



## Effects of Mood Imbalance on Disrupting Coronary Circulation: A Correlation or Speculation?

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**Abstract.** Depression and Coronary Artery disease (CAD) are two highly prevalent diseases seen in general population which affect more than 264 million and 110 million adults worldwide respectively. Modifiable risk factors include smoking, hypertension, dyslipidemia, obesity and one other major risk factor that has caught many researchers' attention: psychological factors. Psychological factors, like depressive symptoms and stress, are known to have a significant effect on CAD. Many patients with CAD suffer from depression and it is believed that depression can increase the mortality rate in CAD. The objective of the current review is to assess the relation of depression and coronary artery disease, analyze different treatment options and determine a potential pathophysiological factor in causing depression in patients with CAD. We searched literature in PubMed with parallel MeSH and Regular Keyword strategy for data collection. Our PubMed search for keywords resulted in finding 5905 articles. After implementing our inclusion and exclusion criteria, a total number of 38 articles from PubMed were selected and reviewed. Our analysis showed that depression can increase chest pains and mortality rate in patients with CAD but on the other hand, patients with CAD were more likely to show depressive symptoms. These patients benefit from cardiac rehabilitation program, Mindfulness-based art therapy and use of Serotonin-norepinephrine reuptake inhibitors (SNRIs). We also found that Sphingolipids are potentially playing a major role in these diseases' pathophysiology.

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**Keywords:** Mood Imbalance, Depression, Major Depression, Major Depressive Disorder, Coronary Artery Disease, CAD, MDD

### 1. Introduction & Background:

Depression and Coronary Artery disease (CAD) are two highly prevalent diseases seen in general population which affect more than 264 million and 110 million adults worldwide respectively (World Health Organization, 2020; Feigin, 2016). Coronary artery disease, which includes non-obstructive CAD (wall irregularities and <60 stenosis), coronary artery ectasia, coronary artery calcification and obstructive CAD (coronary slow flow), can result in major adverse cardiovascular events. Like any other disease, coronary artery disease has modifiable and non-modifiable risk factors. Modifiable risk factors include smoking, hypertension, dyslipidemia, obesity and one other major risk factor that has caught many researchers' attention: psychological factors. Psychological factors, like depressive symptoms and stress, are known to have a significant effect on CAD. Many patients with CAD suffer from depression and it is believed that depression can increase the mortality rate in CAD (Jang et al., 2018).

In Admitted CAD patients only 15-20% meet the full DSM-V criteria of major depressive disorder while about 25-65% of these patients show at least one symptom of depression. The association of depression and CAD is highly complex and multifactorial. It is believed that in people without CAD, depression can increase the risk of developing CAD and can be considered as an independent risk factor for CAD. While in patients with pre-existing CAD, depression can be associated with recurrent cardiac events (Moryś et al., 2016).

Regarding the importance of the recurrence of cardiac events and major adverse events, many researchers use self-reporting questionnaires to detect depressive symptoms. These questionnaires include Beck Depression Inventory-II (BDI-II), the Hospital Anxiety Depression Scale (HADS), the Patient Health Questionnaire (PHQ), the Spielberger State Anxiety Inventory (SSAI), and the Trait (STAI) Anxiety Inventory (Moryś et al., 2016). American Heart Association (AHA) also recommends



doing a routine depression screening among patients with CAD with 9-item patient health questionnaire (PHQ-9) (Morys et al., 2016).

Sphingolipids are a major group of lipids that are made up of sphingoid base and an acyl group such as a fatty acid. Sphingolipids are most seen in brain cell membranes. These sphingolipids are divided in sphingomyelins, sphingosines, ceramides, gangliosides and cerebroside subtypes. Irregularities in concentrations of sphingolipids are commonly seen in patients with coronary artery disease (Lichtman et al., 2008). On the other hand, in patients with depression, disordered levels of sphingolipids are reported as well (Lichtman et al., 2008).

