Mental disorders among cardiac disease patients in a Palestinian population

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ABBREVIATIONS

ACS:	Acute coronary syndrome
AF:	Atrial fibrillation
AHA:	American Heart Association
BMI:	Body mass index
CABG:	Coronary artery bypass graft
CAD:	Coronary artery disease
CATH:	Catheterization
CCU	Coronary care unit
CDS:	Cardiac Depression Scale
CDS-SF:	Cardiac Depression Scale Short-Form
CHD:	Coronary heart disease
CI:	Confidence interval
CMHCs:	Community mental health clinics
CR:	Cardiac rehabilitation
CVDs:	Cardiovascular diseases
DALYs:	Disability-adjusted life years
DASS:	Depression Anxiety Stress Scale
DSM:	Diagnostic and Statistical Manual of Mental Disorders
DV:	Dependent variable
EKNZ:	Ethics Committee of Nordwest-und Zentral Schweiz
ENRICHD:	Enhancing Recovery in Coronary Heart
ESC:	European Society of Cardiology
ESSI:	ENRICHD Social Support Instrument

GAD:	Generalized anxiety disorder
GBD:	Global Burden of Disease
GSEM:	Generalized structural equation model
HDL:	High-density protein
HF:	Heart failure
HICs:	High-income countries
HR:	Hazard ratio
HRQL:	Health-related quality of life
HS:	High school
ICD:	Implantable cardioveter-defribrillator
IRB:	Institutional Review Board
IHD:	Ischemic heart disease
IV:	Independent variable
LDL:	Low-density protein
LICs:	Low income countries
LMIC:	Low-middle income countries
LVEF:	Left ventricular ejection fraction
MACE	Major adverse cardiac events
MCS:	Mental Component Summary
MDD:	Major depressive disorder
MDE:	Major depression episode
MI:	Myocardial infarction
MOH:	Ministry of health
MOS:	Medical Outcomes Survey
NCDs:	Non-communicable diseases
NGO	Non-government organization

NICE	National Institute for Health and Care Excellence
OPT:	Occupied Palestinian territory
OR:	Odds ratio
PCS:	Physical Component Summary
PHQ:	Patient Health Questionnaire
PTSD:	Posttraumatic stress disorder
PCL-S:	Post-Traumatic Stress Disorder Checklist-Specific
QOL:	Quality of life
RS-14:	Resilience Scale-14
SD:	Standard deviation
SISE:	Single-item Self-esteem Scale
SEM:	Structural equation model
SF-12:	The 12-item Short Form Health Survey
WHO:	World Health Organization
YLD:	Years lived with disability

SUMMARY

Mental disorders and cardiovascular diseases (CVDs) are among the leading contributors to the global burden of disease, making them a major public health problem. Mental disorders and CVDs are common conditions, which very often co-occur, and influence each other's etiology. Individuals with cardiac diseases experience higher rates of mental disorders such as depression, anxiety and posttraumatic stress disorder (PTSD) than the general population. Likewise, these mental illnesses are associated with both onset and progression of cardiac diseases. A growing body of evidence has documented the independent association between depression and onset of cardiac disease, morbidity and mortality. There is also compelling evidence that the co-occurrence of depression and cardiac disease leads to worse health-related quality of life (HRQL). However, less is known about the influence of anxiety and PTSD on cardiac outcomes and HRQL. The American Heart Association (AHA) has recommended routine depression screening in cardiac patients and guidelines for cardiac rehabilitation (CR) include that attention is paid to the diagnosis and treatment of mental disorders, yet the uptake of these recommendations remains limited. This situation is expected to be aggravated in low-income countries (LICs) like Palestine, which is affected by the political conflict and rates of CVDs and mental disorders are on a rapid rise. However, mental disorders are stigmatized, and thus not recognized nor treated. The evidence base to promote mental health services is currently lacking. This is the first contribution to assess the relationship between mental disorders and cardiac diseases in Palestine.

This PhD project the "CARMEN Study" was carried out in collaboration between Swiss Tropical and Public Health Institute, (Swiss TPH) and An-Najah National University. The following dissertation is based on three interrelated studies and sought to study the epidemiology and contributions of depression, anxiety, PTSD among cardiac diseases in a

population-based sample of Palestinian adults. This dissertation provides evidence to fill the knowledge gaps to inform treatment and guide optimum management of these comorbid conditions.

Study I used a cross-sectional design to investigate the prevalence of depression and anxiety symptoms among Palestinian cardiac patients. Among the 1022 patients assessed, 54% were categorized as having severe depressive symptoms, while 19% exhibited severe anxiety symptoms. The study also found PTSD symptoms, low level of self-esteem, high somatic symptoms, low physical and mental health component scores, active smoking, physical inactivity, and longer disease duration to be independently associated factors with both depressive and anxiety symptoms. Patients with depressive and anxiety symptoms also reported poor social support and lower resilience and were more prevalent among females and less educated patients.

Study II revealed that women were more likely to suffer from depression than men (28.7% vs. 18.8%). When assessing which characteristics mediate the effect of gender on depression using structural equation modeling (SEM), our results showed that there was no direct effect of gender on depression; however, indirect effects showed that female gender was associated with lower resilience, self-esteem and quality of life, education, prevalence of smoking and physical activity and higher PTSD symptoms, comorbidities, somatic symptoms and smoking.

Study III found 27% of the overall sample at baseline exhibits moderate-to-high PTSD symptoms and at one year follow-up, patients with PTSD reported an approximate 20% lower HRQL. In addition, when assessing the longitudinal association of PTSD with HRQL after one year, the findings suggest this relationship was largely mediated by depression and anxiety.

The overall conclusions drawn from this thesis support the essential need for integrating mental health care into CR in Palestine from disease onset and onwards, considering the alarming rates

of depression and anxiety symptoms in this Palestinian patient population. Depression, anxiety and PTSD should be considered important risk factors for cardiac diseases as much as other traditional cardiac risk factors. To deliver effective treatments for depression, anxiety and PTSD, assessment of the impact of psychological interventions on cardiac outcomes is needed. For clinical practice, future research should apply a more holistic approach in treating both physical and psychological recovery among cardiac patients. Finally, our findings can be considered as first steps to the translational approach of innovation, validation and application, where we can use the current cardiac sample as an entry door to pursue family members of diseased patients whom also could be at risk of onset and progression of cardiac diseases. This could potentially lead to a national mental health program that could be generalizable to similar health care systems in the Middle East region.

LIST OF ARTICLES

This thesis is based on one published article, one accepted article (pending final journal decision) and one article under review, which will be referred to in the text by their Roman numerals.

I. Allabadi H, Alkaiyat A, Alkhayyat A, Hammoudi A, Odeh H, Shtayeh J, Taha M, Schindler C, Zemp E, Haj-Yahia S, Probst-Hensch N: **Depression and anxiety symptoms in cardiac patients: a cross-sectional hospital-based study in a Palestinian population.** *BMC Public Health* 2019, **19:**232.

(Published in BMC Public Health, February 2019)

II. Allabadi H, Probst-Hensch N, Alkaiyat A, Haj-Yahia S, Schindler C, Kwiatkowski M, Zemp E: **Mediators of gender effects on depression among cardiovascular disease patients in Palestine.** *BMC Psychiatry 2019, 19:284.*

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III. Allabadi H , Alkaiyat A, Zahdeh T, Assadi A, Ghanayim A, Hasan S, Abu Al Haj D, Allabadi L, Haj-Yahia S, Schindler C, Kwiatkowski M , Zemp E, Probst-Hensch N. **Posttraumatic stress disorder predicts poor health-related quality of life in cardiac patients in Palestine.**

(*Submitted to the British Journal of Psychiatry, August, 2019)*

DEFINITIONS

Anxiety: an unpleasant emotion that is triggered by anticipation of future events and memories of past events, and it could manifest in different forms (panic disorder, phobic anxiety, generalized anxiety, anxiety reactions, and chronic anxiety).

Atherosclerosis: Atherosclerosis is a disease in which plaque builds up inside your arteries. Arteries are blood vessels that carry oxygen-rich blood to your heart and other parts of your body.

Cardiac Rehabilitation (CR): a multi-factorial intervention recommended for cardiac patients, which aims at improving patients' overall quality of life, as well as reducing the detrimental psychological, emotional and physical burden of cardiac diseases.

Major depressive disorder (MDD): is defined by the presence of depressed mood and/or lack of interest/pleasure in activities, every day for a period of at least two weeks or more, along with the presence of additional symptoms including: significant weight loss/gain; increased/decreased appetite, hypersomnia/insomnia, agitation, fatigue or loss of energy, feelings of worthlessness, difficulty with concentration, presence of suicidal thoughts. (American Psychiatric Association [*DSM-IV-TR*], 2000).

Mental disorders: clinically significant behavioral or psychological set of symptoms, which are commonly associated with distress, pain, disability or loss of freedom and interferes with ability to function effectively and with interpersonal relationships.

Posttraumatic stress disorder (PTSD): Posttraumatic stress disorder is an anxiety disorder initiated by an exposure to a traumatic event, such as combat, natural disaster, or sexual assault, and is characterized by symptoms such as re-experiencing the traumatic event (e.g., intrusive thoughts, nightmares), cognitive or behavioral avoidance of reminders of the event, and physiological hyper arousal.

1

INTRODUCTION

1.1 Non-communicable diseases (NCDs)

In the last century, the world has witnessed an "epidemiologic transition" from infectious disease and nutritional deficiencies to non-communicable diseases (NCDs). As a result of mainly the demographic aging of the population, as well as social detriments of health and globalization, NCD rates are drastically increasing posing major concerns for global health and health care systems around the world (WHO, 2014). According to the World Health Organization (WHO), among the 56 million deaths globally in 2012, 38 million (68%) were due to NCDs, of which 16 million were premature deaths under the age of 70 (WHO, 2014). The Global Burden of Disease (GBD) Study 2015, stated that NCDs contributed to the highest burden measured in disability-adjusted life years (DALYs) (Forouzanfar et al., 2016). Previously, high NCD mortality rates have affected high-income countries (HICs). However, a new trend is emerging as NCDs are rapidly increasing in low- and middle-income countries (LMICs) (Rahim et al., 2014). In 2012, 74% of NCD-related global deaths occurred in LMICs (WHO, 2014).

In recent years, the WHO has focused on the four major NCDs: cardiovascular diseases (CVDs), cancer, chronic respiratory diseases and diabetes. However, the focus has now expanded to a five-by-five approach to also include mental disorders, as the co-occurrence of mental health conditions and NCDs is on a tremendous rise (Stein et al., 2019).

NCDs are now hindering the progress towards the 2030 Agenda for Sustainable Development, which is aimed at reducing NCD-related premature deaths by one-third by 2030.

In response to the NCD epidemic, the WHO is supporting efforts to tackle NCDs through policies and programs that target prevention of NCDs, increase early detection, and ensure sustainable and universal access to appropriate and quality health care (WHO, 2018).

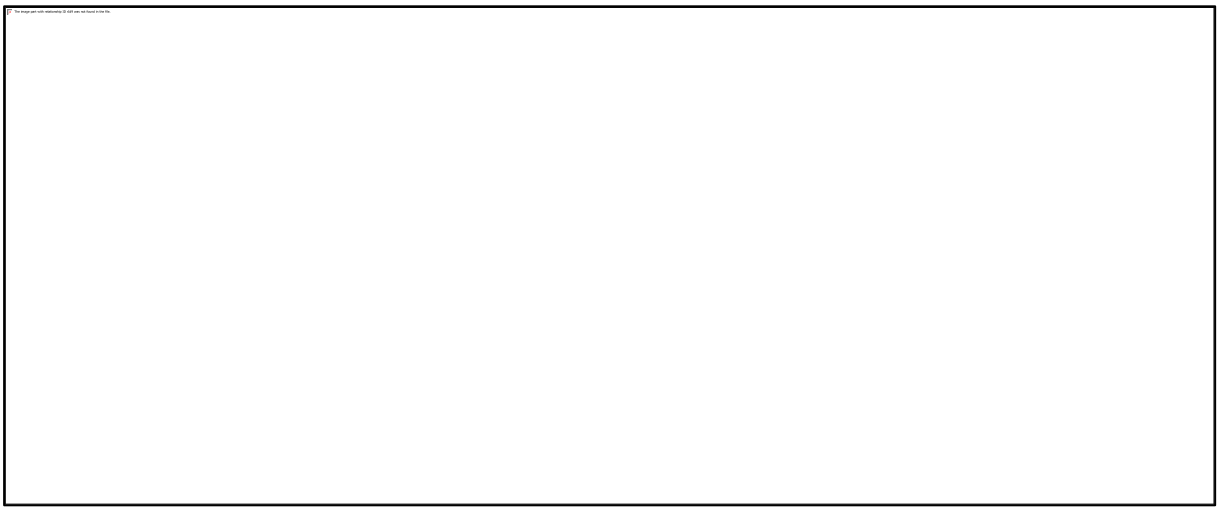
1.2 Global burden of cardiovascular diseases (CVDs)

CVD is an umbrella term comprising a group of disorders of the heart and blood vessels. The main types of CVDs include coronary heart disease (CHD), cerebrovascular disease (e.g. stroke), peripheral vascular disease, and other cardiac-related diseases including rheumatic heart disease, congenital heart disease, heart failure (HF), valvular heart disease, cardiomyopathies (disorders of the heart muscle) and atrial fibrillation (AF) (WHO, 2018) . CVDs are a key contributor to the rise of NCD-related deaths worldwide, accounting for nearly 50% (Mendis et al., 2011). In 2015, CVDs were responsible for over 17 million deaths globally (Figure 1.2), making them the leading cause of death and loss of DALYs in the world (Yusuf et al., 2001, Roth et al., 2017). CHD, also known as ischemic heart disease (IHD) or coronary artery disease (CAD) is projected to be the leading cause of death in the developing world by 2020 (Denollet et al., 2006). The most common clinical manifestations of CHD are stable angina, unstable angina and myocardial infarction (MI). MI is also a major cause of morbidity and mortality worldwide, and it is estimated that more than seven million people suffer from MI each year (White and Chew, 2008). The percentage of premature CVD deaths ranges from 4% in HICs to 42% in low-income countries (LICs) and the rate of CVDs worldwide is predicted to increase as the prevalence CVD risk factors rises in LMICs. Currently, 80% of CVD mortality occurs in LMICs, and is expected to be the major cause of mortality by 2020, overtaking infectious diseases (Perk et al., 2012).

The major traditional risk factors associated with cardiac diseases are hypertension, diabetes, hyperlipidemia, obesity, sedentary lifestyles (e.g. physical inactivity, smoking, poor dietary habits, alcohol consumption), age, gender and family history. It has been established that age,

gender, diabetes and hypertension are greatly contributing to cardiac events such as MI, cardiac readmission, and cardiac death (Stahli et al., 2019, Cole et al., 2019). The WHO states that over 75% of premature CVD is preventable and tackling risk factors can help reduce the increasing CVD burden on both populations and healthcare systems (WHO, 2014).

Figure 1.2. Global distribution of CVD mortality rates in 2015 *(Roth, G.A. et al. J Am Coll Cardiol.2017; 70(1):1–25)*

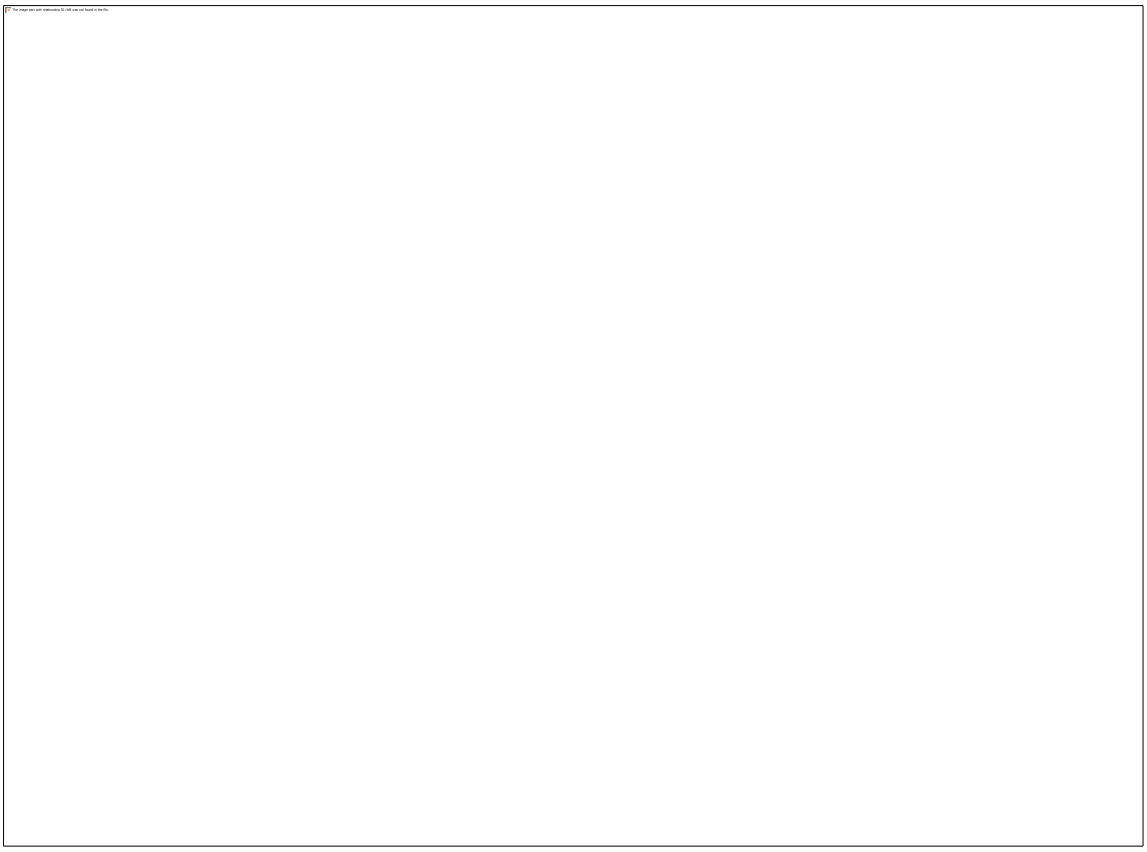


1.3 Global burden of mental disorders

Similar to CVDs, mental disorders also pose a great challenge to the world's health problems, in both HICs and LMICs. According to the GBD study, mental disorders made up 56.7% of global DALYs in 2010, accounting for the fifth leading cause of DALYs and the number one leading cause of years lived with disability (YLD) (Ferrari et al., 2013). Previous research has found that 14.3% of deaths worldwide or eight million deaths each year are related to mental disorders and most of these deaths have been linked to having a co-occurring NCD. Depression and anxiety constitute as two of the most common mental disorders globally, and like CVDs occur at high frequencies in the general population. In 2010, depressive disorders accounted for 40.5% of DALYs, while anxiety disorders accounted for 14.6% of DALYs (Whiteford et al., 2013). The lifetime prevalence rate of depression has been estimated at 14.6% in HICs and 11.1% in LMICs (Bromet et al., 2011), and lifetime incidence rates are approximately 12% and 20% in men and women, respectively (2008, Kessler et al., 2003). The lifetime prevalence of

anxiety disorders is 33.7% (Mensah and Collins, 2015, Ormel et al., 2007). Depression and anxiety have been associated with poor quality of life (Baumeister et al., 2005), increased morbidity and mortality (Rugulies, 2002) and economic burden on society (Ormel et al., 1998). Depression, in particular has a significant impact on psychological (e.g. anxiety, fear, hopelessness), physical and social functioning (e.g. social isolation) (Khawaja et al., 2009) and has been linked to brain damage, cardiac events and poor health-related behaviors (Kessler et al., 2003, Kapfhammer, 2011, Roshanaei-Moghaddam et al., 2009). Posttraumatic stress disorder (PTSD), which is considered a type of anxiety disorder also constitutes as a serious health consequence, and has an estimated lifetime prevalence of 0.3% to 8.7% in HICs (Kessler et al., 1996). PTSD symptoms and clinical PTSD have also been associated with lower quality of life, impaired functioning, short and long-term disability and suicide attempts (Johansen et al., 2007, Sareen et al., 2007). If not treated, these disorders could follow a chronic course, be recurrent and lead to increasing disability over time (Solomon et al., 2000, Andrews, 2001). Diagnostic criteria for depression, anxiety and PTSD according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-V), 5th edition are outlined in Figure 1.2 (de Val D'Espaux et al., 2011).

Figure 1.3. Diagnostic criteria for depression, anxiety and PTSD



1.4 Comorbid mental disorders and CVD

Mental disorders, such as anxiety disorders and depression are highly prevalent among chronic diseases. In particular, mental disorders very often coexist with CVDs and share common features (Hare et al., 2014, Pozuelo et al., 2009, Halaris, 2009). First, they are both chronic conditions in which persist over time and require ongoing management and monitoring over the course of the disease. Second, they arise from a combination of biological, psychosocial, behavioral, and social factors. Likewise, their co-existence of physical and mental morbidity negatively affects the course and outcome of both conditions, and thus results in significant levels of illness, disability and an overall increased burden of disease. This in turn reduces economic productivity, income and socioeconomic opportunities for patients, families and communities (Pozuelo et al., 2009, Halaris, 2009). Comorbid mental and cardiac diseases are associated with noncompliance of treatment, poorer prognosis, poor health-related quality of life (HRQL), and rising medical costs for healthcare systems (Egede, 2007, Dickson et al., 2012, Mensah and Brown, 2007). Additionally, mental disorders result in poor sedentary lifestyles such as reduced physical activity, poor dietary habits, smoking, increased alcohol consumption and increased stress levels (Chaddha et al., 2016).

A body of literature has documented that mental disorders, specifically depression and anxiety are important risk factors for both onset and prognosis of CVD, cardiac morbidity and mortality, independent of traditional cardiac risk factors (Januzzi et al., 2000, Rutledge et al., 2009a, Whooley et al., 2008, Gan et al., 2014, Lichtman et al., 2014b). Patients suffering from mental disorders are even at higher risk for cardiac morbidity and mortality than are their counterparts in the general population (Sowden and Huffman, 2009). The lack of recognition of mental disorders in the development and progression of cardiac disease could explain why they remain the leading causes of death in most countries. This thesis will mainly focus on three mental disorders among cardiac patients; namely depression, anxiety and PTSD.

1.5. Epidemiology, etiological effects, and prognostic implications of DEPRESSION and cardiac disease

Among all mental disorders, depression has received the most attention in the CVD literature given that it is the most prevalent mental illness in patients with CVD, and can tremendously impact treatment and successful management of CVD. The association between depression and CVD has been recognized since the end of the 19th century. An extensive amount of literature has documented the bidirectional relationship between depression and CVD (Katon, 2011, Mensah and Collins, 2015), indicating, depression as a risk factor for CVD and CVD as a risk factor for depression (Mosovich et al., 2008, Chaddha et al., 2016). Interestingly, depression is associated with an increased incidence of new CVD (etiology) and worse outcomes in established CVD (prognosis) (Colquhoun et al., 2013).

1.5.1 Epidemiology

Depression is highly prevalent among cardiac patients in particular. Approximately, 31% to 45% of patients with CAD including those with unstable angina, MI, and stable CAD suffer from some level of depression (Carney and Freedland, 2003, Lesperance et al., 2000, Lesperance and Frasure-Smith, 2000, Thombs et al., 2006, Rudisch and Nemeroff, 2003). The prevalence of MDD among CAD patients ranges from approximately 10% to 30% (Carney and Freedland, 2008, Thombs et al., 2008, Thombs et al., 2006), which is three-fold higher than in the general population (Kessler et al., 2003). Patients with HF, AF, and those undergoing implantable cardioveter-defribrillator (ICD) placements are also at increased risk for elevated depressive symptoms and MDD. A meta-analysis of HF patients found prevalence rates of 36% for increased depressive symptoms and for MDD (Rutledge et al., 2006). Among patients undergoing coronary artery bypass graft (CABG) surgery, 30 to 40% of patients met criteria for minor or major depression and 15% of patients met full MDD criteria (Tully and Baker, 2012).

In the EUROASPIRE III study which investigated over 8500 CHD patients the proportion of men with depression varied form 8.2% to 35.7% and 10.3% to 62.5% in women (Cooney et al., 2013).

