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Depressive Symptoms and First Hospitalization/All-Cause Mortality in the Emory Cardiovascular Biobank Longitudinal Database (2004-2018)

By

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Master of Public Health

Applied Epidemiology

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By

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MSc. (Ag) ANGRA University, 1996

Thesis Committee Chair: Dr. Jose Binongo, PhD

An abstract of A thesis submitted to the Faculty of the
Rollins School of Public Health of Emory University in partial fulfillment of the requirements for the degree of Master of Public Health
In Applied Epidemiology
2023

Abstract

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By Suneela Ramineni

Objective: The goal of this study was to describe the association between depressive symptoms and first hospitalization for reasons related to cardiovascular disease or death among patients at Emory University Hospital and Grady Hospital in Atlanta, GA from 2004 to 2018. Possible risk factors for first hospitalization or death were evaluated.

Design: The data were prospectively collected from date of enrollment. Planned follow-up time was 5 years. The primary endpoint was time to first hospitalization due to re-vascularization, heart failure, or other reasons, or all-cause death.

Methods: Demographic data and other patient characteristics were collected at baseline. During enrollment, patients were asked to complete an eight-question instrument that aimed to quantify their depressive symptoms and mental health condition on a scale from 1 to 4. These responses to the eight questions were added. The patients were then divided into three groups based on this sum: the first group consisted of patients who got a sum of 0, the low depressive symptoms group consisted of patients who had a sum between 1 and 12, and the high depressive symptoms group had a sum between 12 and 24. Competing-risk analysis was then employed to assess the association between depressive symptoms and time to first hospitalization for re-vascularization, heart failure and all other cardiovascular reasons or death, controlling for demographic and other baseline variables.

Results: The sample consisted of 5200 patients, 37.6% of whom were female. The mean ± standard deviation for age was 61.9 ± 13.4 years (range: 18-99). The majority of the patients were white (71.9%), followed by black (23.6%). Assessment of comorbidities was also done at baseline: hypertension (70.1%), hyperlipidemia (63.1%), diabetes (33.4%), BMI (29.8 ± 6.6 kg/m2) and previous myocardial infarction (30.1%). Age and employment status were associated with death and first hospitalization for re-vascularization, heart failure and other reasons. Patients who had high depressive symptoms had a higher rate of first hospitalization due to heart failure and all-cause death. In particular, the hazard ratio comparing high and no depressive symptom groups was 1.69, 95% CI: (1.23, 2.30) for heart failure and 2.86, 95% CI: (1.90, 4.30) for all-cause death.

Conclusion: Patients who have cardiovascular disease with depressive symptoms have a higher rate of hospitalization for heart failure or death. A follow-up study is recommended to further confirm and understand this preliminary finding.

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Chapter 1: Background Literature Review

Introduction

Cardiovascular disease (CVD) is the leading cause of death in United Stated among both men and women accounting for 928,741 deaths in the year 2020. Whereas, depression is the leading cause of disability worldwide and 7.1% of US population, 18 and older are affected by depression disorder which is more prevalent in women. Adults with depression or poor mental health are at 64% greater risk of developing heart disease (1). Research have shown that physiologic effects of the body like increased heart rate and blood pressure may be experienced in people with longterm depression or mental health issues. Increased cardiac reactivity could be due to higher levels of cortisol and decreased blood flow to the heart causing metabolic disease, heart disease and increased calcium buildup in the arteries(3).

Studies have shown that depression and heart disease are inter-related. Depressed individuals showing adoptive behaviors like inactive lifestyle, smoking, alcohol abuse and lack of sleep have increased risk of heart disease and risk of cardiac metabolic disease increases due to drugs used to treat depressive symptoms (2).

We aim to investigate the available literature to examines the risks factors associated with complications of heart disease especially those with depressive symptoms. And finally, we will discuss how self reported depressive symptoms at the baseline plays role in individuals who were hospitalized for reasons like re-vascularization, Heart Failure (HF), other cardiovascular diseases and all cause mortality while controlling for age, race, gender, employment, medication or counseling, and few other risk factors (smoking, BMI, history of depression, diabetes, hypertension, hyperlipidemia and MI). (3,4)

Background

Literature suggests that there is a high comorbidity of depression and CVD resulting in premature death in high income countries (5). In United States, depression is the leading cause of disability especially in young adults and an emerging nontraditional risk factor of CVD(3). Depression in women is two times higher compared to males and this disparity is wide spread due to psychological, social, genetic and biological factors (5). Epidemiologic evidence suggests that depression is a prognostic factor and independent risk factor for cardiovascular disease (CVD). Studies indicate that, primary care intervention for depression in patients aged ≥60 years will reduce the risk of CVD by half (6).

Epidemiology and Economic Burden

Research over the past 3 decades had linked depression as the risk factor for high mortality and morbidity in cardiac patients along with other traditional risk factors. Prevalence of depression is between 31 - 45% in patients with cardiovascular diseases. Nearly 50 -70% of the patients admitted with chronic cardiac events like myocardial infarction (MI) or unstable angina have shown some depressive symptoms preceding the hospitalization. Atrial fibrillation (AF) or heart failure (HF) may increase the risk of elevated depression in 36% of the patients. Approximately 30 - 40% of patients undergoing coronary artery bypass graft (CABG) surgery have shown minor or major depression (7). Nearly 50% of the patients with Heart Failure(HF) die within 5 years of diagnosis causing serious burden of disease to the healthcare system and the patients. Development and progression of HF had been linked to presence of depressive symptoms or anxiety disorder resulting in low quality of life and frequent hospitalizations (36). Recent study indicates that there its 21% increased risk of HF in veterans with depressive

symptoms but no history of CVD (36). The prevalence of comorbids depression and HF is high due to mutual association and shared risks factors (37).

Nearly 60% of the disability-adjusted life years (DALYs) are due to non communicable diseases and 24% of this can be accounted for CVD. Age standardized mortality rate for CVD has been going down globally but the risk still remains high in low and middle income countries. So the economic burden of CVD and hypertension still remains high in relative to healthcare budget in these countries (9). There is significant economic burden due to depression related CVD treatment because of the cost involved with depression medications or counseling and this difference is more evident after the first year of treatment. Adjusted cost for CVD in depressed women is $1500 to $ 3300 higher compared to the women that are not depressed (10).

Risk factors

Traditional risk factors for CVD are lack of physical activity, diabetes, hypertension dyslipidemia and smoking. Whereas anxiety or depression in CVD patients will increase the risk of obesity, dyslipidemia, hypertension and diabetes. Elevated cytokines and inflammatory biomarkers seen in patients with anxiety or depression may increase risk of CVD. Social isolation, behavioral changes and psychological changes seen in depressed people may increase the risk of CVD (11). Men and women with major depression ($P < .001$ vs no depression) face 74.4% and 66.5% high prevalence to lifetime CVD risk respectively. Prevalence of depression in women (61.4%) is high compared to men (50.7%). Women less than age 55 diagnosed with premature CVD and depression are at the highest risk. Few additional risk factors for CVD in women are gestational diabetes, use of oral contraceptives and polycystic ovarian syndrome (PCOS) (12).

Areas of Development

Heart health and depression are intertwined in several ways, depression increases the risk of CVD both by psychological and as well as physiological impacts. Most depressed people have difficulty getting out of bed resulting in lack of exercise and unhealthy life choices leading to poor heart health. Symptoms like chest pain or rapid heart rate are commonly experienced by patients diagnosed with depression along with overlapping symptoms like anxiety and fatigue but more than often they cannot keep up with appointments. Patients diagnosed with heart attack or had heart surgery recently might develop depression due to increased stress, lifestyle changes and medications. Research have shown that depression is the strong predictor of death in patients with CVD. Lack of interest, feeling down or depressed, having suicidal thoughts, sleeping too much or too little are some of the symptoms for depression. To protect mental health and heart health, people with history of CVD should depend on family and friends for emotional support, seek counseling, be physically active, eat nutritious food, meditate and follow routine (13).

