study participants. New variables were created from existing variables, in order to identify the participants with above-normal cholesterol levels, inadequate levels of physical activity, and harmful levels of alcohol consumption, to determine the different BDI categories, and to identify BMI categories. Numerical codes were converted to labelled values for analysis. Several variable names were modified for ease of analysis and to improve interpretability. Participants with incomplete or missing values for the variables of interest were excluded to arrive at the final sample to be included in the analysis. No imputation of data was done.

From the initial dataset, the BDI total score was taken and and a new variable created, categorizing the BDI score based on the scoring of the questionnaire. The new BDI category (bdi_cat) was scaled from 1-5, based on the interpretation where a score of 0-9 indicates that the respondent is not depressed, a score of 10-18 being associated with mild-moderate depression, 19-29 indicating moderate-severe depression, and 30-63 indicating severe depression(37).

Normality Assessment and Transformation

Using Q-Q plots, continuous variables were assessed for normality. Visual assessment was done, and those not following normal distribution were represented with interquartile ranges (IQRs) and medians. A stratified analysis was conducted, comparing those who had an existing diagnosis of depression at baseline and those who did not. The variables of interest (cardiac biomarkers and BDI scores) were assessed for normality using Q-Q plots, and findings were confirmed using the Shapiro-Wilk test. The biomarkers without normal distribution were log-transformed in all further analyses to reduce the effects of skewed distribution and outliers. BDI scores were log-transformed to reduce skewness. However, the transformed values were selectively utilized in further analyses. The original BDI scores were retained in descriptive and categorical analyses to preserve clinical relevance.

Descriptive Analysis

Descriptive statistics were calculated to summarize the characteristics of the study sample. Continuous variables were reported using means and standard deviations or medians and interquartile ranges (IQR), depending on their distribution. Categorical variables were expressed as counts and percentages.

Participant characteristics included demographics (age, sex, education, marital and employment status), lifestyle behaviors (alcohol consumption, physical activity, smoking), and clinical factors (BMI, cholesterol levels, comorbidities, and medication usage). The distribution of BDI scores and each biomarker was also examined.

Descriptive comparisons across subgroups, such as sex and baseline depression status, were performed to explore preliminary differences. Participants were divided into two groups: those with a documented diagnosis of depression at baseline and those without a depression diagnosis.

Bivariate Analysis

Subsequently, the association between BDI scores and each individual biomarker was analyzed using Spearman-Rank correlation, as none of the variables of interest had a normal distribution. A non-parametric analysis was also done using the Wilcoxon two-sample test, stratifying by baseline depression diagnosis.

Multicollinearity Check

Multicollinearity was assessed using Variance Inflation Factor (VIF) analysis. A VIF threshold of >5 was considered to be indicative of problematic collinearity. The variables with high levels of collinearity were removed from the analysis.

Regression Modelling

Multivariate linear regression was conducted to evaluate the association between the BDI scores and the inflammatory marker levels. Linear regression models were constructed to examine the potential association between cardiac biomarkers and depression, with increasing covariates included at each step. The first linear regression model was unadjusted, considering only each biomarker with BDI scores (the crude bivariate analysis mentioned earlier).

The second model included the basic demographic variables of sex, age, BMI, and pre-existing conditions such as nephropathy, diabetes, and hypertension.

The variables from the second linear regression model were retained in the third model, and additional factors such as marital status, employment status, education level, physical activity

levels, and laboratory measures, including cholesterol and triglyceride levels, were incorporated. The third model also contained variables related to their medication usage, alcohol consumption, smoking status, and blood pressure.

A fourth regression model was created, which contained the same variables as the third model but utilized log-transformed covariates. The covariates that did not follow a normal distribution were log-transformed to assess whether they might yield more accurate results. Stratified analysis was done based on sex, and on only those with BDI scores > 9 (greater than minimal depression or normal ups and downs of mood). These four models were applied separately to male and female participants to identify any sex-based differences in association.

To complement the regression analyses, scatterplots were created to visualize the associations between Beck Depression Inventory (BDI) scores and log-transformed cardiac biomarker levels (Figure 2). The regression models were all analyzed using the adjusted R^2 method to determine which models better explained the data and were most suitable.