There are also established risk factors for depression in cardiac patients. Studies suggest that among CVD patients, younger age, female gender and patients with a history of depression are more likely to have depression (Shanmugasegaram, 2012, Mallik et al., 2006, Caro et al., 2012). Among MI patients, social isolation, prior history of MI, and comorbid diabetes may also increase the risk of depression (Spijkerman et al., 2005). In CABG patients, depression is predicted by female gender, younger age, living alone, anxiety and less education (Dunkel et al., 2009). Depression is also associated with many other traditional cardiac risk factors including diabetes, hypertension, smoking, sedentary lifestyle (e.g. physical inactivity, unhealthy diet) and smoking (Huffman et al., 2013).

1.5.2 Etiology

Previous studies have established depression is independently associated with an increased risk of development of CAD in healthy individuals (Wulsin and Singal, 2003). According to a meta-analysis which comprised of 36,000 patients, depression was found to be an independent risk factor for the development of some type of cardiac disease with a relative risk of 1.64 (95% CI: 1.41-1.90), among healthy individuals (Rugulies, 2002). Janszky et al. reported in their study that healthy individuals with depression are at 2.9 (95% CI: 1.8-4.9) times higher risk of having an MI (Janszky et al., 2007). A Danish longitudinal study demonstrated that depression predicted a 70% increase in MI after a 10-year period and a 60% increase in all-cause mortality after a 17-year period (Barefoot and Schroll, 1996).

1.5.3 Prognosis

On another note, a recent meta-analysis found that among patients with already established cardiac disease, depression is associated with a 1.6 to 2.6-fold increased risk of future major adverse cardiac events (MACE), cardiac mortality and all-cause mortality. For example, patients who have acute coronary syndrome (ACS; an umbrella term for MI and unstable angina) and depression have double the risk for future MACE, a rate similar to traditional risk factors such as reduced left ventricular ejection fraction (LVEF) and diabetes (Rozanski et al., 2005), while post-MI patients have a 2.4-fold (95% CI = 1.76–3.22) increased risk for all-cause mortality (Meijer et al., 2011). Subsequently, the American Heart Association (AHA) has recently recommended that development of depression after an MI should be raised to the status of a risk factor for poor prognosis, as evidence also supports its association to reduced secondary prevention behaviors (e.g. smoking, physical activity and CR) and cardiac-mortality (Meijer et al., 2011) (Lichtman et al., 2014a, Frasure-Smith et al., 1995, Barth et al., 2004). Similarly, among patients with unstable CAD, a meta-analysis found MDD to be associated with all-cause mortality (HR= 1.76 [95% CI = 1.27–2.43], two years following a cardiac event, even after adjustment for other risk factors (Barth et al., 2004). Depression also appears to have a detrimental effect on cardiac outcomes in patients with other cardiac diseases. Among HF patients, depression is linked to more frequent hospitalizations, increased heath care costs and utilization and a two-fold increase in mortality risk (Rutledge et al., 2006). Likewise, among CABG patients, depression has been associated with poor functional outcomes, preoperative complications, higher rates of re-hospitalizations, reduced HRQL and progression of atherosclerotic disease (Wellenius et al., 2008, Morone et al., 2010). In addition, depression among cardiac patients is associated with poor compliance to cardiac risk factors and compliance to medication and treatment regimens (Hare et al., 2014).

1.6 Epidemiology, etiological effects, and prognostic implications of ANXIETY and cardiac disease

Anxiety disorders are strongly correlated with depression among cardiac populations. However, in contrast to depression, less research has focused on the association of anxiety with cardiac diseases. Anxiety is highly prevalent in patients with cardiac diseases, including those with CAD, MI and those participating in CR (Frasure-Smith and Lesperance, 2008, De Schutter et al., 2011).

1.6.1 Epidemiology

The most common type of anxiety associated with cardiac diseases is generalized anxiety disorder (GAD), with an 11% point prevalence and 26% lifetime prevalence in CAD patients. The prevalence of elevated symptoms of anxiety in cardiac patients has been reported to be, approximately 30% (Pajak et al., 2013). These rates are higher than the 3-7% lifetime prevalence of GAD in the general population (Tully and Cosh, 2013, Kessler et al., 2005). Among ACS patients, 20 to 30% of patients experience elevated symptoms of anxiety, with symptoms persisting up to one-year after the cardiac event, suggesting that anxiety remains chronic over the course of heart disease (Hanssen et al., 2009). In a recent meta-analysis of 38 studies, 32% of HF patients experience elevated symptoms of anxiety, while 13% met criteria for an anxiety disorder. Furthermore, anxiety affects 20% of patients with advanced HF and 20 to 40% of patients who have undergone implantation of an ICD (Easton et al., 2016, Magyar-Russell et al., 2011).

1.6.2 Etiology

Anxiety is known to be a normal response to a stressful situation or experience, such as cardiac events. A handful of studies have found anxiety to be associated with the development of cardiac disease (Frasure-Smith and Lesperance, 2008, Phillips et al., 2009, Martens et al.,

2010). In a 2010 meta-analysis by Roest et al. including 20 studies and 250,000 patients, anxiety was associated with a 26% (HR = 1.26; 95% CI: 1.15–1.38) increased risk of CAD and a 48% (HR = 1.48; 95% CI: 1.14–1.92) increased risk of cardiac mortality, independent of socio-demographic and traditional cardiac and lifestyle factors (Roest et al., 2010a). However, this meta-analysis did not adjust for depression, which is highly comorbid with anxiety. A prospective national study conducted on men in the military revealed that an anxiety diagnosis was strongly associated with incident CHD (HR= 2.17; 95% CI: 1.28–3.67) and MI (HR= 2.51; 95% CI: 1.38–4.55) over a follow-up of 37 years (Janszky et al., 2007). Additionally, in a large retrospective study among 236,000 patients free of cardiac disease, anxiety disorders increased the risk of HF (HR = 1.19; 95% CI: 1.10–1.28) (Garfield et al., 2014).

1.6.3 Prognosis

Among patients with existing cardiac diseases, a three-year cohort study found anxiety to be independently associated with increased risk of all-cause mortality (HR= 1.83, 95% CI: 1.18-2.83) in CHD patients, particularly in the presence of comorbid depression (Watkins et al., 2013). Additionally, anxiety among cardiac patients has been associated with lower quality of life in patients with MI (Van Beek et al., 2016). Anxiety has also been associated with MACE (OR = 1.71; 95% CI: 1.31–2.23; $p < 0.001$) and cardiac mortality (OR = 1.23; 95% CI: 1.03–1.47; $p = 0.02$) (Roest et al., 2010b). Similarly, in a 10-year follow-up study by Van Dijk et al. on patients with existing CAD, the prevalence of anxiety was 27% and anxiety was associated with an increased risk for all-cause mortality (HR = 1.50; 95% CI: 1.14–1.98) (van Dijk et al., 2016). In a prospective study of 158 patients undergoing CABG surgery, GAD was associated with incident MACE over a five-year period. The associations between GAD and HF outcomes have not yet been investigated (Tully et al., 2015).

1.7 Epidemiology, etiological effects, and prognostic implications of PTSD and cardiac disease

1.7.1 Epidemiology

PTSD symptoms and clinical PTSD also are common in patients with cardiac diseases. Cardiac events including cardiac surgery can be potentially traumatic experiences which could lead to the development of PTSD. PTSD symptoms are present in 10% to 25% of patients with ACS, which is comparable to PTSD rates among those exposed to other traumatic events and the general population (Vilchinsky et al., 2017, Edmondson et al., 2011, Levine et al., 2014). Across other cardiac populations, approximately 20% of patients with ICD and 19% to 38% who have had cardiac arrest suffer from elevated levels of clinical PTSD symptoms (Ladwig et al., 2008, Spindler and Pedersen, 2005, Gamper et al., 2004).

1.7.2 Etiology

It has been established PTSD that occurs as a result of a trauma in non-medical settings is independently associated with increased risk of developing some type of cardiac disease, even after controlling for traditional cardiac risk factors such as smoking, hypertension and diabetes (Edmondson et al., 2013, Edmondson and Cohen, 2013). A meta-analysis evaluating PTSD in healthy individuals found that PTSD was associated with a 27% increased risk for CHD or cardiac-related mortality (HR=1.27,95% CI:1.08-1.49), even after adjusting for confounders, including depression (Edmondson et al., 2013). Another study conducted on twins over a 13-year period found that the incidence of CHD was twice as high among those with PTSD, compared with those without PTSD (22.6% vs 8.9%; $p<0.0001$), after adjustment for depression, lifestyle factors and cardiac risk factors (Vaccarino et al., 2013).

1.7.3 Prognosis

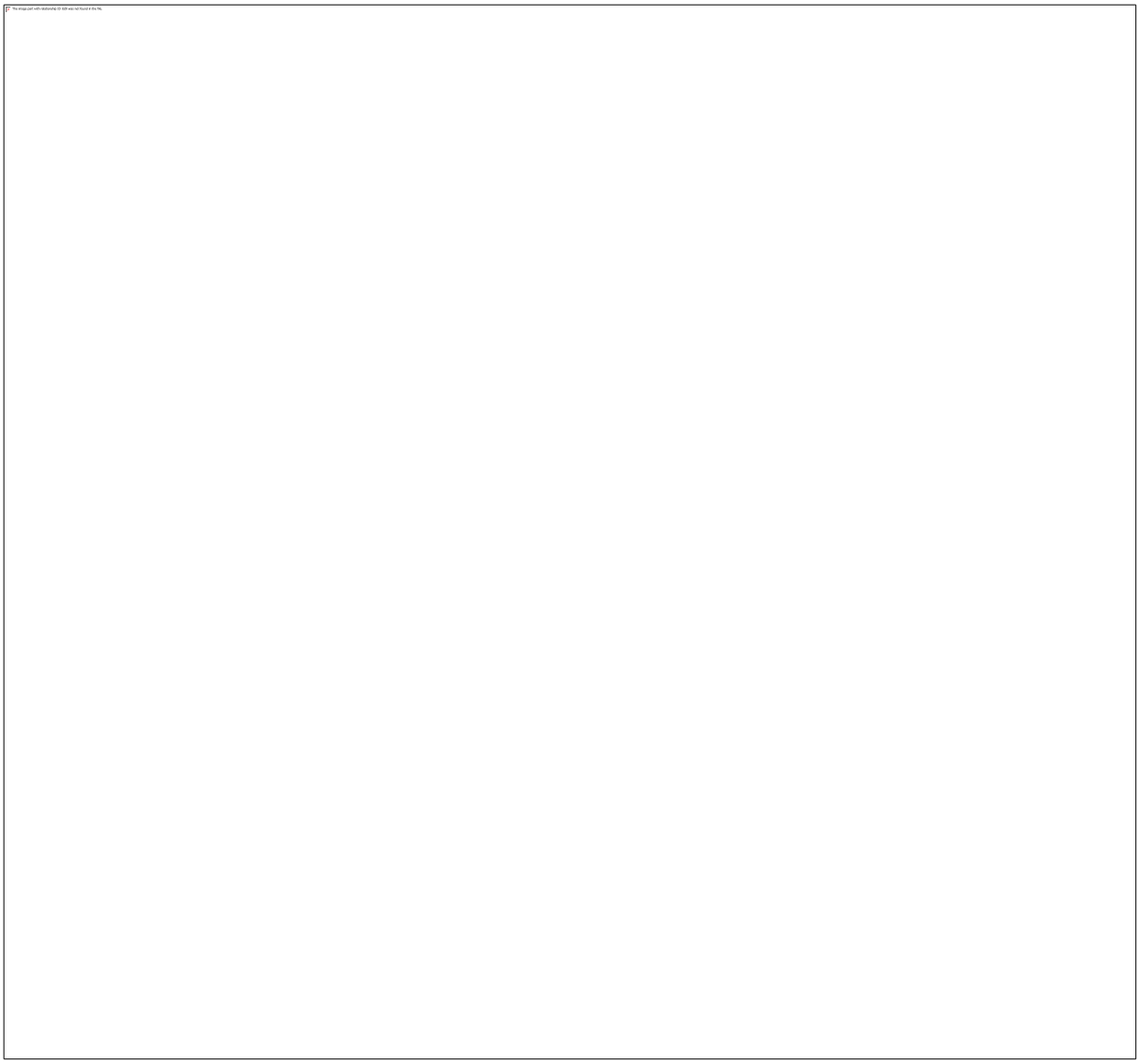
Among patients with clinical PTSD symptoms due to ACS, there is a two-fold increased risk of having another cardiac-related event or mortality within one to three years compared with cardiac patients with no PTSD symptoms (Edmondson et al., 2012a). In a recent Swiss study among MI patients, findings suggest there was a 42% increased risk of ACS recurrence associated with higher levels of PTSD symptoms (von Kanel et al., 2011). Further, the presence

of PTSD due to an ACS has been associated with increased cardiac-related hospitalizations, lower treatment adherence, and lower quality of life. Among patients undergoing CABG, PTSD occurs in approximately 15% of patients (Tully and Baker, 2012) and 18 to 37% among patients with an ICD. Among these subgroups of patients, a recent trial on CABG patients found that those with PTSD also had concomitant depression (Dao et al., 2010, Ladwig et al., 2008).

1.8 Mechanisms linking depression, anxiety and PTSD with cardiac diseases

Mental disorders including depression, anxiety and PTSD share similar biological, behavioral and psychosocial mechanisms in their contribution to the increased risk and prognosis of cardiac diseases (Figure 1.8a, 1.8b). Knowledge of these common mechanisms between the aforementioned mental disorders and CHD could help improve prevention and treatment of these comorbid conditions.

Figure 1.8a Etiological mechanisms linking depression, anxiety and PTSD with onset of cardiac disease



Note. BMI= body mass index; HPA= hypothalamic–pituitary–adrenal; HRV= heart rate variability; PTSD= posttraumatic stress disorder; SES= socioeconomic status.

1.8.1 Biological mechanisms

Depression, anxiety and PTSD have been associated with several biological mechanisms which are involved in the development and progression of atherosclerosis including, autonomic nervous system (ANS) dysfunction, hypothalamic-pituitary adrenal (HPA) axis dysregulation, inflammation and increased platelet reactivity (Rozanski et al., 1999). This, in turn leads to the onset or adverse course of cardiac diseases.

Autonomic nervous system (ANS) dysfunction

The ANS is divided into two systems, the sympathetic and parasympathetic systems that serve to control heart rate, blood pressure and other critical functions. Depression in particular tends to cause activation of the sympathetic system causing increases in heart rate and blood pressure, while affecting the coronary blood flow and increasing the risk of CHD. Another marker of ANS dysfunction is decreased heart rate variability (HRV) which is caused by increased sympathetic tone or decreased parasympathetic tone and is known to be an independent risk factor for cardiac mortality and growing risk of incident CHD (Adibfar et al., 2016, Whooley and Wong, 2013). Several studies have documented that lower HRV has been more frequent among depressed patients compared to non-depressed patients and is associated with increased mortality among depressed patients (Gehi et al., 2005, Kim et al., 2005). Reductions in HRV have also been observed among those with concurrent anxiety (Kemp et al., 2012).

Hypothalamic-pituitary adrenal (HPA) axis dysregulation

Another biological mechanism is the elevated cortisol levels from enhanced activity of the HPA axis (Dinan, 1994). HPA hyperactivity and elevated levels of cortisol have been documented among patients with depression, anxiety and PTSD (Fiedorowicz, 2014, Whooley and Wong, 2013). Meanwhile, depression has been found to cause the stress induced activation of the HPA axis, which causes an increase in levels of glucose, hyperlipidemia and visceral fat mass, ultimately increasing the risk of CHD (Bjorntorp and Rosmond, 2000).

Inflammation

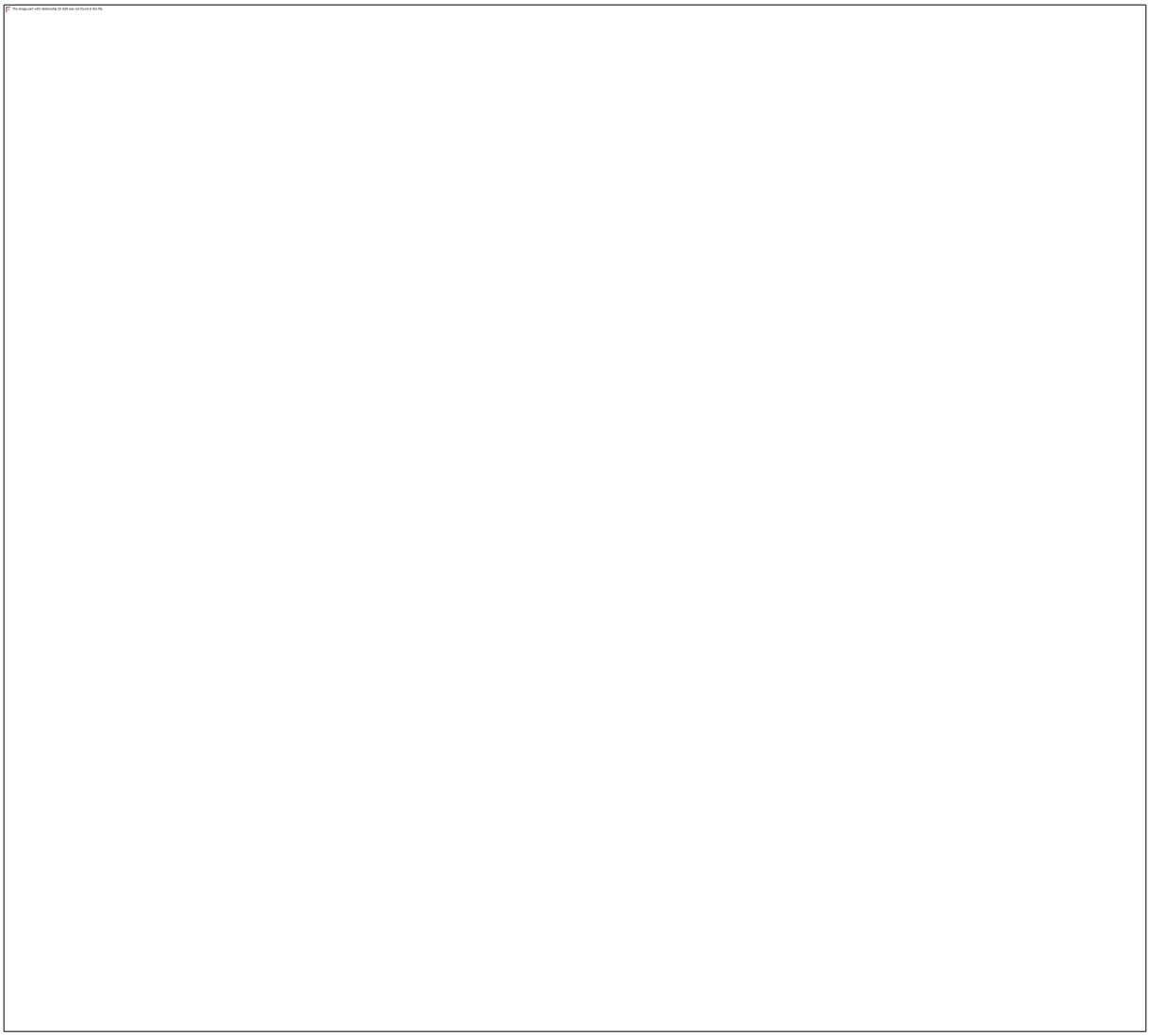
Inflammation which involves endothelial dysfunction has also been established as a causal pathway responsible for depression, anxiety and PTSD leading to an increased risk of CHD, unstable angina and MI through the development of atherosclerosis (Frasure-Smith and Lesperance, 2005). Stress, which is very common in patients with major depression, has been shown to promote endothelial dysfunction, an early sign of cardiac deterioration (Lerman and Zeiher, 2005). Patients with these mental disorders have been found to have elevated levels of

inflammatory markers (e.g. C-reactive protein (CRP); inflammatory cytokines), which have been associated with poor CHD outcomes (Poole et al., 2011, Miller et al., 2002). In a large study of health individuals, higher levels of CRP were found among those with elevated levels of anxiety (Pitsavos et al., 2006).

Increased platelet activity

MDD has been associated with increased platelet activity and aggregation, which can cause thrombus generation, a process involved in atherosclerotic diseases, including CHD. These elevated platelet levels promote clotting. Depressed patients with cardiac disease have been found to have higher platelet activation levels and endothelial dysfunction compared to non-depressed patients (Kim et al., 2014, Spiliopoulos and Pastromas, 2015, Seligman and Nemeroff, 2015, Pozuelo et al., 2009). Similarly, greater levels of platelet aggregation are more frequent among patients with anxiety and PTSD, increasing the risk of cardiac events among these patient populations (Bedi and Arora, 2007, Garvey et al., 1995).

Figure 1.8b Prognostic mechanisms linking depression, anxiety and PTSD with adverse course of cardiac disease



HPA= hypothalamic–pituitary–adrenal; HRV= heart rate variability; MACE= major adverse cardiac events; PTSD= posttraumatic stress disorder

1.8.2 Behavioral mechanisms

It is equally likely that behavioral mechanisms also explain the association between depression, anxiety and PTSD and cardiac diseases. Previous studies suggest that these mental disorders are associated with poor dietary habits, smoking, physical inactivity, obesity and alcohol consumption. These behavioral factors are associated with inflammatory activity, release of inflammatory cytokines, and increased activity in the HPA, which in turn are important drivers in the process of atherosclerosis and can increase the chance of developing cardiac disease and increase the risk of cardiac morbidity and mortality in CHD patients (Bonnet et al., 2005, Berk et al., 2013, Brumpton et al., 2013). Depression, anxiety and PTSD are associated with higher

rates of smoking, leading to three times higher rates of MI among smokers than non-smokers (Berk et al., 2013, Aubin et al., 2012, Chaddha et al., 2016). People with depression and anxiety are also at greater odds of becoming obese and not being physically active. Additionally, hypertension, diabetes, and cholesterol and obesity tend to be present among patients with depression or anxiety, and may be associated with the progression of CHD and poor cardiac outcomes in patients with established cardiac disease and onset of cardiac disease in those without established cardiac disease (Chaddha et al., 2016). Further, and most importantly, there is evidence suggesting depression and anxiety predict poor adherence among CHD patients whom are less likely to adhere to medication and treatment regimens, follow cardiac rehabilitation programs and lifestyle recommendations or practice self-management (e.g. monitor weight and food intake), all of which increase the incidence of cardiac disease and lead to adverse outcomes in those with established cardiac disease. Patients with severe depression and CHD are three times more likely not to take their medication compared to patients that had minor or no depressive symptoms (Fiedorowicz, 2014, Seligman and Nemeroff, 2015, Ziegelstein et al., 2000, Carney et al., 1995). Furthermore, among patients who do not follow behavioral recommendations there is a 10-fold increased risk of MI, compared to those who do (Chaddha et al., 2016).

1.8.3 Psychosocial mechanisms

Additionally, psychosocial factors like social support, social isolation, chronic life stressors, coping styles as well as care giving have been related to depression and anxiety and may play a role in the onset and/or course and outcomes of cardiac diseases (King, 1997, Allman et al., 2009, Kessler, 1997). Evidence indicates that low social support increases the onset and prognosis of CHD in males and females with a relative risk of 1.5 to 2.0 (Khayyam-Nekouei et al., 2013, Lett et al., 2005). Chronic life stressors such as low socio-economic status (SES) and unemployment (e.g. low income) as well as gender have been known to mediate the relationship between depression and onset of cardiac diseases. Individuals with low SES are more likely to

experience cardiac risk factors, are at higher risk for incidence of CHD, and are more likely to suffer from adverse cardiac outcomes than those with a higher SES (Golden et al., 2007, Vieweg et al., 1998). In addition, low SES is linked to poor living conditions (e.g. healthy lifestyles, lack of important resources), which can lead to cardiac risk factors such as overweight, obesity, hyperlipidemia or hypertension, ultimately leading to the development of atherosclerosis ultimately leading to the onset or progression of cardiac disease (Vieweg et al., 1998). Further, Chida et al. found that personality traits such as hostility and anger have been associated with onset of cardiac disease and poorer prognosis in CHD patients (Chida and Steptoe, 2009).

Future research should address the role of negative mood, personality traits and other psychosocial factors increasing the risk of CHD in those with mental disorders, in order to develop effective prevention and treatment strategies.

1.9 Screening of co-morbid mental and cardiac diseases

There is evidence that treating depression and anxiety improves quality of life and daily functioning in cardiac patients (Ormel et al., 2007), thus there needs to be more understanding about the nature of these mental disorders in this population. Unfortunately, health systems around the world have not yet adequately responded to the increasing burden of mental disorders in the cardiac population. As a consequence, there is a gap between the need for treatment and its provision around the world, despite the availability of effective treatments for depression and anxiety in cardiac patients (Collins et al., 2013). Screening and treatment of depression in particular by cardiology physicians continues to be limited due to poor symptom recognition and lack of desire to treat perceived primary care conditions in cardiology practice. Furthermore, physicians often do not consider depression or other mental illness as a risk factor, underestimating their negative effects (Collins et al., 2013, Tesio et al., 2017, Lichtman et al., 2014b).