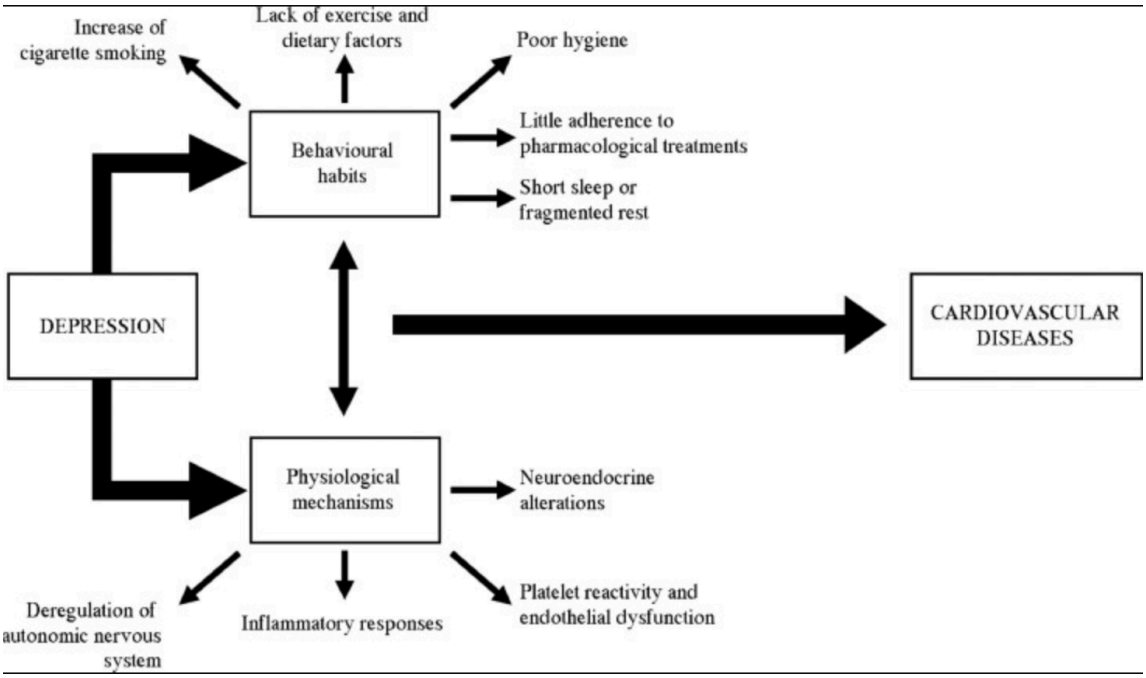

Fig 1: The relationship between Depression and Cardiovascular diseases (14).

Incidence of depression in women cardiac patients is 2 times higher than men and it has been linked to different neuroendocrine setup in women. Treatment to depression has shown to have positive effect on CVD outcomes, but routine screenings for psychosocial risk factors and gender related issues in CVD patients is still not practiced routinely among family practitioners or cardiologists (14). Considering race and ethnic background while studying the link between CVD, depression and anxiety might be beneficial to know the disease pattern and association (15). Recent research showed racial and ethnic discrimination is linked to social determinants of health and CVD. Compared to white population, American Indians, Asian, Blacks and Hispanics are at social disadvantage of receiving poor quality care even if they are from the same demographic background (16).

Statement of Problem

There is a need to identify the link between depressive symptoms and risk of death and hospitalization with cardiovascular disease. Since depression and CVD are interrelated, there is a need to study the risk of hospitalization for various reasons of CVD in relation to self reported depressive symptoms, age sex, race, employment status, smoking and other comorbidities in these patients. A better understanding of these factors may allow to identify at risk populations that may require more support or follow up for managing depressive symptoms and allow for specific interventions based on identified risks.

Purpose of Statement

To investigate the association between depressive symptoms and risk of death, hospitalization due to re-vascularization, heart failure and all other reasons related to CVD in patients enrolled in the study at Emory University Hospital during the 5 year follow up period.

Public Health Implications

Furthermore, a better understanding of the relation between depressive symptoms and risk of death due to all cause mortality, hospitalization due to various reasons of cardiovascular disease to minimize the greater risk of CVD hospitalization will allow for earlier intervention and additional support for those patients to start managing the symptoms during the early visits to the family practitioner and may improve mental health by reducing the associated risk of cardiovascular disease and might lessen risk of hospitalizations related to CVD, while also decreasing costs for families and hospitals within the Emory network. The five-year follow up period with larger sample size will allow for the time needed to assess inter-related affects of depressive symptoms and CVD.

Chapter 2: Journal Article

Abstract

Objective: The goal of this study was to describe the association between depressive symptoms and first hospitalization for reasons related to cardiovascular disease or death among patients at Emory University Hospital and Grady Hospital in Atlanta, GA from 2004 to 2018. Possible risk factors for first hospitalization or death were evaluated.

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baseline: hypertension (70.1%), hyperlipidemia (63.1%), diabetes (33.4%), BMI (29.8 ± 6.6 kg/ m2) and previous myocardial infarction (30.1%). Age and employment status were associated with death and first hospitalization for re-vascularization, heart failure and other reasons. Patients who had high depressive symptoms had a higher rate of first hospitalization due to heart failure and all-cause death. In particular, the hazard ratio comparing high and no depressive symptom groups was 1.69, 95% CI: (1.23, 2.30) for heart failure and 2.86, 95% CI: (1.90, 4.30) for all-cause death.

Conclusion: Patients who have cardiovascular disease with depressive symptoms have a higher rate of hospitalization for heart failure or death. A follow-up study is recommended to further confirm and understand this preliminary finding.

Introduction

Mortality, recurrent cardiac events, and low quality of life related to health are commonly associated with persistent depression in cardiovascular patients. Physiological factors like inflammation, platelet abnormalities, dysfunction of autonomic nervous system and behavioral factors like reduced involvement in health building activities in depressed patients are linked to poor cardiac outcomes. The American Heart Association has recommended routine depression screening of all cardiac patients with the 2- and 9-item Patient Health Questionnaires to track the impact of depression on quality of life and outcomes related to cardiac events. However, depression goes unrecognized and under treated in cardiac patients despite the availability of screening tools and treatments (7).

Therefore in this study we access the depression based on routine screening questionnaire and investigate the relation between incidence of hospitalization and depression in

cardiovascular patients and make specific recommendations on how the intervention for depression would be helpful in this high-risk population.

Methods

Using Emory cardiovascular biobank data obtained from Emory University, Cardiology department in Atlanta, Georgia, we performed a retrospective cohort study of 5200 patients with a median age of 61.7 years (±13.4) ranging from 18 years to 99 years who were hospitalized for the first time after enrollment for cardiovascular related events during the followup period. There were 3250 males and 1949 females in the cohort, patients with missing data on all exposure variables, enrollment date, and follow up data were excluded from the study. One year and 5 year follow ups were done with phone call or email. Study data was collected from Emory University hospital, Grady hospital and elsewhere in Atlanta. Demographics of this cohort can be viewed in Tables 1A and 1B.

Covariates included were date of enrollment, date of last followup, date of first hospitalization, reasons for hospitalization, dead or alive status, age, race, gender, employment status, smoking, depression history, previous myocardial infarction(MI), diabetes, hypertension and hyperlipidemia. During enrollment, patients were asked to complete eight-question instrument that aimed to assess their depressive symptoms and mental health status. Each question assessed for depressive symptoms was assessed at 4-levels on 1-4 scale based on number of days patients reported to have symptoms. Patient Health Questionnaire-9 (PHQ-9) a comprehensive tool a more focused assessment for depressive symptoms was used in our study but the question related to suicide was removed later in the study. To identify high-risk patients with severe symptoms , the overall PHQ-8 score was used to grade the severity of depressive symptoms on a scale of 0-24. Then patients were categorized based on overall score, no

symptoms (Group 0, Score '0'), low (Group 1, Score '1-12') and high (Group 2, Score '>12'). Dummy variables were created for categorical variables, race, employment status, smoking, and medication. All other categorical variables were coded as binary in the data. The patients were divided into 3 groups for employment: both part-time and full-time patients were included in 'employed' group, disabled and unemployed were in 'unemployed' group and the third group 'retired' had retired patients. The patients were categorized as 'No' for non smokers, 'current' for smokers and 'past' for previous smokers. Referent group was set to two in the class statement for race indicating blacks, unemployed for employment, current for smoking, and as zero for all other variables indicated No.