RESULTS

Study Participants and Data

After removing participants with incomplete or absent data related to the variables of interest, 536 participants remained for analysis. Table 1 describes the demographic characteristics of the study participants, grouped by sex. At the onset of the study, 105 (19.59%) of the participants had an existing self-reported diagnosis of depression. The mean age of participants in the data was 65.13 (± 4.86) years. The participants had BMIs ranging from 26.5 to 41.88 kg/m², with a

mean of 32.27 kg/m² (SD 3.34). Of the total participants, 149 were overweight (having a BMI of ≥ 25 kg/m2 and < 30 kg/m2), and 387 participants were obese (having a BMI ≥ 30 kg/m^2).

Participants were categorized based on their total BDI scores into four levels of depression severity. The majority of participants (n = 359, 65.2%) fell into the minimal depression category (BDI score 0–9), followed by mild depression(n = 126, 22.9%; BDI score 10–18), moderate depression (n = 44, 8.0%; BDI score 19–29), and severe depression (n = 7, 1.3%; BDI score 30–63). The characteristics of the participants with minimal depression compared to those with higher levels of BDI scores is shown in Table 2.

Inflammatory Biomarkers and Depression

The association between biomarkers and depression was assessed from two perspectives. The analysis of cardiac biomarkers and baseline depression diagnosis revealed a possible relationship between log-transformed hsTnT and a diagnosis of depression being present at baseline (based on participant self-reporting), through the Wilcoxon two-sample test (Table 3). The test revealed that having a diagnosis of depression was associated with lower levels of hsTnT (7.31 [CI 5.99, 9.39]) compared to those without depression (8.59 [CI 6.62, 11.30]). This association also remained consistent with the untransformed values of the biomarker and the log-transformed hsTnT.

The relationships between BDI scores and log-transformed cardiac biomarker levels were investigated using Spearman's rank correlation, and the same association continued (Table 4). The log transformation of BDI scores was deemed unnecessary due to the non-parametric nature of the Spearman rank correlation. Log-transformed hsTnT levels and BDI scores showed a weak but statistically significant inverse correlation ($\rho = -0.122$, $p = 0.0048$), suggesting that higher BDI scores were associated with lower hsTnT levels. Through performing Spearman’s rank

correlation, a sex-specific association was found. In females, there was a significant positive correlation between BDI scores and log-transformed NT-proBNP ($\rho = 0.161$, $p = 0.0189$).

In males, a borderline significant negative correlation was observed ($\rho = -0.110$, $p = 0.05$), indicating that higher depressive symptoms are associated with lower NT-proBNP levels.

No associations were found between BDI scores and other biomarkers.

Regression Analysis

The first model, considering only the BDI scores and log-transformed hsTnT levels showed a significant negative association ($\beta = –0.0069$, 95% CI: –0.0116 to –0.0022, $p = 0.0037$), similar to the bivariate analysis using Spearman's rank correlation. This association was not found in the second model, which adjusted for sex, age, and BMI. In the second model, After checking for model fit using the adjusted R^2 method, the model with untransformed covariates, untransformed BDI scores, and log-transformed biomarkers was found to be the most appropriate for usage (Table 5).

During the multicollinearity check, total cholesterol, HDL, LDL, and triglyceride variables were found to be highly collinear. Only total cholesterol was retained for the final analysis. In the final reduced models hsTnT and NT-proBNP emerged as biomarkers showing trends suggestive of associations with depressive symptoms, albeit non-significant. The inflammatory markers hsCRP, PICP, and 3-Nitrotyrosine consistently showed negligible associations across all modeling stages, irrespective of adjustment.

In the crude analysis, for every one-unit increase in BDI score, hsTnT decreased by 0.0069 units on the log-scale. This was a statistically significant inverse association, and the only statistically significant association found in the crude analysis (Table 6). No significant associations were

identified for PICP, hsCRP, NT-proBNP, or 3-Nitrotyrosine, as all corresponding p-values exceeded the 0.05 threshold and confidence intervals included zero.

Multivariate linear regression models were conducted to assess the association between BDI scores and log-transformed cardiac biomarkers after adjusting for sex, age, and BMI (Table 7). Across all five biomarkers, no significant associations were observed. For PICP, every one-unit increase in BDI score was associated with a decrease of 0.0031 units on the log-transformed scale (95% CI: -0.0082 to 0.0021, p = 0.2447). For hsCRP, a negligible increase of 0.0001 units was observed per unit increase in BDI score (95% CI: -0.0033 to 0.0036, p = 0.9322). For hsTnT, BDI scores were associated with a decrease of 0.0020 units (95% CI: -0.0064 to 0.0024, p = 0.3677). For NT-proBNP, each unit increase in BDI score corresponded to an estimated increase of 0.0054 units (95% CI: -0.0054 to 0.0163, p = 0.3242). For 3-Nitrotyrosine, a negligible decrease of 0.0004 units was observed (95% CI: -0.0116 to 0.0109, p = 0.9496). These findings indicate that, after adjusting for sex, age, and BMI, depressive symptoms were not independently associated with any of the cardiac biomarkers assessed. The direction of association for NT-proBNP remained positive, while hsTnT showed a negative trend, but neither reached statistical significance.

