University of the Witwatersrand

Faculty of Health Sciences

School of Medicine

THE PREVALENCE OF PSYCHOSOCIAL RISK FACTORS IN ACUTE MYOCARDIAL INFARCTION

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A research report submitted to the Faculty of Health Sciences, University of the Witwatersrand, Johannesburg in the fulfilment of the requirement for the degree of Master of Medicine in the department of Internal Medicine.

Declaration

I Denishan Govender, declare that this Thesis* is my own, unaided work. It is being submitted for the Degree of Master of Medicine in the field of Internal Medicine, at the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at any other University.

Denishan Govender

11th day of March 2021 in Parktown

Dedication

I dedicate this research to my wife Carmel and baby Sheriyana and thank them for standing beside me while doing this research. They have been my inspiration and motivation for continuing to improve my knowledge and move my career forward. The many hours I spent with this research was a sacrifice of Sheriyana's time, and even with me always being so busy she always managed to make me smile. Thank you for understanding when I often worked late and on weekends instead of playing with you. You are my Life. I'd like to thank my parents and sisters who have always taught me hard work, dedication and faith will get you anything. You can get anything you want, but you have to have faith behind all your ideas.

Presentations Arising From This Research Project

South African Heart Congress in November 2017-Sandton

ABSTRACT

Background: Psychosocial risk factors have traditionally been known to be common in patients diagnosed with acute myocardial infarction (MI). Although well studied in developed nations the role of psychosocial risk factors in patients with myocardial infarction in the African continent is extremely sparse.

Aims: The aim of this research study was to assess the prevalence of depression, anxiety and stress in patients presenting with acute MI and to compare the prevalence of these psychosocial factors with matched controls without cardiac disease at a large public academic hospital in Johannesburg, South Africa.

Methods: A case-control prospective study was conducted to determine prevalence of mild to extremely severe levels for each of the three emotional states (depression, anxiety and stress) by using the Depression Anxiety Stress Scale (DASS) as well the INTERHEART Questionnaire. Each of the study patients were matched with control patients by race, sex and with no more than 5 years difference in age. A total of 106 patients were included as study patients and matched with 106 control stable patients without myocardial infarction. Questionnaires were used to interview patients during the same admission. Stressful life events were analysed in two ways: as individual and grouped life events and each was coded as a separate category.

Results: Majority of patients in the case (acute MI) and control (non-MI) groups were between 51 - 60 years. More than 70% of the patients were over the age of 50 years. Over 80% of study patients in both groups were males. In patients with acute MI, over 85% of patients reported no depressive features and 91% did not have features of anxiety, in contrast to what was found in the INTERHEART study, findings which were similar to the control group. Self-reported stress profile of the two groups differed enormously; only 4.7% of MI patients reported normal stress levels, compared to 96.2% of controls. Stress graded as severe or very severe was found in 39.6% of patients with MI with the odds of an MI being extremely high in the group with mild to extremely severe stress compared to those with normal stress (Odds ratio: 515; 95% CI 134 to >999; p=0.0001).

Conclusions:

Depression and anxiety were not significantly more prevalent in patients with acute myocardial infarction as compared to matched controls. However, stress as assessed by both methodologies was significantly higher in patients with acute MI as compared to matched controls. Considering the increase in prevalence of traditional coronary heart disease risk factors recently, it is necessary that attention should also be focused on psychological risk factors and its preventive measures.

Keywords: Psychosocial risk factors; depression; anxiety; stress; acute myocardial infarction.

Acknowledgement:

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Academic Head of Department of Cardiology, University of Witwatersrand and Charlotte Maxeke Johannesburg Academic Hospital (at time of study)
Contribution: Acknowledgement as Study Supervisor

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Definitions and Terminology:

Bio-psychosocial: Pertaining to the complex of biological, psychological, and social aspects of life.

Depression: A mental state of altered mood characterized by feelings of sadness, despair, and discouragement.

Anxiety: Anxiety is a multisystem response to a perceived threat or danger. It reflects a combination of biochemical changes in the body, the patient's personal history and memory and social situation.

Stress: Stress is defined as an organism's total response to environmental demands or pressures.

Anger: A feeling of tension and hostility, usually caused by anxiety aroused by a perceived threat to one's self, possessions, rights or values.

Hostility: An emotional state characterized by enmity toward others and a desire to harm those at whom the antagonism is directed.

Work Stress: Any external force that acts on the body of a worker during the performance of his/her task.

1. INTRODUCTION

Myocardial infarction (MI) is a major cause of death and disability worldwide. Coronary atherosclerosis is a chronic disease with stable and unstable periods. During unstable periods, with activated inflammation in the vascular wall, patients may develop angina or even progress to MI. MI may be a minor event in a lifelong chronic disease but it may also be a major catastrophic event leading to sudden death or severe hemodynamic deterioration.

Many urban communities in South Africa have already progressed to the second phase of epidemiological transition, characterized by the increase in prevalence of coronary artery disease. Currently, 5-7 patients present with acute MI to Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) on a weekly basis. Lifestyle factors such as smoking, lack of physical activity, elevated body mass index, systemic hypertension, diabetes mellitus and dyslipidemia are all well known risk factors for coronary artery disease and have been well studied. Lifestyle modifications are often implemented and are aimed to minimize the impact of these risk factors.

Although not as well studied as the traditional risk factors, some studies have shown that a considerable amount of risk for developing MI is attributable to psychological risk factors (Rosengren *et al.*, 2004). Psychosocial intervention research that aimed at modifying psychological distress to decrease mortality in individuals with CVD have shown mixed results (Berkman *et al.*, 2003; Friedman *et al.*, 1986). It is not known if preventive reduction of psychological distress in a healthy community will ultimately reduce CVD mortality.

There is scientific evidence, dating back four centuries, regarding the brain and emotion-triggered cardiovascular changes. As early as 1628, William Harvey, an English physician, noted that "every affection of the mind that is attended either with pain or pleasure, hope or fear, is the cause of an agitation whose influence extends to the heart" (Goldstein *et al.*, 2004).

Job strain, marital conflict, family care giving, and low socio-economic circumstances are regarded as chronic psychosocial stressors have been shown to be independent risk factors for CVD (Kivimaki *et al.*, 2006; Orth-Gomer *et al.*, 2000; Pollitt *et al.*, 2005).

There is growing evidence that the prevalence of coronary artery disease (CAD) is increasing, especially in communities where the prevalence was previously low. Studies suggest that psychological factors, as independent risk factors, have an important part in physical chronic diseases, particularly coronary heart disease (Albus *et al.*, 2010; Creed *et al.*, 1999).

Psychosocial factors may affect CAD directly through neuroendocrine and platelet activation, or indirectly through higher frequency of adverse health behaviours such as smoking, poor diet, and sedentary lifestyle which in turn increase the risk of CAD.

1.1. Psychosocial Factors

Epidemiological studies in the past have shown that psychosocial factors such as depression, anxiety and stress contribute independently to the risk of coronary heart disease (Rozanski *et al.*, 2005; Dimsdale *et al.*, 2008). In one study, MI following episodes of anger, anxiety, physical activity or coffee consumption was associated with higher all-cause mortality in the following 10 years (Loes *et al.*, 2017).

Clinicians should target behavioral interventions such at smoking cessation, physical exercise and blood pressure management. These are all best achieved with both a psychotherapeutic and psychopharmacologic approach. Multimodal treatment programs will show a benefit to quality of life and a reduction in stress-related CVD morbidity and mortality (Von Kanel *et al.*, 2008).

1.1.1. Stress

Acute psychological stress is associated with increased risk for CAD, and it has been reported that intense grief in the days after death of a significant person may trigger the onset of MI (Mostofsky *et al.*, 2012). A Serbian study found that in persons who

reported that a son or other family member had been mobilized to enter military service had a 138 fold higher risk of acute MI (Deljanin *et al.*, 2007).

Dysregulation of stress response pathways and changes in the sympathetic nervous system, are some of the postulated mechanisms related to neurobiological associations with CAD (Burg *et al.*, 2014; Kendler *et al.*, 2000).

The pathophysiological mechanism of acute emotional stress in the causation of MI remains unclear, but it is assumed to be related to hemodynamic stress in the coronary arteries and rupture of an atherosclerotic plaque, with consequent thrombosis (Muller *et al.*, 1994).

1.1.2. Depression

Depression is a risk factor for morbidity and mortality in patients with coronary heart disease, especially following acute coronary syndrome (Brezinka *et al.*, 1996; Creed *et al.,* 1999; Radloff *et al.,* 1977; Lesperance *et al.*, 2000). Depression results in an increased risk for CVD, hospital admissions and mortality (Jiang *et al.*, 2002). Depression has been found to be a risk factor for coronary artery disease (Jian *et al.*, 2002; Kuper *et al.*, 2002; Musselman *et al.*, 1998; Kubzansky *et al.*, 2000; Rugulies *et al.*, 2002). The exact mechanisms linking depression to increased CAD risk is complex and multifactorial but to date, it is not entirely understood (Penninx *et al., 2017*). A possible mechanism, is chronic inflammation, seen in patients with long standing depression. Chronic inflammation is another well-known risk factor for the development of coronary artery disease and atherosclerosis (Mason *et al.*, 2015). Another possible mechanism related to depression and coronary artery disease is increased platelet activation and resultant thrombosis (Serebruany *et al.*, 2003). The neuroendocrine, immune and inflammatory systems possibly have a common genetic pathway and when disrupted, they increase the risk for both depression and coronary artery disease.

1.1.3. Anxiety

There is increasing evidence suggesting that anxiety is a predictor of cardiovascular events (Olafiranye O *et al.*, 2011). However, the association between anxiety and CAD

has been shown to be less significant than depression and CAD (Roest *et al.*, 2010). With regards to anger and CAD, the relationship is much stronger (Roest *et al.*, 2010). A study of physical and psychological symptoms of anxiety in patients with CAD, demonstrated that anxiety is associated with physical factors such as palpitations without any physical exercise, anger and redness in the face, abnormal heart beat, and muscle tension. These factors could lead to increased risk of CAD especially in women (Suls *et al.*, 2005). Somatic symptoms of anxiety are associated with an increased risk of CAD in women. These findings lend support to the physiological pathway for the relation between psychological factors, anxiety in particular, and coronary heart disease (Nabi *et al.*, 2010). A longitudinal study conducted over a period of 37 years on 49321 young Swedish men aged 18-20 years evaluated the effects of anxiety and early depression on risk factors of coronary artery disease (Janszky *et al.*, 2010). This study revealed that both anxiety and depression were associated with low physical activity and high rate of cigarette smoking. Depression was also associated with high levels of alcohol consumption and anxiety had an association with elevated blood pressure. This study suggested that anxiety is an independent risk factor and can predict subsequent CAD events.

A few mechanisms have been proposed regarding association of anxiety and CAD. These include sympathetic activation, impaired vagal control, reduced heart rate variability, stimulation of the hypothalamic pituitary axis, hyperventilation-induced coronary spasm, oxidative stress, increased inflammatory mediators, neuro-hormonal and behavioural pathways or unhealthy lifestyle (Olafiranye *et al.*, 2011).

