

# Anxiety and Depression as Predictors of Acute Myocardial Infarction in Patients with Pre-Existing Coronary Heart Disease

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## Research Article

### Abstract

**Background:** Cardiovascular disease is the number one cause of death worldwide. Among all cardiovascular diseases, coronary heart disease is the most common manifestation. It has been hypothesized that anxiety and depression increased the incidence of coronary heart disease in healthy individuals and the acute myocardial infarction in patients with pre-existing coronary heart disease. Therefore, the purpose of this study was to investigate the effect of anxiety and depression on the development of acute myocardial infarction in patients with pre-existing coronary heart disease.

**Methods and findings:** This was a prospective study with patients seeking treatment for coronary heart disease. Anxiety and depression were measured before the occurrence of acute myocardial infarction in 1000 patients with pre-existing coronary heart disease. Patients were followed for two years or until they developed an acute myocardial infarction. In a multiple logistic regression, anxiety and depression scores were independent predictors of the occurrence of acute myocardial infarction (OR=1.55, 95% CI: 1.15-2.10, P=0.005) and (OR 1.77, 95% CI: 1.21-2.34, P=0.02), respectively.

**Conclusion:** Anxiety and depression predicted acute myocardial infarction in patients with pre-existing coronary heart disease. Inclusion of assessment and treatment of anxiety and depression in the protocols for those patients is as important as the traditional risk factors.

**Keywords:** Anxiety; Depression; Coronary heart disease and acute myocardial infarction.

### 1. Introduction

In the United States (US), the prevalence of Coronary Heart Disease (CHD) is 6.3% in adults greater than 20 years of age [1]. In 2012, approximately 9 million Americans visited physician for CHD [1]. Over a 4 years period from the beginning of 2011 to the end of 2014, an estimated 16.5 million Americans greater than 20 years of age had CHD [1]. Among all

Americans less than 55 years old, CHD mortality did not decline between 1990 to 2011 [1]. In males and females less than 75 years of age, CHD makes up more than half of all cardiovascular events [2].

Approximately every 40 s, an American will have an acute myocardial infarction (AMI) due to CHD [1]. Coronary Heart Disease was an underlying cause of death in  $\approx 1$  of every 7 deaths in the US in 2014 with an overall age-adjusted death rate 98.8 per 100,000 [3]. Coronary Heart disease is prevalent in developing countries as well. For instant, In Jordan, a developing low income country; where this study was conducted, CHD caused approximately 19% of the total deaths and the rate per 100,000 is 131 leaving Jordan in the rank of 46 worldwide [4]. Acute myocardial infarction due to CHD was found to have a significant prevalence in Jordan according to the Jordan Ministry of Health statistics [5].

Anxiety and depression are the most common prevalent psychiatric disorders among patients with CHD [6]. In patients diagnosed with CHD who have not experienced an AMI event or required an intervention, the prevalence of anxiety is about 20% to 25% [7]. In patients with cardiac diseases, the prevalence of depression is approximately 10% [8]. Fifteen to 20% of patients with AMI due to CHD meet Diagnostic and Statistical Manual of Mental Disorders of depression [8]. Depressive symptoms are much higher among people with CHD living in the society as compared with individuals without CHD [8,9]. For instance, in a meta-analysis of 23 studies about depression in coronary CHD in China, it was found that the prevalence of depression is 51%. This rate ranged between 34.6% to 45.8%, in community participants without CHD [10].

Previous literature reported two major types of studies about the relationship between anxiety/depression and CHD. Firstly, studies that followed healthy persons to detect the occurrence of CHD (i.e., incident CHD). Second: Studies among patients with pre-existing CHD followed up to detect the occurrence of new events related to the CHD (i.e., cardiac mortality, non-fatal AMI).