The AHA has recommended routine screening of cardiac patients for depression using screening instruments as a potential way to improve detection of depression in this patient

population (Huffman et al., 2013). In western countries, the two-item Patient Health Questionnaire (PHQ-2), the PHQ-9 and the Cardiac Depression Scale short form (CDS-SF) have all been recommended as simple and effective depression screening tools in patients with heart disease (Lichtman et al., 2014b, McManus et al., 2005). Thus, it is important for psychiatrists, social workers, mental health experts, and cardiologists to be educated about the bi-directional association between mental disorders and cardiac diseases and about the symptoms and risk factors occurring in the course of both conditions (De Hert et al., 2009, Goldston and Baillie, 2008).

Regardless of the recommendations from the AHA, evidence from settings in HICs points to the fact that even in the context of well-funded health care systems, less than 15% of patients admitted for acute MI are diagnosed for comorbid depression (Lichtman et al., 2014b). Evidence from settings in European and North-American countries, including results from intervention studies, point to the gains in chronic disease outcomes and quality of life obtained from the provision of depression care at different levels. Multiple intervention studies have attempted to examine whether improving psychosocial function improves cardiac outcomes. A Cochrane meta-analysis reported benefits of psychotherapy on CVD outcomes among depressed adults (Whalley et al., 2011, Linden et al., 2007). The evidence stimulated the establishment of guidelines such as the National Institute for Health and Care Excellence (NICE) in the United Kingdom for the treatment of depression at different severity stages in patients with chronic physical conditions (NICE, 2012).

Debates still remain about the optimal screening tools for depression in light of the potentially transient nature of symptoms as well as the optimal disease management of heart disease patients with depression and its associated long-term effect (Ski et al., 2017). There is also controversy whether routine screening for depression alone in cardiac patients in fact, improves patient outcomes. With regard to the management of mental disorders, results from a Cochrane review point to collaborative care being more effective than usual care for depression

and anxiety treatment in general. Collaborative care is delivered by non-medical case managers working with the patient's physicians (e.g. their primary care physician) and with mental health specialists (psychiatrist/psychologist) (Coventry et al., 2015).

1.10 Management strategies for cardiac patients with depression, anxiety and PTSD

1.10.1 Cardiac rehabilitation (CR)

International guidelines strongly recommend the integration of mental health interventions, including diagnosis and treatment into cardiac rehabilitation (CR), yet the uptake of these recommendations remains limited (Anderson et al., 2016, Hare et al., 1995). CR is an important phase to implement psychological interventions in order to stimulate psychological well-being, disease acceptance, and to reduce depressive or anxiety symptoms. There is rich literature which supports CR including psychosocial therapies improving quality of life and health outcomes after an MI. (Oldridge et al., 1988, West et al., 2012). According to a meta-analysis on the effect of CR programs, findings suggest CR programs reduced mortality and hospital readmissions in patients with CAD (Clark et al., 2005). In addition, a home-cased CR program has demonstrated to reduce both depression and anxiety symptoms among patients recovering from CAD (Lewin et al., 1992). CR has also shown to improve prognosis, heart functioning, and HRQL among cardiac patients (Iqbal et al., 2010). More specifically, among all components in CR programs, exercise training has been strongly recommended to improve quality of life and reduce depression in patients with CVD (van Tol et al., 2006, Taylor et al., 1986).

1.10.2 Exercise programs

It has been well-established that exercise programs in a group setting could be an alternative treatment for those with depression, and appear to have the same effect on reduction of depression as anti-depressant medications. In the HF-ACTION trial, it was found that the exercise group had lower levels of depression at three and 12 months and mortality and

hospitalization rates were 10% lower for the exercise group, after adjusting for other relevant variables (Blumenthal et al., 2012).

1.10.3 Cognitive behavioral therapy (CBT)

Cognitive behavioral therapy (CBT) has been the most studied psychotherapy in patients with cardiac disease. CBT aims to treat psychological disorders that arise from negative feelings, thoughts and behaviors which occur due to stress. It has been well established that CBT for CHD or HF patients has led to major improvements and reduction in depressive or anxiety symptoms, compared to other types of care (Cully et al., 2010, Dekker et al., 2012). Further studies have suggested that CBT can have a major effect on reduction of depression in cardiac patients in combination with other management strategies such as exercise programs and anti-depressants (Berkman et al., 2003, Gary et al., 2010, Gulliksson et al., 2011).

1.10.4 Pharmacotherapy and antidepressant medications

Antidepressants are the most commonly used treatments for depression and a variety of anxiety disorders including GAD and PTSD. Selective serotonin reuptake inhibitors (SSRIs), have been found to be the most commonly used and effective for the management of depression, GAD and PTSD in cardiac patients (Berkman et al., 2003).

1.11 Background in the context of Palestine

In Palestine, health is influenced by political, economic and social determinants (Giacaman et al., 2003). The historical Palestinian-Israeli war, which began with the *Nakba* ("catastrophe" in Arabic) in 1948, has caused much suffering and distress for the Palestinian population and has been continuously affecting their lives physically, mentally, emotionally, and economically. Until now, this conflict continues to cause instability and fragmentation throughout the country including the healthcare system (Keelan, 2016, Marie et al., 2016). The Palestinian health care system is controlled by Israel in terms of healthcare budgets, border crossings, and entry

permits. In addition to the occupation, inefficient and underfunding of the existing Palestinian healthcare system has been linked to the lack of skilled health professionals as well as inadequate healthcare services and affordable medicines, all of which raise challenges in tackling the NCD epidemic across the country. Moreover, health care in Palestine including hospitals is very basic in comparison to Israeli and other international health care services. Restriction of movement across the West Bank has resulted in lack of access to quality healthcare to the most vulnerable populations, especially those in rural communities and refugee camps, whom are the most marginalized population and have higher rates of NCDs and associated risk factors (Keelan, 2016) (Husseini et al., 2009).

1.11.1 CVD epidemiology in Palestine

Palestine, a LIC and the focus of this thesis, has been facing the surging burden of NCDs in the past several decades causing an epidemiological shift in the health status of the Palestinian population (Abu-Rmeileh et al., 2012). In particular, CVDs have become highly prevalent in Palestine accounting for 29.5% of all deaths in 2014, making them the largest proportion of disease burden on the population (Murray et al., 2012). Approximately 80% of the ministry of health's (MOH) financial expenses is put to fight NCDs. In 2010, IHD contributed to 40% of all deaths in the Gaza Strip and 36.7% of all deaths in the West Bank (Mosleh et al., 2018). Moreover, Palestine has high rates of CVD-related risk factors: 19.3% for smoking, 46.5% for physical inactivity and 26.8% for obesity (Rahim et al., 2014). These numbers are predicted to increase in the coming decades, ultimately continuing to increase the prevalence of CVDs (Husseini et al., 2009).

1.11.2 Mental health in Palestine

The ongoing-conflict in combination with the violence and continued humiliation among Palestinian citizens has resulted in high levels of psychological stress. Mental disorders are becoming more common, yet are given little attention. Palestinians have been subjected to Israeli checkpoints, physical violence, bombardment, massive demolitions, street closures, blockades, inadequate healthcare, clashes with Israeli occupation forces, imprisonment and discrimination, all of which could be considered risk factors of depressive disorders and have substantially contributed to the burden of mental health in the occupied Palestinian territories (oPt) (Giacaman et al., 2009, Marie et al., 2016). According to the GBD 2013, major depressive disorder (MDD) is the leading cause of YLDs and the third leading cause of DALYs in Palestine (Murray et al., 2012). Espié et al. found that 15.3%, 17.3% and 23.2% of citizens suffered from depression, anxiety and PTSD in the city of Nablus and Gaza Strip from 2005-2008, (Espié et al., 2009). Moreover, Madianos et al. found a prevalence of 24.3% and 10.6% for lifetime and one-month prevalence of major depression episode (MDE), respectively in a 2007 West Bank-based study (Madianos et al., 2012).

Mental health services have been managed in the past by the Israeli government after the 1967 war, and remain underdeveloped and neglected in Palestine. Although there is a need for effective secondary prevention and quality mental health care, there is a lack of resources, infrastructure and trained professionals. In addition, mental health services are underreported, undertreated, under researched and under supported in Palestine.

Currently there are only two psychiatric hospitals and approximately 30 psychiatrists serving the current 4.8 million people in Palestine (Jabr, 2013 , Awwad, 2016). Both the West Bank and Gaza Strip offer governmental and non-governmental services through 42 community mental health clinics (CMHCs), however these are not enough to provide care to the large proportion of the population that is in need (Jabr, 2013). According to the MOH, the CMHCs served 87.7 per 100,000 mental health patients in 2013. Among those who visited the clinics, 24.2% were affected by neurotic disorders, 14.6% schizophrenia, 10.7% epilepsy, 7.8% other

mental disorders and only 1.7% by substance abuse disorders (Marie et al., 2016). In 2015, the MOH reported 76, 018 attended the CMHCs, among those, 2735 were new cases (females more than males). Adding to the inadequate services to meet the mental health needs of the population, the MOH has not considered mental health in its financial budget. Currently only 2% of the MOH budget has gone towards targeting mental health issues (Awwad, 2016).

1.12 Rationale of thesis

It is known from Western European and North-American contexts that mental health problems go largely unrecognized in cardiac patients. This problem is likely aggravated in Palestine, where CVD rates are high and the population faces severe psychological challenges in light of the difficult political situation. In addition, the prevalence of mental disorders in Palestine is increasing (Marie et al., 2016) and mental health services remain scarce both, because of limited resources, but more importantly as a result of the stigmatization of mental diseases in the Middle Eastern culture. The evidence base to promote mental health services is currently dearth in Palestine.

The process towards integrating mental health and cardiac care requires assessment of and customization for the specific platform; identification of tasks and human resources for case findings and delivery of interventions; and application of the principles of collaborative care, care management, and quality improvement. Action needs to be taken through addressing the social and political consequences of the conflict in Palestine and evaluating the well-being of the population (de Val D'Espaux et al., 2011). With that said, research and implementation depend on adequate and reliable screening instruments capable of assessing mental health, well-being and its determinants in the unique sociocultural context of Palestine. No specific screening instruments have been established yet to study the mental health profile in the Palestinian adult population or in the subgroup of heart disease patients.

The alarming increase in prevalence of mental disorders and the drastic rise in rates of CVDs in Palestine, calls for more studies to be conducted in these cultural settings where patients are in particular need for integrated mental health and routine cardiac care. There is a general knowledge gap in understanding the factors that mediate and modify the effect of mental disorders on the course of CVD, and in the case of this thesis, cardiac disease. Shared risk factors between the mental disorders of interest and cardiac disease such as socio-economic status, psychosocial factors and other comorbid conditions have been established, however whether the coexistence of these individual risk factors with depression increase risk of cardiac disease still remains unknown. It is of utmost importance to address these gaps in knowledge in order to prevent and treat these comorbid diseases.

Research into the effect of mental disorders on the health outcomes and quality of life in patients with cardiac disease and also into the effectiveness of screening for and treating mental health problems has not been conducted in Palestine. The studies in this thesis investigate the role of mental disorders among cardiac patients living in Palestine. The findings of this project will increase the awareness of mental health problems and their link to NCD control in various Palestinian organizations, health care workers and in the social networks of the participants.

This project ultimately sets the basis for intervention research and provides local evidence for the need of integrating mental health treatment into cardiac care and to characterize patient sub-groups that are likely to benefit most from mental health screening and intervention. The findings obtained among this Palestinian population have helped deepen our understanding of mental health issues in a unique sociocultural and marginalized setting such as refugee camps, the prevalence of which has become a global health issue of major concern. Refugees and migrants are population groups undergoing fast epidemiological transitions in the context of tremendous mental health pressure. The results from this thesis will provide guidance for integrated care provision to these highly susceptible populations.

2

OBJECTIVES

This PhD thesis aimed to contribute to a better understanding of the role of mental disorders among a well-characterized cohort of cardiac patients in conflict-affected Palestine. Specific objectives of this thesis were as follows (Figure 2.1):

O1. Determine the prevalence and associated factors of depression and anxiety

O2. Identify socio-demographic, clinical, psychosocial, and lifestyle factors associated with a high risk of depressive and anxiety symptoms

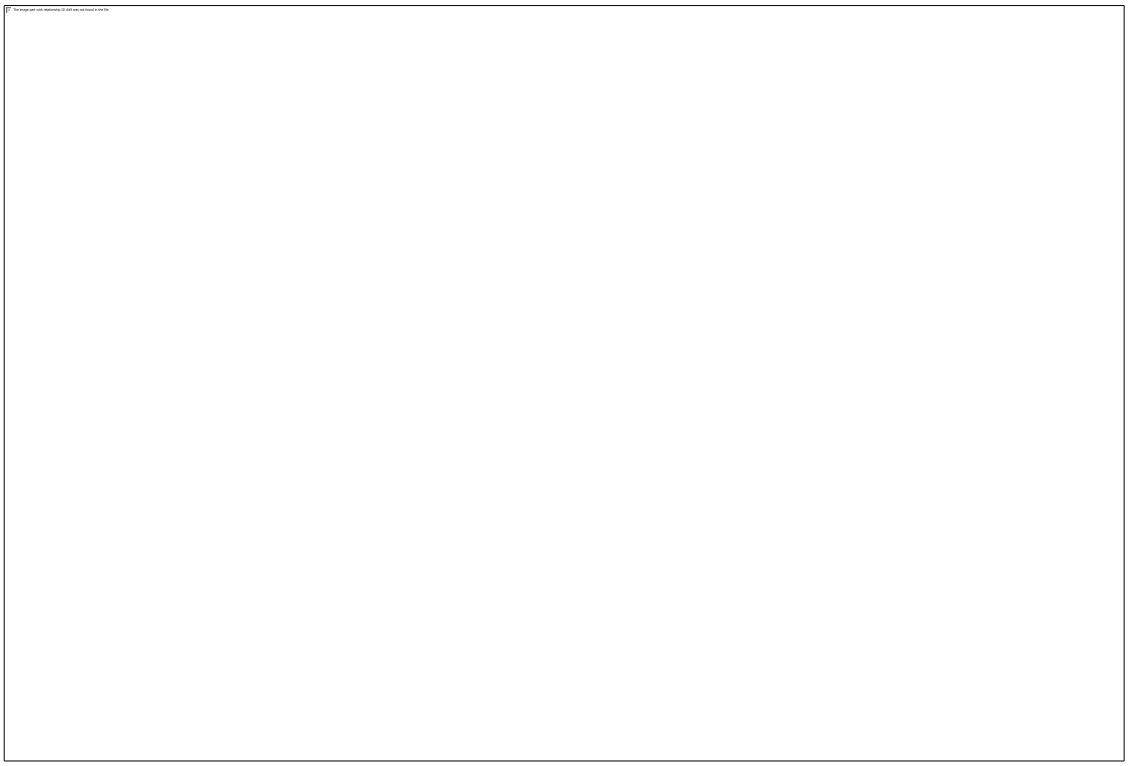
O3. Assess if women are more likely to suffer from depression than men? Determine if and what socio-demographic, clinical psychosocial and lifestyle characteristics mediate the relationship between gender and depression

O4. Investigate the longitudinal association of post-traumatic stress disorder (PTSD) with health-related quality of life (HRQL)

O5. Assess the mediating roles of depression, anxiety and stress in the relationship between PTSD and HRQL to determine patient sub-groups that are likely to benefit most from mental health screening and intervention

In order to answer objectives 1, 2 and 3 a cross sectional design was performed and to answer objectives 4 and 5 a longitudinal design was performed. The results of objectives 1 and 2 are presented in Chapter 4, Article I; the results of objective 3 are presented in Chapter 5, Article II; and the results of objectives 4 and 5 are presented in Chapter 6, Article III.

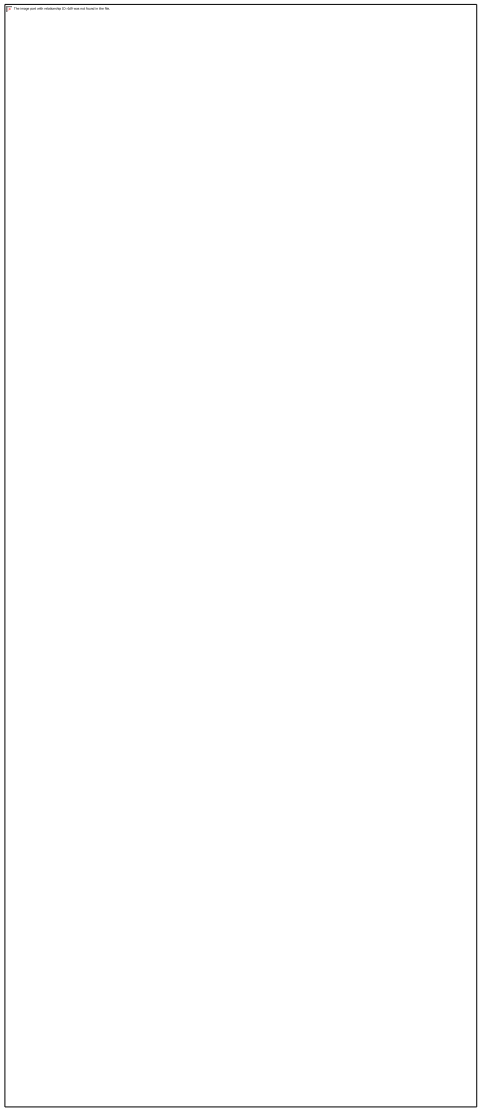
Figure 2.1 Conceptualization of thesis objectives



3

METHODOLOGY

This chapter describes the methodology of the three completed studies of this PhD thesis (Chapters 4-6), including (a) the study design, (b) study setting, (c) study population (d) data collection and instrumentation, and (e) ethical considerations. Study variables, procedures and analytic approaches specific to each study are described within each chapter and their respective supplementary material. As each thesis study was written as a standalone manuscript for publication, some of the methods detailed in this chapter will often be repeated in the subsequent chapters.



3.1 Study setting

The study took place in four hospitals in the city of Nablus, Palestine, which is located in the north of the West Bank (figure 3.1) and 49 kilometers from Jerusalem. The city is home to a population of over 150,000 people. The four participating hospitals were Al-Watani Hospital (governmental), An-Najah National University Hospital (NGO), Arab-Specialized Hospital (private) and Al-Arabi Hospital (private). These hospitals attend a population from both rural

and urban areas coming from different cities, villages, and camps from Jenin, Tubas, Tulkarem, Salfit, Ramallah, and also southern parts of the West Bank. The study is restricted to the city of Nablus for several reasons: budgetary and feasibility constraints given the complications in traveling between different cities in Palestine; the high density of cardiology care in Nablus (there are only ten hospitals in the West Bank that offer cardiac services in which four of the ten are in Nablus and include either some or all cardiac services including a cardiac surgery department, a basic cardiology department and a coronary care unit (CCU); the chosen study sites cover a large proportion of the population residing in the North including those in the refugee camps. This sets the basis and offers the opportunity for a future population-based heart disease registry in the region of Nablus to evaluate and thereby improve quality of cardiac care.

3.2 Study design

A baseline cross-sectional design and a prospective longitudinal design were undertaken to assess the role of mental diseases among cardiac patients (Figure 3.2).

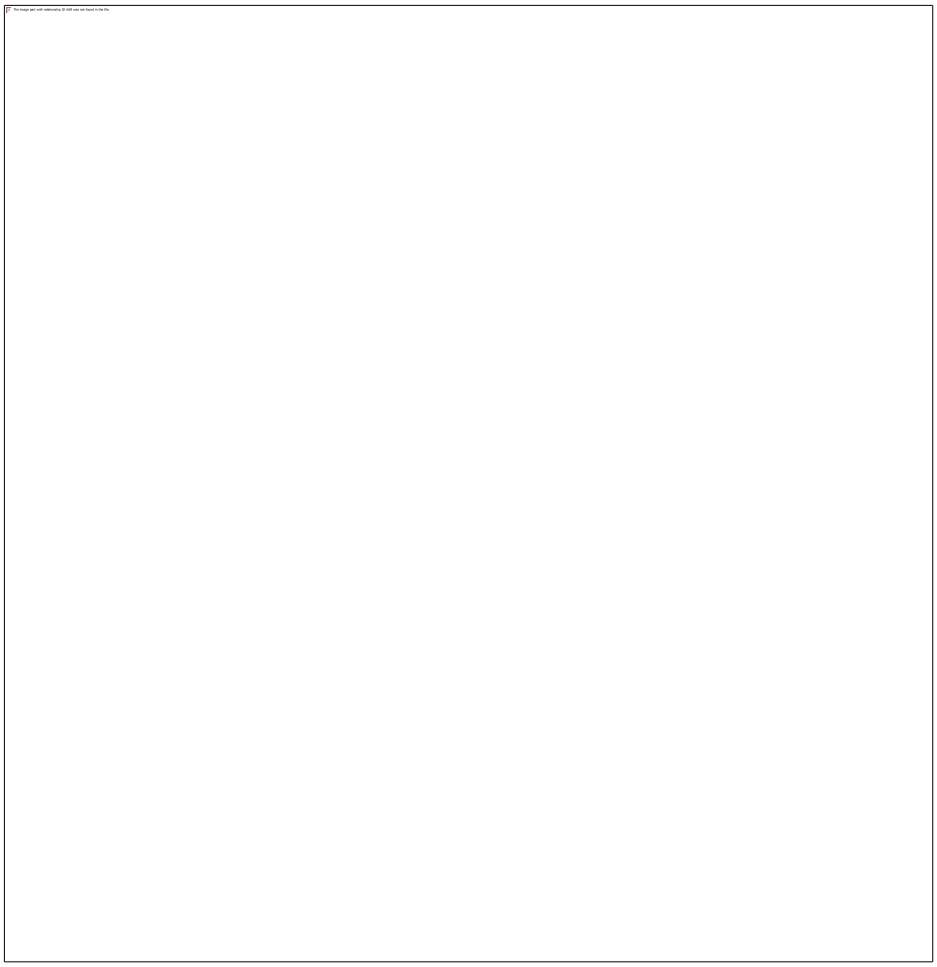


Figure 3.2 Study design for data collection

3.3 Study population

3.3.1 Inclusion criteria

Female and male patients' ages 30 to 80 years consecutively admitted to one of the participating hospitals with a new or pre-existing CVD including CAD, angina, MI, HF, AF or any other cardiac-related disease were invited to participate in the study. Patients were only recruited at cardiac clinics, cardiology departments or cardiac surgery departments at the respective hospitals.

3.3.2 Exclusion criteria

Patients with stroke, peripheral vascular disease, end-stage kidney disease (including dialysis patients), major co-morbidities affecting mental health (alcohol abuse, drug abuse), neurological disorders (dementia, Alzheimers, epilepsy, Parkinson's), cognitive impairment or any severe psychiatric condition or any other condition that will affect the quality of responses.

3.4 Data collection

3.4.1 Pilot study

A pilot study was undertaken at An-Najah National University Hospital in the city of Nablus between July and August, 2016. Patients visiting the cardiology and orthopedic departments of the hospital were considered for the study. Patients in the cardiology department were recruited using convenient sampling if they were newly diagnosed or have had a pre-existing cardiac diagnosis for a minimum of four months. Patients were excluded if they suffered from a severe cardiac disease and were not able to respond to the questionnaire. Patients from the orthopedic department were recruited for the control group using convenient sampling. A total of 120 patients agreed to participate in the pilot study and informed consent was
obtained from all patients prior to the interviews. Interviews were conducted by previously trained field workers and lasted 90 minutes each.

The sole purpose of the pilot was to determine the feasibility of conducting the interviews within a hospital setting in Palestine, to determine patients perception/attitudes towards the questionnaires, time needed to complete the questionnaires, and limitations of the instruments and questions used in the questionnaires. The data from the pilot had not been analyzed, however, findings from the methodology of the pilot assisted and led to the study design of the current studies included in the thesis.