Some patients have higher levels of anxiety and therefore have an increased risk for cardiovascular events. Anxiety can even follow a cardiac event, can impede recovery, and is associated with a higher morbidity and mortality. Mechanisms linking anxiety to CV disease can be categorized broadly into two pathway, that is, the neuro-hormonal and behavioural pathway.

1.2 Neuro-hormonal Pathway

The link between anxiety and cardiovascular disease is manifested by impaired vagal control, elevation in cytokines, high cortisol levels and a reduction in heart rate

variability. This is all a result of activation of sympathetic nervous system (Boyd *et al.*, 1984; Kawachi *et al.*, 1995; Gold *et al.*, 1986; Roberts *et al.*, 1992). Negative emotions can have cumulative effects on the body. This is thought to be through damage from persistent activation of the neurohormonal systems (Everson-Rose *et al.*, 2005; Kubzansky *et al.*, 2000; Rozanski *et al.*, 2005). It has also been shown that there is a decrease in the number of lymphocyte beta-adrenergic receptors (Albus *et al.*, 1986; Aronson *et al.*, 1989) and beta-adrenergic- mediated cyclic AMP generation in patients with anxiety disorder, especially in the context of panic disorder (Charney *et al.*, 1989; Lima *et al.*, 1983).

Patients who have panic attacks often have baseline catecholamine levels that are normal or slightly elevated (Cameron *et al.*, 1988; Cameron *et al.*, 1990). An interesting investigation in which isoproterenol was given to patients with panic disorders and it was found that patients' heart rates increased minimally. This supported the concept that patients with chronic anxiety have an increased sympathetic outflow which in turn leads to beta-adrenergic receptor down regulation and thus poor response to isoproterenol (Nesse *et al.*, 1984). The link between anxiety and reduced heart rate variability has also been shown in a study in patients previously identified as high risk for cardiovascular disease (Kawachi *et al.*, 1995). Thus with increased anxiety symptoms, there is a corresponding decrease in heart rate variability. Interestingly, studies have shown that anxiety and sudden cardiac death, is not necessarily only due to acute myocardial infarction, but may also be related to ventricular arrhythmias (Haines *et al.*, 1987; Kawachi *et al.*, 1994). Autonomic alteration which results in increased sympathetic stimulation has been linked to arrhythmias and sudden death (Lown *et al.*, 1973; Farrell *et al.*, 1987; Rich et al., 1988). Reduced vagal control has also been associated with impaired vagally mediated baro-reflex control of the heart (Vanoli *et al.*, 1991). Thus autonomic dysregulation appears to be a particularly important risk factor for sudden death (Billman *et al.*, 1991; DeFerrari *et al.*, 1995; Watkins *et al.*, 1994). Insomnia, which has been shown to be a form of chronic stress and sympathetic disorder, is in part responsible for the association between anxiety and CV symptoms (Olafiranye *et al.*, 2010). Furthermore, an atherogenic pathway, promoted by recurring activation of the neuro-hormonal system with subsequent endothelial injury and atherosclerosis, has also been suggested (Paterniti *et al.*, 2001).

The mechanism by which depression increases CAD risk is unclear. Depression is associated with stress (Kendler *et al.*, 2000) and patients with major depression show alterations in stress responsive neuro-hormonal systems, including cortisol and norepinephrine (Bremner *et al.*, 2003). Proposed mechanisms linking depression to coronary heart disease via the neuro-hormonal systems include, amongst others, abnormal regulation of stress-response pathways which can contribute to CAD in vulnerable individuals (Kendler *et al.*, 2000). These mechanisms results in changes in sympathetic nervous system and neuro-hormonal function as well as alterations in central brain function (Veith *et al.*, 1994). Stress, whether it being acute or chronic, results in a neurochemical dysfunction, and eventually in abnormalities in the synthesis or activity of neuro-hormones like serotonin, norepinephrine or dopamine (Adell *et al.*, 1988). This may then influence mood and cardiovascular risk (Adell *et al.*, 1988). Neuro-endocrine alterations are related to depression and results from alterations in adrenocorticotropic (ACTH) and the response to corticotropin-releasing factor (CRF), and enhanced adrenal responses to ACTH, elevated circulating cortisol levels and cytokines (Froger *et al.*, 2004).

1.3 Behavioural Pathway

Various lifestyle behaviours, including sedentary diet, physical inactivity and tobacco use, enhance the development and clinical manifestations of CAD (Rozanski *et al.*, 1999). Studies suggest that individuals with anxiety disorders are prone to unhealthy lifestyle behaviours (Rozanski *et al.*, 1999; Kannel *et al.,* 1998). Negative emotions may exacerbate disease progression or reduce survival, either via direct physiological effects or through non-compliance of the recommended medical therapy (Kubzansky *et al.*, 2006; DiMatteo *et al.*, 2000). Negative emotions are also associated with unhealthy lifestyle in patients with CHF (Konstam *et al.*, 2005). Anxiety may demotivate patients to engage in self-care behaviours (Kubzansky *et al.*, 2006). Patients with high levels of anxiety have difficulty making lifestyle changes, coping with challenges and encounter more problems during cardiac rehabilitation (Maeland *et al.*, 1989; Rose *et al.*, 1994; Lane *et al.*, 2001). Patients with anxiety are more prone to be poorly compliant to medical therapy as well as poor adherence to lifestyle change recommendations (Schweitzer *et al.*, 2007). Patients admitted with high levels of anxiety and recent exacerbations of congestive heart failure demonstrated poor self-

care behaviours. Only 34% of patients were compliant on all treatment that was prescribed (Moser *et al.*, 2005).

2. AIMS

The aim of the study was to assess the prevalence of depression, anxiety and stress in patients presenting with acute myocardial infarction to Charlotte Maxeke Johannesburg Academic Hospital and to compare the prevalence of psychosocial factors with matched controls without cardiac disease.

3. METHODS

This was a prospective case-controlled study and the sample size used was based on a prevalence of mild to extremely severe levels for each of the three DASS emotional states (depression, anxiety and stress) of 15%, an odds ratio of 2.6 (based on the INTERHEART study), and 80% power at 5% significance level. The minimal sample size required was 206 (103 patients with MI and 103 control patients).

Patients newly diagnosed with acute MI who were hospitalized at the cardiac unit at CMJAH and who met the inclusion criteria of the study were enrolled over 18 months. Diagnosis of acute MI was made by attending cardiologists and based on typical chest pain symptoms plus either elevations in cardiac enzyme concentrations or diagnostic changes on electrocardiogram according to criteria of the World Health Organization (WHO) (Roffi *et al.*, 2016). Each of the study patients were matched with control patients for race, sex and age (difference of not more than 5 years). The number of study patients included were 106 and these were matched with 106 control patients making a total of 212 patients. Cases were excluded from the study if they had a previous history of MI or if the patients were physically or mentally unable to answer questions. For each study patient, a matched control was selected from stable patients that were being reviewed in other disciplines such as oncology, surgery, hypertension clinics, orthopaedic clinics and gastrointestinal clinics.

Two questionnaires (Appendix A and B) were used to interview patients and controls face-to-face during the index admission. This was done to ensure that the interview was thorough. The first questionnaire was one which was used in the INTERHEART

study (Yusuf S *et al.*, 2004). Permission for use of the INTERHEART questionnaire was granted by the study head (Appendix C) The INTERHEART study questionnaire involves a validated set of questions that evaluate a population of patients with classical cardiac risk factors and psychological risk factors. It also allowed inclusion of demographic data, socioeconomic status, social habits, personal and family history of any cardiovascular disease and risk factors. Standard physical measurements, such as height, weight, waist, hip circumference and pulse rate were collected by the same examiner to maintain standardisation. To avoid homogeneity in the psychological responses, the Depression Anxiety Stress Scale (DASS) was also applied for study patients and controls. The DASS questionnaire was developed by researchers at the University of New South Wales (Australia) for life events (Lovibond et al., 1995). It follows a 3-point Likert scale of frequency or severity of the participants' experiences over the previous week of an event with the intention of emphasizing states over traits. These scores ranged from 0, meaning that the patient believed the item "did not apply to them at all", to 3 meaning that the patient considered the item "applies to them very much, or most of the time".

All patients were interviewed by the author. Stressful life events were analysed in two ways: as individual life events and because the majority of stressful events were rare, or as grouped life events, each was coded as a separate category. Patients were interviewed about the presence of classical cardiovascular risk factors, such as current smoking, drinking alcohol, sedentary occupational physical activity, obesity, hypertension, diabetes, hyperlipidaemia, and family history of cardiovascular disease. Degree of obesity was estimated based on body mass index (BMI) and waist to hip ratio (WHR). According to WHO classifications, subjects with BMI 30 or above were classified as obese. Current smokers were defined as those who had smoked at least one cigarette per day during the previous 12 months. Subjects who had sedentary jobs or were unemployed were classified as a group with sedentary occupational physical activity.

The Ethics Committee of the University of Witwatersrand approved the study (Protocol Number: M 2010115), and oral informed consent was obtained from all participants before participating in the study.

3.1. Patient Selection

The criteria for study patient selection included:

- Patients admitted with a history of an acute MI confirmed with cardiac enzymes and/or electrocardiograph and/or echocardiogram and/or angiogram.
- Only patients who consented to partake in the study were included.

Exclusion criteria for study patients:

- If the patient declined to be part of this study.
- Patients without confirmed myocardial infarction.

The criteria for control patient selection included:

- The patient had to give consent to be part of the study.
- Patient had to have no previous history of heart disease.
- Patient had to have no cardiac symptoms at time of enrollment.
- Patient also had to have a normal ECG

Exclusion criteria for control patients included:

- Unwillingness of patient to be part of this study.
- Patients with a history of cardiac illness/disease.

3.2. Research tools

Two detailed questionnaires (Appendix A and Appendix B) were used to assess emotional and chronic stressors in both index cases and controls. The questionnaires collected data on demographic factors (country of origin, first language), socioeconomic status (education, occupation, income), lifestyle (tobacco use, physical activity, dietary patterns), and personal and family history of cardiovascular disease and risk factors.

The questionnaires were administered before the patient was discharged from hospital. The components of the questionnaire were compiled with previously validated questions included in studies of risk factors for cardiovascular disease (INTERHEART study).

Data on medications (pre-hospital, in-hospital, and discharge) and interventions were collected from hospital charts. Standard physical measurements were performed by

the same examiner on each participant: height, weight, waist, and hip circumference, blood pressure and heart rate.

The data collected included the following:

Demographic data:

- age
- sex
- ethnicity (paternal, maternal, patient)
- religion
- highest level of education (HLOE)
- employment status

Symptoms:

- Onset of symptoms
- Time of arrival at hospital after onset of symptoms

Physical measurements:

- SBP
- DBP
- Weight
- Height
- Waist circumference
- Pulse rate
- Physical activity (frequency per week)
- Duration of exercise (mins per session)

Onset of symptoms

- Time awake prior to onset of symptoms
- Whether or not symptoms woke patient
- Medication

Smoking

- Number of cigarettes smoked per day
- Smoking pack-years
- Tobacco products used

Medical history

- Family history of MI
- Other medical history
- Stress
- Depression
- Anxiety
- Hours of sleep per night
- Snoring frequency
- Snoring description
- Leisure time activity
- Work time activity

DASS questionnaire scores for

- Stress
- Depression
- Anxiety

3.3. Data and Statistical analysis

Descriptive analysis of the data was carried out as follows: Categorical variables were summarised by frequency and percentage tabulation, and illustrated by means of bar charts. Continuous variables were summarised by the mean, standard deviation, median and interquartile range, and their distribution illustrated by means of histograms.