Across both sexes, most associations between BDI scores and cardiac biomarkers were not statistically significant, as indicated by p-values exceeding 0.05 and confidence intervals crossing zero. However, an association was observed for NT-proBNP in female participants. Among females, a statistically significant positive association was observed, where each one-unit increase in BDI score was associated with a 0.0168 unit increase in log-transformed NT-proBNP levels (95% CI: 0.0016 to 0.0321, p = 0.0305). This suggests that among female participants, higher depressive symptoms were significantly associated with elevated NT-proBNP levels

(Table 10). In males, for every one-unit increase in BDI score, NT-proBNP decreased by 0.0135 units (95% CI: -0.0294 to 0.0025, p = 0.097), although this was marginally significant.

Multivariate linear regression analyses were performed to examine the association between depressive symptoms, measured by BDI scores, and log-transformed cardiac biomarkers after adjusting for a comprehensive set of covariates. These covariates included demographic characteristics (age, sex), clinical factors (BMI, diabetes, nephropathy, baseline depression diagnosis), lifestyle behaviors (smoking status, alcohol intake, physical activity), medication use (tranquilizers, antihypertensive and cholesterol-lowering drugs), socioeconomic status (education, marital status, employment), lipid profile (total cholesterol), and blood pressure measurements. The results of these fully adjusted models are presented in Table 8. Across all five biomarkers assessed, no statistically significant associations were observed between BDI scores and biomarker levels after full adjustment. Consistent with previous findings, no significant associations were observed between log-transformed biomarkers and BDI scores, even after conducting a fully adjusted, sex-stratified analysis (Table 11).

With the visual assessment done using scatterplots (Figure 2), a slight positive linear trend was observed between BDI scores and NT-proBNP levels, consistent with the significant association identified in male participants during sex-stratified analysis. Conversely, a negative trend between BDI scores and high-sensitivity hsTnT levels, as was found in the crude analysis. For hsCRP, PICP, and 3-nitrotyrosine, no clear patterns or associations were visually discernible, reflecting the non-significant results obtained from multivariate regression models.

DISCUSSION

Key Findings

The study aimed to evaluate the association between depressive symptoms, measured by BDI scores, and cardiac biomarkers reflecting inflammation, cardiac strain, fibrosis, and oxidative stress in overweight adults.

The analysis's findings overall suggest the presence of an association between Beck Depression Inventory scores and the biomarkers high-sensitivity hsTnT and NT-proBNP in crude analyses. However, these associations became nonsignificant after adjustment for potential confounders. There were no significant associations between the depression scores and the biomarkers hsCRP, 3-nitrotyrosine, or PICP.

This is in line with existing findings showing a relationship between the two biomarkers and cardiovascular disease in patients with psychological stress, where higher levels of hsTnT and NT-proBNP were found to be linked to mental stress-induced myocardial ischemia(38).

The analysis showing higher BDI scores to be associated with lower hsTnT levels were supported by previous studies, which found similar results in their unadjusted analyses(39,40). In the bivariate analysis of the entire study sample, no associations were found between depression scores and biomarkers, which suggests that depression scores alone cannot explain variations in inflammatory markers. However, when male and female study participants were analyzed separately, a sex-specific association was found with BDI scores, with opposite directions of correlation. While females had a positive association between BDI scores and NT-proBNP, males displayed an inverse correlation. This implies possible biological differences in how depressive symptoms are linked to cardiac stress markers between men and women. It could also be explained by the complex interaction of sex, hormonal influences, or possible menopausal

effects on NT-proBNP(41). The Dallas Heart Study also found levels of NT-proBNPs to be elevated in women, and found the elevation may also be due to the complex interaction of androgens and estrogens(42).