With regard to anxiety and CHD, a meta-analysis

investigated anxiety and risk of incident of CHD between the years 1980 and 2009 [11]. The study examined twenty prospective studies on 249,846 persons who were followed for an average of 11.2 years with a range from 2.0 to 20.9 years. Results showed that anxious persons were at risk of CHD (hazard ratio: 1.26; 95% confidence interval: 1.15 to 1.38;  $p < 0.0001$ ) after controlling for their demographic variables, biological risk factors, and health behaviors. Five studies [12-16] in a meta-analysis about cardiac mortality and AMI, found that anxiety was significantly associated with cardiac mortality, among which three remained significant after controlling for the covariates [12,15,16]. The pooled hazard ratio for cardiac mortality was 1.48 (95% CI: 1.14 to 1.92;  $p = 0.003$ ). In patients with pre-existing CHD, five studies used non-fatal AMI as an end-point. Two of them [17,18], found a significant association between general anxiety and AMI, among which one did not adjust for confounders [18] and excluded from the analysis. The hazard ratio was 1.23 (95% CI: 0.74 to 2.05;  $p = 0.416$ ).

A large Swedish survey on 49,321 young men investigated the long term association (over 37 years) between anxiety and subsequent CHD and development of AMI. The results showed that the multi adjusted hazard ratios were 2.17 (95% CI: 1.28 to 3.67) and 2.51 (95% CI: 1.38 to 4.55) for CHD and for AMI, respectively [19]. This indicates that anxiety independently predicted subsequent CHD events. A contradicting result was reported by other studies [20-22] which showed no relationship between anxiety and CHD.

With regard to depression and CHD, different prospective studies found that there is a moderately strong association between depression and the incidence of CHD [23-30]. Moreover, other studies found that there is a dose-response relationship between the severity of depression and the earlier and more severe cardiac events [31,32]. In a prospective study of 314 patients (age range, 19-79 years) who had presented with chest pain, every 1-point increase in the depression score was associated with an average of 6% increase in coronary artery stenosis, after controlling for sex differences and other confounding variables [20]. In a meta-analysis about the impact of depression on the development of CHD in initially healthy subjects, 11 studies met the inclusion criteria. It was found that the overall relative risk for the development of CHD in depressed subjects was 1.64 (95% CI=1.29-2.08,  $p < 0.001$ ) [33].

Previous literature found that there is an association between base line depression and the development of CHD events. A meta-analysis of 21 prospective studies on 124,509 participants was conducted. The meta-analysis examined the relationship between depression and development of CHD events. In 11 studies which adjusted for cardiac risk factors, relative risk was 1.90 (95% CI: 1.49-2.42) [23]. In another meta-analysis quantifying the impact of depressive symptoms on cardiac mortality in healthy

people, depressed patients were two times higher than non-depressed for developing cardiac mortality [31].

In a recent study conducted in Brazil, an upper-middle-income country, major depressive disorder was associated with a two-fold increase in CHD after full adjustment for covariates [34]. However, other studies failed to find an association between depression and CHD. For instance, in a Swedish survey [19] depression did not predict subsequent CHD events. Another study conducted in Netherlands on 2807 patients concluded that no associations were found for persons with depressive disorders and increased prevalence of CHD [35].

Most of the previous research has been restricted to high-income developed countries including Australia, Canada, Denmark, Finland, Netherlands, UK and US stressing the need for research in low to middle-income countries. This need was also highlighted by the authors of a meta-analysis [36] of prospective studies about depression and risk of CHD who recommended that results should not be extended to developing countries. Furthermore, they concluded that in order to generalize the findings to other populations, additional studies should be conducted in other populations from Asia, Africa and South America. Therefore, the purpose of this study was to examine if there is an association between anxiety and depression with CHD in Jordan.

## 2. Materials and Methods

### 2.1 Research hypotheses

After controlling for sociodemographics and clinical variables (i.e., age, gender, history of diabetes, history of hypertension, smoking history, hypercholesterolemia, family history of CHD, and body mass index (BMI)); 1) Anxiety and depression scores will be independent predictors for the development of AMI, and 2) Anxiety and depression scores will be independent predictors for the percentage of coronary artery stenosis.

### 2.2 Design, sample and setting

A prospective observational design was used in patients with a pre-existing diagnosis of CHD. One thousand three hundred fifty patients were approached when they visited out patients' clinics for treatment or follow up from three private and two governmental hospitals in Amman, Jordan. Among them, 1000 agreed to participate and filled in the questionnaires. Those 1000 patients composed the sample and were followed up for two years or until the development of any AMI event.