The DASS scores were categorised in Table 1 below as follows: **Depression Anxiety and Stress Scale (DASS) Rating Scale**

The **DASS** is a 42-item questionnaire which includes three self-report scales designed to measure the negative emotional states of depression, anxiety and stress. Each of the three scales contains 14 items, divided into subscales of 2-5 items with similar content. The Depression scale assesses dysphoria, hopelessness, devaluation of life, self-deprecation, and lack of interest/involvement, anhedonia, and inertia. The Anxiety scale assesses autonomic arousal, skeletal muscle effects, situational anxiety, and subjective experience of anxious affect. The Stress scale (items) is sensitive to levels of chronic non-specific arousal. It assesses difficulty relaxing, nervous arousal, and being easily upset/agitated, irritable/over-reactive and impatient. Respondents are asked to use 4-point severity/frequency scales to rate the extent to which they have experienced each state over the past week.

Scoring: Scores of Depression, Anxiety and Stress are calculated by summing the scores for the relevant items. The depression scale items are 3, 5, 10, 13, 16, 17, 21, 24, 26, 31, 34, 37, 38, 42. The anxiety scale items are 2, 4, 7, 9, 15, 19, 20, 23, 25, 28, 30, 36, 40, 41. The stress scale items are 1, 6, 8, 11, 12, 14, 18, 22, 27, 29, 32, 33, 35, 39. The score for each of the respondents over each of the sub-scales, are then evaluated as per the severity-rating index below.

Table 1: The categories of DASS scores on depression, anxiety and stress from CVD patients

	Depression	**Anxiety**	**Stress**
Normal	0-9	0-7	0-14
Mild	10-13	8-9	15-18
Moderate	14-20	10-14	19-25
Severe	21-27	15-19	26-33
Extremely Severe	28+	20+	34+

Between-group comparisons were undertaken as matched-pairs analyses using logistic regression. The odds ratio for the presence of each risk factor in the MI group, compared to the control group, was calculated together with its 95% confidence intervals. A 5% significance level was used.

4. RESULTS:

Demographics

Age

The patients were divided into different age groups for the questionnaire and the age distribution of the patients in the case (MI) and control (non-MI) groups is shown below. More than 70% of the patients were over the age of 50 years. Majority of patients that entered the study (cases and controls) fell into the age group of 51 to 60 years being 38.7% for the cases and 31.1% for the controls.

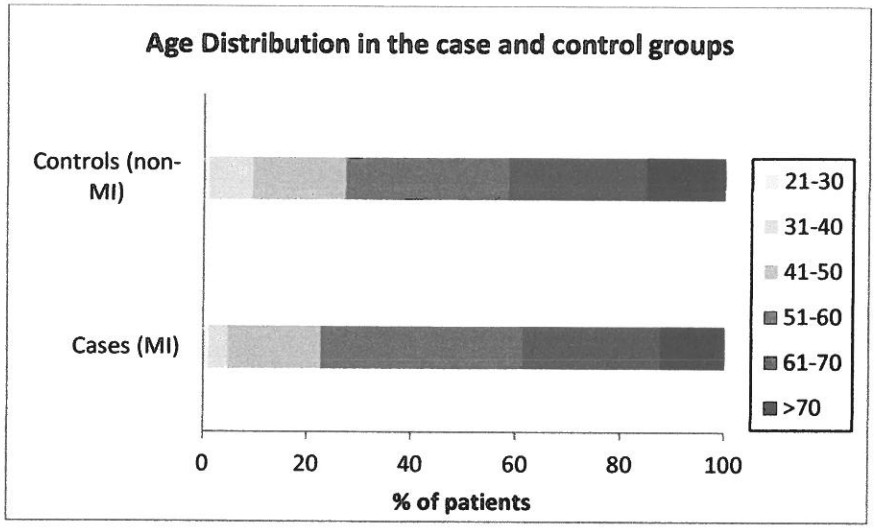

Figure 1: Age distribution in the case and control patient groups

Gender:

Both groups comprised of 81.1% males.

Ethnicity

The ethnic composition of the study group is shown below. In patients with MI, Caucasians comprised 47.2% of the cohort, followed by Indian patients who made up 24.5%.

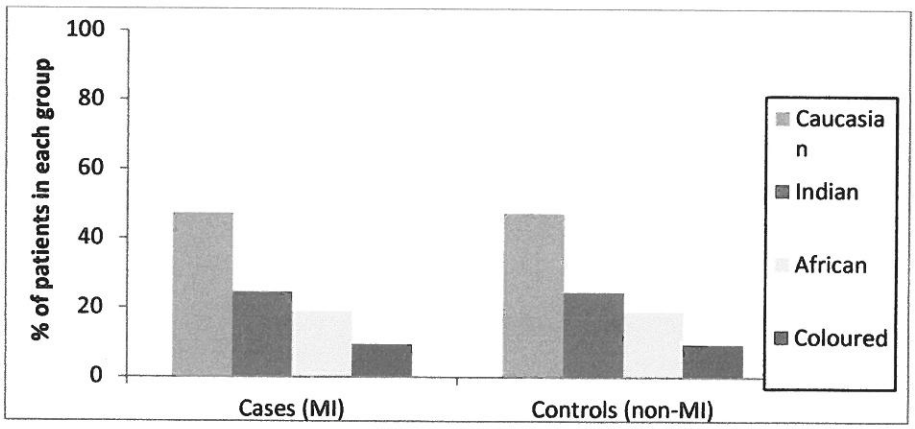

Figure 2: Patient distribution on race and ethnicity

Highest level of education (HLOE)

A HLOE of less than Grade 12 predominated in both groups.

Grade 12 (G12) was chosen as the reference category for analysis (although those with less than Grade 12 predominate, this covers a wide range of HLOE). The Degree and Diploma categories were combined, due to small group sizes.

- The odds of an MI was higher for those with less than G12 education compared to those with G12 education (Odds ratio: 3.48; 95% CI 1.82-6.65; p=0.001).
- The odds of an MI was higher for those with Degrees/Diplomas compared to those with G12 (Odds ratio: 2.96; 95% CI 1.17-7.50; p=0.022).

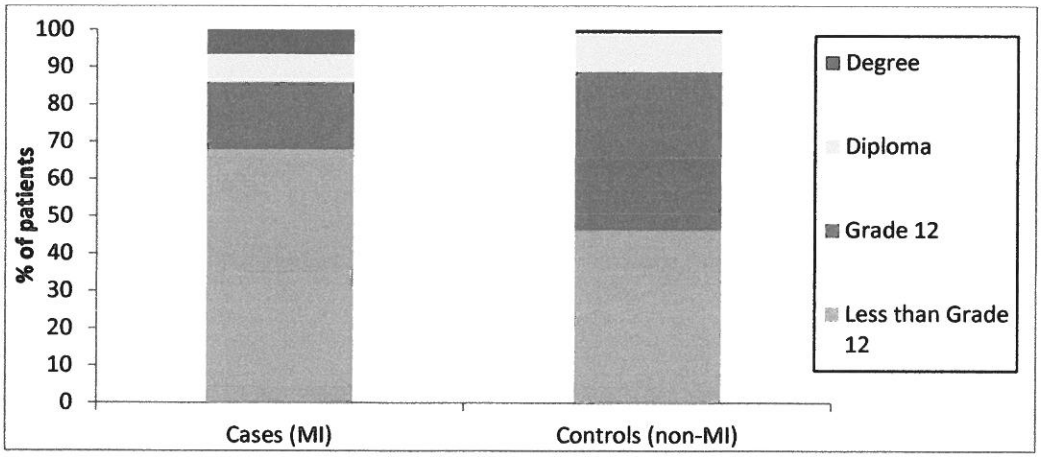

Figure 3: Level of education in patients from case (MI) and Controls (non-MI) groups

Employment

Unemployment predominated in both groups. Permanent employment was chosen as the reference category for analysis and the odds of MI were not significantly affected by employment status.

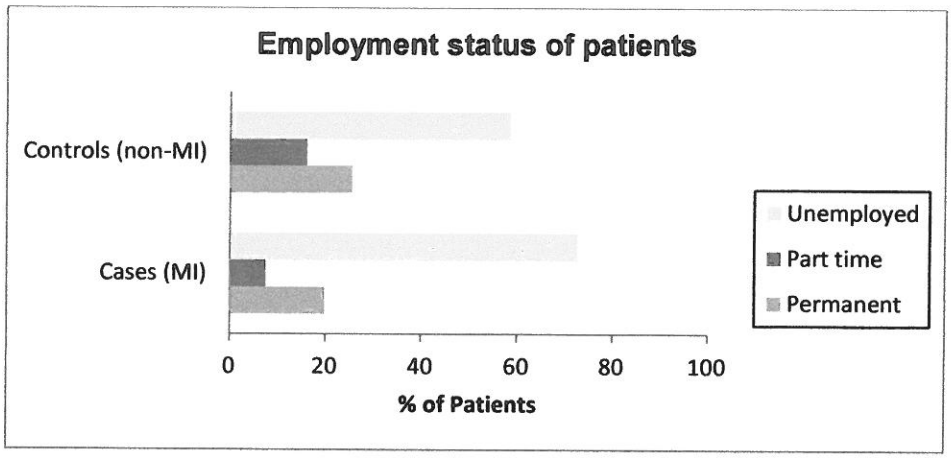

Figure 4: Showing the employment status of cases and control patient groups

MI diagnosis and factors affecting prevalence

Symptoms

The prevalence of each of the symptoms in the MI group is shown below; the most prevalent symptoms were chest pain (92.5%) and shortness of breath (70.8%).

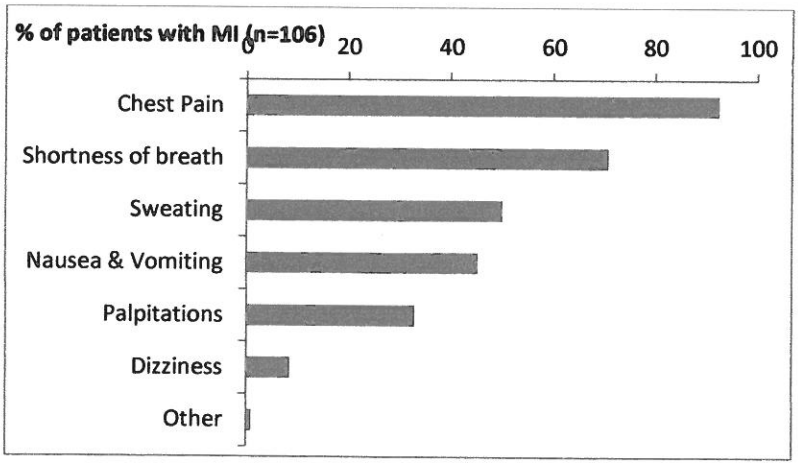

Figure 5: Symptoms experienced by case (MI) patients

Systolic blood pressure

Over 70% of the patients on both groups had SBP in the normal range.