Although it is clear that the association between CAD and depression exists, the potential pathophysiological trigger, the effects of depression on progression of CAD, how these two diseases correlate, and effects of the different treatment modalities is yet to be studied. Our aim in this study is to assess the relation of depression and coronary artery disease, to assess different treatment options and determine a potential pathophysiological factor in causing depression in patients with CAD.

## 2. Method:

We searched literature in PubMed with parallel MeSH and Regular Keyword strategy for data collection. Table 1 demonstrates MeSH and regular keywords for our literature search.

Table 1. Regular and MeSH Keywords for literature search

Regular Keyword "Depression" AND "Coronary Artery Disease"	
Total Records	5905
Selected Records	198
MeSH Keyword "Depression" AND "Coronary Artery Disease"	
Total Records	426
Selected Records	40
MeSH Keyword "Depressive Disorder" AND "Coronary Artery Disease"	
Total Records	158
Selected Records	14
MeSH Keyword "Depressive Disorder, Major" AND "Coronary Artery Disease"	
Total Records	64
Selected Records	3

The following inclusion and exclusion criteria were applied to select studies.

### 2.1. Inclusion Criteria:

Humans, Papers published in English, Ages of 19 and older Papers published in the last five years, Diagnosis of Coronary Artery Disease, Free Full Text Articles, Observational Studies, Clinical Trials, Cohort Studies, Review Studies

### 2.2. Exclusion Criteria:

Animal Studies, Younger than 19 years of age, Case Reports, Case series and Meta-analysis, Non-English Articles

## 3. Result

Table 2 demonstrates inclusion and exclusion criteria and the number of articles selected.

Regular Keywords "Depression" AND "Coronary Artery Disease"	
Total number of records	5905
Inclusion/Exclusion Criteria application	
Human studies	5077
English Language	4461
Published in the last five years	587
Ages of 19 and older	496
Free Full Texts Online	198
MeSH Keyword "Depression" AND "Coronary Artery Disease"	
Total number of records	426
Inclusion/Exclusion Criteria application	
Human studies	424
English Language	405
Published in the last five years	142
Ages of 19 and older	119
Free Full Text Online	40
MeSH Keyword "Depressive Disorder" AND "Coronary Artery Disease"	
Total Records	158
Inclusion/Exclusion Criteria application	
Human studies	155
English Language	142
Published in the last five years	40
Ages of 19 and older	40
Free Full Text Online	14
MeSH Keyword "Depressive Disorder, Major" AND "Coronary Artery Disease"	
Total number of records	64
Inclusion/Exclusion Criteria application	
Human studies	64
English Language	61
Published in the last five years	16
Ages of 19 and older	16
Free Full Text Online	3

A total number of 6 articles were removed due to having duplicates in searches. A total number of 14 papers were removed due to lack of mentioning our interest in the study. The total number of papers collected after a focused search has been 37 free full texts. All 37 articles were analyzed and at last the total number of 2 articles were removed because of the following reason: Meta-analysis study.

Finally, the total number of 35 articles from PubMed, with having free full text available online, were reviewed which included:

- 5 studies as Clinical Trials (Ma et al., 2019; Chan et al., 2018; Mazereeuw et al., 2016; Nikrahan et al., 2016; Vitinius et al., 2019)
- 20 studies as Cohort studies (Liu et al., 2013; Mommersteeg et al., 2017; Jani et al., 2016; Rahmani et al., 2018; Poole et al., 2016; Bellettiere et al., 2016; Janssen et al., 2016; Carroll et al., 2017a; Carroll et al., 2017b; Rutledge et al., 2016; Hayek et al., 2017; Grace et al., 2018; Gharacholou et al., 2016; Batika et al., 2017; Van Geffen et al., 2015; Edward et al., 2016; Gu et al., 2016; Wilcox et al., 2016; Zhang et al., 2017)



- 7 Studies as Cross Sectional (Jang et al., 2018; Lichtman et al., 2008; Pelletier et al., 2015; Bremner et al., 2019; Ho et al., 2018; El-Baz et al., 2018; Sun et al., 2018).
- 3 studies as Case Control (Feigin, 2016; Elamragy et al., 2019; Karataş et al., 2015).