Differences in the survival time were accounted for by taking the difference between date of enrollment and date of first hospitalizations in the patients who were hospitalized, the difference between date of enrollment and date of last followup who were not hospitalized, and the difference between date of enrollment and date of death who died during the followup. This number was used as the model offset.

Patients were placed in one of the 2 categories in all demographics and risk factors, based on the answers to depression related questions. Patients who reported to have no symptoms were placed in one group ('1') and those who reported symptoms from several days to everyday of the week were placed in another group ('2, 3, 4') for depressive symptoms. Similar pattern was followed for all questions in eight-question instrument.

Study participants hospitalized for the first time during the followup, were analyzed for reason and categorized into 3 outcome groups based on the reasons for hospitalization. Outcome '1' includes re-vascularization (MI, Cardiac Cath, PCI, PIA and CABG), outcome'2' for HF (HF,

Heart transplant and Valve surgery), and outcome '3' for all other cardiovascular related events. Participants who died after enrollment, before first hospitalization and during the followup were included in outcome '4' for all cause mortality. Patients who were alive and not hospitalized during the followup were included in the reference group as outcome '0'.

Using SAS 9.4, we calculated date of first hospitalization and survival time from the difference between the date of enrollment, date of first hospitalization, date of last follow up and date of death. SAS 9.4 was also used for descriptive analyses to know the frequency distribution, mean, median, variance and range on each covariate, all exposure variables and then modeled each with each outcome to better understand its characteristics and its relationship to the outcome. We opted for the univariable analysis of the survival data by performing regression analysis based on competing risks model, to obtain hazard ratios (HR) for each covariate and level of covariate (Tables 3A, 3B, 3C and 3D).

We then performed multivariable analysis of each outcome category with all covariates and depressive symptoms 'Group' as exposure. We included depressive symptoms into the model with referent group as '0' in the class statement, along with other covariates (Table 2). Using these models for each h outcome, we assessed for statistically significant interactions (covariates with p-values less than 0.05) among clinically significant covariate combinations. We assessed for confounding effects of individual variables on our outcome by comparing the Chi-square estimates of our exposure and risk factors in models with and without the variable we were assessing (Tables 4A, 4B, 4C and 4D).

Results

We had 8408 patients enrolled in the study and only 5200 patients were included in this study after initial clean up, due to missing demographics data, enrollment date, exposure time, one or more exposure variables, follow up time and date of first hospitalization prior to date of enrollment (Fig 2). The demographics of the study population, exposure and outcome variables after univariable analysis were summarized in Table 1 under the appendix section.

The mean age of our study population was 61.7 ±13.4, 62.5% of them were males, 71.9% were white, 23.6% were black and 4.5% were categorized as other. Distribution of study population were analyzed for each exposure variable. The majority of the patients were white (3732), followed by black (1227) and other races (233). There were 1775 (34.7%) employed patients, 1156 (22.6%) unemployed and 2187 (42.7%) retired patients in the study population. The mean follow up time was 5 years with number of reasons for hospitalization ranging between 0 to 18. In univariable analysis, known traditional risk factor for cardiovascular disease, age (p-value <.0001) (HR 1.04 (95% CI: 1.03, 1.06)) was significant in all outcome categories, diabetes, hypertension, and previous MI (p-value <.0001) were significant for all outcomes except HF. BMI and severe depressive symptoms (p-value <.0001) were significant for HF and death outcomes. Hyperlipidemia (p-value <.0001) (HR 1.35 (95% CI: 1.20, 1.51)) was significant and males (p-value <.0001) (HR 1.63 (95% CI: 1.43, 1.86)) were at higher risk for re-vascularization. In all the patients who reported to be depressed by nine-question instrument all the variables related were highly significant (p-Value of 0.001 or <0.0001). Hazard ratio of less than one and significant p-value for medication or counseling in re-vascularization patients might be indicating that medication might be protective in those patients (Table 3A).

For multivariable analysis of the survival data we performed regression analysis based on Cox proportional hazards model starting with a full model for each outcome. In the first reduced model for re-vascularization, age, sex, previous MI, and diabetes were significant. Males were at 63% more risk and patients with previous MI were at 56% increased risk. Employed vs unemployed was significant with p-value of 0.0052 (Table 4A) (Fig 3). Our next model for heart failure includes 3 significant variables, depressive symptoms, age, and hyperlipidemia. For depressive symptoms, High Vs None was significant (p-value 0.0055) (HR 1.64 (95% CI: 1.15, 2.31)) indicating having severe depressive symptoms might be a predictor for heart failure (Table 4B) (Fig 4). Our model for all other cardiovascular related events of hospitalization includes age, race employment status, smoking and previous MI. Both white (p-value 0.0023) and other (p-value 0.0296) races seem to be at less risk for CVD compared to black patients based on significant p-values and negative estimates indicating white and other races were protective. Similarly, being employed vs unemployed was protective and both past and current smokers were increased risk for CVD (Table 4C) (Fig 5). Our final model for all cause mortality or death includes depressive symptoms, age, sex, employment status, BMI, diabetes, hyperlipidemia, and previous MI as significant risk factors. Highly significant p-value in patients with higher score for depressive symptoms (p-value <0.0001) (3.31 (95% CI : 2.02, 5.42)) shows that they were at increased risk for death. Both employed and retired patients were shown to be at lower risk (68% and 49% respectively) for all cause mortality compared to unemployed patients in our cohort. Significant traditional risk factors in our model were BMI, diabetes, hyperlipidemia and previous MI. (Table 4D) (Fig 6). Age was significant in all 4 outcome models, ranging between 1-4% risk indicating hospitalization or death increases with age in patients. Analysis for each outcome

model was performed by removing less significant variables from the full model, analyzing one after another based on the chi-square values and p-values.

Discussion

The inter relationship between cardiovascular disease and depression has been well established and depression is listed as a risk factor but the implication of antidepressants remain very contentious (17 - 19). Use of certain class of antidepressants that inhibit serotonin reuptake have shown to reduce the risk of myocardial infarction whereas, the risk was increased with Lofepramine (19). One more study suggests that adverse events and contraindications should be studied in older patients with CVD before treating them with new antidepressants by constantly monitoring blood pressure(17). Study published in Journal of American heart association indicated that there is no reduced risk of CVD when different classes of antidepressants were prescribed and concluded that there is no protective effect when selective serotonin reuptake inhibitors (SSRI) were used compared to the other antidepressants. High affinity of SSRI's for the Serotonin transporter have shown to lower the risk of ischemic stroke by reducing platelet activity in patients (20).

Various studies imply that 67% of the adults older than 50 years diagnosed with depressive disorders were reported to have a heart disease or stroke. Even though there are other traditional risk factors and genetic reasons for CVD, age has an impact of depressive symptoms and the severity of symptoms and influences the outcome in HF patients (37). Treatment for depressive symptoms followed by a stroke have shown to improve cognitive and motor skills in older adults (30). Our study indicates that age was a risk factor for all outcomes, adult patients were at increases risk for HF hospitalization and all cause mortality. Focusing on psychosocial

stress and making lifestyle changes while mitigating for depressive symptoms should be a routine practice for controlling CVD in older adults.

Studies have shown that sex hormone alterations, exposure to stress during pregnancy trigger inflammatory response in women may contribute to depression and increases the risk of CVD in women (23, 24). Contradicting this, our investigation showed males were at higher risk of hospitalization for re-vascularization and death for all cause mortality. Our analysis does not include level of physical activity and other preexisting comorbidities. Inflammation has been linked to several traditional risk factors for CVD like hypertension, diabetes, and obesity. Women were 2 times likely to be depressed compared to males and there is a complex relationship between depression and CVD in women leading to more morbidity and mortality. This can be improved by better understanding the reasons for inflammatory response and the mechanisms leading to it (23, 25).