The 120-139 mmHg category was chosen as the reference group. The 160-179 and 180-199 mmHg groups were combined, due to small group sizes. The odds of MI were not significantly affected by SBP. Odds ratio: 1.61; CI 0.37-6.94; p=0.52)

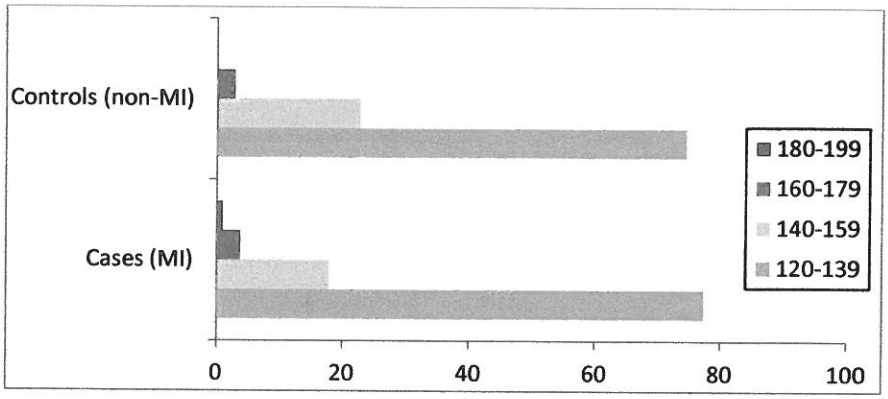

Figure 6: Showing the range of SBP in both the cases and control groups

Pulse rate

The pulse rate profile of the two groups were quite different – Fig 7.

The 60-69 bpm category was chosen as the reference group. The top three groups were collapsed due to small group sizes.

- The odds of an MI was lower for those with pulse rate 70-79 bpm compared to 60-69 bpm (Odds ratio: 0.27; 95% CI 0.12-0.62; p=0.0.02).
- The odds of MI were not significantly affected by pulse rate 80-89 bpm compared to 60-69 bpm.
- The odds of an MI was higher for those with pulse rate 90+ bpm compared to 60-69 bpm (Odds ratio: 5.24; 95% CI 1.03-26.6; p=0.046); note the wide confidence interval due to the small group size for the controls).

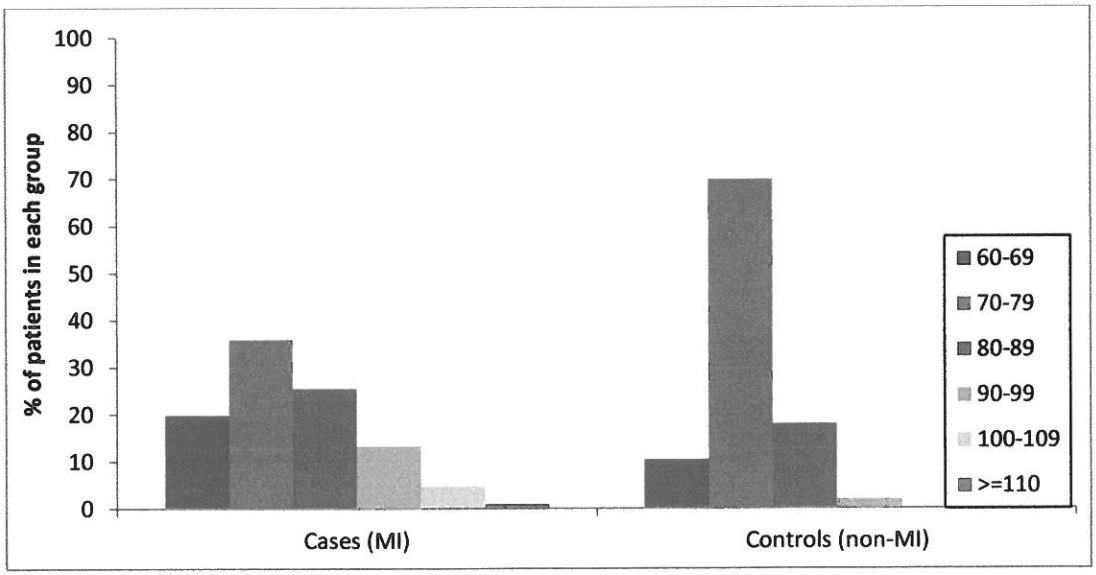

Figure 7: Distribution of pulse rate in patients in the cases and control groups

Physical exercise (sessions per week)

More than 75% of the patients in both groups did not perform any physical exercise.

The 'none' category was chosen as the reference group. The top three groups were collapsed due to small group sizes. The odds of MI were not significantly affected by exercise.

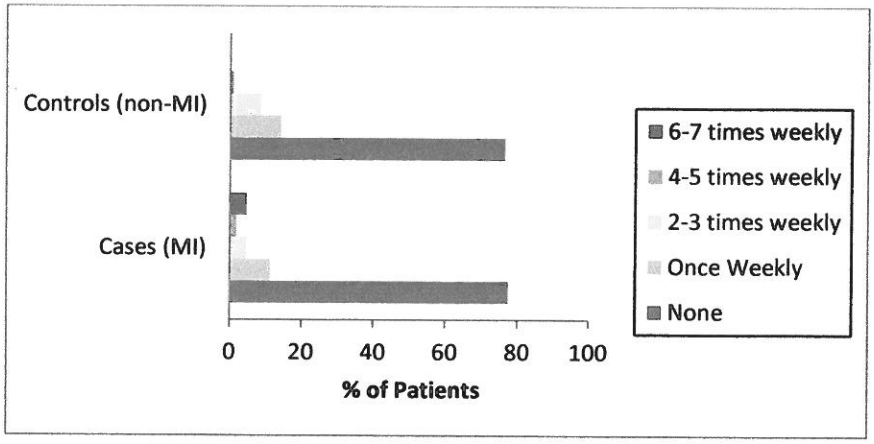

Figure 8: Weekly exercise by patients in the case (MI) and control (non-MI) groups

Daily cigarette consumption

A total of 38.7% of the cases and 60.4% of the controls patients were non-smokers. Non-smoking was used as the reference category so that 1-5 and 6-10 cigarettes per day were combined, due to small group sizes. The 'unsure' group was omitted from the analysis. The odds of MI were higher for patients who smoked, compared to non-smokers, at all three levels of cigarette use (Fig 9).

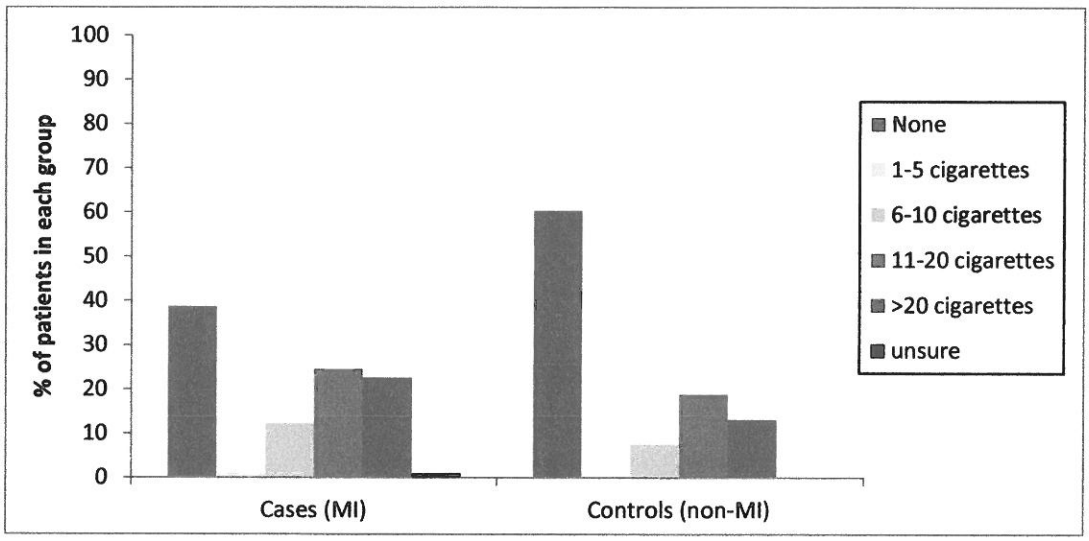

Figure 9: Showing the prevalence of smokers and non-smokers in the cases and control groups.

Smoking pack-years

Of the patient groups 39.6% of the cases and 60.4% of the controls had zero pack-years. Zero pack-years was used as the reference category such that 1-2 and 2-5 pack-years were combined, due to small group sizes (Fig 10).

- The odds of MI were not significantly affected by smoking pack-years up to 20, compared to zero pack-years.
- The odds of an MI in patients with > 20 pack year smoking history was highest (Odds ratio: 2.68; 95% CI 1.24-5.76; p=0.012).

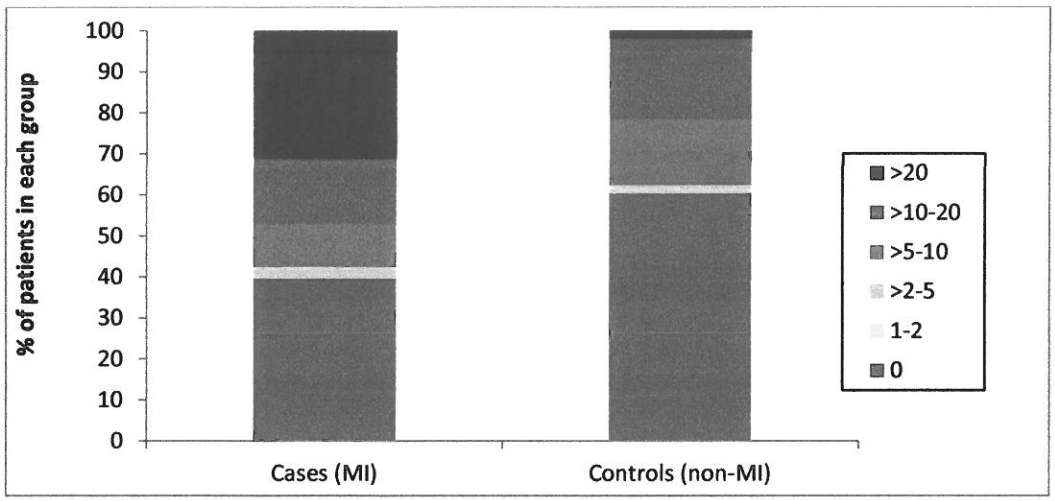

Figure 10: The number of years patients in the cases and control grops have been smoking

There were very few non-cigarette tobacco users, so no further analysis was done.

Stress *(based on the INTERHEART questionnaire)*

Patients were asked if they thought they had any stress.

It is clear that stress in the two groups differed enormously; only 4.7% of MI patients reported normal stress levels, compared to 96.2% of controls.

For analysis, the normal group was used as reference, and the mild to extremely severe groups were combined due to small group sizes.