The maximum number of the patients in these studies were 35537 with the minimum of 83.

#### 4. Discussion

Studies on Depression and Coronary artery disease mainly focused on the following aspects: patients' functional status, correlation of depression and coronary artery disease and the adverse effects of them, the potential etiology of this correlation, treatment of depression and interventions done to improve them.

One study performed an analysis to determine the functional status of depressed patients with coronary artery disease. It was found that patients with persistent depressive symptoms had a major decline in their functional status following a cardiac intervention while patients with no depression only showed minor changes to

Hospital anxiety and depression scale (HADS) method underestimates depressed symptomatic patients with coronary artery disease compared to the other questionnaire and scales (Jang et al., 2018).

Many articles suggested a strong correlation between depression and coronary artery disease.

There were some studies working on the potential etiology of the mentioned association. It is suggested that pro-inflammatory phospholipids are associated with presence and the severity of depression (Ma et al., 2019). Another study on the same subject shows that Sphingolipids (ceramide species C16:0 and C18:0 and the SM18:1) are the probable triggering factor in the pathophysiology of depression in patients with coronary artery disease (Lichtman et al., 2008).

There are many different interventions done to improve psychological and cardiac health of patients. One study suggests Community health service cardiac rehabilitation for CAD patients as it has shown to have reduced the score of depression and has significant effect on improving the quality of life in patients (Zhang et al., 2017). Likewise, another study shows that cardiac

Table 3 demonstrates the studies selected for this review and their important findings.

Author	Year of publication	Sample size	Age range	subjects	Major points
Roxanne Pelletier et al. [31]	2015	2390	18-75	Men and Women	Patients with CAD who had depression were three times more likely to die compared to patients without depression over a period of nine years. If CAD patients compared to non CAD patients, no solid evidence of increased risk of major adverse cardiovascular events was found in patients with depression.
Mehmet Baran Karataş et al. [37]	2015	94	43.2-63.5	Men and Women	Patients with coronary slow flow, a type of coronary artery disease, had considerably elevated rates of depression, psychological distress compared to control group with normal coronary flow.
John Belletiere et al. [17]	2016	417	60-84	Men and Women	depression has a non-linear U-shaped, gender-specific association with coronary artery calcifications but no association with its progression
Imke Janssen et al. [18]	2016	528	46-59	Women	Persistent depressive symptoms have been seen to be strongly linked to higher calcification in coronary arteries indicating they are more likely to have adverse effects on subclinical coronary artery disease than a single episode of depression
Bhautesh Dinesh Jani et al. [14]	2016	35537	18-90	Men and Women	Hypertensive patients with depression had a 83% higher adjusted risk for developing major adverse cardiovascular event compared to hypertensive patients who do not have depression.
Paula M.C. Mommersteeg et al. [13]	2017	523	52-70	Men and Women	Non obstructive coronary artery disease in men and women was associated with compromised health, more psychological distress and Type D personality compared to a control group
Salim S. Hayek et al. [22]	2017	5158	51-75	Men and Women	There is a strong association between angina and depression. Patients with depression suffer more from angina regardless of the severity of coronary artery disease. Whether treatment depressive disorder ameliorates angina was not studied.
Guo-Zhe Sun et al. [35]	2019	11956	43.1-62.5	Men and Women	Positive association of depressive symptoms with cardiovascular disease, especially in women
Ahmet Seyfeddin Gurbuz et al. [38]	2019	83	49-67.9	Men and Women	Patients with coronary artery ectasia, which is an atypical form of CAD, had higher depression scores based on HADS compared to people with no coronary artery deformity.
Ahmed A. Elamragy et al. [36]	2019	100	41.3-63	Men and Women	Depression and Male gender are strongly related to coronary slow flow in patients undergoing elective coronary angiography. It was found that there is a strong link between severity of depression and the severity of coronary artery disease.

their functional status (Wilcox et al., 2016). However, in another study we found that prevalence of depression decreases over time after cardiac interventions (Gu et al., 2016).