A total of 157 patients developed AMI events and met the following criteria were included in the final analyses. a) signed an informed consent, b) greater than 18 years old, c) can read and write Arabic, d) not on anti-anxiety or anti-depressant treatment and e) did not have a previous AMI event or heart failure

due to myocardial infarction. To make sure that the sample size is sufficient, a-priori Sample Size Calculator for Multiple Regression was used [37]. The assumptions were: number of predictors was 9, a power of 0.9, an alpha of 0.05, and a small effect size of 0.15. Accordingly, the needed sample size was 141 participants. Therefore, 157 participants were considered enough to perform the analyses and reach a statistical significant result.

### 2.3 Ethical consideration

The institutional review board (IRB) committee at the Applied Science Private University, Amman, Jordan granted the approval for this study (faculty 005B). The principal investigator presented the study proposal to the medical and nursing directors of the previously mentioned hospitals, and submitted the IRB approval letter. These hospitals accepted the IRB approval from the Applied Science Private University. Then, permissions to conduct the study within these hospitals were issued to the principal investigator by the medical directors.

### 2.4 Procedure

Five research assistants were trained to collect data (one for each selected hospital) and authorized to work in the settings in the current study. Regular meetings were held between the principal investigator and research assistants to reduce recruitment bias and to answer their questions. They all agreed on a recruitment script in order to recruit participants identically.

The study was explained by research assistants to the participants. They guaranteed the participants that their participation was voluntary and they could withdraw from the study at any time. Participants then signed an informed consent if they agreed to participate including an approval to review their medical record if they were admitted to the hospital due to an AMI event. An initial interview with those who agreed to participate was held, during which the participants completed the required questionnaires. Then, patients were followed for 2 years or until they developed an AMI event. Patients and other family members were asked to contact the principal investigator/research assistant after they were discharged from an admission for an AMI event. Since it is difficult that all patients and family members would remember to call, patients were followed-up at 3, 6, 12 and 24 months by phone calls. During these phone calls, patients were queried about whether they experienced any hospital admissions. If any of them have been hospitalized for an AMI event, the medical records were obtained and reviewed by principal investigator/research assistant to collect data about the results of the cardiac catheterization.

### 2.5 Measurement of variables

#### Sociodemographics and clinical characteristics

Data were obtained either during the interview or

from medical record review including: age, gender, history of diabetes, history of hypertension, smoking history, hypercholesterolemia, family history of CHD, BMI, which coronary artery disease was stenosed and the percentage of the stenosis.

### Anxiety and depression

The Arabic version of Hospital Anxiety and Depression Scale (HADS) was used to measure anxiety and depression. The psychometric proprieties of this version have been checked in previous studies [38-42]. The Cronbach's alpha was 0.78 for anxiety subscale and 0.87 for depression subscale. Each subscale has seven items that were rated by patients on a 0-3 scale, with 3 indicating higher symptom frequency and severity. Each subscale score ranges from 0-21. Patients were considered normal if the anxiety/depression scores were between 0 and 7; mildly anxious/depressed if the scores were between 8 and 10; moderately anxious/depressed if the scores were between 11 and 14; and severely anxious/depressed if the scores were between 15 and 21 [38-42].

### 2.6 Data analysis

Data were analyzed using SPSS software version 21.0 (SPSS Inc., Chicago, Illinois). Statistical significance was defined as  $p < 0.05$ . The socio demographics and clinical characteristics of the sample were described using descriptive statistics with frequencies and percentages or mean  $\pm$  standard deviation (SD).