In our study, race being a significant predictor for higher hospitalization incidence for CVD related reasons in black patients, indicating the importance of routine screening for depressive symptoms. Several factors like economic instability, physical environment, health care system that play a role in racial disparities associated with CVD, blacks are at social disadvantage resulting in implications for CVD morbidity and mortality(16). Depressive symptoms were related to traditional CVD risk factors by several studies indicating the that depression might be a precursor in developing CVD (21), and the need to use antidepressants or counseling before the onset of symptoms.

In regard to the employment status, our study indicated that being employed part time or full time is protective in the study population in all outcome models except in HF hospitalization.

This supports the study showing higher rates of mortality in unemployed due to CVD. Mental health deteriorates in unemployed individuals significantly increasing the risk of depression which is a known non traditional risk factor for CVD (22).

Globally, diabetes impacts 425 million adults causing significant burden of disease and a major risk factor for CVD. Individuals with type 2 diabetes are 2 times more likely to be depressed suggesting an association of CVD and depression with diabetes. Adults with diabetes are at increased stress to make life style changes to manage the chronic disease (31). Our study indicated that the risk of re-vascularization hospitalization was more 16% more and the risk of death was 45% more in patients with diabetes. Studies have shown that depressed adults have worse prognosis for MI and managing depression with anti depressants have not shown any difference in the mortality rate of patients . But managing depression in acute MI survivors might be an important step towards improving quality of life (32, 33). Our preliminary investigation suggests that patients with previous MI were at 56% increased risk for re-vascularization, 23% higher risk for other CVD related hospitalizations and 50% higher risk for death.

Our results indicated that there was increased risk for HF and death in patients with higher levels of cholesterol (Hyperlipidemia). In support to our findings, studies have also shown increased incidence of CVD in hyperlipidemia patients with pre existing depression. Depressive symptoms in adolescents leads to unhealthy levels of lipids, changing the lipid profile. In presence of other comorbidities, depressed adolescents with dyslipidemia have shown increased risk for CVD (34, 35).

Our results have shown current smokers were at increased risk for several cardiovascular related hospitalizations. No smokers and past smokers were at 28% and 21% less risk

respectively when compared to current smokers. Research indicates heart attack or stroke might be the first sign of heart disease in people who smoke (39). Obesity and high BMI are known risks of CVD but studies have shown that people with underweight vs Normal weight (low BMI) are at 2.3 times more risk for CVD. Increased risk of heart disease in obese people could be related to other comorbidities whereas BMI<18.5kg/m^2 is a risk factor for CVD alone. (38) Our results indicated that BMI was significant for all cause mortality but with a negative estimate. Our study showed that increased cholesterol was significant in hospitalized patients for HF and those who died during follow up. But the negative estimate for this variable might be attributed to the variation in study data (Number of patients answered Yes Vs no compared to hypertension and diabetes).

However, our results were insignificant for few known risk factors like, hypertension, and history of depression. Hypertension was significant in univariable analysis for death and all reasons of hospitalizations except HF. Few of the limitations of the study are, even with the large sample size this study cannot be generalized to other populations or geographical locations as the study population was only from one hospital system. Racial distribution of the study population is not the true demographic representation with 71.9% whites, 23.6% black and only 4.5% representing all other races. However the specific study population may represent the socioeconomic and racial disparities in Georgia. The longer follow up period in a large cohort of patients might be a true implication of importance to screen for depressive symptoms as they play significant role in hospitalization for HF and death, there by reducing morbidity and mortality associated with CVD. There are other covariants like physical activity, obesity, alcohol consumption, sleeping habits and eating habits if added into the analysis might provide better understanding and significant differences. Depression questionnaire based on Beck's inventory

of depression was included in the study but majority of patients skipped that questionnaire after answering initial PHQ-8 on depressive symptoms. If all the questionnaires included in the study were answered, more comprehensive and significant results would have been possible. However this study is helpful in identifying the disparities in healthcare to eliminate gaps by screening for depressive symptoms and addressing depression during the primary care and to identify inflammation response and underlying mechanisms in females.

In summary, among patients who reported high depressive symptoms, we observed an increased risk of hospitalization for HF in patients. Patients reporting high depressive symptoms with significant BMI, diabetes, previous MI and high cholesterol, unemployed or retired were at increased risk for death or all cause mortality.

Future Directions:

This study can be considered as a pilot study to assess the all cause death, hospitalization in patients for re-vascularization, Heart Failure and other reasons related to heart disease, who reported depressive symptoms at baseline. Management of depressive symptoms clinically is important to minimize the harmful effects of heart disease. There is a need to categorize patients to assess the risk in patients with no history of CVD (28). Prevalence of heart disease is 40% more in patients having major depressive disorder. Complexity and cost involved will make it harder to study exact mortality rates but understanding biological and clinical mechanisms involved in the bidirectional relation between CVD and depression will reduce health care costs (29). Females are disproportionately effected when both depression and CVD are present, and prevalence of CVD is 70% more in females diagnosed with depression. Studies indicated multidisciplinary approach with systematic screening for depression, use of antidepressants,

behavioral cognitive therapy might be beneficial and cost effective rather than therapeutic intervention alone(31).