The absence of associations found between BDI scores and other biomarkers in the analysis (hs-CRP, 3-Nitrotyrosine, and PICP) may indicate a lack of association between BDI scores and more generalized inflammatory markers. Any association present may also have been masked by the presence of obesity, wherein there is a state of chronic low-grade inflammation associated with higher levels of inflammatory markers such as hsCRP, higher levels of oxidative stress, and the production of more pro-inflammatory substances by adipose tissue(43).

Public Health and Clinical Implications

The presence of associations between depressive scores and cardiac biomarkers suggest that there may be clinical and public health benefits to early cardiac biomarker screening among older, overweight adults with signs of depression or diagnosed depression. Depression screening could also be made a routine part of cardiovascular disease screening. Identifying at-risk individuals can help in risk stratification, implementing early interventions, and reducing the global health burden of cardiovascular disease. While bodies such as the American Heart Association advocate for depression screening in individuals with cardiovascular disease, there may be a benefit in extending this practice to those even at risk of cardiovascular disease(44). Tailoring screening protocols based on sex may also offer further insight.

Furthermore, including mental health treatments or stress reduction programs as part of the prevention and therapy for cardiovascular disease could be impactful in slowing the progression of disease or preventing cardiovascular events, and reducing mortality and morbidity.

LIMITATIONS

The analysis was limited due to the cross-sectional nature of the analysis, since only baseline data was utilized for the analysis. Longitudinal data, with repeated BDI and biomarker measurements, would improve the reliability of the findings by accounting for mood fluctuations and transient variations in biomarkers. There was a limited range of distribution in the depression scores, with the majority of patients (66.98%) belonging to the first category of having normal variations in mood. If the population had more participants with higher depression scores, it might have improved the ability of the analysis to detect any meaningful associations between depressive symptoms and cardiac biomarkers. Furthermore, the Beck Depressive Inventory is a self-reported questionnaire with an intended use of being a screening tool. While it is validated, it is not as strong a method of detecting depression as a clinical diagnosis. A more specific screening tool, such as the Cardiac Depression Scale, may have yielded different results or offered further insight(45).

Despite the adjustment for many covariates, residual confounding may remain due to other variables not part of the analysis, such as sleep quality, psychosocial factors, and genetic factors. While the study identified sex-specific patterns, it is important to acknowledge that menopausal status, a key modifier of NT-proBNP levels in women, was not accounted for in the analysis.

Furthermore, many of the variables considered in the analysis were self-reported. Factors such as physical activity, smoking status, alcohol consumption, and sociodemographic factors were all self-reported. While this yielded more information due to the ease of completing a self-administered questionnaire, the data may have been affected by participant recall issues and reporting bias. Eliminating participants without complete data related to BDI scores and biomarker information may have introduced selection bias.

Another limitation is that the study sample consisted of only overweight and obese individuals between the ages of 55 and 70. Therefore, it is doubtful that the associations found in this study can be generalized to a broader population. The selection of only overweight and obese individuals may also have introduced selection bias, as obesity/metabolic syndrome may be a confounding or mediating variable despite the adjustment for BMI in the analysis.

CONCLUSION AND FUTURE DIRECTIONS

The current thesis investigated the possible association between depressive symptoms, measured as Beck Depression Inventory (BDI) scores, and cardiac biomarkers among overweight and obese adults free from pre-existing cardiovascular disease. The biomarkers were assumed to be indicators of possible future cardiovascular disease or cardiovascular disease risk. Positive and significant correlations were found between BDI scores and cardiac-specific biomarkers in crude analyses, including hsTnT and NT-proBNP. No statistically significant associations were found with generalized inflammatory markers, such as hsCRP, PICP, or 3-nitrotyrosine. These findings suggest that depressive symptoms may be a causal factor in early myocardial stress or damage independent of systemic inflammatory or oxidative stress mechanisms.

The results are in line with the growing literature indicating shared biological mechanisms between cardiovascular disease and depression. The positive correlation between depression scores and NT-proBNP may be an expression of neurohormonal activation and myocardial strain due to chronic stress and HPA axis dysregulation. Similarly, the correlation with hsTnT, a subclinical marker of myocardial damage, may indicate chronic cardiac strain even in the absence of overt cardiovascular disease.

These findings emphasize the importance of adding mental health assessment to cardiovascular risk assessment, especially in older or overweight patients with metabolic risk factors. Depression screening tools like the Beck Depression Inventory can play a key role in the detection of early risk and prevention strategies. These findings also provide additional evidence for incorporating psychological and behavioral treatments, such as stress management and depression management, into integrated cardiovascular disease prevention programs.