3.4.2 Baseline study

Eligible patients were recruited for in-person interviews from March 2017 until November, 2017 by the study team which included the PhD student and trained medical research assistants. Patients were identified using hospital registries and medical records. Interviews were conducted while patients were awaiting treatment (after CATH) or after their treatment, within one week of their admission to the hospital. Data was collected using a structured questionnaire consisting of two parts (see Appendix II). The first part included detailed socio-demographic and clinical information obtained from patients' administrative and medical charts. The second part was administered during a private face-to-face interview and consisted of a sequence of screening instruments (see Appendix I) and lifestyle-related questions. Interview responses were entered directly into an electronic software (OpenDataKit) using tablets. The questionnaire, including the instruments, was translated from English to Arabic and back-translated from Arabic to English by two bilingual experts.

3.4.3 Longitudinal study

All patients that were recruited for the baseline assessment and were included in the baseline analysis were invited to participate in a follow-up assessment between June and December, 2018, approximately 12-months (on average) after initial enrollment. Patients were re-contacted by telephone and asked to attend an in-person interview at a medical facility in Nablus, Palestine. Patients refusing in-person interviews were asked to provide relevant information during a phone interview.

3.4.4 Study variables and Instruments

All study variables including outcome variables are presented in detail in the upcoming thesis chapters 4, 5, and 6. Screening instruments used for both baseline and longitudinal studies are described in detail below:

Cardiac Depression (CDS). The Cardiac Depression Scale (CDS), by Hare et al., is a 26-item questionnaire used to measure depression in patients with CVD (Hare and Davis, 1996). It has been used and validated in cardiac patients with a range of diagnoses such as HF, post-MI, CAD, and arrhythmias. The CDS has accurate psychometric properties including internal and external reliability and validity. Items on the scale are measured on a seven-point Likert scale from 1 (strongly disagree) to 7 (strongly agree). CDS scores range from 26-182. The CDS can be used as a continuous measure, where higher scores indicate higher depressive symptoms or as an ordinal indicator of possible depression using cut-off points previously used in literature (Shi et al., 2010).

Depression, anxiety, stress (DASS-42). Depression, anxiety and stress were additionally measured using the Depression Anxiety Stress Scale-42 (DASS-42) by Lovibond & Lovibond. The 42-item scale has been validated for clinical and non-clinical samples and has been proven to be a reliable screening tool for symptoms of depression, anxiety and stress. Prior studies have demonstrated high internal consistency and convergent and discriminant validity of the DASS. The questionnaire is divided into three scales (one for each state) each containing 14 items. Items are scored on a four-point Likert scale ranging from 0 (did not apply to me at all) to 3 (applied to me very much) measuring the extent to which each state was experienced over the past week. Scores for each of the three scales are determined by summing up the scores and categorized into: depression 0-9 (normal), 10-20 (mild-moderate), >21 (severe-very severe); anxiety 0-7 (normal), 8-14 (mild-moderate), >15 (severe-very severe); stress 0-14 (normal); 15-25 (mild-moderate), >26 (severe-very severe) (Lovibond SH, 1995).

Health-related quality of life (HeartQoL Questionnaire). HRQL at follow-up was assessed using the HeartQoL Questionnaire, a 14-item IHD-specific scale, which measures overall quality of life. The global HeartQoL score indicates how the patient perceives being bothered by their heart disease (Oldridge et al., 2012). In this thesis, the total score was determined by

summing up the scores of all 14 items which were assessed on a four-point scale from 0 to 3 (0=poor and 3=good quality of life). The overall score range was 0-42, with higher scores indicating better HRQL.

Somatic symptoms (PHQ-15). The Patient Health Questionnaire-15 (PHQ-15) is a 15-item, somatic symptom scale derived from the full Patient-Health-Questionnaire to measure the severity of somatization in patients. Patients were asked to indicate the severity of 15 physical symptoms they may have experienced during the past four weeks on a three-point scale 0 ("not bothered at all") to 2 ("bothered a lot"). The total PHQ-15 score was obtained by summing the scores of each item and classified as minimal (0-4); mild (5-9); moderate (10-14); and high (15-30) with higher scores indicating greater severity of somatic symptoms. Prorated scores were calculated if there were unanswered items on the measure (Kroenke et al., 2002).

Quality of life (SF-12-PCS; SF-12-MCS). Quality of life at baseline was assessed using the 12-item Short Form Health Survey (SF-12), an alternative to the SF-36 that measures overall health status. The SF-12 is comprised of two components, the Mental Component Summary (MCS) score and the Physical Component Summary (PCS) score. The SF-12 consists of 12 items including mental health items (vitality, role-emotional, social function, and mental health) and physical health items (physical functioning, physical role, bodily pain). The possible scores of the 12 questions range from 0-100, in which lower scores reflect lower levels of health and higher scores reflect higher levels of health. The MCS and PCS scores were standardized based on data of a US general population using a mean score of 50 and a standard deviation (SD) of 10 (Ware et al., 1996).

Post-traumatic stress disorder (PTSD-PCL-S). The Post-Traumatic Stress Disorder Checklist (PTSD-PCL-S) is a 17-item scale used to assess PTSD symptoms based on the DSM-IV criteria. Each item in the checklist is scored from 1 (not at all) to 5 (extremely), indicating the extent to which the patient has been bothered by the symptom in the past month. A total

symptom severity score is calculated. The range of the total score is divided into four categories of PTSD symptom severity: "little" (17-29), "some" 28-29 "moderate-moderately high" (30-44), and "high" (45-85) (Blanchard et al., 1996).

Social Support (ESSI). Social support was assessed using the seven-item ENRICHD (Enhancing Recovery in Coronary Heart) Social Support Instrument (ESSI) comprised from the Medical Outcomes Survey (MOS) and assesses for four components of social support including emotional, instrumental informational and appraisal. The ESSI has been used in previous studies on cardiac populations with post-MI and CAD. It has demonstrated high internal consistency, reliability, and good convergence. Items on the ESSI are summed up for a total score with item categories ranging from 1 (none of the time) to 5 (all of the time). Patients who score ≤18 on the scale are considered to have low social support and meet the ENRICHED eligibility criteria (The ENRICHD investigators, (2000b, 2001)).

Self-esteem (SISE).The Single-Item Self-Esteem Scale (SISE) is a one-item scale developed as an alternative of the Rosenburg Self-Esteem scale, which is used to measure self-esteem. It is based on a seven-point Likert scale from 1 (not very true of me) to 7 (very true of me) (Lett et al., 2004).

Resilience (RS-14). Resilience Scale-14 (RS-14) is a 14-item questionnaire that assesses resilience in a general population. The RS-14 is comprised of five characteristics of the resilience core, including purpose, perseverance, self-reliance, equanimity, and authenticity. Items of the RS-14 are scored on a seven-point Likert scale from 1 (strongly disagree) to 7 (strongly agree). Total scores range from 14 to 98, and are categorized as very low (14-56); low (57-64); on the low end (65-73); moderate (74-81); moderately high (82-90) and high (91-98) resilience levels (Wagnild and Guinn, 2009).

3.5 Ethical considerations

The studies of this PhD thesis were carried out in accordance with the principles of ethics of the Declaration of Helsinki (DoH). The study protocols and questionnaires were submitted to the responsible ethics committees. Ethical approval was obtained from the Ethics Committee of Basel-Stadt and Basel-Land in Basel, Switzerland and from the Institutional Review Board (IRB) committee at An-Najah National University in Nablus, Palestine. Informed consent forms in Arabic, stating study objectives, purpose and significance of study were distributed to all participating patients prior to the beginning of the cross-sectional study and longitudinal study.

4

ARTICLE I

Depression and anxiety symptoms in cardiac patients: a cross-sectional hospital-based study in a Palestinian population

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Please refer to Appendix III for published article.

Abstract

Background. Mental health problems have an adverse effect on the course of cardiac disease. The integration of their diagnosis and treatment into cardiology care is generally poor. It is particularly challenging in cultural environments where mental health problems are stigmatized. The objective of the current study was to investigate the proportion of cardiac patients with depression and anxiety as well as factors associated with the presence of these symptoms in a Palestinian population.

Methods. This cross-sectional hospital-based study was conducted on patients consecutively admitted with a new or existing cardiac diagnosis to one of the four main hospitals in Nablus, Palestine over an eight-month period. Data was obtained from hospital medical charts and an in-person interview, using a structured questionnaire with a sequence of validated instruments. All subjects were screened for depression and anxiety using the Cardiac Depression Scale (CDS) and the Depression Anxiety Stress Scale (DASS-42). Multivariate ordered logistic regression analyses were performed to identify factors among four categories (socio-demographic, clinical, psychosocial, lifestyle) independently associated with depression and anxiety.

Results. In total, 1053 patients with a confirmed cardiac diagnosis were included in the study with a participation rate of 96%. Based on the CDS and DASS-42, 54% met the criteria for severe depression (CDS >100) and 19.2% for severe-to-very severe anxiety (DASS-anxiety >15), respectively. Symptoms of depression and anxiety were more prevalent among females and less educated patients. Factors independently associated with both depressive and anxiety symptoms were post-traumatic stress disorder symptoms, low levels of self-esteem, high somatic symptoms, low physical and mental health component scores, active smoking, physical inactivity, and longer disease duration. Patients with depressive and anxiety symptoms also reported poor social support and lower resilience.

Conclusion. There was a high level of depression and anxiety in this sample of cardiac patients. The results point to characteristics of patients in particular need for mental health screening and suggest possible targets for intervention such as strengthening of social support and of physical activity. The integration of mental health services into cardiac rehabilitation in Palestine and comparable cultural settings is warranted from the time of first diagnosis and onward.

Keywords: Depression, anxiety, cardiovascular diseases, predictors, prevalence, cardiac rehabilitation

4.1 Background

Cardiovascular diseases (CVDs) and depression are among the leading causes of the global disease burden (Murray et al., 2012). CVDs are the most common cause of death accounting for 17.9 million deaths globally, in 2015 (Roth et al., 2017). Depression affects over 300 million people around the world (WHO, 2012), and is expected to become the main cause of disability globally, in 2030 (Mensah and Collins, 2015). Similarly, in 2010, anxiety affected approximately 272 million people, worldwide (Baxter et al., 2014).

There is a high prevalence of mental disorders, particularly depression and anxiety, in CVD patients (Rutledge et al., 2009b). The bidirectional link between CVDs and these mental disorders has been extensively documented in literature (Lippi et al., 2009, Holt et al., 2013, Riba M, 2011). Approximately, 15-30% of patients with CVD suffer from depressive disorders (Lesperance and Frasure-Smith, 2000, Frasure-Smith and Lesperance, 2006a, Rudisch and Nemeroff, 2003, Thombs et al., 2008, Carney and Freedland, 2008). These rates of depression are two to three times higher than in the general population (Kessler et al., 2003). Moreover, depression and anxiety have been found to worsen prognosis and quality of life in patients with coronary artery disease (CAD), myocardial infarction (MI), heart failure (HF), unstable angina, and coronary artery bypass grafting (CABG) (Lett et al., 2004, Nicholson et al., 2006, Rutledge et al., 2006, Jiang et al., 2001, de Jonge et al., 2006, Blumenthal et al., 2003, de Jager et al., 2018). CABG is defined as a surgical procedure that is performed to treat people who have severe coronary heart disease, which improves blood flow to the heart (Harris et al., 2013). They were also found to be the biggest driver of health care costs in coronary heart disease (CHD) patients (Palacios et al., 2018).

Mental health problems have a direct physiological effect on the course of cardiac disease and their adverse effect may be mediated by non-compliance to lifestyle interventions, treatment and medication (Chaddha et al., 2016, Lichtman et al., 2008). Furthermore, these

mental disorders add to the burden of managing CVD, from a perspective of treatment complexity and emotional distress. This problem is further aggravated by the high rate of additional co-morbidities such as diabetes, hypertension and obesity (Leon and Maddox, 2015).

The American Heart Association (AHA) has recommended routine depression screening in cardiac patients (Lichtman et al., 2008). However, health systems have not yet adequately responded and less than 15% of cardiac patients are being diagnosed and treated for depression (Huffman et al., 2006). Integrating mental health into cardiac treatment is of particular relevance in low-middle-income countries (LMICs), where the burden of depression and anxiety is often high and aggravated by adverse life and political conditions. Similarly, mental health problems are stigmatized in many of these non-western cultures (Rathod et al., 2017). Little is known on the prevalence of depression and anxiety among cardiac patients in LMICs (Ormel et al., 2007). This also applies to Palestine, where mental disorders commonly are not recognized, diagnosed or treated, despite the increase in their prevalence (Marie et al., 2016). Unaddressed mental care needs may be an important barrier to the successful management of cardiac patients in Palestine, where CVD remains the leading cause of death (Mosleh et al., 2018).

Mental health problems have not been studied in cardiac patients in the Palestinian population. Therefore, the aim of the current study was to determine the proportion of patients with depression and anxiety symptoms admitted with a cardiac diagnosis, to one of the four main hospitals in Nablus, Palestine. To guide physicians in effective mental health screening in the future, we also identified socio-demographic, clinical, psychosocial, and lifestyle factors associated with a high risk of depression and anxiety symptoms.

4.2 Methods

4.2.1 Study design and population

This cross-sectional hospital-based study was conducted on patients consecutively admitted to the cardiology and cardiac surgery departments of An-Najah National University Hospital, Arab-Specialized Hospital, Watani Hospital and Nablus Specialized Hospital in the Northern West Bank city of Nablus, Palestine. Patients were eligible for the study if they were between 30 and 80 years of age and had an existing or newly confirmed cardiac diagnosis warranting hospitalization during the period between March and November 2017. In the present study, cardiac diagnoses considered included CAD, ST elevation or non-ST elevation MI, angina, HF, cardiac arrhythmia, valve disease or any other cardiac disease. Diagnoses were confirmed using hospital medical charts. Patients were excluded if they had a normal cardiac catheterization (CATH), an acute or past stroke, end-stage kidney disease (including dialysis patients), peripheral vascular disease, major co-morbidities affecting mental health (alcohol abuse, drug abuse), neurological disorders (dementia, Alzheimer's disease, epilepsy, Parkinson's disease), cognitive impairment, a severe clinically diagnosed psychiatric condition or any other condition affecting the quality of their responses.

Eligible patients were recruited for in-person interviews by trained medical research assistants. Patients were identified using hospital registries and medical records. Interviews were conducted while patients were awaiting treatment (after CATH) or after their treatment, within one week of their admission to the hospital. Eligible patients were informed about the study objectives and benefits and written informed consent was obtained from those who agreed to participate. The study was approved by the Ethics Committee of Nordwest-und Zentral Schweiz (EKNZ) in Basel, Switzerland, and by the Institutional Review Board (IRB) committee at An-Najah National University in Nablus, Palestine.

4.2.2 Study assessments and measures

Data was collected using a structured questionnaire consisting of two parts (Table 4.1). The first part included detailed socio-demographic and clinical information obtained from patients' administrative and medical charts.

Table 4.1. Predictor blocks used in bivariate and ordered logistic regression analyses

Block	Variable
1 Socio-demographic factors	Age, gender, marital status, residence, education level, occupation
2 Clinical factors	Current diagnosis, previous cardiac diagnoses, years with cardiac disease, cardiac treatment (at admission), co-morbidities, medications, somatic symptoms (PHQ-15), family history of CVD, QoL (SF-12-PCS)
3 Psychosocial factors	PTSD (PTSD-PCL-S), social support (ESSI), resilience (RS-14), self-esteem (SISE), QoL (SF-12-MCS)
4 Lifestyle factors	Smoking status, currently on diet, fat consumption, vegetable and fruit consumption, alcohol use, physical activity, BMI

Note. CVD= cardiovascular disease; QoL= quality of life; PHQ-15= Patient Health Questionnaire-15; PCS= Physical Component Summary; PTSD=post-traumatic stress disorder; PTSD-PCL-S=Post-Traumatic Stress Disorder Checklist; ESSI= ENRICHD Social Support Instrument; RS-14= Resilience scale-14; MCS= Mental Component Summary; BMI= body mass index

The second part was administered during a private interview and consisted of a sequence of screening instruments. These validated tools have demonstrated to be suitable for clinical populations to assess for depression and anxiety symptoms, quality of life, posttraumatic stress disorder (PTSD), social support, resilience, self-esteem, somatic symptoms and lifestyle behaviors. The questionnaire, including the instruments, was translated from English to Arabic and back-translated from Arabic to English by two bilingual experts.

Table 4.2. Study Instruments (see Chapter 3, p. 32 for further descriptions)

Instrument	Description

Outcomes - assessment of depression, anxiety and stress	
Cardiac Depression (CDS)	The primary outcome of the study was measured using the Cardiac Depression Scale (CDS) by Hare et al., a disease-specific, 26-item questionnaire used to measure depression in patients with CVDs. CDS scores range from 26-182, and items are scored on a seven-point Likert scale from 1 (strongly disagree) to 7 (strongly agree) (Hare and Davis, 1996). The CDS can be used as a continuous measure, where higher scores indicate higher depressive symptoms or as an ordinal indicator of possible depression using cut-off points previously used in literature. In this study, the presence of mild-to-moderate depression was defined as a CDS score of 90-100 and the presence of severe depression as a score >100. Scores below 90 indicated no-to-minimal depression (Wise et al., 2006).
Depression, anxiety, stress (DASS-42)	Depression (DASS-depression), anxiety (DASS-anxiety) and stress (DASS-stress) were measured using the Depression Anxiety Stress Scale-42 (DASS-42) by Lovibond & Lovibond, a 42-item questionnaire consisting of three subscales, each containing 14 items scored on a four-point Likert scale ranging from 0 (did not apply to me at all) to 3 (applied to me very much), measuring the extent to which each item was experienced over the past week. The scores are classified as: depression 0-9 (normal), 10-20 (mild-moderate), >21 (severe-very severe); anxiety 0-7 (normal), 8-14 (mild-moderate), >15 (severe-very severe); stress 0-14 (normal); 15-25 (mild-moderate), >26 (severe-very severe) (Lovibond SH, 1995).
Predictors – correlates of depression and anxiety	
Somatic Symptoms (PHQ-15)	The Patient Health Questionnaire (PHQ-15) is a 15-item somatic symptom scale derived from the full Patient-Health-Questionnaire to measure the severity of somatization in patients (Kroenke et al., 2002).
Quality of life (SF-12-PCS; SF-12-MCS)	Quality of life was assessed using the 12-item Short-Form Health Survey (SF-12), which is a generic measure of overall health status. The SF-12 is comprised of two components, the Mental Component Summary (MCS) score and the Physical Component Summary (PCS) score (Ware et al., 1996).
Post-traumatic stress disorder (PTSD-PCL-S)	The Post-Traumatic Stress Disorder Checklist (PTSD-PCL-S) is a 17-item scale used to assess PTSD symptoms based on the Diagnostic and Statistical Manual of Mental Disorders (DSM IV) criteria. The PTSD-PCL-S is used to link symptom endorsements to a specific stressful or traumatic event or experience (Blanchard et al., 1996).
Social Support (ESSI)	The ENRICHD (Enhancing Recovery in Coronary Heart) Social Support Instrument (ESSI) is a seven-item scale comprised from the Medical Outcomes Survey (MOS). It assesses four components of social support including emotional, instrumental, informational and appraisal (2000b, 2001).
Self-esteem (SISE)	The Single-Item Self-Esteem Scale (SISE) is a one-item scale developed as an alternative of the Rosenburg Self-Esteem scale (Robins et al., 2001).
Resilience (RS-14)	Resilience Scale (RS-14) is a 14-item questionnaire that assesses individual resilience in a general population (Wagnild and Guinn, 2009).

4.2.3 Statistical analyses

The primary endpoints in the present study were depression and anxiety. The four predictor blocks investigated for association with depression and anxiety were socio-demographic, clinical, psychosocial and lifestyle factors (Table 4.S1). Descriptive statistics for stress as an endpoint are presented in Table 4.S2, with no further description. Endpoints and predictors were described as means and standard deviations (SD) for quantitative variables and as absolute values and percentages for categorical variables. Differences in predictor variables according to presence or absence of depression and anxiety symptoms were described using chi-squared test and the Wilcoxon rank sum test, as appropriate. Fisher's exact test was used for results presenting a frequency below five. Multivariate ordered logistic regression analyses were performed to examine the independent association between predictor variables and depression or anxiety symptoms. All variables were entered in each of the models at once. Results are presented in separate models for depression and anxiety and are expressed as odds ratio (OR) and 95% confidence intervals (95% CI). The cut-offs for the respective outcome variables were normal, mild/moderate, and severe/very severe according to standardized cut-offs. Correlations between the outcome variables and other instruments used in the study were assessed using Spearman's rank correlation coefficient. Cronbach alpha was used to assess the internal consistency of the different scales. Statistical significance was defined as a two-sided p-value <0.05. All data was analyzed using the STATA Data Analysis and Statistical Software, version 14.

4.3 Results

In total, 1092 patients were eligible and approached for an interview. Among the 1053 (96%) patients which agreed to participate in the study, 1022 patients with complete outcome and predictor information were used in the analysis.

4.3.1 Characteristics of study population

Characteristics of the participants are presented in Table 4.3.

Socio-demographic factors. Among the 1022 patients, 73.4% were males. The mean age of patients was 58.9±10.1 years (range 30-80 years). The majority of participants were married (90.6%), 37% were unemployed, and 58.7% did not have a high school diploma. Most of the study population lived in cities (46.4%) or villages (46.3%), while 7.3% resided in refugee camps.

Clinical factors. The primary diagnoses among the sample were MI (39.7%), CAD (32.7%), angina (15.9%) and other diagnoses (11.7%), including mitral or aortic valve stenosis, valve regurgitation, heart block and others. Among the category of other diagnoses, 29 (2.8%) patients had heart failure. Over 60% of participants had a previous cardiac diagnosis and had been diagnosed with a cardiac disease for one year or less. About half of participants underwent a CATH with a stent (52.2%), while others underwent a CATH with a CABG (23.5%), or some kind of other procedure (24.3%), which was not yet performed at the time of the interview. Forty one percent of participants reported having two or more co-morbidities (mainly diabetes and hypertension) and 72.2% were on three or more medications. In addition, more than half of the participants' reported a family history of CVD. Approximately 37% of participating patients exhibited high somatic symptoms on the PHQ-15. The mean score of the participants on the SF-12- PCS score was 37.6 ±12.4.

Psychosocial factors. Forty Percent of patients reported having PTSD symptoms on the PTSD-PCL-S. Social support was generally high (64%) among participants, according to the ESSI. Almost half of the participants presented with moderate to moderately-high resilience. The mean score for self-esteem was 5.8±1.4, while the mean score for the SF-12-MCS was 39.7±13.2.

Lifestyle factors. Almost half of the participants were current smokers while 35.6% had never smoked before. The vast majority of participants (83.4%) reported not being on a diet, 47% low fat consumption, and 55.5% high vegetable and fruit consumption. The reported alcohol consumption was very low with 95% of participants not consuming any alcohol. Almost half of the patients reported no-to-minimal daily physical activity. Eighty percent of patients were either overweight or obese.