Appendix: Figures and Tables

Figure 2: Flow Diagram

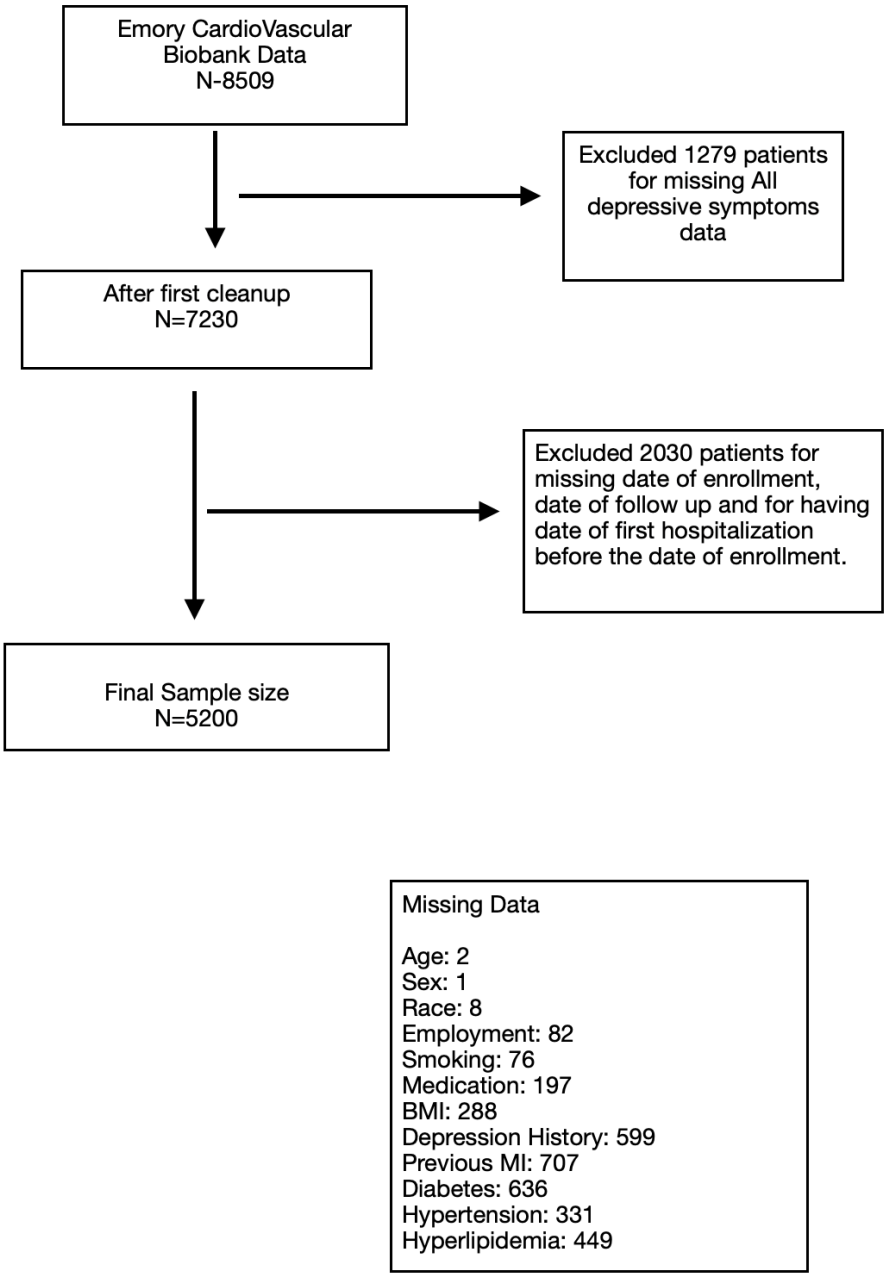
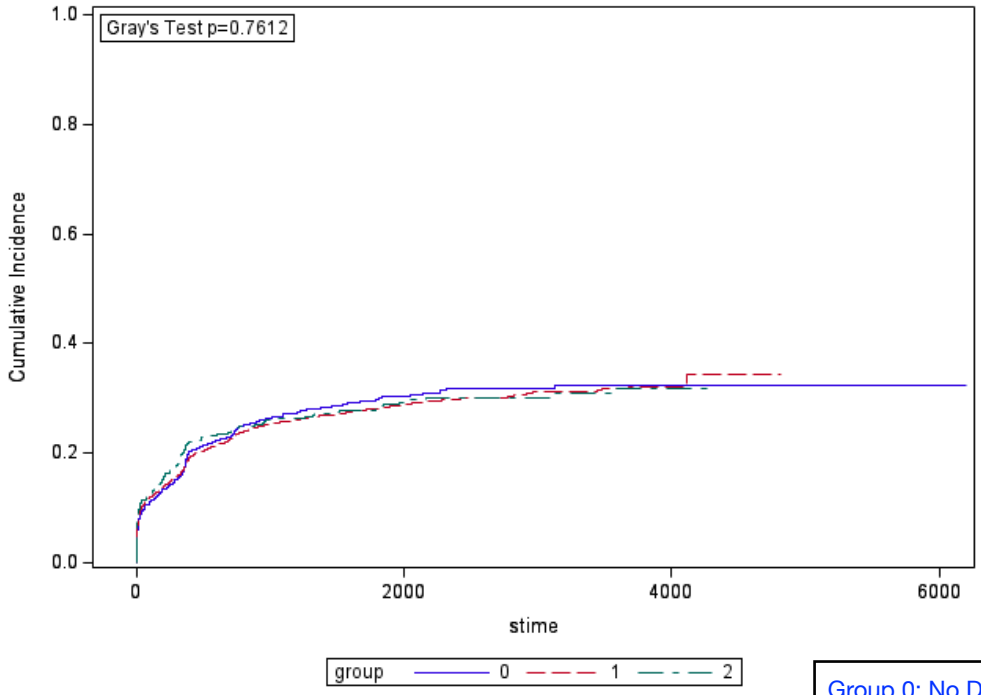


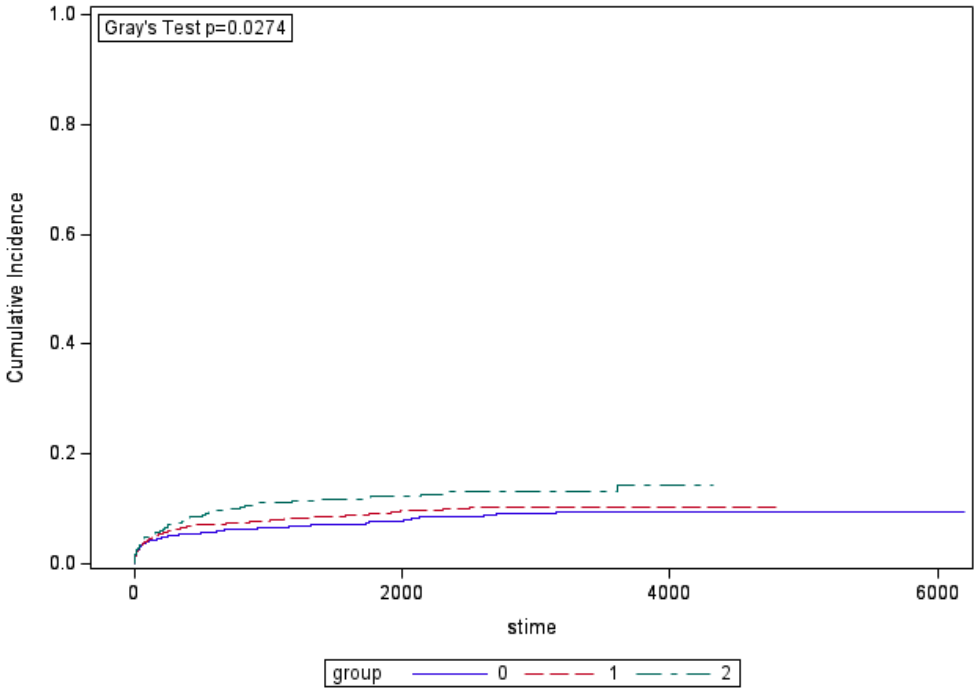
Figure 3: Cumulative Incidence Functions

A. Hospitalization due to Re-Vascularization

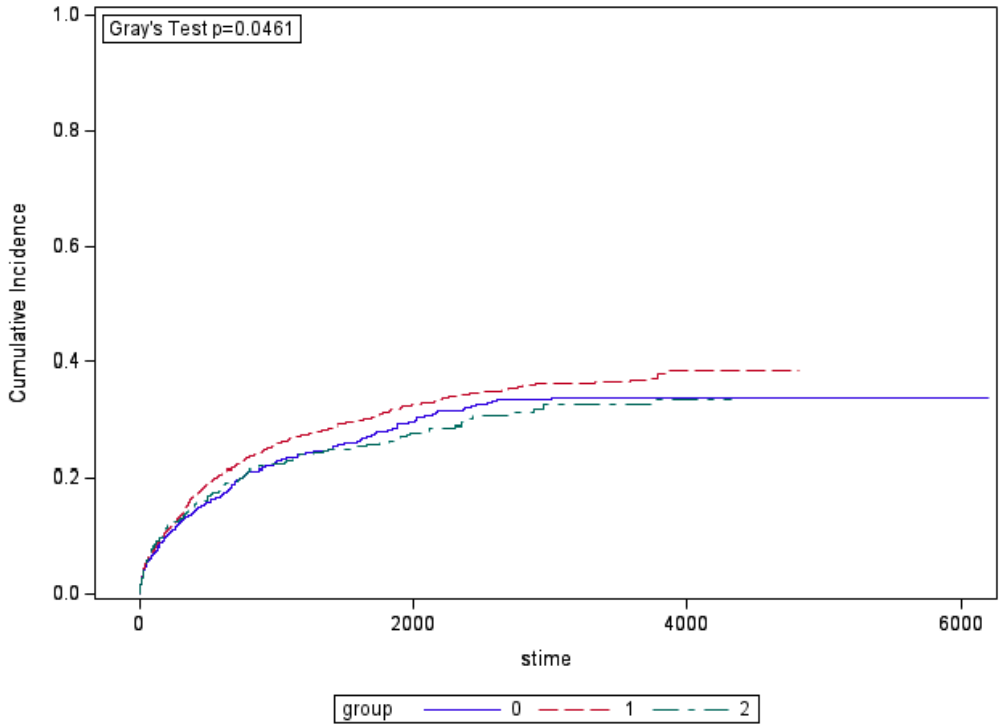


Group 0: No Depressive symptoms
Group 1: Low Depressive symptoms
Group 2: High Depressive symptoms