In another study we figured out that if self-report measures are used, e.g., questionnaire, the result will vary based on the different methods used. It was evident that

rehabilitation program for patients after Percutaneous Coronary Intervention (PCI) decreases depression scores and suggests that not joining a cardiac rehab program can itself be a potential risk factor for developing depression or exacerbating pre-existing depressive symptoms (Mommersteeg et al., 2017). Another study suggests Mindfulness-based art therapy as a method to improve



psychological stability in patients with coronary artery disease as it has shown vast improvement in depression scores (Feigin, 2016).

Use of antidepressant drugs are a common practice to target and control the depression. However, this practice can be complicated by cardiac side effects of some antidepressants. In a study, effects of different antidepressants were observed on CAD. It was evident that antidepressants improve depressive symptoms but on the other hand, all the antidepressants except for Serotonin-norepinephrine reuptake inhibitors (SNRIs) were linked to more major cardiovascular events (Grace et al., 2018). While patients taking Tricyclic Antidepressants (TCA) have shown to have 2.5 times increase in risk of developing major adverse cardiovascular events, patients taking Selective Serotonin Reuptake Inhibitors (SSRIs) or atypical antidepressants showed 1.5 times increased risk of developing major adverse cardiovascular events than the general population. Some drugs in SSRIs category have shown to increase the QT interval and bleeding time (Grace et al., 2018). In one clinical trial, effects of Omega-3 poly unsaturated fatty acids (n-3 PUFA) on depressive symptoms of CAD patients was assessed and showed that n-3 PUFA has not any effect on improving depression in patients with coronary artery disease (Chan et al., 2018).

It is evident that there is a close association between depression and coronary artery disease. While many researchers have worked on this correlation, there are not many studies on potential etiology of this correlation and treatment of a major depressive disorder in presence of coronary artery disease which can be challenging due to the cardiac side effects of antidepressants and patients' noncompliance in these cases. More studies are needed in order to determine the potential etiology, analyze the effects of sphingolipids and safety of each antidepressant in different types of coronary artery disease based on age, sex and other pre-existing disorders and illnesses. These are the aspects that need more attention in order to prevent major adverse cardiovascular events and improve the quality of life in patients.

### 5. What new information is this article highlighting?

It is known for a fact that depression in patients with CAD is higher than it is in the general population, and it could also be known as an independent risk factor for developing CAD. However, the reason that these two diseases are related is more than a cause-and-effect association and quite complex. Sphingolipids are the potential etiological factors that need to be studied more in order to confirm this effect and to develop new methods and modalities of treatment based on targeting the causing factors not just based on symptoms and signs.

Since we know that using SSRIs are challenging in CAD patients, more studies are needed on safety of SNRIs, and using rehabilitation and psychotherapy can be uneconomical and result in noncompliance, studying more

on the role of sphingolipids is suggested to confirm this association. Once confirmed, more studies on targeting the sphingolipids in treatments would be helpful for these patients.

This literature review has some limitations: the study limits its analysis in terms of year of publication (last five years), papers published in English, type of studies included (Observational Studies, Clinical Trials, Cohort Studies, Review Studies, no meta-analysis, case report or case series) and many other factors that need to be assessed and analyzed in future studies.

### 6. Conclusion:

Our aims in this study, were to assess the link between depression and coronary artery disease, the outcomes of it, the potential cause and means of treating and improving it. This current literature review has concluded that with depression, the functional status of patients is lowered, risk of major adverse cardiovascular events is increased, and vice versa, patients with coronary artery disease were more likely to suffer from depressive disorders than other patients. However, it is important to know that many of depressive symptoms might be underestimated based on the type of self-reporting questionnaire used. For the etiology, it is probable that Sphingolipids play a part in pathophysiology of this association, yet more studies are needed to confirm. To improve depressive symptoms, we have seen those patients joining a cardiac rehabilitation program have shown improvements in mood manifestations and functional status. Treatment with antidepressants except for SNRIs, however necessary to improve depression, can increase the risk of adverse cardiac events. Nevertheless, more studies are needed in order to confirm the safety of SNRIs.

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