However, the cross-sectional nature of the analysis prohibits inferences about causality. The limited availability of depression scores and reliance on self-reported data might have further diminished the ability to detect more subtle associations. Future research should employ longitudinal measurements on clinically validated scales of depression and examine whether longitudinal changes in depressive symptoms are associated with changes in cardiac biomarker profiles. Multiple measurements can also confirm consistent elevations and help reduce any coincidental fluctuations in biomarkers.

Long-term follow-up based on PREDIMED-Plus trial data also might help determine whether depression is predictive of incident cardiovascular disease in this patient group. More research will be needed to examine whether these associations hold true for more heterogeneous groups and to elucidate the mediating roles of sleep, genetic risk, and other psychosocial stressors. Larger scale extensions of this research could eventually help determine and develop individualized prevention strategies for cardiovascular disease based on both psychological and physical risk factors.

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TABLES

Table 1: Demographic Summary of Study Participants

	Female	Male
n (%)	213 (39.7)	323 (60.3)
Weight, kg (mean (SD))	78.98 (9.99)	92.81 (11.84)
Height, cm (mean (SD))	155.73 (5.32)	169.93 (6.51)
BMI, kg/m^2 (mean (SD))	32.55 (3.63)	32.08 (3.12)
Age, years (mean (SD))	66.31 (3.81)	64.35 (5.30)
Total Cholesterol, mg/dL (mean (SD))	204.05 (36.37)	196.58 (35.30)
Alcohol consumption, mean grams/day (median [IQR])	1.46 [0.00, 6.24]	14.69 [4.53, 35.43]
Beck Depression Inventory Score (mean (SD))	10.12 (7.91)	6.80 (6.20)
Smoking Status (%)		
Former smoker > 5 years	54 (25.4)	189 (58.5)
Former smoker 0 - 1 year	2 (0.9)	4 (1.2)
Former smoker 1 - 5 years	7 (3.3)	17 (5.3)
Insufficient data	0 (0.0)	2 (0.6)
Never smoker	134 (62.9)	75 (23.2)
Yes	16 (7.5)	36 (11.1)
Previous Diabetes Diagnosis (%)	62 (29.1)	88 (27.2)
Previous Nephropathy Diagnosis (%)	11 (5.2)	21 (6.5)
Diagnosis of Depression at Baseline (%)	61 (28.6)	44 (13.6)
Marital Status (%)		
Divorced	14 (6.6)	11 (3.4)
Married	144 (67.6)	278 (86.3)
Not divorced	1 (0.5)	5 (1.6)
Single	9 (4.2)	21 (6.5)
Widower	45 (21.1)	7 (2.2)
Schooling (%)		
Graduated	17 (8.0)	59 (18.3)
High school	50 (23.5)	121 (37.5)
Illiterate	1 (0.5)	0 (0.0)
Primary education	139 (65.3)	119 (36.8)
Technical studies	6 (2.8)	24 (7.4)
Employment Status (%)		
Currently on leave for more than three months	2 (0.9)	6 (1.9)
Currently working	22 (10.3)	74 (23.1)
Housewife	57 (26.8)	1 (0.3)
Insufficient data	1 (0.5)	2 (0.6)
Permanent disability	5 (2.3)	10 (3.1)
Retired	112 (52.6)	216 (67.5)
Unemployment with subsidy	11 (5.2)	6 (1.9)
Unemployment without subsidy	3 (1.4)	5 (1.6)