- The odds of an MI was higher for those with mild to extremely severe stress compared to those with normal stress (Odds ratio: 515; 95% CI 134 to >999; p=0.0001).
- In the study, 37.7% of patients graded their stress as moderate followed by 26.4% of patients grading it as severe followed by mild at 17.9% and extremely severe was only 13.2%.

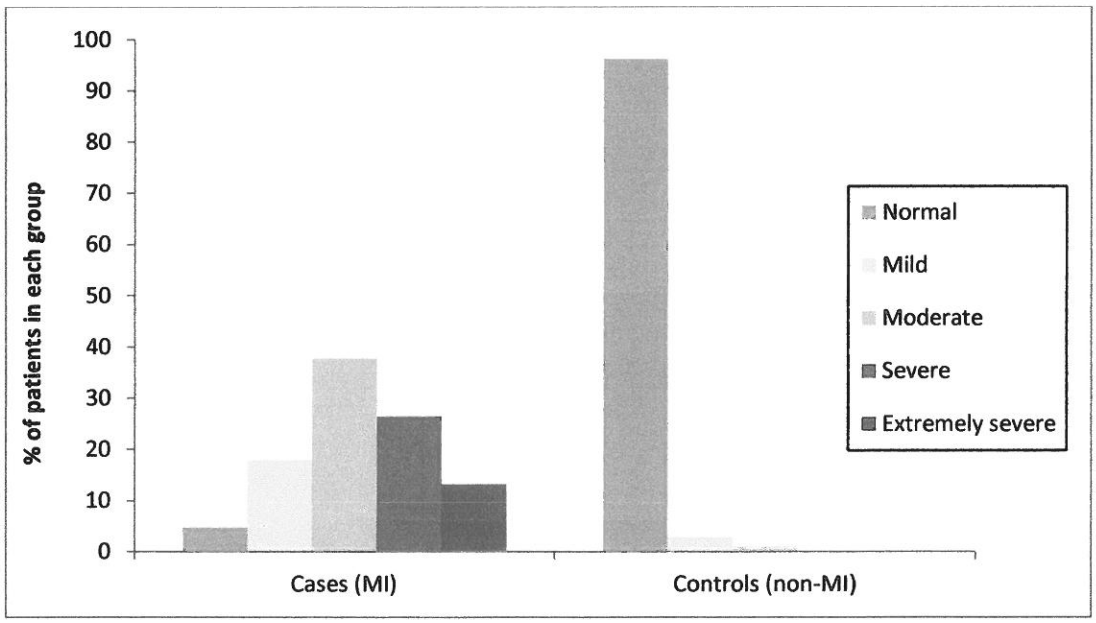

Figure 11: Percentage of patients experiencing the stress in the case and control groups

Depression *(based the INTERHEART questionnaire)*

More than 85% of both groups reported no abnormal levels of depression during the interview.

For analysis, the normal group was used as reference, and the mild to extremely severe groups were combined due to small group sizes. The odds of an MI was higher for those with mild to extremely severe depression compared to those with normal levels of depression (Odd ratio: 3.26; 95% CI 1.02-10.4; p=0.046).

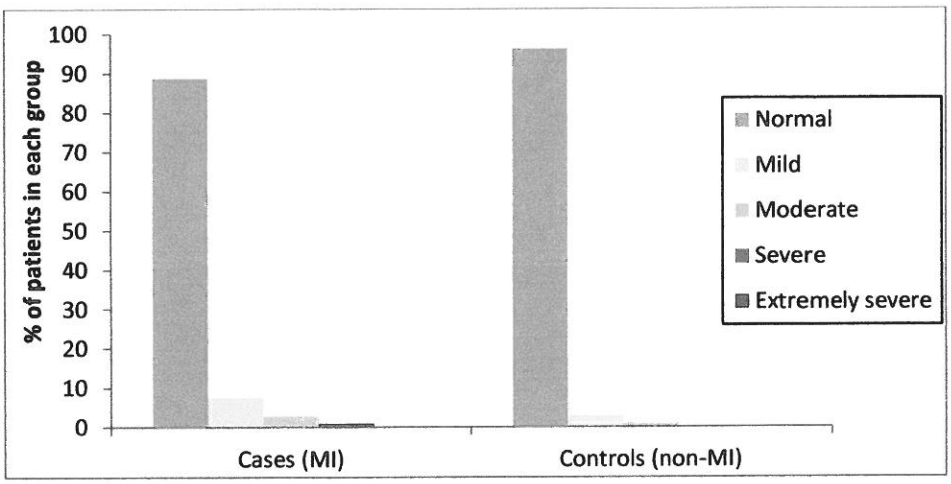

Figure 12: Percentage number of patients with depression in the cases and control factors.

Anxiety *(based on the INTERHEART questionnaire)*

- 91.5% of patients reported having no anxiety symptoms.
- No analysis was possible since there were no patients with non-normal levels of anxiety in the control group.

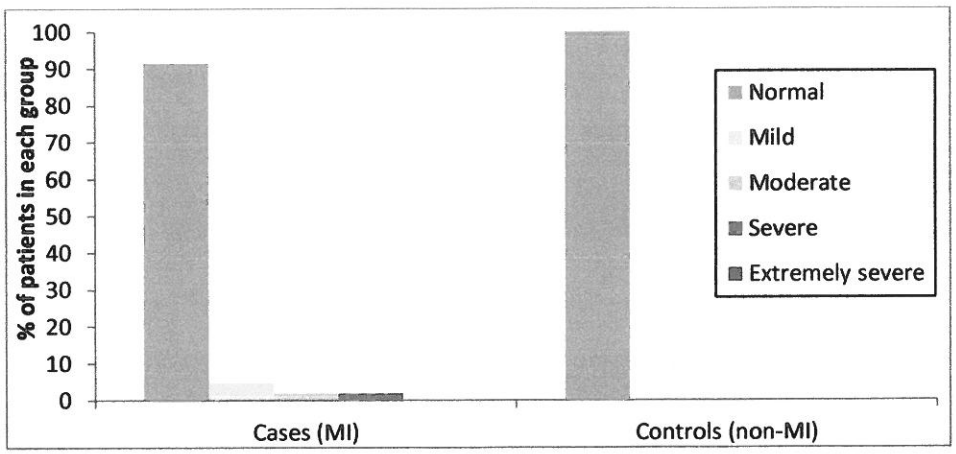

Figure 13: Percentage of patients who suffered from anxiety in the case and control groups

Work stress *(based on the INTERHEART questionnaire)*

Patients were given the opportunity to grade their work stress according to their own discretion. 29.3% of patients related severe stress to work.

- 48.1% of cases reported nil or minimal work stress levels, compared to 84.0% of controls.
- For analysis, the nil/minimal group was used as reference, and the moderate and severe groups were combined due to small group sizes.
- The odds of an MI was higher for those with moderate/severe work stress compared to those with nil/minimal stress (Odds ratio: 5.65; 95% CI 2.97-10.8; p=0.0001).

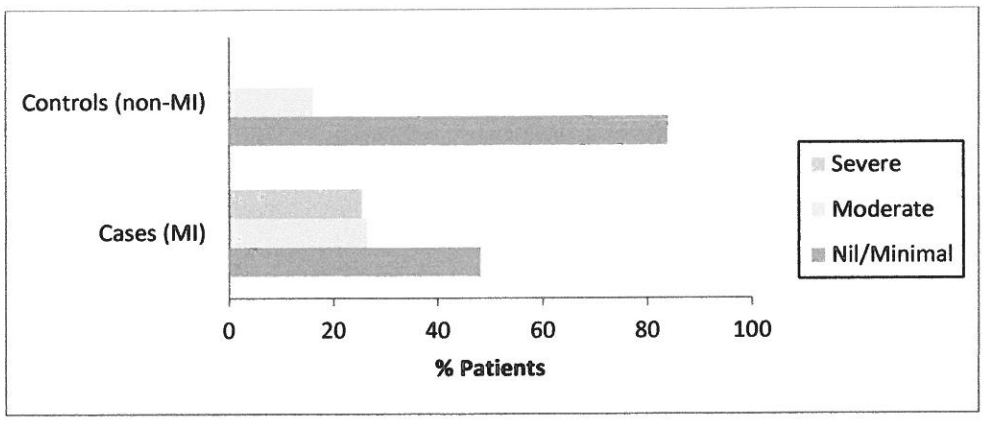

Figure 14: Patients who experience work stress in the cases and controls groups

Marital stress *(based on the INTERHEART questionnaire)*

- 73.6% of cases reported minimal marital stress levels, compared to 97.2% in the control patients.
- For analysis, the minimal group was used as reference, and the moderate and severe groups were combined due to small group sizes.
- The odds of an MI was higher for those with moderate/severe marital stress compared to those with minimal stress (Odds ratio: 12.3; 95% CI 3.62-42.0; p=0.0001).

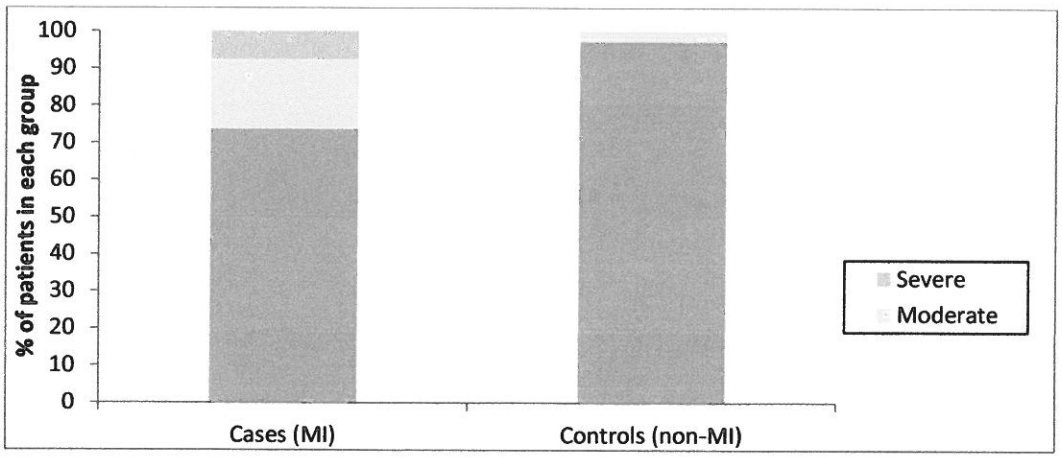

Figure 15: Patients who experience marital stress in the cases and controls groups

Financial stress *(based on the INTERHEART questionnaire)*

- Only 22.6% of cases reported minimal financial stress levels, compared to 79.3% in the control patients.
- The odds of an MI was higher for those with moderate/severe financial stress compared to those with minimal stress (Odds ratio: 13.1; 95% CI 6.79-25.1; p=0.0001).