Table 4.3. Socio-demographic, clinical, psychosocial and lifestyle characteristics of study population, (*n*=1022)

Variable	n (%)	Variable	n (%)
Socio-demographic factors		***Psychosocial factors***	
Age, mean (SD)	58.9±10.1	PTSD (PTSD-PCL-S)	
Gender		Minimal	611 (59.7)
Female	272 (26.6)	Some	95 (9.3)
Male	750 (73.4)	Moderate	253 (24.8)
Marital status		High	63 (6.2)
Married	926 (90.6)	Social support (ESSI)	
Not married	96 (9.4)	Low	364 (35.6)
Residence		High	658 (64.4)
City	474 (46.4)	Resilience (RS)	
Village	473 (46.3)	Very low	92 (9.0)
Camp	75 (7.3)	Low	103 (10.1)
Education degree		Low-end	204 (20.0)
No HS diploma	600 (58.7)	Moderate	257 (25.1)
HS diploma	167 (16.3)	Moderately-high	274 (26.8)
College degree	255 (25.0)	High	92 (9.0)
Occupation		Self-esteem (SISE) score, mean (SD)	5.8±1.4
Professional	209 (20.5)		
Non-professional	307 (30.0)	QoL,(SF-12-MCS score), mean (SD)	39.7±13.2
Unemployed	378 (37.0)		
Retired	81 (7.9)		
House wife	47 (4.6)		
Clinical factors		***Lifestyle factors***	
Cardiac diagnosis		Smoking status	
CAD	334 (32.7)	Never	364 (35.6)
MI	406 (39.7)	Former	170 (16.6)
Angina	162 (15.9)	Current	488 (47.8)
Other	120 (11.7)	Currently on diet	
Previous cardiac diagnosis		Yes	170 (16.6)
Yes	690 (67.5)	No	852 (83.4)
No	332 (32.5)	Fat consumption	
Years with cardiac disease		Low	480 (47.0)
≤1 year	628 (61.5)	Medium	323 (31.6)
2-9 years	255 (24.9)	High	219 (21.4)
≥10 years	139 (13.6)	Vegetable & fruit consumption	
Cardiac treatment (at admission)		Low	102 (10.0)
CATH/stent	534 (52.2)	Medium	353 (34.5)
CATH/CABG	240 (23.5)	High	567 (55.5)
CATH/other & unknown	248 (24.3)	Alcohol use, (n=1019)	

Co-morbidities		Yes	49 (4.8)
None	299 (29.3)	No	973 (95.2)
One	303 (29.6)	Physical activity	
Two or more	420 (41.1)	None	337 (33.0)
Medications		Not daily	189 (18.5)
None	132 (12.9)	Daily	496 (48.5)
1-2	152 (14.9)		
3-4	738 (72.2)		
Somatic symptoms (PHQ-15)			
Minimal	91 (8.9)		
Low	241 (23.6)		
Medium	314 (30.7)		
High	376 (36.8)		
Family history			
Yes	614 (60.1)		
No	408 (39.9)		
QoL, (SF-12-PCS score), mean (SD)	37.6±12.4		

Note. HS= high school; MI= myocardial infarction; CAD= coronary artery disease; CATH= catheterization; CABG= coronary artery bypass graft; CVD= cardiovascular disease; PHQ-15= Patient Health Questionnaire-15; PCS= Physical Component Summary; QoL= quality of life; SD= standard deviation; PTSD=post-traumatic stress disorder; PTSD-PCL-S=Post-Traumatic Stress Disorder Checklist; ESSI= ENRICHD Social Support Instrument; RS-14= Resilience scale-14; MCS= Mental Component Summary; BMI= body mass index

4.3.2 Proportion of patients with depressive and anxiety symptoms at different severity levels

Table 4.4 shows the proportion of patients with depression (CDS), depression (DASS-depression), anxiety (DASS-anxiety) and stress (DASS-stress) symptoms at different severity levels. Cutoffs for the levels of CDS and DASS subscales are also presented in Table 4.4. Based on our findings, the mean ± SD depression score on the CDS was 101.3±15.6 and the overall proportion of patients with depression was 78.7%. According to the recommended cutoffs for the CDS, 21.3%, 25.2% and 53.5% of the sample had no, mild-to-moderate and severe-to-very severe depression symptoms, respectively. The means ± SDs on the DASS-42 were 9.4±8.6, 9.4± 6.8 and 15.2± 9 for depression, anxiety, and stress, respectively. It was found that the overall proportion was 52.9%, 53.1% and 37.4% for the presence of depressive, anxiety and stress symptoms according to the DASS-42. Based on recommended cutoffs, 47.1%, 33.4% and 19.5% of patients reported normal, mild-to-moderate and severe-to-very severe depressive symptoms (DASS-depression). In addition, 46.9% patients did not report any anxiety, while 33.9% reported mild-to-moderate anxiety and 19.2% reported severe-to-very severe anxiety

symptoms. According to the stress scale, 62.6% reported having no stress, 30% reported having mild-moderate stress symptoms and 7.4% severe-very severe stress symptoms. Patients that had mild-moderate and severe-very severe symptoms of depression or anxiety according to the DASS-42 were more likely to have severe depressive symptoms on the CDS. Nevertheless, 8 (4.0%) and 9 (4.6%) patients without any signs of depressive symptoms on the CDS, showed symptoms of depression and anxiety, respectively, on the DASS-42.

Table 4.4. Proportion of patients with CDS-depression, DASS-depression, DASS-anxiety, DASS-stress at different severity levels, (*n*=1022)

	Depression, anxiety, stress according to CDS levels			
	Normal n (%)	Mild-Moderate n (%)	Severe-very severe n (%)	Percentage above normal level
CDS	CDS<90	CDS 90-100	CDS>100	**78.7**
	218 (21.3)	**257 (25.2)**	**547 (53.5)**	
DASS-depression (D≥10)	**481 (47.1)**	**341 (33.4)**	**200 (19.5)**	**52.9**
Normal (0-9)	166 (34.5)	164 (35.1)	151 (31.4)	
Mild/moderate (10-20)	44 (12.9)	82 (24.1)	215 (63.1)	
Severe/very severe (21-42)	8 (4.0)	11 (5.5)	181 (90.5)	
DASS-anxiety, (A≥7)	**479 (46.9)**	**347 (33.9)**	**196 (19.2)**	**53.1**
Normal (0-6)	152 (31.7)	164 (34.2)	163 (34.0)	
Mild/moderate (7-14)	57 (16.4)	77 (22.2)	213 (61.4)	
Severe/very severe (15-42)	9 (4.6)	16 (8.2)	171 (87.2)	
DASS-stress, (S≥15)	**640 (62.6)**	**307 (30.0)**	**75 (7.4)**	**37.4**
Normal (0-14)	178 (27.8)	206 (32.2)	256 (40.0)	
Mild/moderate (15-25)	36 (11.7)	44 (14.3)	227 (73.9)	
Severe/very severe (26-42)	4 (5.3)	7 (9.3)	64 (85.3)	

Note. CDS= Cardiac Depression Scale; DASS= Depression, Anxiety, Stress Scale

4.3.3 Unadjusted correlations between continuous scores of the scales used in study

Spearman correlation coefficients were calculated between the CDS and other instruments used in the study (figure 4.1). The correlation of the CDS with the DASS-depression was =0.57 (p=<0.001), with DASS-stress =0.51 (p<0.001), and with DASS-anxiety =0.50 (p<0.001). The correlations between the DASS subscales were as follows: DASS-depression and DASS-anxiety (0.65, p<0.001); DASS-depression and DASS-stress (0.63, p<0.001); DASS-anxiety

and DASS-stress (0.61, p<0.001). CDS was positively correlated with the PHQ-15 (0.44, p<.001) and the PTSD-PCL-S (0.37, p<.001) and the DASS-depression was also positively correlated with the PTSD-PCL-S (0.57, p<.001).

The above cluster of positively associated factors were weakly correlated to the physical and mental quality of life components of the SF-12, social support, resilience, and self-esteem, which were strongly correlated among each other. Specifically, weak correlations were observed between CDS and the SF-12-MCS (-0.39, p<0.001), SF-12-PCS (-0.29, p<0.001), ESSI (-0.12 p<0.001), RS-14 (-0.24, p<0.001) and with the self-esteem scale (-0.23, p<0.001).

4.3.4 Association between socio-demographic, clinical, psychosocial, lifestyle factors and depressive and anxiety symptoms

The bivariate distribution of socio-demographic, clinical, psychological, and lifestyle characteristics according to the presence or absence of depression symptoms (CDS), anxiety symptoms (DASS-anxiety) and stress symptoms (DASS-stress) is presented in Table 4.S1 (depression (CDS) and anxiety)] and Table 4.S2 (stress)]. Briefly, with regard to socio-demographic factors, bivariate analysis revealed depressive and anxiety symptoms were more frequent among females than males (depression: 84.9% vs. 76.4%, p=0.003; anxiety: 72.4% vs. 55.6%, p=<0.001) and among those with lower educational level (depression: 81.0% [no high school diploma] vs. 78.0% [high school diploma] and 71.1% [college degree], p=0.02; anxiety: 63.2% [no high school diploma] vs. 59.8% (high school diploma) and 52.8% (college degree), p<0.05). Both, depressive and anxiety symptoms were most prevalent among those unemployed and housewives (depression: p<0.001; anxiety: p<0.001).

Multivariable ordered logistic regression was performed to determine the independent association of factors in the four predictor blocks with a) depressive symptoms, categorized as no depressive symptoms, moderate depressive symptoms, and severe depressive symptoms

according to the CDS and b) anxiety symptoms, categorized as minimal anxiety symptoms, mild-moderate anxiety symptoms, and severe-severe anxiety symptoms according to the DASS-anxiety subscale. The results for the four blocks of variables are presented in table 4.5.

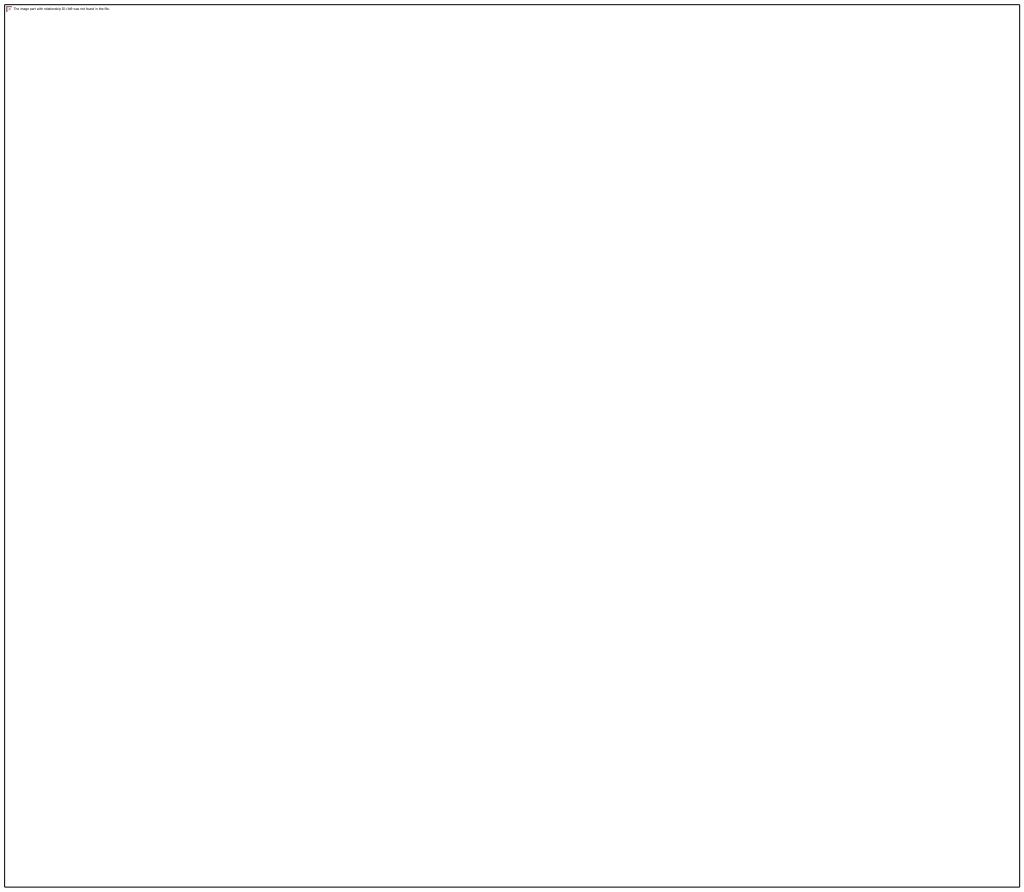
Overall, most of the psychosocial factors were consistently associated with both, depression and anxiety. Participants with depression or anxiety were more likely to exhibit at least some symptoms of PTSD. Odds ratios tended to be higher for anxiety than for depression (moderate symptoms vs. minimal symptoms: $OR_{depresssion}$ 1.87 (95% CI 1.29-2.71) vs. $OR_{anxiety}$ 3.01 (95% CI 2.12-4.27). Patients with depression or anxiety had a lower score for the mental component of quality of life (SF-12-MCS) [$OR_{depression}$ 0.96 (95% CI 0.95-0.97); $OR_{anxiety}$ 0.98 (95% CI 0.97-0.99)]. High resilience and high social support were inversely associated with depression and anxiety [high vs. low social support: $OR_{depression}$ 0.71 (95% CI 0.52-0.97); $OR_{anxiety}$ 0.74 (95% CI 0.54-1.00)]. The inverse association with resilience tended to be stronger in the presence of anxiety [high vs. very low resilience: $OR_{depression}$ 0.42 (95% CI 0.18-0.94); $OR_{anxiety}$ 0.22 (95% CI 0.11-0.48)].

In addition to psychosocial factors, the physical component of quality of life (SF-12-PCS) and somatic symptoms (PHQ-15) also showed consistent associations with both depression and anxiety [high vs. minimal somatic symptoms: $OR_{depression}$ 3.00 (95% CI 1.73-5.18); $OR_{anxiety}$ 7.64 (95% CI 3.96-14.78)]; [SF-12-PCS: $OR_{depression}$ 0.98 (95% CI 0.97-1.00); $OR_{anxiety}$ 0.97 (95% CI 0.96-0.99)]. Current smoking was associated with depression with the strongest odds ratio observed for depression and former smoking: OR 1.87 (95% CI 1.17-2.97). Finally, patients with depression and anxiety were more likely to be physically inactive compared to patients without the respective psychological problems.

A few factors exhibited associations with only one of the two mental health outcomes. For example, patients residing in villages or camps were less likely to show symptoms of anxiety compared to patients living in the city [($OR_{village}$ 0.74 (0.54-1.00); OR_{camp} 0.56 (0.31-1.01)].

Unemployment was positively associated with depression, but not anxiety. The presence of previous cardiac diagnoses was positively associated with anxiety, but inversely associated with depression [($OR_{depression}$ 0.67 (95% 0.47-0.96); $OR_{anxiety}$ 1.52 (95% 1.05-2.21)]. Symptoms of depression were more frequent among patients with a cardiac diagnosis for more than ten years compared to patients with a diagnosis for a year or less [years since first diagnosis ≥10 vs. ≤ 1 year OR 1.71 (95% 1.06-2.75)]. Patients who were diagnosed with angina were more likely to have anxiety symptoms than those diagnosed with an MI. Underweight and obese participants were more likely to exhibit symptoms of anxiety than those of normal weight and overweight.

Figure 4.1 Spearmen correlations between CDS, DASS-depression, DASS-anxiety, DASS-stress and other instruments used in the study



Note. CDS= Cardiac Depression Scale; PHQ= Patient Health Questionnaire-15; PTSD= Post-Traumatic Stress Disorder; MCS= Mental Component Summary; PCS= Physical Component Summary; RS= Resilience Scale-14; SE= Self-esteem; ESSI= ENRICHD Social Support Instrument.
Blue colors represent positive correlations and red colors represent negative correlations. Correlations measured are expressed as rho spearman.

Table 4.5 Factors associated with DEPRESSION and ANXIETY in multivariate ordered logistic regression

	Depression (CDS)			**Anxiety (DASS-anxiety)**		
Variable	OR	95% CI	*P* value	OR	95% CI	*P* value
Socio-demographic factors						
Age, mean (SD)	0.99	(0.98-1.00)	0.393	**0.96**	**(0.95-0.99)**	**<0.001**
Gender						
Female	(reference)			(reference)		
Male	0.83	(0.51-1.36)	0.469	0.68	(0.43-1.10)	0.117
Marital status						
Married	(reference)			(reference)		
Not married	**0.38**	**(0.22-0.65)**	**0.001**	1.28	(0.76-2.13)	0.350
Residence						
City	(reference)			(reference)		
Village	1.22	(0.91-1.64)	0.191	0.74	(0.54-1.00)	0.054
Camp	1.35	(0.76-2.40)	0.308	0.56	(0.31-1.01)	0.054
Education degree						
No HS diploma	(reference)			(reference)		
HS diploma	1.15	(0.82-1.62)	0.421	0.93	(0.65-1.31)	0.666
College degree	1.19	(0.76-1.87)	0.449	1.09	(0.68-1.76)	0.715
Occupation						
Professional	(reference)			(reference)		
Non-professional	0.85	(0.55-1.31)	0.472	1.15	(0.73-1.81)	0.544
Unemployed	1.12	(0.67-1.88)	0.662	0.89	(0.54-1.48)	0.660
Retired	0.71	(0.38-1.33)	0.289	1.44	(0.75-2.73)	0.269
House wife	**0.33**	**(0.14-0.80)**	**0.014**	0.65	(0.27-1.56)	0.335
Clinical Factors						
Cardiac diagnosis						
CAD	0.89	(0.63-1.25)	0.508	0.75	(0.53-1.07)	0.111
MI	(reference)			(reference)		
Angina	1.26	(0.83-1.92)	0.271	0.54	(0.35-0.86)	0.009
Other	0.82	(0.49-1.37)	0.440	1.23	(0.76-1.99)	0.407
Previous cardiac diagnosis						
Yes	**0.67**	**(0.47-0.96)**	**0.028**	**1.52**	**(1.05-2.21)**	**0.026**
No	(reference)			(reference)		
Years with cardiac disease						
≤1 year	(reference)			(reference)		
2-9 years	**1.46**	**(1.00-2.13)**	**0.048**	1.10	(0.76-1.59)	0.663
≥10 years	**1.71**	**(1.06-2.75)**	**0.028**	0.95	(0.60-1.50)	0.832
Cardiac treatment (at admission)						
CATH/stent	(reference)			(reference)		
CATH/CABG	1.42	(0.98-2.04)	0.065	0.89	(0.62-1.29)	0.558
CATH/other & unknown	1.34	(0.95-1.89)	0.097	**1.44**	**(1.02-2.04)**	**0.036**
Co-morbidities						
None	(reference)			(reference)		
1	0.93	(0.64-1.34)	0.695	0.96	(0.65-1.43)	0.860
2+	1.39	(0.94-2.04)	0.096	1.36	(0.92-2.01)	0.127
Medications						
None	(reference)			(reference)		
1-2	1.33	(0.78-2.29)	0.293	1.20	(0.68-2.10)	0.521
3-4	1.19	(0.74-1.92)	0.470	1.31	(0.79-2.18)	0.299
Somatic symptoms (PHQ-15)						
Minimal						
Low	(reference)			(reference)		
Medium	1.18	(0.72-1.94)	0.506	1.41	(0.74-2.72)	0.296
High	**1.86**	**(1.12-3.08)**	**0.015**	**3.35**	**(1.76-6.35)**	**<0.001**
Family history	**3.00**	**(1.73-5.18)**	**<0.001**	**7.64**	**(3.96-14.78)**	**<0.001**

Yes						
No	1.03	(0.77-1.38)	0.824	0.76	(0.57-1.03)	0.075
QoL, (SF-12-PCS score)	(reference)			(reference)		
	0.98	**(0.97-1.00)**	**0.015**	**0.97**	**(0.96-0.99)**	**<0.001**
Psychosocial factors						
PTSD (PTSD-PCL-S)						
Minimal						
Some	(reference)			(reference)		
Moderate	1.32	(0.83-2.10)	0.247	**2.34**	**(1.47-3.71)**	**<0.001**
High	**1.87**	**(1.29-2.71)**	**0.001**	**3.01**	**(2.12-4.27)**	**<0.001**
Social support (ESSI)	1.28	(0.00)	0.974	**7.37**	**(3.89-14.0)**	**<0.001**
Low						
High	(reference)			(reference)		
Resilience (RS-14)	**0.71**	**(0.52-0.97)**	**0.032**	**0.74**	**(0.54-1.00)**	**0.049**
Very low						
Low	(reference)			(reference)		
Low-end	1.05	(0.49-2.25)	0.896	0.76	(0.41-1.41)	0.381
Moderate	0.78	(0.39-1.56)	0.479	**0.43**	**(0.25-0.77)**	**0.004**
Moderately-high	0.60	(0.30-1.21)	0.154	**0.37**	**(0.20-0.66)**	**0.001**
High	**0.48**	**(0.23-0.98)**	**0.044**	**0.19**	**(0.10-0.36)**	**<0.001**
Self-esteem (SE) score	**0.42**	**(0.18-0.94)**	**0.035**	**0.22**	**(0.11-0.48)**	**<0.001**
QoL,(SF-12-MCS score)	0.97	(0.85-1.10)	0.640	0.85	(0.76-0.96)	**0.007**
	0.96	**(0.95-0.97)**	**<0.001**	**0.98**	**(0.97-0.99)**	**<0.001**
Lifestyle factors						
Smoking status						
Never						
Former	(reference)			(reference)		
Current	**1.87**	**(1.17-2.97)**	**0.008**	0.71	(0.44-1.14)	0.154
Currently on diet	**1.61**	**(1.11-2.33)**	**0.013**	1.37	(0.93-2.02)	0.106
Yes						
No	**0.59**	**(0.40-0.86)**	**0.007**	1.45	(0.98-2.13)	0.060
Fat consumption	(reference)			(reference)		
Low						
Medium	(reference)			(reference)		
High	0.73	(0.53-1.00)	0.054	1.09	(0.79-1.51)	0.583
Vegetable & fruit consumption	0.79	(0.55-1.14)	0.206	1.28	(0.88-1.86)	0.187
Low						
Medium	(reference)			(reference)		
High	0.83	(0.50-1.37)	0.466	**0.52**	**(0.31-0.86)**	**0.011**
Alcohol use	0.73	(0.45-1.19)	0.207	0.80	(0.49-1.30)	0.375
Yes						
No	1.31	(0.66-2.61)	0.439	1.19	(0.63-2.24)	0.591
Physical activity	(reference)			(reference)		
None						
Not daily	(reference)			(reference)		
Daily	**0.64**	**(0.42-0.98)**	**0.040**	**0.57**	**(0.37-0.87)**	**0.009**
BMI	**0.43**	**(0.30-0.60)**	**<0.001**	0.98	(0.70-1.38)	0.908
Underweight						
Normal weight	0.63	(0.05-7.7)	0.720	2.09	(0.22-19.9)	0.522
Overweight	(reference)			(reference)		
Obese	0.81	(0.55-1.18)	0.272	**0.61**	**(0.42-0.89)**	**0.010**
	0.95	(0.63-1.43)	0.824	0.87	(0.59-1.29)	0.495

Note. Multivariate ordered logistic regression reported for **socio-demographic, clinical, psychosocial and lifestyle** factors associated with depression, CDS (not depressed; mild-moderate depression; severely-very severe depression) and DASS-anxiety (no anxiety, mild-moderate anxiety; severe-very severe anxiety). Analyses were performed in two separate models for depression and anxiety, mutually adjusting for all factors in the four predictor blocks in both models. Analyses are also adjusted for the hospital to which patients were admitted. OR= odds ratio; CI= confidence Interval; SD=standard deviation; HS= high school; MI= myocardial infarction; CAD=

coronary artery disease; CATH= catheterization; CABG= coronary artery bypass graft; PHQ-15= Patient Health Questionnaire-15; PCS=Physical Component Summary; PTSD=Post-Traumatic Stress Disorder; PTSD-PCL-S=Post-Traumatic Stress Disorder Checklist; ESSI= ENRICHD Social Support Instrument; RS-14= Resilience Scale-14; MCS=Mental Component Summary; BMI= body mass index; *P* values in bold are significant at $p < 0.05$.

4.3.5 Reliability assessment (Cronbach's alpha) of the study instruments

Cronbach α for the primary outcome variable, CDS was 0.86 and 0.92 (DASS-depression), 0.82 (DASS-anxiety), and 0.89 (DASS-stress) for the DASS subscales, respectively, indicating high consistency for the relevant psychometric scales. This indicates all scales exhibit acceptable internal consistency with little likelihood of item redundancy. Inter-item correlations between the 26 items of the CDS and the total CDS scores ranged from 0.08 to 0.58, and all correlations were statistically significant at the 0.01 level. Cronbach α for the other scales used in the study was: 0.78 for PHQ-15, 0.86 for PTSD-PCL-S, 0.82 for ESSI and 0.88 for RS-14.

4.4 Discussion

In the present study, the observed rates of depressive and anxiety symptoms were high. Only 21% (CDS) and 46% (DASS-anxiety) of patients did not exhibit any symptoms of depression and anxiety, respectively. Our findings point to the need for integrating mental health care into cardiac treatment. It is noteworthy that several factors found to be associated with depression and anxiety may serve as screening and possibly as intervention targets.

Rates of mental health problems reported in earlier studies for patients with different cardiac diagnoses and in different cultural and health system settings ranged from 14-73% (Hanssen et al., 2009, Meneghetti et al., 2017, Liang et al., 2014, Akhtar et al., 2004, Bayani et al., 2011, Goudarzian et al., 2016) for depressive symptoms and 15 to 48% (Hanssen et al., 2009, Meneghetti et al., 2017, Liang et al., 2014, Akhtar et al., 2004, Bayani et al., 2011) for anxiety symptoms. These varying rates are explained in part by differences in sample sizes, the

instruments and cutoffs used for classifying depression and anxiety and the type of cardiac disease targeted in studies.