B. Hospitalization due to Heart Failure



C. Hospitalization due to all Other Reasons



D. All cause Death

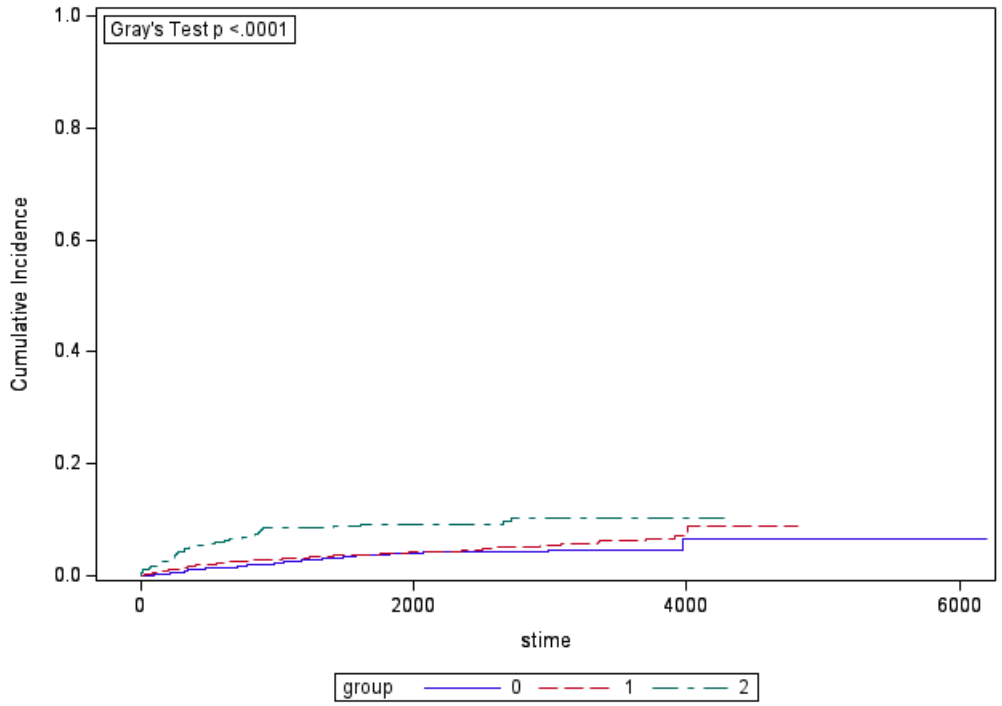


Table 1A: Baseline Characteristics by Depressive Symptom

Baseline Characteristics	All N=5200	No Interest (0) n=3545	No Interest (1,2,3) n=1572	Feeling Bad (0) n=4103	Feeling Bad (1,2,3) n= 1000	Depression (0) n=3610	Depression (1,2,3) n=1530	Sleep (0) n=2794	Sleep (1,2,3) n=2327
Age (Years)	61.7±13.4	62.1 ±13.2	60.5 ±13.6	62.4 ±13.2	57.7 ±13.4	62.4 ±13.2	59.6 ±13.3	62.4 ±12.9	60.5 ±13.8
Female	1949 (37.5%)	1257 (35.5)	655 (41.7)	1493 (36.4)	408 (40.8)	1260 (34.9)	668 (43.7)	935 (33.5)	989 (42.5)
Race									
White	3732 (71.9%)	2566 (72.4)	1110 (70.6)	2974 (72.4)	689 (68.9)	2584 (71.6)	1112 (72.7)	2009 (72.0)	1668 (71.7)
Black	1227 (23.6%)	805 (22.7)	399 (25.4)	948 (23.1)	254 (25.4)	851 (23.6)	357 (23.3)	645 (23.1)	564 (24.2)
Other	233(4.5%)	171 (4.8)	59 (3.7)	178 (4.3)	42 (4.2)	174 (4.8)	55 (3.6)	138 (4.9)	89 (3.8)
Employment									
Employed	1775 (34.7%)	1330 (38.1)	419 (26.7)	1463 (36.2)	293 (29.3)	1330 (37.4)	429 (28.0)	1041 (37.8)	711 (30.6)
Retired	2187 (42.7%)	1525 (43.7)	621 (39.5)	1816 (44.9)	317 (31.7)	1591 (44.9)	568 (37.1)	1226 (44.6)	921 (39.6)
Unemployed	1156 (22.6%)	634 (12.6)	508 (32.3)	763 (18.9)	372 (37.2)	637 (17.9)	506 (33.1)	484 (17.6)	656 (28.2)
Smoking									
No	1911 (37.3%)	1365 (39.0)	518 (33.0)	1542 (38.2)	340 (34.0)	1402 (39.4)	486 (31.8)	1038 (37.7)	842 (36.2)
Current	371 (7.2%)	212 (6.1)	153 (9.7)	256 (6.3)	109 (10.9)	203 (5.7)	165 (10.8)	158 (5.7)	210 (9.0)
Past	2842 (55.5%)	1920 (54.9)	875 (55.7)	2240 (55.5)	541 (54.1)	1951 (54.9)	860 (56.2)	1559 (56.6)	1239 (53.2)
Medication	874 (17.5%)	418 (12.2)	548 (34.9)	505 (12.7)	350 (35.0)	342 (9.8)	529 (34.6)	309 (11.5)	557 (23.4)
BMI (kg/m^2)	29.8 ±6.6	29.8 ±6.6	30.3 ±6.9	29.6 ±6.4	30.9 ±7.3	29.5 ±6.3	30.5 ±7.2	29.4 ±6.3	30.2 ±6.9
Depression History	883 (19.2%)	415 (13.2)	660 (43.1)	487 (13.5)	380 (38.0)	322 (10.1)	550 (32.3)	312 (12.6)	562 (24.2)
Previous MI	1350 (30.1%)	861 (27.9)	567 (36.1)	1021 (28.8)	308 (30.8)	863 (27.6)	473 (30.9)	676 (28.0)	651 (28.0)
Diabetes	1526 (33.4%)	984 (31.4)	507 (32.3)	1171 (32.5)	317 (31.7)	1030 (32.4)	474 (31.0)	756 (30.9)	740 (31.8)
Hypertension	3411 (70.1%)	2292 (68.8)	1064 (67.7)	2669 (69.4)	676 (67.6)	2346 (69.3)	1023 (66.9)	1776 (68.0)	1584 (68.1)

Baseline Characteristics	All N=5200	No Interest (0) n=3545	(1,2,3) n=1572	Feeling Bad (0) n=4103	(1,2,3) n= 1000	Depression (0) n=3610	(1,2,3) n=1530	Sleep (0) n=2794	(1,2,3) n=2327
Hyperlipidemia	2996 (63.1%)	2011 (63.1)	944 (60.1)	2371 (63.0)	581 (58.1)	2053 (62.0)	910 (59.5)	1608 (62.8)	1349 (58.0)

*Age and BMI are continuous variables. All categorical variables in parenthesis are in percentages.