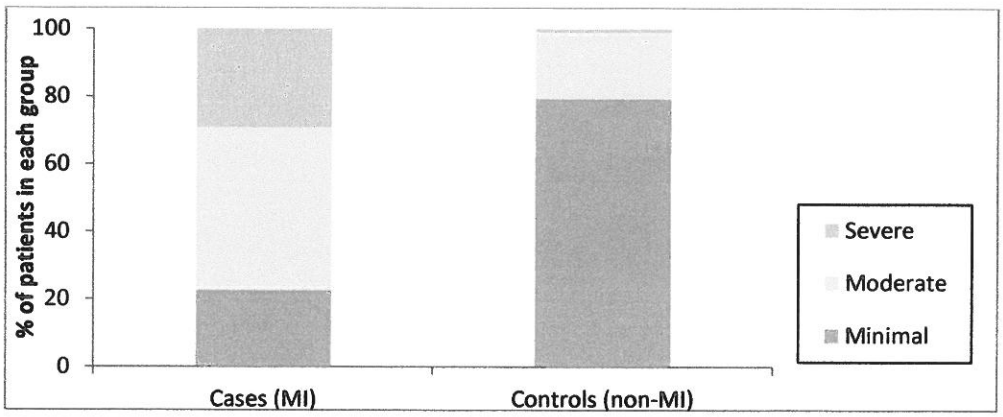

Figure 16: Percentage number of patients who experience financial stress in the cases and control groups

Hours of sleep per night

Only 74.5% of cases reported at least 6h of sleep per night, compared to 94.3% of controls.

For analysis, the >6-8h group was used as reference, and the <=6h groups were combined due to small group sizes.

- The odds of an MI was higher for those with <=6h sleep compared to those with >6-8h sleep (Odds ratio: 3.47; 95% CI 1.34-8.96; p= 0.010).
- The odds of an MI was lower for those with >8h sleep compared to those with >6-8h sleep (Odds ratio: 0.09; 95% CI 0.03-0.24; p=0.0001).

Leisure time activity

Over 80% of patients in both groups reported sedentary leisure time.

For analysis, the sedentary group was used as reference, and the other groups were combined due to small group sizes. The odds of MI were not significantly affected by leisure time activity.

***Depression** (DASS scale)*

- Using the DAS scale, 92.5% of patients scored values for depression equivalent to having no symptoms or minimal symptoms.
- For analysis, the normal group was used as reference, and the mild to extremely severe groups were combined due to small group sizes.
- The odds of MI were not significantly affected by depression, as measured by the DASS scale.

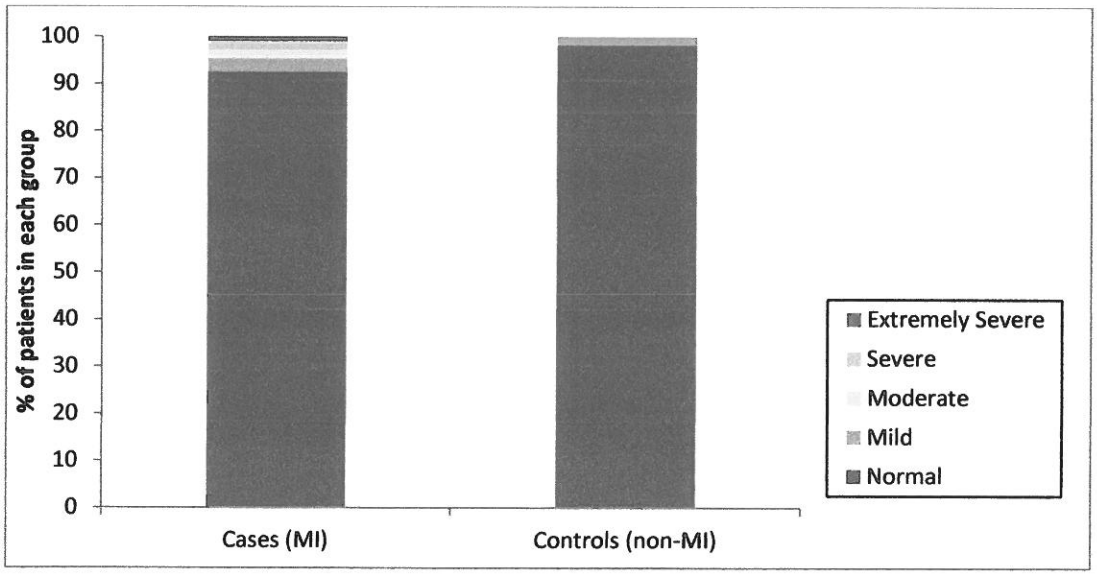

Figure 17: Levels of depression experienced by the patients in the cases and control groups

Anxiety *(DASS scale)*

- More than 85% of both groups reported normal levels of anxiety.
- The results were not different for the control patients scoring 98.1%.
- 89.6% of patients scored values for anxiety which is suggestive of no or minimal anxiety symptoms.
- 100% of control patients reported having no anxiety symptoms.
- No analysis was possible since there were no patients with non-normal levels of anxiety in the control group.

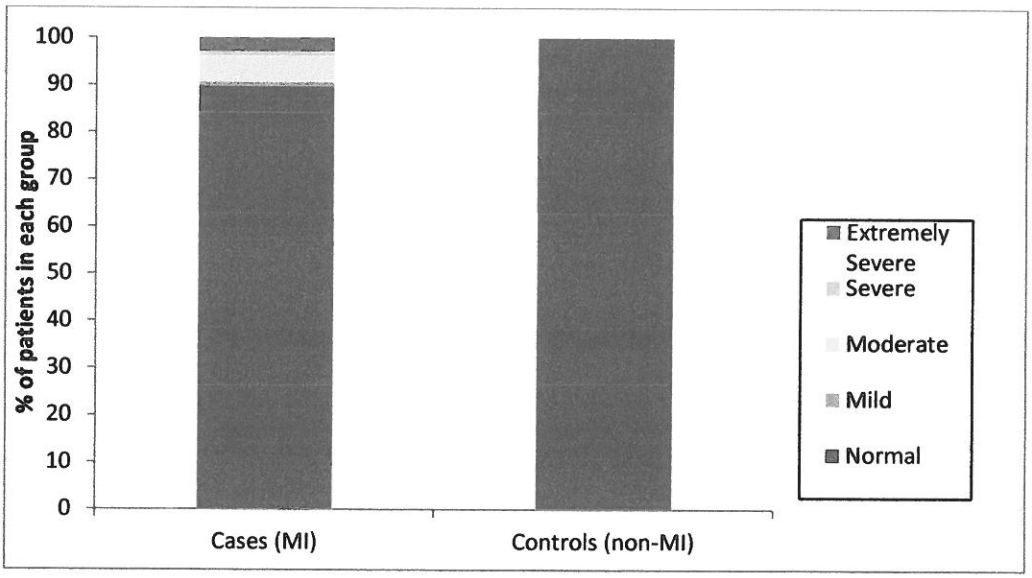

Figure 18: Levels of anxiety experienced by the patients in the cases and control groups

Stress *(DASS scale)*

It is clear that the stress profile of the two groups differed significantly; only 8.5% of MI patients reported normal stress levels, compared to 98.1% of controls. For analysis, the normal group was used as reference, and the mild to extremely severe groups were combined due to small group sizes.

- The odds of an MI was higher for those with mild to extremely severe stress, as measured by the DASS scale, compared to those with normal stress (Odds ratio: 560; 95% CI 118 to >999; p=0.0001).
- Case patients have a significant amount of stress with 46.2% of patients scoring extremely severe, followed by 31.1% of patients falling into the severe category and 9.4% falling into the moderate category. 98.1% of non-MI patients scored in the normal range for the stress questions.

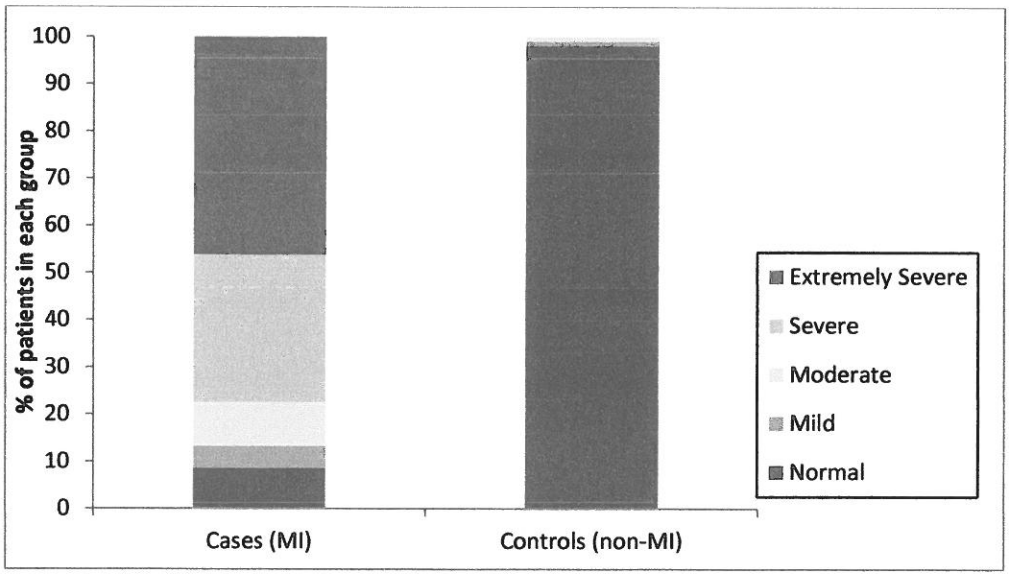

Figure 19: Levels of stress experienced by the patients in the cases and control groups

5. Discussion

As cardiovascular diseases are one of the leading cause of death worldwide, primary and secondary prevention of CAD remains the primary objective in the reduction of cardiac events such as acute MI (Khayam *et al.*, 2012). As alluded to earlier, previous studies have attributed a significant contribution of this CAD risk is due to psychological stress (Rosengren *et al.,* 2004, Yusuf et al., 2004). One of the major findings of the INTERHEART study suggested that the effects of psychosocial distress on CVD outcomes was similar to the impact of demographic characteristics (age, sex, and race) and risk factors such as hypertension, obesity, alcohol, dyslipidaemia and tobacco use (Yusuf *et al.*, 2004). As a result, physicians began implementing behavioural changes and risk factor modifications with the aim of reducing CVD events (Yousefy *et al.,* 2006; Khayam *et al.*, 2012). Psychosocial intervention research, aimed at modifying psychological distress to decrease mortality in individuals with CVD have shown mixed results (Berkman *et al.,* 2003; Friedman *et al.*, 1986). It is not known if preventive reduction of psychological distress in a healthy community will ultimately reduce CVD mortality.

The impression is that the role of psychosocial factors in the progression of cardiovascular diseases has been under-appreciated and thus may be a reason as to why CVD is still the leading cause of death in most developed countries.

Patients with depression have an increased risk of developing CAD when compared to those without depression (Rugulies *et al.*, 2002). As discussed earlier there is a noted pathological pathway associated with the hypothalamic-pituitary-adrenal axis dysfunction. Depressed patients also have a lack of interest in pleasurable activities and in activities that would decrease risk of CAD such as exercise. In the current study more than 85% of patients with acute MI reported no depression based on the INTERHEART questionnaire and over 90% with acute MI had no significant levels of depression using the DASS depression scale. The results of the current study are at odds with previous reported findings. Most of the data on the role of psychosocial factors and CAD emanate from first world countries where psychiatry is well established and services more accessible and conditions such as depression are well understood. Patients in developing countries such as those in this study, are not very aware of depressive symptoms, English is often not the home language, negative

cultural attitudes to psychiatric terminology and possibly poor understanding of the questionnaire could be some of the reasons why this study did not find depression to be a risk factor for acute MI (Carney *et al.*, 2009). In this study, in the small number of patients with acute MI with self-reported depression, the risk of AMI was 3 fold higher (OR 3.26; CI 1.02-10.4; $p < 0.046$), hence suggesting that depression increases the risk for AMI.