Lower rates of depression than in the current study were observed in other settings including Norway (14%) (Hanssen et al., 2009), USA (15%) (Moraska et al., 2013), Brazil (26.4%) (Meneghetti et al., 2017) and Pakistan (14%) (Akhtar et al., 2004). Similar among these studies, was the common psychiatric instruments used to assess for depression, all of which were not specific for cardiac populations. In contrast, a different study assessing depression using the CDS found a rate of 73.2% of severe depression in Iranian patients with acute coronary syndrome (ACS), a rate even higher than in this study (Goudarzian et al., 2016).

Similar anxiety rates to the current study were observed in Iran (28.5%) (Bayani et al., 2011) and Pakistan (18%) (Akhtar et al., 2004). Interestingly, in another study conducted in Brazil, Meneghetti et al. found a very high prevalence of 48.4% for anxiety symptoms among ACS patients using the Hospital Anxiety and Depression Scale (HADS) (Meneghetti et al., 2017). A study in the USA also reported, 37% of patients with MI due to spontaneous coronary artery dissection screened for anxiety using the Generalized Anxiety Disorder 7-Item Scale (GAD-7) (Liang et al., 2014).

Mental health problems are generally high in the Palestinian population (Marie et al., 2016). In the absence of a healthy control group the results of this study do not allow to conclude that depression and anxiety are more common in cardiac patients. However, cardiac patients are in particular need of treatment for depression and anxiety given that existing evidence points to their adverse effect on the course of heart disease. Furthermore, cardiac rehabilitation may be an efficient starting point to address mental health issues beyond the patient and to the extended family and social network. Given the shortage of mental health services available and the local economic instability in Palestine, the provision of additional services needs to be implemented

in a cost-effective way. The identification of subgroups of cardiac patients at higher risk of depression and anxiety can guide screening and interventions.

In perspective of mental health screening among cardiac patients, focus should be given to females and less educated patients. The higher rates of depression and anxiety seen in these sub-groups were previously described in literature (Bayani et al., 2011, Dogar et al., Alexandri et al., 2017, Meneghetti et al., 2017). Women seem to be more vulnerable to the trauma caused by cardiac events, which leads to a deterioration in depression and anxiety symptoms (Bayani et al., 2011). As observed in some (Meneghetti et al., 2017, Shokrgozar et al., 2015, Su et al., 2018), but not all studies (Bayani et al., 2011, Al-Abbudi et al., 2018, Goudarzian et al., 2016), the association between gender and social status may not be direct as suggested by the disappearance of gender and social status differences in the fully adjusted models (Meneghetti et al., 2017, Shokrgozar et al., 2015, Bayani et al., 2011, Goudarzian et al., 2016).

The presence of the following additional characteristics in cardiac patients should be a red flag for cardiologists to consider mental health care in cardiac practice: symptoms of PTSD, low levels of self-esteem, somatic symptoms, low quality of life components, active smoking, physical inactivity, and longer disease duration. In contrast, a high level of resilience seems to reduce symptoms of psychological problems, as previously observed in patients with heart failure (Toukhsati et al., 2017, Chang et al., 2017). Unlike findings reported previously, comorbidities were not consistently more common in the presence of mental health disorders (Eng et al., 2011). Little is known about the association of PSTD symptoms with depression and anxiety in cardiac patients. A study conducted on 813 patients who received angiograms at a large U.S. Veterans Administration Medical Center found depression to be positively associated with PTSD, smoking and alcohol consumption (Shankman et al., 2012). Low MCS and PCS scores on the SF-12, smoking, and chest pain were recently identified as the strongest

predictors of longitudinally sustained high levels of depression and anxiety in CHD patients (Palacios et al., 2018).

Factors serving as targets for intervention include smoking, physical activity and social support. Smoking cessation interventions are crucial for cardiac rehabilitation, however in the presence of depression, results are less successful and interventions may need to be adapted (Doyle et al., 2014). Sedentary behavior, a risk factor for depression in the general population (Hamer and Stamatakis, 2014), was previously associated with depression according to the Beck Depression Inventory-II in patients hospitalized for ACS (Zhu et al., 2018). In a small non-randomized intervention study with heart failure patients, aerobic interval training decreased symptoms of depression over a period of 12-weeks (Isaksen et al., 2016). In studies on breast cancer (Segar et al., 1998), promotion of physical activity may have the additional benefit of improving self-esteem, a factor associated with depression and anxiety in this study and a predictor of mortality in the general population (Stamatakis et al., 2004). In addition, according to previous studies (Su et al., 2018, Compare et al., 2013, Bucholz et al., 2014, Notara et al., 2015, Zarbo et al., 2013), the inverse association between high social support and low levels of anxiety and depression points to another important target for prevention as it is supported by firm evidence from previous studies. Poor social support among patients with ACS was observed in secondary analyses of a randomized trial to reduce the effectiveness of treatment with antidepressants (Kim et al., 2018). The quality of social support plays an important role, as overprotective behaviors of partners can have an adverse effect (Zarbo et al., 2013). Interestingly, in the current study marital status and social support were associated with presence of depressive symptoms independently and in opposite directions.

The current study has several strengths. First, it utilized a broad set of validated instruments to identify depression and anxiety symptoms as well as associated factors. The overall validity of the CDS in this study was almost similar to levels originally reported by Hare and Davis

(Hare and Davis, 1996). The validity of the DASS-42 was satisfactory, in line with other findings of other studies, including those originally reported by Lovibond and Lovibond (Lovibond and Lovibond, 1995). Furthermore, the CDS is the only psychometric scale suitable for the comparative depression assessment in heart disease patients, subjected to different interventions (Shi et al., 2010, Hare and Davis, 1996) . This is evident in the present study, as depression rates were lower when assessed by the DASS-42. The CDS, also has excellent properties for the diagnosis of MDD, a score of ≥95 having a 97% sensitivity at 85% specificity (AUC 0.96) (Shi et al., 2010). Second, the large sample size provided sufficient statistical power for testing independent associations. Third, the study subjects are well characterized, which allowed for addressing confounding. Fourth, the high participation rate decreased the likelihood of selection and participation bias. Finally, the findings of the study despite being hospital-based are likely generalizable to the entire cardiac patient population in the city of Nablus and surrounding cities of Palestine, considering the study sites provide cardiac care to a large percentage of cardiac patients in the area.

Nonetheless, the cross-sectional nature of the study does not enable us to make causal inferences. A long-term follow-up is foreseen to investigate the predictive effect of the study characteristics and predictors with regard to the course of depression, anxiety and heart disease. While the reliability of the previously validated instruments was confirmed in our study, the instruments have not been validated specifically for the context of cardiac patients in Palestine. Furthermore, some of the risk factors could only be captured broadly to avoid lengthy interviews. This likely caused some misclassification, as in the case of physical activity. Recall bias may have added to the misclassification of risks, given the retrospective nature of the interview. Also, the study was not sufficiently powered to investigate differences in the frequency of depression and anxiety as well as associated factors between relevant subgroups of clinical diagnoses, for example MI and HF. Finally, some patients were recruited at the time

of admission and for the most part before receiving their intervention or diagnosis, and thus were under much pressure and stress. The level of depression and anxiety could have been overestimated and may decrease in part over the course of disease. The most appropriate time point to assess depression and anxiety from a prognostic perspective is unknown.

4.5 Conclusions

The alarmingly high rate of depression and anxiety symptoms observed in cardiac patients in Palestine points to the need for integrating mental health care into cardiac rehabilitation. The prognostic value of depression and anxiety with regard to the course of heart disease, adherence to treatment and quality of life needs to be investigated. Treatment of psychological problems from the disease onset and onwards is crucial considering longer disease duration puts individuals at higher risk of being depressed. The expertise of social scientists and medical anthropologists is needed for identifying efficient means to overcome barriers related to the stigmatization of psychological disorders.

Declarations

Ethics approval and consent to participate

This study was approved by the Ethics Committee of Nordwest- und Zentral Schweiz (EKNZ) in Basel, Switzerland and by the Institutional Review Board (IRB) committee at An-Najah National University in Nablus, Palestine. All patients enrolled in the study provided written informed consent.

Consent for publication

Not applicable.

Availability of data and material

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

HA conducted data collection, analyzed and interpreted data, and wrote the manuscript. AA[1] supervised the data collection and the implementation of the study in Palestine and edited the manuscript. AA[2], AH, HO, JS, MT assisted in data collection. EZ and SHY contributed to designing the study. EZ and CS participated in planning the data analysis. CS supervised the statistical analysis. EZ, SHY, and CS contributed to the interpretation of the results. NPH designed the study, directed its implementation, data analysis and result interpretation. She edited all versions of the manuscript. All authors read and approved the final manuscript.

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4.6 Supplementary Material

Table 4.S1. Socio-demographic, clinical, psychosocial, lifestyle factors by DEPRESSION and ANXIETY status, (*n*=1022)

Variable	Depression (CDS)			Anxiety (DASS-anxiety)		
	NO n=218 (%)†	YES n=804 (%)††	*P* value	NO n=408 (%)†††	YES n=614 (%)††††	*P* value
Socio-demographic factors						
Age, mean (SD)	58.9±10.6*	59±10.0*	0.560	59.2±9.8*	58.8±10.3*	0.66
Gender			**0.003**			**<0.001**
Female	15.1	84.9		27.6	72.4	
Male	23.6	76.4		44.4	55.6	
Marital status			0.088			0.109
Married	20.6	79.4		40.7	59.3	
Not married	28.1	71.9		32.3	67.7	
Residence			0.158			0.893
City	23.0	77.0		40.1	59.9	
Village	20.9	79.1		40.2	59.8	
Camp	13.3	86.7		37.3	62.7	
Education degree			**0.024**			**0.036**
No HS diploma	19.0	81.0		36.8	63.2	
HS diploma	22.1	77.9		42.5	57.4	
College degree	28.9	71.1		47.2	52.8	
Occupation			**0.004**			**<0.001**
Professional	22.5	77.5		45.0	55.0	
Non-professional	25.1	74.9		47.6	52.4	
Unemployed	15.9	84.1		31.0	69.0	
Retired	32.1	67.9		49.4	50.6	
House wife	17.0	83.0		23.4	76.6	
Clinical factors						
Cardiac diagnosis			0.101			**<0.001**
CAD	24.9	75.1		39.5	60.5	
MI	21.7	78.3		37.9	62.1	
Angina	17.3	82.7		54.3	45.7	
Other	15.8	84.2		28.3	71.7	
Previous cardiac diagnosis			**0.008**			**<0.001**
Yes	19.0	81.0		33.5	66.5	
No	26.2	73.8		53.3	46.7	
Years with cardiac disease			**0.022**			**0.020**
≤1 year	24.0	76.0		43.3	56.7	
2-9 years	18.0	82.0		34.1	65.9	
≥10 years	15.1	84.9		35.2	64.8	
Cardiac treatment (at admission)			**0.048**			**0.003**
CATH/stent	24.3	75.7		44.2	55.8	
CATH/CABG	17.9	82.1		38.2	60.8	
CATH/other & unknown	18.1	81.9		31.4	68.6	
Co-morbidities			**<0.001**			**<0.001**
None	28.4	71.6		48.2	51.8	
One	21.8	78.2		40.9	59.1	
Two or more	16.0	84.0		33.3	66.7	
Medications			0.080			**0.025**
None	28.8	71.2		50.0	50.0	
1-2	19.7	80.3		34.9	65.1	
3-4	20.3	79.7		39.2	60.8	
Somatic symptoms (PHQ-15)			**<0.001**			**<0.001**
Minimal	40.7	59.3		72.5	27.5	
Low	36.9	63.1		61.4	38.6	

Medium	18.1	81.9		39.2	60.8	
High	9.3	90.7		18.9	81.1	
Family history			0.752			0.114
Yes	20.8	79.2		42.9	57.1	
No	21.7	78.3		37.9	62.1	
QoL, (SF-12-PCS score), mean (SD)	42.7±12.7*	36.3±11.9*	**<0.001**	43.1±11.8*	34.0±11.3*	**<0.001**
Psychosocial factors						
PTSD (PTSD-PCL-S)			**<0.001**			**<0.001**
Minimal	29.0	71.0		53.5	46.5	
Some	14.7	85.3		25.3	74.7	
Moderate	10.7	89.3		20.2	79.8	
High	0.0	100.0		9.5	90.5	
Social support (ESSI)			**<0.001**			**0.007**
Low	19.2	80.8		34.3	65.7	
High	22.5	77.5		43.0	57.0	
Resilience (RS-14)			**<0.001**			**<0.001**
Very low	9.8	90.2		7.6	92.4	
Low	9.7	90.3		14.6	85.4	
Low-end	19.6	80.4		31.4	68.6	
Moderate	22.2	77.8		42.4	57.6	
Moderately-high	26.6	73.4		58.8	41.2	
High	31.5	68.5		56.5	43.5	
Self-esteem (SISE) score, mean (SD)	6.2±1.0*	5.7±1.5*	**<0.001**	6.3±0.9*	5.4±1.5*	**<0.001**
QoL, (SF-12-MCS score), mean (SD)	46.3±12.5*	37.9±12.9*	**<0.001**	44.4±12.8*	36.7±12.6*	**<0.001**
Lifestyle factors						
Smoking status			0.701			**<0.001**
Never	22.3	77.7		42.6	57.4	
Former	19.4	80.6		49.4	50.6	
Current	20.9	79.1		31.9	68.1	
Currently on diet			**0.046**			0.062
Yes	27.1	72.9		33.5	66.5	
No	20.2	79.8		41.1	58.9	
Fat consumption			0.674			0.184
Low	22.1	77.9		42.9	57.1	
Medium	21.7	78.3		37.2	62.8	
High	19.2	80.8		37.4	62.6	
Vegetable & fruit consumption			0.340			**0.035**
Low	17.7	82.3		41.2	58.8	
Medium	19.8	80.2		45.0	55.0	
High	22.9	77.1		36.5	63.5	
Alcohol use			0.840			0.434
Yes	22.5	77.5		34.7	65.3	
No	21.2	78.8		40.3	59.7	
Physical activity			**<0.001**			**<0.001**
None	12.5	87.5		31.0	69.0	
Not daily	19.1	81.9		48.7	51.3	
Daily	28.2	71.8		42.5	57.5	
BMI			<0.063			**<0.001**
Underweight	25.0	75.0		0.0	100.0	
Normal weight	21.1	78.9		36.2	63.8	
Overweight	25.1	74.9		47.1	52.9	
Obese	17.4	82.6		34.4	65.6	

Note. Bivariate analysis was performed using chi-squared test to assess the association of depression with factors of the four predictor blocks. Analysis was adjusted for hospital site. HS= high school; MI= myocardial infarction; CAD= coronary artery disease; CATH= catheterization; CABG= coronary artery bypass graft; CVD=

cardiovascular disease; PHQ-15= Patient Health Questionnaire-15; PCS= Physical Component Summary; QoL= quality of life; SD= standard deviation; PTSD= post-traumatic stress disorder; PTSD-PCL-S=Post-Traumatic Stress Disorder Checklist; ESSI= ENRICHD Social Support Instrument; RS-14= Resilience
Scale-14; MCS= Mental Component Summary; BMI= body mass index *= Wilcoxon rank sum test; † Scores 26-89 (no depressive symptoms); †† Scores ≥90 (depressive symptoms); ††† Scores of 0-6 (no anxiety); †††† Scores ≥7 (mild, moderate, severe, very severe anxiety); *P* values in bold are significant at p <0.05.

Table 4.S2. Socio-demographic, clinical, psychosocial, lifestyle factors by STRESS status, (*n*=1022)

Variable	Stress (DASS-stress)		
	No n= 370 (%)†	Yes n=652 (%)††	*P* value
Socio-demographic factors			
Age, mean (SD)	60.3±10.1*	58.3±10.1*	**0.002**
Gender			0.944
Female	36.0	64.0	
Male	36.3	63.7	
Marital status			0.866
Married	36.3	63.7	
Not married	35.4	64.6	
Residence			**0.027**
City	40.3	59.7	
Village	33.4	66.6	
Camp	28.0	72.0	
Education degree			0.171
No HS diploma	35.2	64.8	
HS diploma	34.6	65.4	
College degree	42.8	57.2	
Occupation			0.172
Professional	33.0	67.0	
Non-professional	41.0	59.0	
Unemployed	36.2	63.8	
Retired	29.6	70.4	
House wife	29.8	70.2	
Clinical factors			
Cardiac diagnosis			**<0.001**
CAD	28.1	71.9	
MI	38.4	61.6	
Angina	51.2	48.8	
Other	30.8	69.2	
Previous cardiac diagnosis			0.055
Yes	34.2	65.8	
No	40.4	59.6	
Years with cardiac disease			**0.009**
≤1 year	39.7	60.3	
2-9 years	32.6	67.4	
≥10 years	27.3	72.7	
Cardiac treatment (at admission)			0.826
CATH/stent	37.1	62.9	
CATH/CABG	35.0	65.0	
CATH/other & unknown	35.5	64.5	
Co-morbidities			**0.027**
None	42.5	57.5	
One	34.0	66.0	
Two or more	33.3	66.7	
Medications			0.209
None	33.3	66.7	
1-2	30.9	69.1	
3-4	37.8	62.2	
Somatic symptoms (PHQ-15)			**<0.001**
Minimal	56.0	44.0	
Low	50.2	49.8	
Medium	34.7	65.3	
High	23.7	76.3	

Family history			0.333
Yes	38.0	62.0	
No	35.0	65.0	
QoL, (SF-12-PCS score), mean (SD)	40.0±12.3*	36.3±12.2*	**<0.001**
Psychosocial factors			
PTSD (PTSD-PCL-S)			**<0.001**
Minimal	52.9	47.1	
Some	17.9	82.1	
Moderate	10.3	89.7	
High	6.3	93.7	0.915
Social support (ESSI)			
Low	36.0	64.0	
High	36.3	63.7	
Resilience (RS-14)			**<0.001**
Very low	14.1	85.9	
Low	23.3	76.7	
Low-end	38.2	61.8	
Moderate	43.2	56.8	
Moderately-high	41.2	58.8	
High	33.7	66.3	
Self-esteem (SISE) score, mean (SD)	6.0±1.2*	5.7±1.5*	**<0.001**
QoL, (SF-12-MCS score), mean (SD)	44.6±12.4*	37.0±12.9*	**<0.001**
Lifestyle factors			
Smoking status			0.777
Never	37.6	62.4	
Former	35.3	64.7	
Current	35.4	64.6	
Currently on diet			0.546
Yes	38.2	61.8	
No	35.8	64.2	
Fat consumption			0.506
Low	35.4	64.6	
Medium	38.7	61.3	
High	34.2	65.8	
Vegetable & fruit consumption			0.676
Low	32.3	67.7	
Medium	37.1	62.9	
High	36.3	63.7	
Alcohol use			**0.003**
Yes	16.3	83.7	
No	37.3	62.7	
Physical activity			**0.002**
None	28.8	71.2	
Not daily	39.7	60.3	
Daily	39.9	60.1	
BMI			**0.049**
Underweight	0.0	100.0	
Normal weight	32.7	67.3	
Overweight	40.5	59.5	
Obese	33.7	66.3	

Note. Bivariate analysis was performed using chi-squared test to assess the association of depression with factors of the four predictor blocks. Analysis was adjusted for hospital site. HS= high school; MI= myocardial infarction; CAD= coronary artery disease; CATH= catheterization; CABG= coronary artery bypass graft; CVD= cardiovascular disease; PHQ-15= Patient Health Questionnaire; PCS= Physical Component Summary; QoL= quality of life; SD= standard deviation; PTSD=post-traumatic stress disorder; PTSD-PCL-S=Post-Traumatic Stress Disorder Checklist; ESSI= ENRICHD Social Support Instrument; RS-14= Resilience Scale-14; MCS=Mental Component Summary; BMI= body mass index *=Wilcoxon rank sum test; † Scores 0-14 (no stress); †† Scores 15-42 (mild, moderate, severe, very severe stress); *P* values in bold are significant at p <0.05.

5

ARTICLE II

Mediators of gender effects on depression among cardiovascular disease patients in Palestine

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Abstract

Background. Among patients suffering from coronary heart disease (CHD) and comorbid depression, women experience a higher burden compared to men. Little is known on the characteristics that differentiate men and women with both diseases and whether these factors mediate gender effects on depression. This study assessed whether women are more likely to suffer from depression and which characteristics mediate gender effects on depression among a cardiac population in Palestine, specifically addressing the role of PTSD.

Methods. Using a cross-sectional design, patients consecutively admitted with a CHD to one of the four main hospitals in Nablus, Palestine, were interviewed using a structured questionnaire with validated instruments. Data was also obtained from hospital medical records. Patients were assessed for depression using the Cardiac Depression Scale (CDS). Bivariate analysis was conducted to compare characteristics of women and men with and without depressive symptoms. Mediators (direct and indirect effects) of the association between gender and depression were evaluated using a structural equation model (SEM).

Results. Women were more likely to suffer from severe depression than men (28.7% vs. 18.8%). Female gender was positively associated with higher PTSD symptoms, comorbidities, somatic symptoms and income, and with lower resilience, self-esteem, quality of life, education, prevalence of smoking and physical activity. Structural equation modeling revealed negative indirect effects of gender on depression (CDS score) through resilience, self-esteem and physical activity, whereas positive indirect effects of gender on depression were observed through PTSD, comorbidities, somatic symptoms and smoking. There was no direct effect of gender on depression.

Conclusion. This study found a higher prevalence of severe depression in female patients with cardiac disease compared to male cardiac patients. Our findings provide novel information on

mediating factors of the association between gender and depression among cardiac patients, in particular PTSD. The results emphasize the need for further research on potential mediating factors that could account for gender differences in depression and the need to provide support programs for female patients with comorbid CHD and depression to improve their psycho-social well-being.

Keywords: Gender, depression, cardiovascular disease, mediators, post-traumatic stress disorder

5.1 Introduction

Depression is an increasingly recognized risk factor for cardiovascular disease (CVD), particularly coronary heart disease (CHD) (Barth et al., 2004, Frasure-Smith and Lesperance, 2006b). The prevalence of depression among cardiac patients ranges from 15% to 30%, which is considerably higher than in the general population (Lesperance and Frasure-Smith, 2000). Depression in cardiac patients is associated with poor outcomes (Nicholson et al., 2006), long-term prognosis (Lett et al., 2004), overall quality of life (Barrett-Connor, 2013), mortality (Barth et al., 2004), and a dose-response relationship has been reported between depressive symptom level and subsequent mortality (Lesperance et al., 2002).

Depression is up to two times higher in women than in men (Piccinelli and Wilkinson, 2000, Nolen-Hoeksema et al., 1999). Many factors could explain these differences including biological, genetic, psychological and social differences between women and men (Kornstein, 1997). Gender and sex are often used interchangeably suggesting biological and psychosocial attributes vary with one another (Möller-Leimkühler, 2007). While sex denotes genetic and biological characteristics, gender refers to the array of socially constructed roles and relationships, personality traits, attitudes, behaviors and values that society ascribes to the sexes on a differential basis (Krieger, 2003). However, the use of the term sex as a 'stand-alone indicator of biology' is rejected as gendered experiences materialize in the body and measures of sex can include effects of gender (Springer et al., 2012). In the case of depression and in the presence of sex differences, biology alone cannot provide an accurate explanation. Higher depression rates are found in women than men due to stressors related to social roles whereas lower rates of depression are found among men because male-attributed symptoms of depression such as anger, aggression, irritation, and abusive behavior are commonly not recognized as depressive symptoms (Moller-Leimkuhler et al., 2004). Evidence suggests that women underprivileged in different aspects of life suffer from greater stressors and poorer

health than men, including mental disorders and chronic diseases (Rahman et al., 1994). Women also report poorer health than men due to lack of access to healthcare and due to the stressors caused by their gender and marital roles (McDonough and Walters, 2001, Matthews et al., 1999).