The first hypothesis of the study was tested by three different logistic regression analyses, each included three blocks. Variables entered in the first and second block in each analysis were the followings: In the first block, age and gender were entered; in the second block, BMI, history of hypertension, history of diabetes, smoking history, hypercholesterolemia, and family history of CHD were entered. The third block is different in the three analyses. In the first analysis, anxiety scores formed the third block, in the second analysis, depression scores were entered as the third block, in the third analysis, depression and anxiety scores together were entered as the third block. To check if anxiety and depression scores were independent predictors of coronary artery stenosis (i.e., the second hypothesis); first a serial bivariate correlation between (anxiety, depression) scores and the percentage of the coronary artery stenosis was done. Then, three different stepwise regression analyses were done in the same method done in the logistic regression.

## 3. Results

One thousand three hundred fifty patients were asked to participate in the study among which 1000 agreed to participate. The final analysis included only 157 patients who had AMI event during the follow up period. Sociodemographics and clinical characteristics of the patients are presented in

**Table 1.** Sociodemographics and clinical characteristics of the patients.

Variable	N (%) or M ± SD
Male/female	109 (69.4%)/48 (30.6%)
Age	66.6 ± 11.1
History of hypertension	124 (79.0%)
History of diabetes	55 (35.0%)
Family history of CHD	46 (29.3%)
History of smoking	
Never smoked	51 (32.5%)
Former smoker	63 (40.1%)
Current smoker	43 (27.4%)
Hypercholesterolemia	112 (71.3%)
BMI	27.4 ± 5.0
Anxiety levels	9.5 ± 5.8
Depression levels	10.9 ± 4.7
Percentage of coronary artery stenosis	42.2 ± 9.2

CHD: Coronary Heart Disease, BMI: Body Mass Index

Table 1. Approximately 70% of the patients were males, more than three-quarters of the sample had hypertension, and more than one-third of the patients were diabetic. Patients were mildly anxious and depressed based on a mean ± (SD) for the HADS.

As shown in Table 2, anxiety levels, depression levels, hypercholesterolemia, and male gender were independent predictors of AMI events. Both anxiety and depression have a strong positive significant correlation with the percentage of coronary artery stenosis;  $r=0.72$ ,  $p<0.001$  and  $0.69$ ,  $p<0.001$ , respectively. Tables 3 and 4 show the results of the stepwise regression. Male gender was an independent predictor in all models. Anxiety and depression levels also were independent predictors for stenosis. Hypercholesterolemia was an independent predictor in the anxiety model, anxiety and depression model but not in the depression model.

#### 4. Discussion

This was the first study to examine the relationship between anxiety, depression and the development of AMI events in patients with pre-existing CHD in Jordan. The major findings of this study were that

**Table 2:** Independent predictors of myocardial infarction anxiety model, depression model, depression and anxiety model respectively.

Predictor	OR	95% CI	β	SE	Wald	p
Anxiety Model						
Hypercholesterolemia	1.98	1.06- 3.24	1.01	0.33	6.22	0.004
Anxiety levels	1.55	1.15-2.10	0.45	0.67	7.49	0.005
Depression Model						
Hypercholesterolemia	2.31	1.44- 5.85	1.06	0.34	9.15	0.002
Depression levels	1.77	1.21-2.34	0.76	0.31	5.79	0.02
Anxiety and Depression Model						
Male gender	2.16	1.17-3.97	0.76	0.36	8.66	0.002
Hypercholesterolemia	2.39	1.07-5.95	1.08	0.35	9.01	0.001
Depression scores	1.52	1.12-2.07	.041	0.61	6.99	0.005
Anxiety scores	1.14	1.03-1.29	0.13	0.06	4.63	0.03

OR: Odd Ratio, CI: Confidence Interval, B: Beta, SE: Standard Error of the mean, P: P value

**Table 3.** Predictors of coronary artery stenosis when anxiety scores alone were entered in the third block, then when depression scores entered alone in the third block respectively.

Predictor	Standardized β	T	Model statistics
Male gender*	0.14	2.1	R2=0.50; F (9,148)=
Hypercholesterolemia*	0.16	2.4	
Anxiety scores**	0.72	12.2	
Male gender*	0.13	1.9	R2=0.51; F (9,148)=
Depression scores**	0.73	12.4	

\*  $p<0.05$ , \*\*  $p<0.001$

**Table 4.** Predictors of coronary artery stenosis when anxiety and depression scores were entered together in the third block.