It has been noted that depression leads to increased smoking and other forms of sedentary lifestyles. Even though in this study the majority of patients with acute MI had low levels of depression, smoking was a significant risk factor. In the current study, 61% of the cases and 40% of the controls were smokers. The odds of MI were higher for patients who were smokers, compared to non-smokers, at all three levels of cigarette use. Also 33% of AMI patients had calculated pack years of more than 20. The odds of MI were 25 times higher for patients with smoking pack-years >20, compared to zero pack-years (Odds ratio: 25.13; 95% CI: 5.73-110; p= 0.0001).

Sleep deprivation and sleep disorders like obstructive sleep apnoea are prevalent in the community and is associated with uncontrolled blood pressure, inflammation, and psychological distress, such as depression (Phillips *et al.,* 2007; Lopez-Jimenez *et al.,* 2008; Mills *et al.,* 2007; Brown *et al.,* 2005). Low-grade inflammation, platelet hyperactivity, autonomic imbalance and endothelial dysfunction are some of the biological changes associated with depression (Skala *et al.,* 2006). There is well a known interplay between depressive disorders and sleep quality. Although the current study failed to show significant levels of depression in the cohort of patients studied, it did find that the odds of MI were 3.47 times higher for those with less than 6 hours of sleep compared to those with more than 6-8 hours of sleep (Odds ratio: 3.47; 95% CI: 1.34-8.96; p= 0.010).

Anxiety is well known in the field of psychology and is defined as an emotion of feeling unpleasant and is triggered by anticipation of future events or memories of past events. It can manifest in various forms such as phobic anxiety, chronic anxiety, generalized anxiety and a panic disorder (Boyd *et al.,* 1984; Zimmerman *et al.,* 2003). A few studies have examined associations between anxiety and cardiovascular disease. Some researchers have demonstrated at least between 40% to 70% of patients with congestive heart failure have some degree of anxiety. Other studies

estimate that in more elderly patients with congestive heart failure, anxiety levels are somewhat higher at about 60% as compared to patients without congestive cardiac failure symptoms (De Jong *et al.,* 2004; Moser *et al.,* 2005). Anxiety is directly related to and is a risk factor for CAD (Zafar *et al.*, 2010). Both anxiety and depression have been shown to predict a greater risk of major adverse cardiac events including cardiac deaths, myocardial infarction, cardiac arrest, atrial fibrillation and urgent revascularization (Frasure-Smith *et al.*, 2008). In the current study, anxiety contributed minimally to the presenting cardiac event. It was potentially a confusing point for patients as the anxiety symptoms were close to symptoms experienced with acute myocardial infarction.

The most relevant psychological factor that was associated with an increased risk of MI in the current study was stress defined as either work stress, marital stress of financial stress. This was supported by the DASS stress scale that found that only 8.5% with AMI had normal stress levels compared to 98% of control patients. Thus as measured by the DASS scale, the odds of an acute MI was extremely elevated (OR 560; 95% CI 118to >999; p=0000.1) in those MI patients with mild to severe stress as compared to those MI patients with no stress. In the INTERHEART questionnaire stress category, the risk of MI was increased 5 fold (OR 5.65; CI 2.97-10.8; p= 0.0001) in those patients who reported moderate/severe work stress levels, increased 12 fold (OR 12.3;CI 3.62-4.20; p= 0.0001) in those who reported moderate to severe marital stress and increased by 13 fold (OR 13.1; 6.79-25.2; p=0001) in those who reported financial stress.

The findings of this current study are consistent with those found in the INTERHEART study that reported a statistically significant higher prevalence of all forms of stress factors in patients with acute MI (Yusuf *et al.,* 2004). The mechanism of acute emotional stress causing MI is postulated to be related to hemodynamic instability in coronary arteries and rupture of an atherosclerotic plaque, followed by thrombosis (Muller *et al.*, 1994). Classical risk factors may also play a role in stress through neuroendocrine and platelet activation as well as from adverse health behaviours such as smoking, poor diet, and sedentary lifestyle (Wenger *et al.*, 2012).

6. CONCLUSION

This study using a modern psychological perspective aimed to evaluate the role of psychological factors in the aetiology of myocardial infarction in a cohort of patients presenting with acute MI at a large public hospital in Johannesburg, South Africa. The findings of this study failed to show that depression and anxiety were significantly associated with myocardial infarction, but stress, in its various forms, was an important psychological risk factor for coronary heart disease. The rise in coronary heart disease risk factors in recent years, makes it necessary that more attention be given to preventive measures and the psychological factors to improve CVD morbidity and mortality. Considering the increase in coronary heart disease risk factors during recent years, it is necessary that attention should also be paid to psychological factors and its preventive measures. This includes, improving psychological and educational interventions in the community, as well as increasing people's awareness on the effects of good cardiac health. The results from this study are pertinent and hopefully it may influence an integrative approach of psychiatry and internal medicine.

Physicians should aim to treat patients using targeted behavioural modification such as smoking reduction or cessation, improving physical activity, improved blood pressure management and relaxation techniques. This will alleviate psychological distress. To achieve this, a combination of both psychotherapeutic and psychopharmacologic intervention in needed. More clinical trials are needed, to prove the hypothesis that such psychotherapeutic and psychopharmacologic interventions are needed to decrease stress-related CVD.

7. Recommendations

As psychosocial factors have been demonstrated to be a major risk factor for acute myocardial infarction, a multidisciplinary interventional approach is recommended. This approach should target emotional and chronic stressors and should include psychotherapy, behavioral therapy, appropriate drug therapy, social intervention, occupational health, exercise programs and stress management. All of these may be of major benefit in reducing the incidence of coronary heart disease.

It is clear that better screening tools are needed for proper evaluation of patients with

suspected depression, anxiety and stress symptoms. Patients need to be made aware and educated about these psychiatric manifestations. This study found that stress is by far the most important factor amongst the 3 and definitely early detection and evaluation with appropriate steps will hopefully lead to a reduction in acute myocardial infarction precipitated by stress. The bio-psychosocial approach needs to be re-emphasized amongst health care providers. Adequate early screening of patients at risk in a primary health care setting, leading to early identification and referral would be the ideal primary prevention modality.

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Appendix A

DASS QUESTIONNAIRE

http://www2.psy.unsw.edu.au/groups/dass/down.htm
The DASS questionnaire forms may be downloaded and copied without restriction. However, the scales may not be modified)

Depression Anxiety and Stress Scale (DASS) Rating Scale

Please read each statement and circle a number 0, 1, 2 or 3 which indicates how much the statement applied to you over the past week. There are no right or wrong answers. Do not spend too much time on any statement.

Scoring: Scores of Depression, Anxiety and Stress are calculated by summing the scores for the relevant items. The depression scale items are 3, 5, 10, 13, 16, 17, 21, 24, 26, 31, 34, 37, 38, 42. The anxiety scale items are 2, 4, 7, 9, 15, 19, 20, 23, 25, 28, 30, 36, 40, 41. The stress scale items are 1, 6, 8, 11, 12, 14, 18, 22, 27, 29, 32, 33, 35, 39. The score for each of the respondents over each of the sub-scales, are then evaluated as per the severity-rating index below.

The rating scale is as follows:

0 Did not apply to me at all
1 Applied to me to some degree, or some of the time
2 Applied to me to a considerable degree, or a good part of time
3 Applied to me very much, or most of the time

1.	I found myself getting upset by quite trivial things	0	1	2	3
2.	I was aware of dryness of my mouth	0	1	2	3
3.	I couldn't seem to experience any positive feeling at all	0	1	2	3
4.	I experienced breathing difficulty (eg, excessively rapid breathing, breathlessness in the absence of physical exertion)	0	1	2	3
5.	I just couldn't seem to get going	0	1	2	3

6. I tended to over-react to situations	0	1	2	3
7. I had a feeling of shakiness (eg, legs going to give way)	0	1	2	3
8. I found it difficult to relax	0	1	2	3
9. I found myself in situations that made me so anxious I was most relieved when they ended	0	1	2	3
10. I felt that I had nothing to look forward to	0	1	2	3
11. I found myself getting upset rather easily	0	1	2	3
12. I felt that I was using a lot of nervous energy	0	1	2	3
13. I felt sad and depressed	0	1	2	3
14. I found myself getting impatient when I was delayed in any way (eg, lifts, traffic lights, being kept waiting)	0	1	2	3
15. I had a feeling of faintness	0	1	2	3
16. I felt that I had lost interest in just about everything	0	1	2	3
17. I felt I wasn't worth much as a person	0	1	2	3
18. I felt that I was rather touchy	0	1	2	3
19. I perspired noticeably (eg, hands sweaty) in the absence of high temperatures or physical exertion	0	1	2	3
20. I felt scared without any good reason	0	1	2	3
	0	1	2	3

21. I felt that life wasn't worthwhile

22. I found it hard to wind down | 0 | 1 | 2 | 3 |

23. I had difficulty in swallowing | 0 | 1 | 2 | 3 |

24. I couldn't seem to get any enjoyment out of the things I did | 0 | 1 | 2 | 3 |

25. I was aware of the action of my heart in the absence of physical exertion (eg, sense of heart rate increase, heart missing a beat) | 0 | 1 | 2 | 3 |

26. I felt down-hearted and blue | 0 | 1 | 2 | 3 |

27. I found that I was very irritable | 0 | 1 | 2 | 3 |

28. I felt I was close to panic | 0 | 1 | 2 | 3 |

29. I found it hard to calm down after something upset me | 0 | 1 | 2 | 3 |

30. I feared that I would be "thrown" by some trivial but unfamiliar task | 0 | 1 | 2 | 3 |

31. I was unable to become enthusiastic about anything | 0 | 1 | 2 | 3 |

32. I found it difficult to tolerate interruptions to what I was doing | 0 | 1 | 2 | 3 |

33. I was in a state of nervous tension | 0 | 1 | 2 | 3 |

34. I felt I was pretty worthless | 0 | 1 | 2 | 3 |

35. I was intolerant of anything that kept me from getting on with | 0 | 1 | 2 | 3 |

what I was doing

36. I felt terrified

0	1	2	3

37. I could see nothing in the future to be hopeful about

0	1	2	3

38. I felt that life was meaningless

0	1	2	3

39. I found myself getting agitated

0	1	2	3

40. I was worried about situations in which I might panic and make a fool of myself

0	1	2	3

41. I experienced trembling (eg, in the hands)

0	1	2	3

42. I found it difficult to work up the initiative to do things

0	1	2	3

APPENDIX B: INTERHEART QUESTIONNAIRE (Yusif S et al., 2004)