Table 1B: Baseline Characteristics by Depressive Symptom

Baseline Characteristics	All N=5200	Feeling Tired (0) n=1784	(1,2,3) n=3358	No Appetite (0) n=3612	(1,2,3) n=1509	Prob Speaking (0) n=4282	(1,2,3) n=822	No Concentration (0) n=4000	(1,2,3) n=1131
Age (Years)	61.7 ±13.4	61.3 ±13.0	61.9 ±13.4	62.0 ±13.1	60.9 ±14.0	61.7 ±13.3	61.4 ±13.6	62.0 ±13.4	60.0 ±13.2
Female	1974 (37.6%)	516 (28.9)	1412 (42.0)	1227 (34.0)	695 (46.1)	1550 (36.2)	346 (42.1)	1411 (35.3)	507 (44.8)
Race									
White	3732 (71.9%)	1186 (66.5)	2512 (74.8)	2644 (73.2)	1035 (68.6)	3074 (71.9)	589 (71.7)	2866 (71.7)	818 (71.6)
Black	1227 (23.6%)	499 (28.0)	707 (21.1)	801 (22.2)	403 (26.7)	1005 (23.5)	198 (24.1)	948 (23.7)	261 (23.1)
Other	233(4.5%)	98 (5.5)	132 (3.9)	166 (4.6)	64 (4.2)	197 (4.6)	33 (4.0)	182 (4.8)	48 (4.2)
Employment									
Employed	1775 (34.7%)	709 (40.4)	955 (28.4)	1347 (37.9)	410 (27.2)	1567 (37.2)	191 (23.2)	1443 (36.6)	325 (28.7)
Retired	2187 (42.7%)	744 (42.4)	1413 (42.1)	1553 (43.7)	591 (39.2)	1809 (42.9)	325 (39.5)	1723 (43.8)	427 (37.8)
Unemployed	1156 (22.6%)	302 (17.2)	838 (24.9)	655 (18.4)	484 (32.1)	842 (20.0)	291 (35.4)	772 (19.6)	372 (32.9)
Smoking									
No	1911 (37.3%)	676 (38.5)	1219 (36.3)	1361 (38.2)	522 (34.6)	1608 (38.1)	271 (33.0)	1489 (37.9)	499 (44.1)
Current	371 (7.2%)	95 (5.4)	274 (8.2)	228 6.4)	139 (9.2)	283 (6.7)	82 (10.0)	260 (6.6)	106 (9.4)
Past	2842 (55.5%)	985 (56.1)	1819 (54.2)	1971 (55.4)	826 (54.7)	2327 (55.2)	459 (55.8)	2185 (55.5)	617 (54.6)
Medication	874 (17.5%)	161 (9.4)	699 (20.8)	438 (12.6)	427 (28.3)	605 (14.6)	258 (31.4)	477 (12.3)	384 (34.0)
BMI (kg/m^2)	29.8 ±6.6	29.2 ±6.1	30.1 ±6.7	29.5 ±6.3	30.4 ±7.1	29.7 ±6.5	30.2 ±6.9	29.7 ±6.5	30.1 ±6.9

Baseline Characteristics	All N=5200	Feeling Tired (0) n=1784	Feeling Tired (1,2,3) n=3358	No Appetite (0) n=3612	No Appetite (1,2,3) n=1509	Prob Speaking (0) n=4282	Prob Speaking (1,2,3) n=822	No Concentration (0) n=4000	No Concentration (1,2,3) n=1131
Depression History	883 (19.2%)	168 (10.6)	701 (20.9)	459 (14.3)	413 (27.4)	598 (15.8)	272 (31.2)	492 (14.0)	379 (33.5)
Previous MI	1350 (30.1%)	416 (27.4)	920 (27.4)	899 (28.4)	441 (29.2)	1080 (29.0)	249 (30.3)	1012 (29.2)	324 (20.7)
Diabetes	1526 (33.4%)	475 (30.6)	1033 (30.8)	993 (31.2)	507 (33.6)	1215 (32.2)	282 (34.3)	1153 (32.8)	349 (30.9)
Hypertension	3411 (70.1%)	1137 (68.7)	2234 (66.5)	2328 (68.9)	1032 (68.4)	2785 (69.3)	564 (68.6)	2603 (69.5)	763 (67.5)
Hyperlipidemia	2996 (63.1%)	974 (60.0)	1997 (59.5)	2056 (62.2)	902 (59.8)	2450 (62.3)	496 (60.3)	2300 (62.8)	666 (58.9)

*Age and BMI are continuous variables. All categorical variables in parenthesis are in percentages.

Table 2: Baseline Characteristic by Depressive Symptom Group

Baseline Characteristics	None N=1278	Low N=3394	High N=528
Age (Years)	62.0 ±13.0	61.9 ±13.5	59.4 ±13.7
Female	360 (28.2%)	1339 (39.5%)	250 (47.4%)
Race			
White	863 (67.6%)	2490 (73.5%)	379 (72.1%)
Black	345 (27.0%)	754 (22.3%)	128 (24.3%)
Other	69 (5.4%)	145 (4.3%)	19 (3.6%)
Employment Status			
Employed	513 (41.0%)	1146 (34.2%)	116 (22.3%)
Retired	544 (43.5%)	1464 (43.7%)	179 (34.4%)
Unemployed	193 (15.4%)	738 (22.0%)	22.5 (43.3%)
Smoking			
No	490 (39.0%)	1258 (37.6%)	163 (31.2%)
Current	60 (4.8%)	241 (7.2%)	70 (13.4%)
Past	708 (56.3%)	1844 (55.2%)	290 (55.5%)
Medication	82 (6.7%)	558 (17.1%)	234 (45.6%)
BMI (kg/m^2)	29.0 ±6.0	30.0 ±6.6	30.8 ±7.4
Depression History	83 (7.4%)	553 (18.4%)	247(51.4%)
Previous MI	279 (26.1%)	904 (30.4%)	167 (37.1%)
Diabetes	324 (29.4%)	1023 (34.0%)	180 (39.0%)
Hypertension	792 (67.2%)	2251 (70.3%)	368 (75.3%)
Hyperlipidemia	693 (60.2%)	1985 (63.4%)	318 (67.5%)

*Depression Symptoms combined and treated as categorical Variable for analysis.

Table 3A: Univariable Competing Risk Analysis of Hospitalization for Re-vascularization

Baseline Characteristics	HR	95% CI	p-Value
Age	1.02	1.01, 1.02	<.0001
Sex	1.65	1.47, 1.85	<.0001
Race			
White Vs Black	1.25	1.11, 1.43	0.0009
Other Vs Black	0.95	0.71, 1.26	0.7337
Employment			
Retired vs Unemployed	0.85	0.74, 1.00	0.0335
Employed vs Unemployed	1.21	1.05, 1.38	0.0070
Smoking			
No vs current	0.84	0.68, 1.05	0.1113
Past vs current	1.04	0.85, 1.28	0.7183
Medication	0.83	0.71, 0.95	0.0104
BMI	1.00	0.99, 1.00	0.1919
Depression History	0.89	0.77, 1.02	0.0956
Previous MI	1.80	1.61, 2.02	<.0001
Diabetes	1.33	1.18, 1.48	<.0001
Hypertension	1.23	1.09, 1.39	0.0007
Hyperlipidemia	1.35	1.20, 1.51	<.0001
Depressive Symptoms			
Low vs None	1.01	0.90, 1.14	0.8903
High Vs None	1.11	0.92, 1.34	0.2804

*Age and BMI are continuous variables, depressive symptoms and outcome were combined and treated as categorical variables.

Table 3B: Univariable Competing Risk Analysis of Hospitalization for Heart Failure

Baseline Characteristics	HR	95% CI	p-Value
Age	1.02	1.01, 1.03	<.0001
Sex	0.87	0.73, 1.05	0.1585
Race			
White vs Black	0.81	0.66, 1.00	0.0454
Other vs Black	1.04	0.68, 1.56	0.8375
Employment			
Retired vs Unemployed	0.68	0.53, 0.87	0.0024
Employed vs Unemployed	1.12	0.89, 1.41	0.3305
Smoking			
No vs current	1.55	1.02, 2.48	0.0514
Past vs current	1.44	0.96, 2.29	0.1008
Medication	1.00	0.73, 1.27	0.9857
BMI	0.99	0.97, 1.00	0.0450
Depression History	1.11	0.87, 1.40	0.3746
Previous MI	0.89	0.70, 1.12	0.3115
Diabetes	1.10	0.89, 1.35	0.3664
Hypertension	0.97	0.80, 1.19	0.7574
Hyperlipidemia	0.84	0.69, 1.03	0.0847
Depressive Symptoms			
Low vs None	1.20	0.96, 1.51	0.1103
High Vs None	1.69	1.23, 2.30	0.0011

*Age and BMI are continuous variables, depressive symptoms and outcome were combined and treated as categorical variables.