The role of gender for CHD has been addressed extensively in literature since the 1980's (Mosca et al., 2011, Barrett-Connor, 2013). Studies have reported that being female is associated with higher mortality and morbidity after cardiac events compared to being male (Khan et al., 1990, Penckofer and Holm, 1990) and that women are likely to develop more depressive symptoms associated with CHD than men (Naqvi et al., 2005). A meta-analysis found an overall prevalence of comorbid major depression of 18.7% in women compared to 12.0% in men. In particular, women are more vulnerable after coronary artery bypass graft (CABG) compared to men, suffer from more comorbid illness (Mickleborough et al., 1995), are more likely to experience anxiety and more likely to be socially isolated (Shanmugasegaram, 2012). Among myocardial infarction (MI) patients, women report less social support and more role disruption during recovery (Kristofferzon et al., 2003) and are two times more prone to depression post-MI than men (Mallik et al., 2006). Therefore, female cardiac patients have a higher risk of suffering from adverse effects of depression on the prognosis of their disease (Nolen-Hoeksema et al., 1999, Barth et al., 2004, Frasure-Smith et al., 1999). In addition, women have greater symptom frequency, experience greater risk of re-infarction, have lower survival rates after CABG and higher rates of subsequent heart failure (HF) compared to men (Regitz-Zagrosek et al., 2016, Vaccarino et al., 2002, Gruberg and Beyar, 2003). In several studies, the worse cardiac outcomes in women persist after adjustment for age, medical history, clinical severity, hospital treatment, and cardiac procedures (Vaccarino et al., 2002, Vaccarino and Mallik, 2004, Wenger, 2003, Czajkowski et al., 1997). Despite the burden observed in women due to comorbid CHD and depression, they continue to

be understudied in research and data are often not presented by gender. The high burden of CVD and the rise of depression rates among women in the general population as well as in CHD populations call for assessment of the gender gap in depression. There is scarce literature on characteristics that distinguish men and women with comorbid CHD and depression. Furthermore, whether these factors mediate gender effects on depression in cardiac patients remains unclear. This ultimately makes it difficult to identify women at higher risk of adverse outcomes associated with both CHD and depression. In this paper, the terms sex and gender as well as women and men are used: 'gender' as an overarching notion; 'sex' when referring to associations reported in the literature for being female and male respectively; and the terms 'women' and 'men' to denote population subgroups.

Post-traumatic stress disorder (PTSD) is also a common co-morbid condition in cardiac patients (Tulloch et al., 2014) and rates are higher among female cardiac patients. PTSD has been associated with recurrent MI, hospitalizations and mortality (Ladwig et al., 2008, Edmondson et al., 2012b). Similarly, PTSD exhibits gender-specific patterns and is known to be comorbid with depression (O'Donnell et al., 2004).

Previous literature has focused on gender differences in depression among heart disease patients mainly in high income countries (Mosca et al., 2011, Regitz-Zagrosek et al., 2016). In Middle Eastern countries, CVD accounts for 34% of all deaths and PTSD is high among individuals living in regions of conflict (Marie et al., 2016). The Occupied Palestinian Territories (oPt) in particular, report high rates of depression in response to the stressful living conditions. The different societal roles of women and the evidence based CVD-gender differences call for more research into the understanding of gender-related factors with regard to depression and mediating factors among cardiac patients. In this study, we sought to assess whether Palestinian women are more likely to suffer from depression than Palestinian men among a sample of 1022 consecutively admitted cardiac patients at one of the four major

hospitals in the West Bank city of Nablus, Palestine, and to investigate whether socio-demographic, clinical, psychosocial and lifestyle characteristics mediate gender effects on depression, especially addressing the role of PTSD.

5.2 Methods

5.2.1 Study design and population

This cross-sectional hospital-based study was conducted on consecutive patients aged 30-80 years admitted to the cardiology and cardiac surgery departments at one of the four main hospitals in Nablus, Palestine, during their stay in the hospital (1-7 days) between March 2017 and November 2017. They were included in the study if they were diagnosed with CHD, ST elevation or non-ST elevation MI, angina, HF, cardiac arrhythmia, valve disease or any other cardiac disease. Patients with a normal cardiac catheterization (CATH), an acute or past stroke, end-stage kidney disease (including dialysis patients), peripheral vascular disease, psychological disorders, cognitive deficit, neurological disorders (dementia, Alzheimer's disease, epilepsy, Parkinson's disease), use of antidepressant or any other condition affecting the quality of their responses were excluded from the study. A total of 1092 patients were approached and met initial eligibility requirements, and 1053 agreed to participate in the study. The analytic sample included 1022 subjects. The study was approved by the Ethics Committee of Nordwest-und Zentral Schweiz (EKNZ) in Basel, Switzerland, and by the Institutional Review Board (IRB) committee at An-Najah National University in Nablus, Palestine.

5.2.2 Data Collection

Eligible patients were approached for private in-person interviews using hospital registries and written informed consent was obtained from those who agreed to participate. Prior to completion of the interview, socio-demographic and clinical characteristics including: age,

gender, marital status, residence, education level, occupation, income; current diagnosis, previous cardiac diagnoses, years with cardiac disease, cardiac treatment (at admission), co-morbidities, medications and family history of CVD were retrieved from patients' medical records and were ascertained via patient interview. In-person interviews consisted of a sequence of validated instruments assessing physical and psychosocial factors and questions assessing lifestyle factors.

5.2.3 Study Measurements

Depressive symptoms were assessed by the Cardiac Depression Scale (CDS), a disease-specific, 26-item questionnaire used to accurately measure depression in patients with CVD. The CDS is scored based on a Likert scale ranging from strongly disagree (1) to strongly agree (7). Total scores are calculated as the sum of the scores of each item and range from 26 to 182 (Shi et al., 2010). The CDS can be used as a continuous measure, where higher scores indicate more severe depressive symptoms, or as an ordinal indicator of possible depression using previously established cut-off points which include: <90 for no depression; 90-100 for mild to moderate depression; and >100 for severe depression. These cut offs were used in the current study to categorize depressive symptoms. The CDS has a sensitivity of 88% and a specificity of 84% for severe depression when a cutoff of >100 is used, and 84% sensitivity and 78% specificity for cutoff scores of 90-100 (Wise et al., 2006). Further instruments used include the Post-Traumatic Stress Disorder Checklist (PTSD-PCL-S) (Blanchard et al., 1996); Enhancing Recovery in Coronary Heart Social Support Instrument (ESSI) (2000b, 2001); Resilience Scale-14 (RS-14) (Wagnild GM, 2009); Single-Item Self-Esteem Scale (SISE) (Robins et al., 2001); Short-form 12 Health Survey (SF-12-PCS; SF-12-MCS) (Ware et al., 1996) and the Patient Health Questionnaire-15 (PHQ-15) (Kroenke et al., 2002). The instruments have been described in detail elsewhere (Allabadi et al., 2019).

5.2.4 Statistical Analyses

Depressive symptoms were examined both as a continuous variable (CDS score) and as a dichotomous variable (presence of moderate-severe depressive symptoms using the standard cutoff of CDS ≥90). Characteristics of women and men with and without depressive symptoms were compared using Chi-squared or Fisher exact tests for categorical variables, and independent *t*-tests for continuous variables, as appropriate.

A structural equation model (SEM) was built to assess direct and indirect (i.e. mediated) effects of gender on depression. Mediators are variables which transfer part of the effect of an independent variable (IV) on a dependent variable (DV). In our analysis, the IV was gender (used as a binary variable, with "being female" coded as 1), the DV was depression (CDS score, used as a continuous variable), and the potential mediator variables were socio-demographic, clinical, psychosocial and lifestyle factors (Cole and Hernan, 2002). First, mediator groups (i.e. socio-demographic, clinical, psychosocial and lifestyle factors) were assessed in separate models. In a second step, the final model was built (reference model, n=1022), including education, income, comorbidities, somatic symptoms, quality of life, PTSD, resilience, self-esteem, smoking, physical activity. These potential mediators were chosen based on 1) their statistical significance in the preceding analyses, using a cut-off level of $p<0.10$ 2) the magnitude of their association 3) whether the associations were significant between gender and the potential mediator, as well as between the potential mediator and depression (CDS score). The SEM was estimated using the maximum likelihood method and included continuous, binary and ordinal variables which were all treated as continuous. Inclusion of a larger number of potential mediators reduces bias in estimating the true direct effect of gender on depression (CDS score). Potential confounding factors assessed were age, marital status, occupation, social support, and lifestyle factors (i.e. BMI, alcohol consumption). A further SEM-analysis was then conducted stratifying by age, running separate models for two age groups (those aged below and above the median age of 59 years; see figure 6.S1). Moderation by age was assessed

by testing the differences between corresponding age-specific effects using Chi-squared tests. In further analyses, two additional SEM's were computed to assess whether resilience and smoking could be potential mediators and/or moderators of the effect of PTSD on depression, adding the respective factor as mediator between PTSD and depression and testing its interaction with PTSD to assess potential moderation. This additional analysis was based on general conceptualization and literature on psychological comorbidity of PTSD and depression (O'Donnell et al., 2004, Dao et al., 2010). Analysis was conducted using the STATA Statistical Software Release 15 (StataCorp., College Station, U.S.A.).

5.3 Results

5.3.1 Patient characteristics

This sample consisted of 750 (73.4%) men and 272 (26.6%) women. Among the cardiac patients with depressive symptoms, 231 (28.7%) were women. In contrast, among patients without depressive symptoms, 41 (18.8%) were women. Socio-demographic, clinical, psychosocial and lifestyle factors of depressed and non-depressed men and women are presented in Table 5.1. In terms of socio-demographic factors, among those with depressive symptoms, women were on average older than men, more likely to be unmarried (i.e. single, widowed), less educated, unemployed and have no income compared to men.

Differences among women and men with depressive symptoms in terms of clinical factors were also found. Women with depressive symptoms were more likely to have a severe cardiac disease (i.e. heart failure, mitral or aortic valve stenosis) compared to men with depressive symptoms who had mostly CHD or a MI diagnosis, more likely to report a previous cardiac diagnosis, undergo a CATH/complex procedure (i.e. valve replacement), have two or more comorbid conditions (i.e. diabetes, hypertension, the combination of both), take three to four

medications, have higher somatic symptoms and to score lower on the SF-12-PCS for quality of life.

Table 5.1. Bivariate comparison of study characteristics in men and women with CVD, by presence and absence of depressive symptoms, *n*=1022

	Sample with depressive Symptoms (CDS ≥90) (*n*=804)			**Sample without depressive symptoms (CDS<90) (*n*=218)**		
Variable	Male (*n*=573) *n* (%)	Female (*n*=231) *n* (%)	*P* value	Male (*n*=177) *n* (%)	Female (*n*=41) *n* (%)	*P* value
Socio-demographic factors						
Age, mean (SD) †	57.9±9.6	61.6±10.5	**<0.001**	57.8±10.2	63.7±10.7	**0.001**
Marital status			**<0.001**			**<0.001**
Married	564 (98.4)	171 (74.0)		166 (93.8)	25 (60.7)	
Not married	9 (1.6)	60 (26.0)		11 (6.2)	16 (39.0)	
Residence			0.456			0.723
City	261 (45.5)	104 (45.0)		89 (50.3)	20 (48.8)	
Village	270 (47.1)	104 (45.0)		79 (44.6)	20 (48.8)	
Camp	42 (7.3)	23 (10.0)		9 (5.1)	1 (2.4)	
Education degree			**<0.001**			**0.004**
No HS diploma	298 (52.0)	188 (81.4)		84 (47.4)	30 (73.2)	
HS diploma	173 (30.2)	32 (13.8)		49 (27.7)	9 (21.9)	
College degree	102 (17.8)	11 (4.8)		44 (24.9)	2 (4.9)	
Occupation			**<0.001**			**<0.001**
Professional	153 (26.7)	9 (3.9)		47 (26.6)	0 (0.0)	
Non-professional	226 (39.4)	4 (1.7)		76 (42.9)	1 (2.4)	
Unemployed	143 (25.0)	175 (75.8)		31 (17.5)	29 (70.8)	
Retired	51 (8.9)	4 (1.7)		23 (13.0)	3 (7.3)	
House wife	0 (0.0)	39 (16.9)		0 (0.0)	8 (19.5)	
Income			**<0.001**			**<0.001**
Yes	442 (77.1)	77 (33.3)		146 (82.5)	12 (29.3)	
No	131 (22.9)	154 (66.7)		31 (17.5)	29 (70.7)	
Clinical Factors						
Cardiac diagnosis			**<0.001**			**0.010**
CHD	188 (32.8)	63 (27.3)		70 (39.6)	13 (31.7)	
MI	242 (42.2)	76 (32.9)		73 (41.2)	15 (36.6)	
Angina	96 (16.8)	38 (16.4)		24 (13.6)	4 (9.8)	
Other	47 (8.2)	54 (23.4)		10 (5.6)	9 (21.9)	
Previous cardiac diagnosis			**0.036**			0.898
Yes	386 (67.4)	173 (74.9)		106 (59.9)	25 (61.0)	
No	187 (32.6)	58 (25.1)		71 (40.1)	16 (39.0)	
Years with cardiac disease			0.356			0.800
≤1 year	347 (60.6)	130 (56.3)		124 (70.1)	27 (65.8)	
2-9 years	148 (25.8)	61 (26.4)		37 (20.9)	9 (22.0)	
≥10 years	78 (13.6)	40 (17.3)		16 (9.0)	5 (12.2)	
Cardiac treatment (at admission)			**0.005**			0.872
CATH/stent	306 (53.4)	98 (42.4)		107 (60.5)	23 (56.0)	
CATH/CABG	139 (24.3)	58 (25.1)		34 (19.2)	9 (22.0)	
CATH/other & unknown	128 (22.3)	75 (32.5)		36 (20.3)	9 (22.0)	
Co-morbidities			**<0.001**			**0.021**
None	182 (31.8)	32 (13.9)		73 (41.2)	12 (29.3)	
1	169 (29.5)	68 (29.4)		57 (32.2)	9 (22.0)	
2+	222 (38.7)	131 (56.7)		47 (26.6)	20 (48.7)	
Medications			**0.003**			0.471

None	81 (14.1)	13 (5.6)		32 (18.1)	6 (14.6)	
1-2	85 (14.9)	37 (16.0)		22 (12.4)	8 (19.5)	
3-4	407 (71.0)	181 (78.4)		123 (69.5)	27 (65.8)	
Somatic symptoms (PHQ-15)			**<0.001**			**0.046**
Minimal	48 (8.4)	6 (2.6)		35 (19.8)	2 (4.9)	
Low	118 (20.6)	34 (14.7)		74 (41.8)	15 (36.6)	
Medium	193 (33.7)	64 (27.7)		43 (24.3)	14 (34.1)	
High	214 (37.3)	127 (55.0)		25 (14.1)	10 (24.4)	
Family history			0.356			0.033
Yes	236 (41.2)	87 (37.7)		63 (35.6)	22 (53.7)	
No	337 (58.8)	144 (62.3)		114 (64.4)	19 (46.3)	
QoL, (SF-12-PCS score), mean (SD) †	38.2±12.1	31.4±10.1	**<0.001**	44.6± 12.1	34.4±1.9	**<0.001**
Psychosocial factors						
PTSD (PTSD-PCL-S)			**<0.001**			0.282
Minimal	329 (57.4)	105 (45.4)		147 (83.1)	30 (73.2)	
Some	66 (11.5)	15 (6.5)		11 (6.2)	3 (7.3)	
Moderate	141 (24.6)	85 (36.8)		19 (10.7)	8 (19.5)	
High	37 (6.5)	26 (11.3)		0 (0.0)	0 (0.0)	
Social support (ESSI)			**<0.001**			0.293
Low	186 (32.5)	108 (46.7)		54 (30.5)	16 (39.0)	
High	387 (67.5)	123 (53.3)		123 (69.5)	25 (61.0)	
Resilience (RS-14)			**<0.001**			**0.002**
Very low	45 (7.9)	38 (16.4)		3 (1.7)	6 (14.6)	
Low	55 (9.6)	38 (16.4)		8 (4.5)	2 (4.9)	
Low-end	118 (20.6)	46 (19.9)		37 (20.9)	3 (7.3)	
Moderate	148 (25.8)	52 (22.5)		45 (25.4)	12 (29.3)	
Moderately-high	156 (27.2)	45 (19.5)		58 (32.8)	15 (36.6)	
High	51 (8.9)	12 (5.1)		26 (14.7)	3 (7.3)	
Self-esteem (SISE), mean (SD) †	5.9 ±1.3	5.2 ±1.6	**<0.001**	6.2±1.0	6.1±1.2	0.633
QoL,(SF-12-MCS score), mean (SD) †	39.1±12.5	35.3± 3.3	**<0.001**	46.2±12.6	47.0±1.9	0.724
Lifestyle factors						
Smoking status			**<0.001**			**<0.001**
Never	106 (18.5)	182 (78.8)		42 (23.7)	34 (82.9)	
Former	126 (22.0)	11 (4.8)		105 (59.3)	4 (9.8)	
Current	341 (59.5)	38 (16.4)		30 (17.0)	3 (7.3)	
Currently on diet			0.767			0.483
Yes	87 (15.2)	37 (16.0)		39 (22.0)	7 (17.1)	
No	486 (84.8)	194 (84.0)		138 (78.0)	34 (82.9)	
Fat consumption			**<0.001**			**0.075**
Low	247 (43.1)	127 (55.0)		85 (48.0)	21 (51.2)	
Medium	176 (30.7)	77 (33.3)		53 (30.0)	17 (41.5)	
High	150 (26.2)	27 (11.7)		39 (22.0)	3 (7.3)	
Vegetable & fruit consumption			0.920			0.789
Low	59 (10.3)	25 (10.8)		15 (8.5)	3 (7.3)	
Medium	200 (34.9)	83 (35.9)		55 (31.1)	15 (36.6)	
High	314 (54.8)	123 (53.3)		107 (60.4)	23 (56.1)	
Alcohol use			**0.004**			0.100
Yes	35 (6.1)	3 (1.3)		11 (6.2)	0 (0.0)	
No	536 (93.9)	228 (98.7)		165 (93.8)	41 (100.0)	
Physical activity			**<0.001**			**0.008**
None	178 (31.1)	117 (50.7)		31 (17.5)	11 (26.8)	
Not daily	116 (20.2)	37 (16.0)		24 (13.6)	12 (29.3)	
Daily	279 (48.7)	77 (33.3)		122 (68.9)	18 (43.9)	
BMI			**0.083**			0.230
Underweight	3 (0.5)	0 (0.0)		1 (0.6)	0 (0.0)	

Normal weight	118 (20.6)	39 (16.9)	38 (21.5)	4 (9.8)
Overweight	236 (41.2)	84 (36.4)	87 (49.1)	20 (48.8)
Obese	216 (37.7)	108 (46.7)	51 (28.8)	17 (41.4)

Note. Gender differences were assessed using Chi-squared and t-tests, respectively, both in patients with and without depressive symptoms.

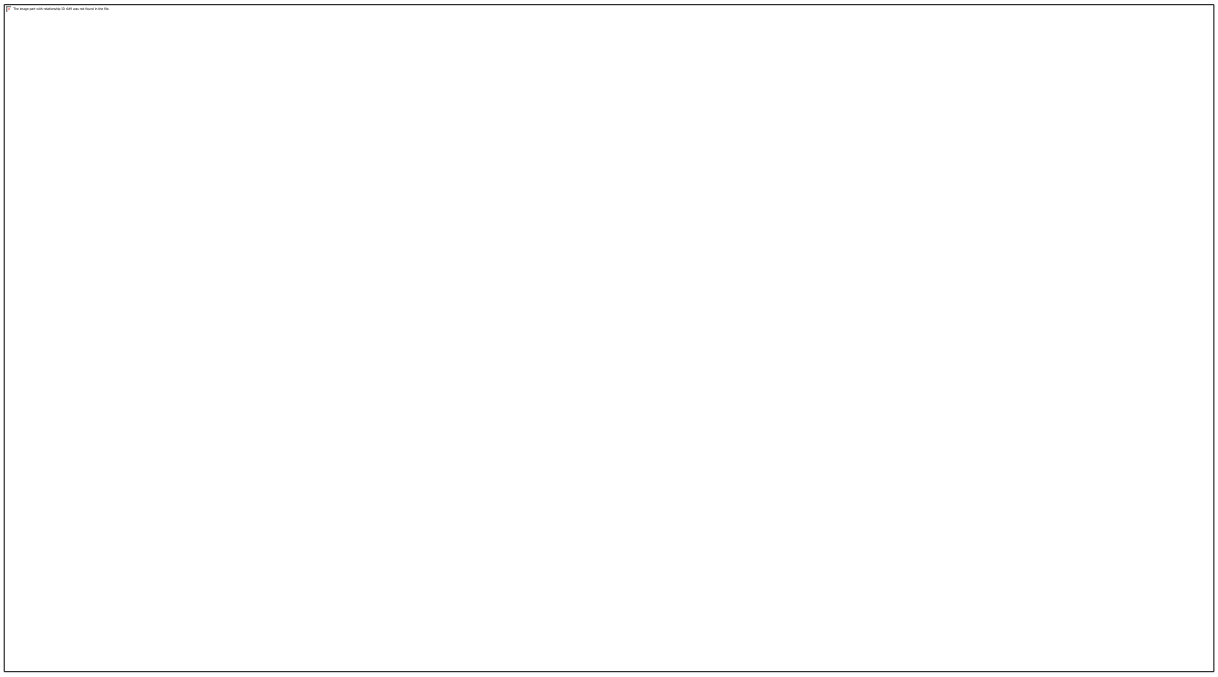
CDS=Cardiac Depression Scale, HS= High school, MI= Myocardial infarction, CHD= Coronary heart disease, CATH= catheterization, CABG= coronary artery bypass graft, PHQ-15= Patient Health Questionnair-15, QoL=quality of life, SF-12= Short-form 12 Health Survey, PCS= Physical Component Summary, SD= standard deviation, PTSD=Post-Traumatic Stress Disorder, PTSD-PCL-S=Post-Traumatic Stress Disorder Checklist, RS-14=Resilience Scale-14, SISE=Single-Item Self-Esteem Scale, ESSI= ENRICHD Social Support Instrument, MCS=Mental Component Summary, BMI= body mass index; †=Independent *t* test; P values in bold are significant at $p < 0.05$.

Bivariate comparisons of psychosocial factors between depressed men and women revealed that depressed women were more likely to have higher levels of PTSD symptoms, lower social support, lower resilience, lower self-esteem and a lower score on the SF-12-MCS for quality of life than their male counterparts.

Regarding lifestyle factors, women with depressive symptoms were less likely to be smokers and have a high fat intake, while more likely to be physically inactive and to be obese than men with depressive symptoms.

In the sample without depressive symptoms, the pattern of gender differences was similar, but with the small sample of women without depression (*n*=41), significant differences were observed less frequently.

Figure 5.1. Distribution of scores for symptoms of depression (CDS score) and PTSD score, by gender



Note. CDS=Cardiac Depression Scale (Possible score range: 26-182; Actual score range: 47-155); PTSD=Post-Traumatic Stress Disorder (Possible score range: 0-85; Actual score range: 0-71)

The presence of depressive symptoms as defined by a CDS score ≥90 among the total sample was 78.7%. The proportion of severe depressive symptoms (CDS >100) was higher in women compared to men (61.4% versus 50.7%, P=0.003), while the proportion of women without depressive symptoms was 15.1% versus 23.6% for men (Table 5.2). Comparison of depressive and PTSD symptoms assessed as continuous variables (means of CDS and PTSD scores) by gender revealed that women had significantly higher CDS (104.6±15.9; t=4.1; P<0.001) and PTSD scores (29.4±10.6; t=4.4; P<0.001) (Figure 5.1).