1. History and Vitals

DOB: ☐☐☐☐ year ☐☐ month ☐☐ day ☐ Not Known → Age ☐☐ yrs

a) When did the symptoms begin? (Collect from medical record) Date ☐☐☐☐ year ☐☐ month ☐☐ day Time ☐☐ : ☐☐ (00:00-23:59)

b) When did patient arrive at hospital? (Collect from medical record) Date ☐☐☐☐ year ☐☐ month ☐☐ day Time ☐☐ : ☐☐ (00:00-23:59)

Date of interview: ☐☐☐☐ year ☐☐ month ☐☐ day

5. Sex: ☐ Female ☐ Male

Place Subject File Blood Label Here

Physical Measurements

a) Blood Pressure

#1 ☐☐☐ Systolic ☐☐☐ Diastolic

#2 ☐☐☐ Systolic ☐☐☐ Diastolic

b) Waist (cm)

#1 ☐☐☐.☐

#2 ☐☐☐.☐

c) Hip (cm)

#1 ☐☐☐.☐

#2 ☐☐☐.☐

d) Weight ☐☐☐.☐ kg

e) Height ☐☐☐.☐ cm

f) Heart Rate ☐☐ beats/minute

Were you engaged in heavy physical exertion:

a) in the hour prior to the onset of your symptoms? ☐ No/Unknown ☐ Yes

b) during the same hour on the previous day? ☐ No/Unknown ☐ Yes

Were you angry or emotionally upset:

a) in the hour prior to the onset of your symptoms? ☐ No/Unknown ☐ Yes

b) during the same hour on the previous day? ☐ No/Unknown ☐ Yes

a) On the day of your heart attack:

i) At what time did you wake up, prior to the onset of your symptoms? ☐☐ : ☐☐ (00:00-23:59)

ii) At that time, were you waking up from a nap? ☐ No ☐ Yes

iii) Did you wake up because of your symptoms? ☐ No ☐ Yes

b) On the day before your heart attack:

i) At what time did you wake up from your longest, or nocturnal, sleep? ☐☐ : ☐☐ (00:00-23:59)

2. Medication

	No	Yes	No	Yes	No	Yes
a) ACE-I	☐	☐	☐	☐	☐	☐
b) ASA/ anti-platelet	☐	☐	☐	☐	☐	☐
c) Beta Blocker	☐	☐	☐	☐	☐	☐
d) Ca Channel Blocker	☐	☐	☐	☐	☐	☐
e) Cholesterol ↓	☐	☐	☐	☐	☐	☐
f) Digoxin	☐	☐	☐	☐	☐	☐
g) Diuretic	☐	☐	☐	☐	☐	☐
h) Heparin → LDH			☐	☐		
h) Heparin → FDH			☐	☐		

	No	Yes	No	Yes	No	Yes
i) Low Molecular Weight Heparin	☐	☐	☐	☐	☐	☐
j) Hormone Replacement	☐	☐	☐	☐	☐	☐
k) Insulin	☐	☐	☐	☐	☐	☐
l) Nitrates	☐	☐	☐	☐	☐	☐
m) Oral Hypoglycemics	☐	☐	☐	☐	☐	☐
n) Thrombolysis			☐	☐		
o) Oral Anticoagulants	☐	☐	☐	☐	☐	☐

3. Ethnicity

Ethnicity: (see Users Guide) Subject ☐☐ + ☐☐ Mother ☐☐ + ☐☐ Father ☐☐ + ☐☐

4. Religion

Religion: **check one** ☐ Christianity ☐ Hinduism ☐ Islam ☐ Buddhism ☐ Judaism ☐ Atheist/ Agnostic ☐ Sikhism ☐ Traditional Chinese ☐ None ☐ Other *(specify)* _____

→ Do you practice your religion regularly? ☐ No ☐ Yes ☐ N/A

→ How often do you visit your place of worship in one month? ☐☐☐ visit(s) ☐ Religious holidays only

5. Education

How many years of formal education have been completed by (check highest level only):

Subject	☐ None	☐ 1-8	☐ 9-12	☐ Trade School	☐ College/University	
Mother	☐ None	☐ 1-8	☐ 9-12	☐ Trade School	☐ College/University	☐ Unknown
Father	☐ None	☐ 1-8	☐ 9-12	☐ Trade School	☐ College/University	☐ Unknown

6. Occupation

How many years of formal education have been completed by (check highest level only):

Subject	☐ None	☐ 1-8	☐ 9-12	☐ Trade School	☐ College/University	
Mother	☐ None	☐ 1-8	☐ 9-12	☐ Trade School	☐ College/University	☐ Unknown
Father	☐ None	☐ 1-8	☐ 9-12	☐ Trade School	☐ College/University	☐ Unknown

7. Income

Current annual household income ☐ Range 1 ☐ Range 2 ☐ Range 3 ☐ Range 4 ☐ Range 5

Check each of the following objects owned by household members: (check all that apply)

☐ Home ☐ Car/Auto ☐ Motorcycle/Scooter ☐ Bicycle ☐ Radio/Stereo ☐ Television
☐ Other Land/Property ☐ Computer ☐ Livestock/Cattle ☐ _____ ☐ _____

8. Losses

Marital separation/Divorce	☐ No	☐ Yes	Major personal injury or illness	☐ No	☐ Yes
Loss of job/retirement	☐ No	☐ Yes	Death/major illness of a close family member	☐ No	☐ Yes
Loss of crop/ business failure	☐ No	☐ Yes	Death of a spouse	☐ No	☐ Yes
Violence	☐ No	☐ Yes	Other major stress_____ (if yes, please specify)	☐ No	☐ Yes
Major Intra-family conflict	☐ No	☐ Yes			

9. Stress

Please answer the following:

For the following question, stress is defined as feeling irritable or filled with anxiety, or as having sleeping difficulties as a result of conditions at work or at home. (Note for cases: Please respond as you would have prior to having this MI.)

	Never Experienced Stress	Some Period of Stress	Several Periods of Stress	Permanent Stress
a) How often have you felt stress at work in the past year? (Mark here if not applicable, i.e. no longer working ☐)	☐	☐	☐	☐
b) How often have you felt stress at home in the past year?	☐	☐	☐	☐

c) What level of financial stress do you feel?

☐ Little/none ☐ Moderate ☐ High/Severe

d) How much autonomy do you have in organizing the events of your work day?

☐ None ☐ Little ☐ Moderate ☐ Substantial ☐ Complete ☐ Not Applicable (i.e. no longer working)

10. Past Medical and Family History

	Subject		Mother		Father	
	No	Yes	No	Yes	No	Yes
Hypertension	☐	☐	☐	☐	☐	☐
Diabetes	☐	☐ Age Dx? → ☐ <20 ☐ ≥20; On Ins? → ☐ No ☐ Yes	☐	☐ Age Dx? → ☐ <20 ☐ ≥20; On Ins? → ☐ No ☐ Yes	☐	☐ Age Dx? → ☐ <20 ☐ ≥20; On Ins? → ☐ No ☐ Yes
Angina	☐	☐ Age Dx? → ☐ <50 ☐ ≥50	☐	☐ Age Dx? → ☐ <50 ☐ ≥50	☐	☐ Age Dx? → ☐ <50 ☐ ≥50
MI	☐	☐ Age Dx? → ☐ <50 ☐ ≥50	☐	☐ Age Dx? → ☐ <50 ☐ ≥50	☐	☐ Age Dx? → ☐ <50 ☐ ≥50
Stroke	☐	☐ Age Dx? → ☐ <50 ☐ ≥50	☐	☐ Age Dx? → ☐ <50 ☐ ≥50	☐	☐ Age Dx? → ☐ <50 ☐ ≥50
Other Vascular	☐	☐	☐	☐	☐	☐
Cancer	☐	☐ Site? → ☐	☐	☐ Site? → ☐	☐	☐ Site? → ☐

11. Smoking

Which best describes your history of tobacco use?

☐ Formerly used tobacco products ☐ Currently uses tobacco products ☐ **Never used tobacco products** → ***Go to #28***

a) At what age did you start? ☐☐ yrs

b) If former, at what age did you quit? ☐☐ yrs ☐ N/A (still smoking)

c) Have you ever regularly used any of the following tobacco products? (check all that apply)

☐ Cigarettes ☐ Beedies ☐ Pipes/ cigars ☐ Chewing tobacco ☐ Paan ☐ Snuff ☐ Other _____
☐ Sheesha/water pipe

If use Cigarettes or Beedies:
→ How many per day? ☐☐☐
→ Type of cigarettes? (Check one only) ☐ Filter ☐ Non-Filter ☐ Both
→ What brand of cigarettes do/did you most commonly smoke? _____

12. Sleep

a) How many hours do you usually sleep during your longest/nocturnal sleep? ☐☐ hrs

b) Do you usually take naps/siestas? ☐ No ☐ Yes → *Total nap duration* ☐☐☐ mins
→ Usual time of day to the nearest hour ☐☐:00 (00:00 - 23:00)

c) How often during sleep do you snore in any way?

☐ Never ☐ A few times ☐ Sometimes ☐ Often ☐ Always or almost always ☐ Don't know

d) Select a category which best describe your usual snoring:

☐ Not applicable ☐ Mild/light ☐ Moderately disturbing ☐ Loud & disruptive ☐ Don't know

13. Leisure

How active are you at work and during your leisure time?

a) At work (check one):

☐ 1. Mainly sedentary
☐ 2. Predominately walking on one level, no heavy lifting
☐ 3. Mainly walking, including climbing stairs, or walking uphill or lifting heavy objects
☐ 4. Heavy physical labour
☐ 5. Subject does not work

b) During your leisure time (check one):

☐ 1. Mainly sedentary (sitting e.g. reading, watching television)
☐ 2. Mild exercise (minimal effort eg. yoga, archery, sport fishing, easy walking)
☐ 3. Moderate exercise (e.g. walking, bicycle riding, or light gardening at least 4 hours per week)
☐ 4. Strenuous exercise (heart beats rapidly e.g. running/jogging, football, vigorous swimming)

Appendix C

Dear Sir

I am a postgraduate Internal Medicine Registrar of the University of the Witwatersrand and as is mandatory to my MMed degree, I am required to do a research study.

I am working in Johannesburg, South Africa and will be doing my study at Charlotte Maxeke Academic hospital Johannesburg under the supervision of Professor P Manga.

I am humbly requesting permission to please use the questionnaire that was used in the INTERHEART study for the patients in my study. Please advise me on the correct procedure to do so and if in fact it is permissible. Rest assured that acknowledgment will be granted respectfully to this questionnaire from the INTERHEART study.

Thank You

Dr D Govender
cel: +27745885889
Internal Medicine Registrar
Johannesburg
South Africa

Yusuf, Salim

To

Me

CC

Lindeman, Judy

Today at 8:05 PM

Sure. We can send it to you.

SUMATHY: Please can u send him infor on how to access this?

thnx

Dr. Salim Yusuf, DPhil, FRCPC, FRSC, O.C.
Professor of Medicine, McMaster University
Executive Director, Population Health Research Institute
McMaster University, Hamilton Health Sciences
Vice President Research, Hamilton Health Sciences
Heart and Stroke Foundation/Marion W. Burke Chair in Cardiovascular Disease