Table 3C: Univariable Competing Risk Analysis of Hospitalization for all Other Reasons

Baseline Characteristics	HR	95% CI	p-Value
Age	1.01	1.01, 1.02	<.0001
Sex	0.91	0.83, 1.01	0.0788
Race			
White vs Black	0.8	0.71, 0.89	<.0001
Other vs Black	0.6	0.45, 0.79	0.0005
Employment			
Retired vs Unemployed	0.61	0.53, 0.7	<.0001
Employed vs Unemployed	0.95	0.84, 1.08	0.4319
Smoking			
No vs current	0.74	0.61, 0.90	0.0021
Past vs current	0.86	0.72, 1.04	0.1148
Medication	1.05	0.92, 1.19	0.4700
BMI	1.00	0.99, 1.01	0.6790
Depression History	1.06	0.92, 1.21	0.4067
Previous MI	1.36	1.20, 1.53	<.0001
Diabetes	1.28	1.14, 1.43	<.0001
Hypertension	1.22	1.09, 1.37	0.0009
Hyperlipidemia	1.12	1.00, 1.25	0.0432
Depressive Symptoms			
Low Vs None	1.17	1.04, 1.33	0.0091
High Vs None	1.12	0.92, 1.36	0.2489

*Age and BMI are continuous variables, depressive symptoms and outcome were combined and treated as categorical variables.

Table 3D: Univariable Competing Risk Analysis of All cause Mortality-Death

Baseline Characteristics	HR	95% CI	p-Value
Age	1.04	1.03, 1.06	<.0001
Sex	1.22	0.94, 1.59	0.1448
Race			
White vs Black	1.53	1.10, 2.18	0.0159
Other vs Black	0.59	0.21, 1.37	0.2734
Employment			
Retired vs Unemployed	0.28	0.18, 0.41	<.0001
Employed vs Unemployed	1.07	0.8, 1.45	0.6637
Smoking			
No vs current	0.56	0.35, 0.93	0.019
Past vs current	0.83	0.54, 1.34	0.4124
Medication	1.32	0.96, 1.78	0.0754
BMI	0.96	0.93, 0.98	0.0002
Depression History	1.26	0.91, 1.71	0.1474
Previous MI	2.00	1.51, 2.63	<.0001
Diabetes	1.47	1.12, 1.93	0.0052
Hypertension	1.38	1.03, 1.87	0.0326
Hyperlipidemia	0.86	0.66, 1.12	0.2561
Depressive Symptoms			
Low Vs None	1.30	0.94, 1.82	0.1243
High Vs None	2.86	1.90, 4.30	<.0001

*Age and BMI are continuous variables, depressive symptoms and outcome were combined and treated as categorical variables.

Table 4A: Multivariable Competing Risk Analysis of Hospitalization for Re-vascularization

Parameter	Estimate	HR	CI	p=Value
Age	0.014	1.01	1.01, 1.02	<0.0001
Sex	0.49	1.63	1.43, 1.86	<0.0001
Status				
Employed Vs Unemployed	-0.23	0.79	0.67, 0.93	0.0052
Retired Vs Unemployed	-0.14	0.87	0.73, 1.05	0.1385
MI History	0.45	1.56	1.38, 1.76	<0.0001
Diabetes	0.15	1.16	1.03, 1.31	0.0163

Table 4B: Multivariable Competing Risk Analysis of Hospitalization for Heart Failure

Parameter	Estimate	HR	CI	p=Value
Group				
Low Vs None	0.17	1.18	0.94, 1.51	0.168
High Vs None	0.49	1.64	1.15, 2.31	0.0055
Age	0.02	1.02	1.01, 1.03	<0.0001
Hyperlipidemia	-0.3	0.74	0.61, 0.9	0.0029

*For group, depressive symptoms and outcome were combined and treated as categorical variables.

Table 4C: Multivariable Competing Risk Analysis of Hospitalization for all Other Reasons

Parameter	Estimate	HR	CI	p=Value
Age	0.01	1.01	1.01, 1.02	<0.0001
Race				
White Vs Black	-0.21	0.81	0.71, 0.93	0.0023
Other Vs Black	-0.35	0.71	0.51, 0.96	0.0296
Status				
Employed Vs Unemployed	-0.41	0.66	0.57, 0.78	<0.0001
Retired Vs Unemployed	-0.17	0.85	0.71, 1.01	0.0608
Smoking				
No Vs Current	-0.28	0.75	0.61, 0.94	0.0101
Past Vs Current	-0.21	0.81	0.66, 1.00	0.0460
MI History	0.2	1.23	1.08, 1.39	0.0012

*For group, depressive symptoms and outcome were combined and treated as categorical variables.

Table 4D: Multivariable Competing Risk Analysis of All cause Mortality-Death

Parameter	Estimate	HR	CI	p=Value
Group				
Low Vs None	0.25	1.28	0.88, 1.92	0.2133
High Vs None	1.20	3.31	2.02, 5.42	<0.0001
Age	0.04	1.04	1.03, 1.06	<0.0001
Sex	0.47	1.60	1.16, 2.22	0.0048
Status				
Employed vs Unemployed	-1.15	0.32	0.20, 0.50	<0.0001
Retired Vs Unemployed	-0.68	0.51	0.33, 0.79	0.0027
BMI	-0.04	0.96	0.93, 0.99	0.0036
Diabetes	0.37	1.45	1.05, 2.01	0.0243
MI History	0.41	1.50	1.08, 2.07	0.0134
Hyperlipidemia	-0.49	0.61	0.45, 0.84	0.0018

*Depressive symptoms and outcome were combined and treated as categorical variables.

Chapter 3

Future Directions and Public Health Implications

This study can be considered as a pilot study to assess all cause death, hospitalization in patients for re-vascularization, Heart Failure and other reasons related to heart disease, who reported depressive symptoms at baseline. Management of depressive symptoms clinically is important to minimize the harmful effects of heart disease. There is a need to categorize patients to assess the risk in patients with no history of CVD (28). Prevalence of heart disease is 40% more in patients having major depressive disorder. Complexity and cost involved will make it harder to study exact mortality rates but understanding biological and clinical mechanisms involved in the bidirectional relation between CVD and depression will reduce health care costs (29). Females are disproportionately effected when both depression and CVD are present, and prevalence of CVD is 70% more in females diagnosed with depression. Studies indicated multidisciplinary approach with systematic screening for depression, use of antidepressants, behavioral cognitive therapy might be beneficial and cost effective rather than therapeutic intervention alone(31). Focusing on psychosocial stress and making lifestyle changes while mitigating for depressive symptoms should be a routine practice for controlling CVD in older adults.

The inter relationship between cardiovascular disease and depression has been well established and depression is listed as a risk factor but the implication of antidepressants remain very contentious (17 - 19). Use of certain class of antidepressants that inhibit serotonin reuptake have shown to reduce the risk of myocardial infarction whereas, the risk was increased with Lofepramine (19). One more study suggests that adverse events and contraindications should be studied in older patients with CVD before treating them with new antidepressants by

constantly monitoring blood pressure(17). Study published in Journal of American heart association indicated that there is no reduced risk of CVD when different classes of antidepressants were prescribed and concluded that there is no protective effect when selective serotonin reuptake inhibitors (SSRI) were used compared to the other antidepressants. High affinity of SSRI's for the Serotonin transporter have shown to lower the risk of ischemic stroke by reducing platelet activity in patients (20).

Various studies imply that 67% of the adults older than 50 years diagnosed with depressive disorders were reported to have a heart disease or stroke. Even though there are other traditional risk factors and genetic reasons for CVD, age has an impact of depressive symptoms and the severity of symptoms and influences the outcome in HF patients (37). Treatment for depressive symptoms followed by a stroke have shown to improve cognitive and motor skills in older adults (30).

Furthermore, a better understanding of the relation between depressive symptoms and all cause death, hospitalization due to various reasons of cardiovascular disease to minimize the greater risk of CVD hospitalization will allow for earlier intervention and additional support for those patients to start managing the symptoms during the early visits to the family practitioner and may improve mental health by reducing the associated risk of cardiovascular disease and might lessen risk of hospitalizations related to CVD, while also decreasing costs for families and hospitals within the Emory network. The five-year follow up period with larger sample size will allow for the time needed to assess inter-related affects of depressive symptoms and CVD.

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