Table 2: Study Participant Characteristics Based on Baseline Depression Scores

	BDI > 9	**BDI ≤ 9**	**p-value**
n	177	359	
Weight, kg (mean (SD))	86.19 (13.98)	87.87 (12.52)	0.16
Height, cm (mean (SD))	162.13 (9.98)	165.35 (8.64)	<0.001
BMI, kg/m^2 (mean (SD))	32.67 (3.43)	32.07 (3.28)	0.05
Age, years (mean (SD))	65.13 (5.15)	65.13 (4.72)	0.99
Physical activity (METs/Week) (mean(SD))	2165.68 (2000.76)	2730.64 (2372.95)	0.01
Alcohol consumption (mean grams/day)	14.04 (19.53)	17.12 (20.63)	0.10
Sex (Male)	86 (48.6)	237 (66.0)	<0.001
Smoking Status (%)			0.34
Former smoker > 5 years	71 (40.1)	172 (47.9)	
Former smoker 0 - 1 year	1 (0.6)	5 (1.4)	
Former smoker 1 - 5 years	8 (4.5)	16 (4.5)	
Insufficient data	0 (0.0)	2 (0.6)	
Never smoker	76 (42.9)	133 (37.0)	
Yes	21 (11.9)	31 (8.6)	
Previous Diabetes Diagnosis (%)	56 (31.6)	94 (26.2)	0.22
Previous Nephropathy Diagnosis (%)	18 (10.2)	14 (3.9)	0.01
Diagnosis of Depression at Baseline (%)	57 (32.2)	48 (13.4)	<0.001
Marital Status (%)			0.13
Divorced	11 (6.2)	14 (3.9)	
Married	132 (74.6)	290 (80.8)	
Not divorced	0 (0.0)	6 (1.7)	
Single	11 (6.2)	19 (5.3)	
Widower	23 (13.0)	29 (8.1)	
NA	0 (0.0)	1 (0.3)	
Schooling (%)			0.03
Graduated	19 (10.7)	57 (15.9)	
High school	46 (26.0)	125 (34.8)	
Illiterate	0 (0.0)	1 (0.3)	
Primary education	102 (57.6)	156 (43.5)	
Technical studies	10 (5.6)	20 (5.6)	
Beck Depression Inventory (BDI) Score (mean(SD))	2 (1.1)	1 (0.3)	
BDI Score Category			<0.001
BDI Score ≤ 9 (Minimal depression)	0 (0.0)	359 (100.0)	
BDI Score 10 – 18 (Mild Depression)	126 (71.2)	0 (0.0)	
BDI Score 19 – 29 (Moderate Depression)	44 (24.9)	0 (0.0)	
BDI Score 30 – 63 (Severe Depression)	7 (4.0)	0 (0.0)	

Table 3: Association Between Cardiac Biomarkers and Baseline Depression Diagnosis

	No	**Yes**	**p-value***
n	431	105	
High-sensitivity Troponin T, ng/L (median [IQR])	8.59 [6.62, 11.30]	7.31 [5.99, 9.39]	**0.005**
3-Nitrotyrosine, nmol/L (median [IQR])	611.00 [337.00, 986.96]	568.00 [320.00, 970.00]	0.79
Serum carboxy-terminal Propeptide of type I Procollagen, ng/mL (median [IQR])	88.08 [72.78, 111.47]	89.07 [69.61, 108.53]	0.47
NT-proBNP, pg/mL (median [IQR])	49.26 [25.72, 89.56]	53.60 [28.38, 100.60]	0.50
High-sensitivity C-Reactive Protein, mg/L (median [IQR])	0.21 [0.12, 0.39]	0.25 [0.10, 0.50]	0.44

*p-values from the Wilcoxon two-sample test.

Table 4: Spearman's Rank Correlation of Log-transformed Biomarkers and BDI Scores

Biomarker	**Spearman's ρ**	**p-value**
High-sensitivity C-Reactive Protein	0.063	0.14
High-sensitivity Troponin T	-0.122	**0.0048**
NT-ProBNP	0.031	0.48
Serum carboxy-terminal propeptide of type I procollagen	0.008	0.84
3-Nitrotyrosine	0.007	0.87

Table 5: Adjusted R^2 Comparison Across Full Models

Model	hsCRP	hsTnT	NT-ProBNP	PICP	3-Nitrotyrosine
Untransformed BDI and Covariates	0.0257	0.1982	0.1081	-0.0298	0.0191
Untransformed BDI and log-transformed Covariates	0.0194	0.2050	0.1126	-0.024	0.0125
Log-transformed BDI and untransformed covariates	0.0257	0.1973	0.1055	-0.0303	0.0235
Log Transformed BDI and Covariates	0.0194	0.2041	0.1101	-0.0244	0.0166

Note: All biomarkers were log-transformed in the models. Adjusted R^2 indicates the proportion of variance explained, accounting for model complexity.