Predictor	Standardized β	t	Model statistics
Male gender*	0.14	2.1	R2=0.54; F <sub>(10,148)</sub> =18.3, $p<0.001$
Hypercholesterolemia*	0.13	2	
Depression scores**	0.41	3.4	
Anxiety scores**	0.36	2.9	

\*  $p<0.05$ , \*\*  $p<0.01$

anxiety and depression independently predicted the occurrence of AMI and increased the risk for coronary artery stenosis after adjusting for covariates. Moreover, the results indicated that depression was stronger than anxiety in this relationship. Male gender and hypercholesterolemia also were independent predictors.

This study was conducted in a low-income Arabic developing country to duplicate or counter the findings from developed countries. The results of the current study are fairly comparable to those in developed countries, suggesting that anxiety and depression are predictors of an AMI events and important risk factors for coronary artery stenosis across a broad diversity of cultures.

The results of this study are consistent with previous studies checking the effect anxiety and depression on CHD patients [12,15,16,23-30]. It has been suggested that anxiety and depression are as important as other traditional risk factors (i.e., age, gender, smoking, and family history) in the development of CHD and increasing risk of cardiac events among patients diagnosed with CHD [6,19]. Anxiety and depression may affect the heart in biological and behavioral pathways. Biologically, anxiety and depression stimulate the sympathetic nervous system (SNS) and decrease heart rate variability due to higher epinephrine and nor-epinephrine levels [43-45]. Moreover, anxiety and depression are associated with hypercoagulation due to increased plasma platelet factor 4 and thromboglobulin (suggesting enhanced platelet activation) [46,47]. Furthermore, anxiety and depression are associated with hyperlipidemia [48] and immune suppression [48]. In addition, depression was associated with low levels of omega-3 fatty acid [49] and enhancing inflammatory processes [50,51]. Behaviorally, anxiety and depression might negatively affect adherence to specific diet and medication [43,52,53] decrease physical activity [43,54] and enhance (smoking [55], social isolation and chronic life stress) [56].

Different explanations have been made why anxiety and depression did not predict AMI events or coronary artery stenosis in previous studies. First, uncertainty concerning causal inferences [19]. Second, concerns about reverse causation (the possibility that both depression and subsequent CHD are caused by subclinical manifestations of cardiovascular disease) [19,57] which means that, when a prospective clinical study includes individuals free from clinical heart disease, they might not be free from atherosclerosis which may assist depressive symptoms even before generating cardiac ischemia creating a fake association between depression and atherosclerosis [57]. Third, incomplete adjustment to CHD risk supply factors and publication bias [23]. Fourth, instruments used included a broad depressive symptom band, such as sleep problems, being short of energy and troubled appetite [25]. These symptoms significantly go beyond with symptoms of common physical

illnesses, including subclinical coronary artery disease [25,57].

The instrument which has been chosen in this study (HADS) was initially intended to detect anxiety and depression in patients with physical illness. Therefore, it methodically excludes somatic symptoms which can imitate heart disease [58]. For this reason, our study is the first study in a low-income country to link core psychological and cognitive symptoms of anxiety and depression to increased AMI risk. Yet, using this style, some patients with mostly somatic symptoms of depression might go invisible. Consequently, we are more likely to have underestimated, rather than overestimated, the association between depression and AMI in our study. Anxiety and depression can be treated effectively with different management strategies [59]. Unluckily, a lot of patients do not receive sufficient treatment [59]. In addition to the effect that anxiety/depression has on disability and decreased quality of life, clinicians must be alert about the association between anxiety/depression with incident CHD. Future randomized control trials checking whether the treatment of anxiety/depression has a significant beneficial effect on the incidence CHD is warranted.

## 5. Conclusion

Anxiety and depression independently predict the occurrence of AMI events and coronary artery stenosis among patients with pre-existing CHD in a low-income Arabic developing country. These results are comparable with those from developed countries, indicating that anxiety and depression are important global risk factors to develop AMI events in patients with pre-existing CHD. Interventional studies to control the effect of anxiety and depression in this population are needed.

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