Table 6: Unadjusted Analysis of Beck Depression Inventory Scores and Cardiac Biomarkers

Biomarker	Estimate	95% CI Lower	95% CI Upper	Std. Error	t-value	p-value
Serum Carboxy-terminal Propeptide of type I Procollagen	-0.0020	-0.0070	0.0030	0.0025	-0.7911	0.43
High-sensitivity C-Reactive Protein	0.0013	-0.0021	0.0046	0.0017	0.7417	0.46
High-sensitivity Troponin T	-0.0069	-0.0116	-0.0022	0.0024	-2.9132	**0.0037**
NT-ProBNP	0.0061	-0.0047	0.0170	0.0055	1.1059	0.27
3-Nitrotyrosine	0.0004	-0.0104	0.0113	0.0055	0.0778	0.94

Table 7: Association between Log-transformed Biomarkers and BDI Scores After Adjusting for Sex, Age, and BMI

Biomarker	Estimate	95% CI Lower	95% CI Upper	Std. Error	t-value	p-value
Serum Carboxy-terminal Propeptide of type I Procollagen	-0.0031	-0.0082	0.0021	0.0026	-1.1646	0.24
High-sensitivity C-Reactive Protein	0.0001	-0.0033	0.0036	0.0018	0.0851	0.93
High-sensitivity Troponin T	-0.0020	-0.0064	0.0024	0.0022	-0.9015	0.37
NT-ProBNP	0.0054	-0.0054	0.0163	0.0055	0.9868	0.32
3-Nitrotyrosine	-0.0004	-0.0116	0.0109	0.0057	-0.0632	0.95

Table 8: Association of Log-transformed Biomarkers with BDI Scores, All Covariates*, After Reducing Multicollinearity

Biomarker	Estimate	95% CI Lower	95% CI Upper	Std. Error	t-value	p-value
Serum Carboxy-terminal Propeptide of type I Procollagen	-0.0028	-0.0084	0.0029	0.0029	-0.9569	0.34
High-sensitivity C-Reactive Protein	0.0003	-0.0034	0.0040	0.0019	0.1380	0.89
High-sensitivity Troponin T	-0.0017	-0.0064	0.0029	0.0024	-0.7257	0.47
NT-ProBNP	0.0064	-0.0053	0.0181	0.0059	1.0790	0.28
3-Nitrotyrosine	0.0050	-0.0072	0.0171	0.0062	0.8055	0.42

*All Covariates: Age, Sex, BMI, Previous Diagnosis of Diabetes, Previous Diagnosis of Nephropathy, Previous Diagnosis of Depression, Use of Tranquilizer Drugs (Sedatives, Anti-anxiety medication, sleep aids), Blood Pressure Medication, Cholesterol Medication, Mediterranean Diet Score, Physical Activity, Total Cholesterol, Alcohol consumption (mean grams/day), Systolic Blood Pressure, Diastolic Blood Pressure, Smoking History, Marital Status, Education Level, Employment Status

Table 9: Sex-Stratified Spearman's Rank Correlation

Biomarker	Sex	Spearman ρ	p-value
Serum Carboxy-terminal Propeptide of type I Procollagen	Male	0.037	0.51
	Female	-0.049	0.48
High-sensitivity C-Reactive Protein	Male	0.007	0.90
	Female	0.083	0.23
High-sensitivity Troponin T	Male	-0.061	0.28
	Female	-0.030	0.66
NT-proBNP	Male	**-0.110**	**0.0492**
	Female	**0.161**	**0.0189**
3- Nitrotyrosine	Male	-0.014	0.80
	Female	0.005	0.94

Table 10: Unadjusted Analysis by Sex, with Log-transformed Biomarkers and BDI Scores

Biomarker	Sex	Estimate	95% CI Lower	95% CI Upper	Std. Error	t-value	p-value
Serum Carboxy-terminal Propeptide of type I Procollagen	Male	-0.0024	-0.0096	0.0047	0.0036	-0.6707	0.50
	Female	-0.0022	-0.0097	0.0053	0.0038	-0.573	0.57
High-Sensitivity C-Reactive Protein	Male	-0.0009	-0.0061	0.0043	0.0026	-0.3261	0.74
	Female	0.0023	-0.0021	0.0067	0.0022	1.0426	0.30
3-Nitrotyrosine	Male	-0.0049	-0.0213	0.0116	0.0084	-0.5816	0.56
	Female	0.0016	-0.0134	0.0166	0.0076	0.2141	0.83
NT-ProBNP	Male	-0.0135	-0.0294	0.0025	0.0081	-1.6646	0.10
	Female	**0.0168**	**0.0016**	**0.0321**	**0.0077**	**2.1782**	**0.0305**
High-sensitivity Troponin T	Male	-0.0041	-0.0106	0.0024	0.0033	-1.2455	0.21
	Female	-0.0014	-0.0077	0.005	0.0032	-0.4232	0.67

Table 11: Fully Adjusted Sex-stratified Analysis of Log-transformed Biomarkers and BDI Scores, With All Covariates*, After Reducing Collinearity

Biomarker	Sex	Estimate	95% CI Lower	95% CI Upper	Std. Error	t-value	p-value
Serum carboxy-terminal propeptide of type I procollagen	Male	-0.0024	-0.0107	0.0059	0.0042	-0.58	0.57
	Female	-0.0028	-0.0117	0.0062	0.0045	-0.61	0.54
High-sensitivity C-Reactive Protein	Male	0.0003	-0.0055	0.0062	0.0030	0.11	0.91
	Female	0.0007	-0.0041	0.0054	0.0024	0.28	0.78
3-Nitrotyrosine	Male	0.0014	-0.0173	0.0200	0.0095	0.14	0.89
	Female	0.0064	-0.0108	0.0236	0.0087	0.73	0.47
High-sensitivity Troponin T	Male	-0.0033	-0.0102	0.0036	0.0035	-0.94	0.35
	Female	-0.0003	-0.0074	0.0068	0.0036	-0.08	0.93
NT-ProBNP	Male	-0.0087	-0.0261	0.0087	0.0089	-0.98	0.33
	Female	0.0135	-0.0038	0.0309	0.0088	1.54	0.12

All Covariates*: Age, Sex, BMI, Previous Diagnosis of Diabetes, Previous Diagnosis of Nephropathy, Previous Diagnosis of Depression, Use of Tranquilizer Drugs (Sedatives, Anti-anxiety medication, sleep aids), Blood Pressure Medication, Cholesterol Medication, Mediterranean Diet Score, Physical Activity, Total Cholesterol, Alcohol consumption (mean grams/day), Systolic Blood Pressure, Diastolic Blood Pressure, Smoking History, Marital Status, Education Level, Employment Status

FIGURES

Figure 1: Flowchart of Methodology

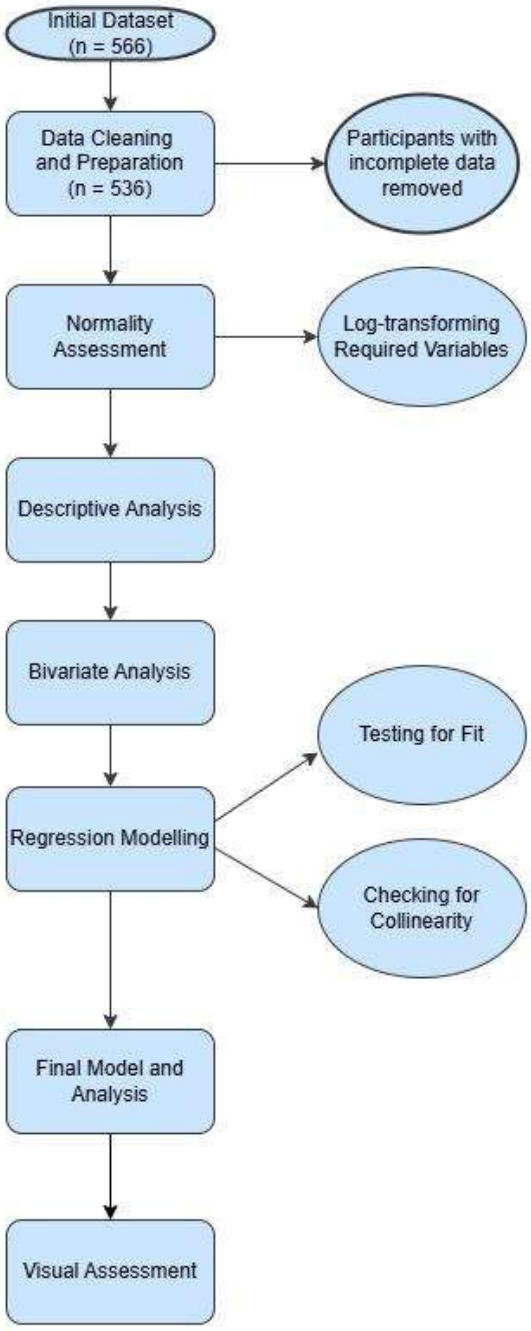

Figure 2: Scatterplots of Log-transformed Biomarkers and Beck Depression Inventory (BDI) Scores