Table 5.2. Frequency of levels of severity of depressive symptoms, by gender

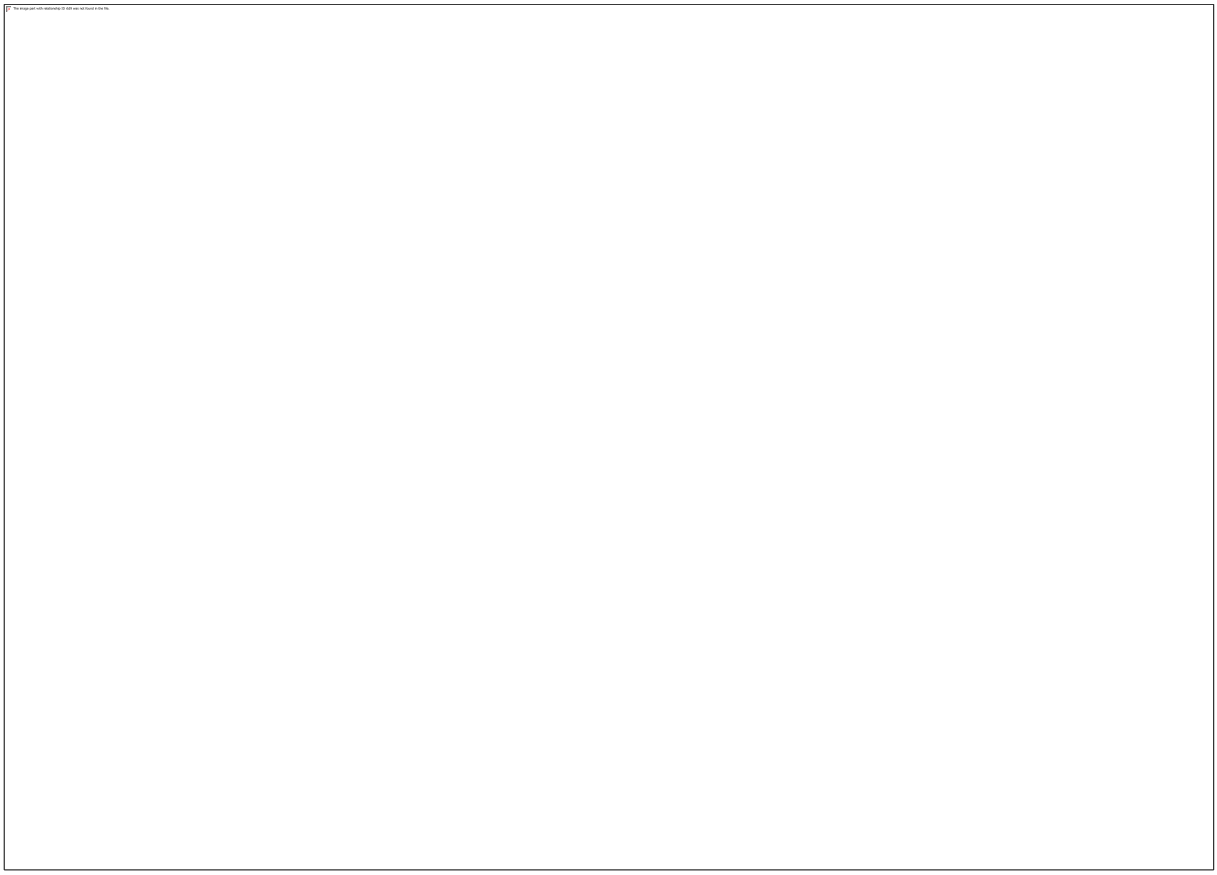
CDS score	Total Population (*n*=1022)	Men (*n*=750)	Women (*n*=272)	*P* value
<90: no depression	218 (21.3)	177 (23.6)	41 (15.1)	0.003
90-100:mild-to-moderate depression	257 (25.2)	193 (25.7)	64 (23.5)	
>100: severe depression	547 (53.5)	380 (50.7)	167 (61.4)	

Note. CDS=Cardiac Depression Scale

5.3.2 Direct and indirect effects of gender on depression (CDS score)

The pooled SEM of the direct effect of gender on depression (CDS score) and the indirect effects when mediators were added was conducted for the overall sample. Figure 6.2 illustrates the pathways between gender and depression with the tested mediators. Parameters reported in the figure include coefficients and confidence intervals (CI). They demonstrate the associations of gender with each potential mediating factor and between each potential mediating factor and outcome variable, after adjusting for the effect of gender. Results from the SEM showed both positive and negative mediators, where positive mediators mediating the gender difference on depression are associated both with being female and higher levels of depression. In the pooled SEM of gender and depression, there was no direct effect of gender on CDS score (coefficient: 0.0, 95% CI: -2.2-2.2, p=1.0). There were significant direct effects of gender on the mediators as shown in figure 6.2. On the one hand, female gender was positively associated with higher PTSD symptoms, comorbidities, somatic symptoms and income. On the other hand, female gender was associated with lower resilience, self-esteem, quality of life, education, less smoking and lower physical activity. Negative indirect effects of gender on depression were observed through resilience, self-esteem, quality of life, (SF-12-PCS), education, income and physical activity, whereas positive indirect effects of gender on depression were observed through PTSD, comorbidities, somatic symptoms, and smoking. Quality of life, education, and income were not significant mediators for the indirect effect of gender on depression. No evidence of moderation was found for the direct effect of gender on CDS score, the effects of gender on mediators and the effects of mediators on CDS score.

Figure 5.2. SEM of the direct and indirect effects of gender on depression (CDS score), (*n*=1022)



Note. The pathways represented by arrows correspond to direct and indirect effects of gender on depression (CDS score). Solid arrows (in bold) represent statistically significant associations between variables and dashed arrows represent non-significant associations. Each arrow is labeled with the respective effect estimate and its 95%-confidence interval. The effect magnitudes on the arrows are not comparable to each other because the mediators have different scale ranges.
Gender was coded as 0=male, 1=female; IV=independent variable, DV= dependent variable, CDS=Cardiac Depression Scale, PTSD-PCL-S=Post-Traumatic Stress Disorder Checklist, RS-14=Resilience Scale-14, SISE= Single-Item Self-Esteem Scale, SF-12-PCS= Short-form 12 Health Survey-Physical Component Summary, PHQ-15= the Patient Health Questionnaire-15; *p<0.05, **p<0.01, ***p<0.001

There was no indication of confounding or moderation by age. In the pooled model, age was not significant when a direct effect of age on CDS score was added to the model. There were also no significant differences between corresponding effect estimates after SEM's were conducted separately for the two age groups <59 years and ≥59 years. These results are presented in Figure 5.S1.

The SEM conducted to assess whether resilience could also be a mediator and/or moderator between PTSD and depression (CDS score) revealed a significant direct association between PTSD and depression and a small positive moderating effect of resilience on this association was observed. There were negative yet significant associations between PTSD and resilience and between resilience and depression (Figure 5.S2). Thus, in this SEM, resilience appeared both as a mediator of the total effect of PTSD on depression and a moderator of the respective direct effect.

Figure 5.3. Association of PTSD and CDS stratified by level of resilience

Note. CDS= Cardiac Depression Scale; PTSD=Post-traumatic stress disorder

Figure 5.3 illustrates the interaction between PTSD and resilience, in which the difference in predicted depression (CDS score) between those with low and high resilience decreases slightly with increasing PTSD symptoms. This suggests that resilience shows a clearer protective role at lower levels of PTSD, becoming less protective at higher levels of PTSD.

No mediation by smoking of the association between PTSD and depression (CDS score) was found (data not shown).

5.4 Discussion

In our sample of cardiac patients, women with CVD have a higher prevalence of severe depressive symptoms (61.4%) compared to men (50.7%). The association of gender with depression was entirely explained by a number of mediators. The strongest positive mediator was PTSD, which was more prevalent in women and positively associated with depression. While resilience itself was a negative mediator of the gender-depression association, it mediated and moderated the PTSD-depression (CDS score) association. Besides mediation by psychosocial parameters, lifestyle factors such as physical activity and smoking also explained part of the gender-depression association.

Our findings that women with CVD were more likely to experience depressive symptoms and at higher levels than men with CVD were consistent with other studies (Kao et al., 2014, Frasure-Smith and Lesperance, 2005, 2006). This finding is also consistent with the respective sex difference observed in the general population (Nolen-Hoeksema et al., 1999).

Previously, there has been evidence on gender being linked to PTSD and comorbid depression as well as PTSD and associated outcomes in cardiac patients. However, to our knowledge, this is the first study to assess direct and indirect effects of gender on depression among a cardiac population, with a particular focus on PTSD as a mediator. Previous studies have found that women are at higher risk of comorbid PTSD and depression symptoms compared to men (Cohen et al., 2016, Horesh et al., 2015), similar to our findings which showed a direct significant association of female gender with PTSD and a significant indirect effect of gender on depression mediated by PTSD. Reasons for these gender differences could be attributed to the different types of traumatic or stressful situations which men and women are exposed to, different responses to trauma, and different symptom-related responses, all of which may affect the course and severity of symptoms (Nolen-Hoeksema, 1987). In addition, higher rates of PTSD and depression among women could be due to women's lower social

position which can lead to greater exposure to trauma and stressors compared to men (Van de Velde et al., 2010). This could particularly be true among our sample and in the cultural context of Palestine, where women have much lower social positions compared to men. In the present study, women had more severe diagnoses, comorbidities and complicated treatment procedures along with other negative daily stressors, suggesting that women were more vulnerable to traumatic stress which arises from both PTSD and depression and their comorbidity. Dao et al., found increased mortality among comorbid PTSD and depression patients after CABG to be linked to female gender (Dao et al., 2010). These results have implications for early assessment of these mental health disorders, as their comorbidity is becoming more frequently observed and prevalent in cardiac patients.

Our findings also reveal that low resilience is associated with being female and higher depressive symptoms among our cardiac sample. This finding supports the results of a study by Carvalho et al. (Carvalho et al., 2016), which found that among a CVD sample, lower scores of resilience were associated with depressive symptoms and with female gender, compared to men. This finding could indicate that men tend to have more motivation to focus on problem solving coping strategies, whereas women tend to use emotion-focused coping strategies (Bazrafshan et al., 2014, Möller-Leimkühler, 2007). Additionally, another study which assessed for depression using the CDS found a strong association between low resilience and depression (CDS>95) among CVD patients (Toukhsati et al., 2017). In our further analysis assessing mediation of resilience between PTSD and depression (CDS score), we found a significant effect for the interaction by resilience of the association between PTSD and depression (CDS score). We also found the difference in CDS score between those with low and high resilience decreased with increasing PTSD symptoms, potentially meaning that higher levels of PTSD partly override the protective effects of resilience. These findings suggest the need for intervention targets such as group cardiac rehabilitation and interventions to improve coping

with adversities, which could ultimately reduce the risk of depression and strengthen resilience among cardiac patients. Furthermore, promoting physical activity among CVD patients is recommended as resilience also has been linked to exercise (Fleshner et al., 2011) and has been known to reduce the risk of depression among resilient patients with CVD (Toukhsati et al., 2017).

Higher somatic symptoms were also associated with being female and higher depression levels in this study, consistent with previous reports which found females with major depression showed higher rates of somatic symptoms compared to men (Dessotte et al., 2015, Dekker et al., 2007). A study conducted in Spain, which also used the PHQ-15 to assess for somatic symptoms, found women reported higher total scores than men and were more concerned in 8 out of 15 items of the PHQ-15 (Gonzalez et al., 2009). Nonetheless, these findings should be interpreted with caution since somatic symptom scales vary in different studies.

Our results also reveal that physical inactivity is associated with being female and higher depressive symptoms among our cardiac sample. It has been previously reported that female cardiac patients frequently engage in less exercise compared with their male counterparts, despite the increasing evidence to support the beneficial role of exercise among cardiac patients (Hunt-Shanks et al., 2009). Physical inactivity has been associated with depression and has been shown to mediate the relationship between depression and cardiovascular events and mortality (Bonnet et al., 2005, Whooley et al., 2008). A recent systematic review found that depression could lead to a sedentary lifestyle and lower levels of physical activity (Roshanaei-Moghaddam et al., 2009). These data along with our findings suggest that there is need for exercise programs for CVD patients, especially women and those with depression.

Furthermore, our findings shed light on gender differences for socioeconomic factors among men and women with both CVD and depressive symptoms. In the present study, and

similar to other studies, women were more likely to be not married, unemployed, and less educated (Vaccarino et al., 2003, Doering et al., 2011), compared to men with CVD and comorbid depressive symptoms. These findings are supported by previous studies on CHD patients that female gender is linked to lower education, which increases the risk of onset of CHD (Thurston et al., 2006), whereas employment and higher education play a protective role against depressive symptoms (Bjerkeset et al., 2005). Those with high socioeconomic status have more self-esteem, more resources and social support, all of which reduce the stress that comes with depression compared to those with low socioeconomic status, whom have less access to social and personal resources, which increases stress levels. However, occupation and marital status were not significant in the final SEM and thus were not mediating effects of gender on depression (CDS score).

Furthermore, in our sample, women had more coexisting illnesses (i.e. diabetes and hypertension) compared with men with cardiac disease, a finding consistent with other studies (Anand et al., 2005, Doering et al., 2011, Vaccarino et al., 2003). There were no major differences in rates of angina as an initial cardiac diagnosis between men and women, which is inconsistent with results in other studies, which found higher angina rates among women compared with men (Daly et al., 2006) (Milner et al., 2002).

Strengths

This study had several strengths. First, the high participation rate decreased the likelihood of selection and participation bias. Second, our sample of women was relatively large, compared to other studies, which provided sufficient statistical power for testing gender differences. Third, the CDS used in the study is the only psychometric scale suitable for the comparative depression assessment in heart disease patients, subjected to different interventions and has excellent properties for the diagnosis of severe depression, a score >100 having a sensitivity of 88% and a specificity of 84%. Finally, the findings of our study are likely generalizable as our

sample was recruited from four main hospitals of Nablus, Palestine, which provide cardiac care to a large percentage of individuals in the area.

Limitations

The limitations of our study are due to several sources. First, depression was not formally diagnosed by a psychological interview and was rather assessed using the CDS, thus we cannot conclude that our sample had clinical depression. However, the identification of certain mediating factors of gender on depression among cardiac patients can serve as a basis for developing the best intervention targeting depression among women and men with cardiac disease. Second, some patients were recruited at the time of admission and for the most part before receiving their intervention or diagnosis, and thus were under stress and anxiety. As some of the anxiety observed may have been transient, the level of depression and anxiety could have been overestimated. Finally, due to the cross-sectional design of the study the direction of associations cannot be derived with certainty and causality cannot be inferred.

5.5 Conclusion

This study demonstrated that, similar to the general population, the prevalence of severe depression is greater in female patients with cardiac disease compared to male patients. Overall, our findings provide new information documenting mediating factors, in particular PTSD, of the association between gender and depression among cardiac patients. These findings emphasize the need to devote more attention to identify and address potential mediating factors that could account for gender differences in depression. Providing supportive programs for female patients with CVD to improve their psychosocial well-being in cardiac rehabilitation seems of particular importance in conflict-prone areas, like Palestine.

Declarations

Ethics approval and consent to participate

This study was approved by the Ethics Committee of Nordwest- und Zentral Schweiz (EKNZ) in Basel, Switzerland and by the Institutional Review Board (IRB) committee at An-Najah National University in Nablus, Palestine. All patients enrolled in the study provided written informed consent.

Consent for publication

Not applicable.

Availability of data and material

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

HA conducted data collection, analyzed and interpreted data, and wrote the manuscript. AA and SHY supervised the data collection and the implementation of the study in Palestine and edited the manuscript. NPH, EZ, MK and CS participated in planning the data analysis. CS supervised the statistical analysis. NPH, EZ, MK and CS contributed to the interpretation of the results. NPH designed the study and directed its implementation. EZ directed the data

analysis and interpretation of results. She edited all versions of the manuscript. All authors read and approved the final manuscript.

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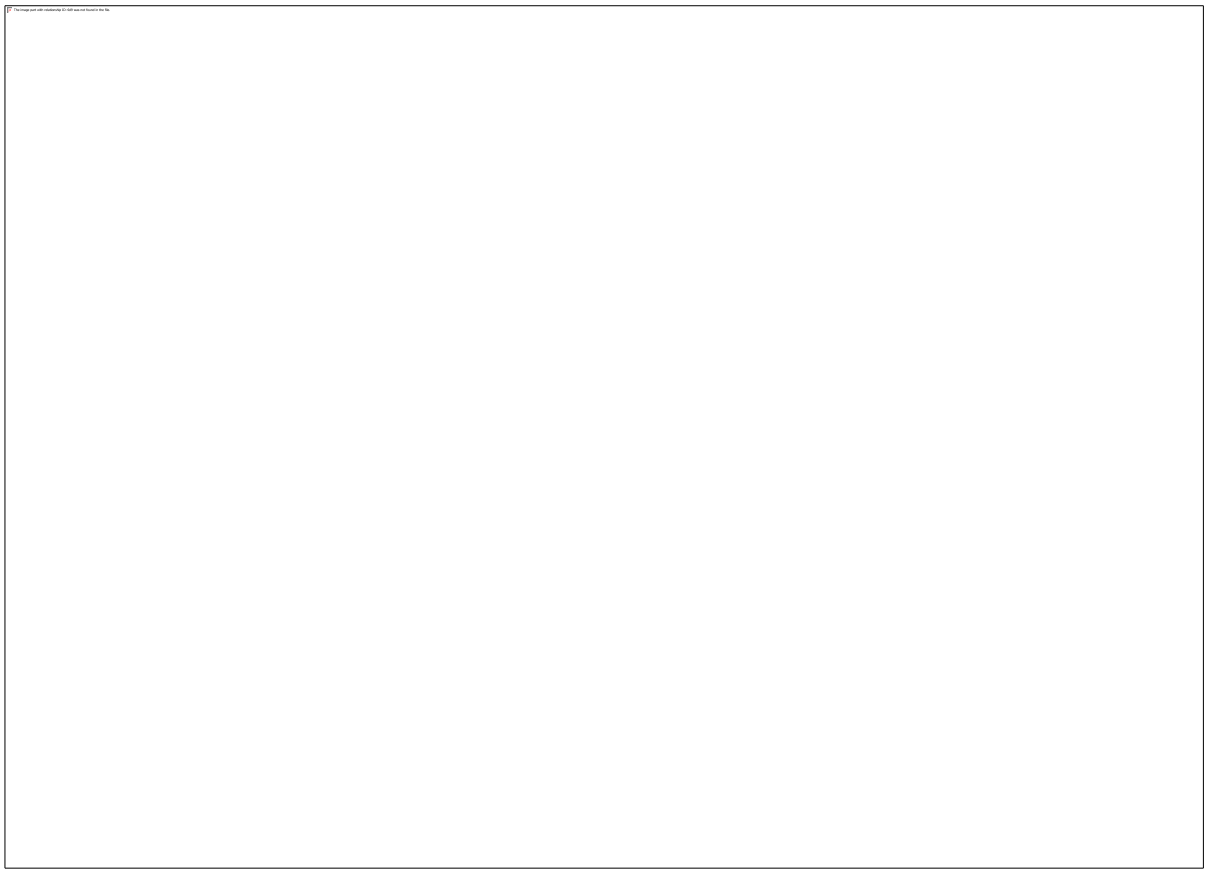
5.6 Supplementary material

Figure 5.S1. SEM of the direct and indirect effects of gender on depression (CDS score) for age groups <59 (*n=500*) and ≥59 (*n=522*).

Age group <59

Note. The pathways represented by arrows correspond to direct and indirect effects of gender on depression (CDS score). Solid arrows (in bold) represent statistically significant associations between variables and dashed arrows represent non-significant associations. Each arrow is labeled with the respective effect estimate and its 95%-confidence interval. The effect magnitudes on the arrows are not comparable to each other because the mediators have different scale ranges.
Gender was coded as 0=male, 1=female; IV=independent variable, DV= dependent variable, CDS=Cardiac Depression Scale, PTSD-PCL-S=Post-Traumatic Stress Disorder Checklist, RS-14=Resilience Scale-14, SISE= Single-Item Self-Esteem Scale, SF-12-PCS= Short-form 12 Health Survey-Physical Component Summary, PHQ-15= the Patient Health Questionnaire-15; *p<0.05, **p<0.01, ***p<0.001

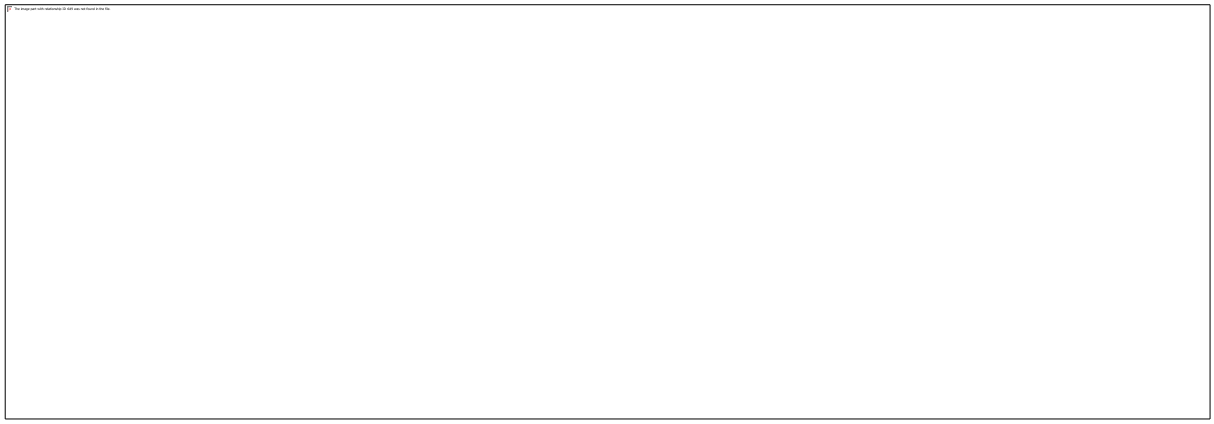
Age group ≥59



Note. The pathways represented by arrows correspond to direct and indirect effects of gender on depression (CDS score). Solid arrows (in bold) represent statistically significant associations between variables and dashed arrows represent non-significant associations. Each arrow is labeled with the respective effect estimate and its 95%-confidence interval. The effect magnitudes on the arrows are not comparable to each other because the mediators have different scale ranges.

Gender was coded as 0=male, 1=female; IV=independent variable, DV= dependent variable, CDS=Cardiac Depression Scale, PTSD-PCL-S=Post-Traumatic Stress Disorder Checklist, RS-14=Resilience Scale-14, SISE= Single-Item Self-Esteem Scale, SF-12-PCS= Short-form 12 Health Survey-Physical Component Summary, PHQ-15= the Patient Health Questionnaire-15; *p<0.05, **p<0.01, ***p<0.001

Figure 5.S2. SEM of association between resilience, PTSD and depression (CDS score**)**



Note. CDS= Cardiac Depression Scale; PTSD=Post-traumatic stress disorder

6

ARTICLE III

Posttraumatic stress disorder predicts poor health-related quality of life in cardiac patients in Palestine

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Abstract

Background: The longitudinal association of posttraumatic stress disorder (PTSD) with health-related quality of life (HRQL) in cardiac patients' remains poorly studied, particularly in conflict-affected settings.

Methods: For this cohort study, we used baseline and one-year follow-up data collected from patients 30 to 80 years old consecutively admitted with a cardiac diagnosis to four major hospitals in Nablus, Palestine. All subjects were screened for PTSD and HRQL using the PTSD Checklist Specific and the HeartQoL questionnaire. We used a generalized structural equation model (GSEM) to examine the independent predictive association of PTSD at baseline with HRQL at follow-up. We also examined the mediating roles of depression, anxiety, and stress at baseline.

Results: The prevalence of moderate-to-high PTSD symptoms among 1022 patients at baseline was 27·0%. Patients with PTSD symptoms reported an approximate 20·0% lower HRQL at follow-up. The PTSD and HRQL relationship was largely mediated by depressive and anxiety symptoms. It was not materially altered by adjustment for socio-demographic, clinical, and lifestyle factors.

Discussion: Our findings suggest that individuals with a combination of PTSD and depression, or anxiety are potentially faced with poor HRQL as a longer term outcome of their cardiac disease. In Palestine, psychological disorders are often stigmatized; however integration of mental health care with cardiac care may offer an entry door for addressing psychological problems in the population. Further studies need to assess the effective mental health interventions for improving quality of life in cardiac patients.

Keywords: Posttraumatic stress disorder, cardiovascular diseases, health-related quality of life

6.1 Introduction

Cardiovascular diseases (CVDs) account for 31% of all global deaths (Roth et al., 2017). The Middle East has a high burden of CVD morbidity, mortality, and premature cardiac events (Dugani et al., 2019), leading to a substantial proportion of patients experiencing disability (Lisy et al., 2018). Subsequently, there is a strong need for cardiac rehabilitation with a special focus on improving health-related quality of life (HRQL). There is evidence that HRQL predicts adverse health outcomes including mortality and hospitalizations in cardiac patients (Bosworth et al., 1999).

Targets for intervention in cardiac rehabilitation include psychosocial stressors and mental health disorders, which tremendously impact overall HRQL. Depression in particular is not only an established risk factor for CVD (Barth et al., 2004), but is increasingly recognized for its adverse prognostic effect in cardiac patients (Carney and Freedland, 2008). Less is known about the prognostic role of posttraumatic stress disorder (PTSD), a common psychiatric disorder in individuals who experience a traumatic event (e.g. war, natural disasters, physical assault, life threating illness) (2000a).

Numerous cross-sectional studies have found CVD and its risk factors are more prevalent among individuals with PTSD than those without PTSD (Pietrzak et al., 2011). This higher CVD prevalence can reflect both the etiological role of PTSD and the traumatic effect of a cardiac event. On the one hand, a recent meta-analysis has shown that PTSD is associated with a 55% increased incidence of cardiac disease or cardiac-related mortality, even after adjustment for demographic, clinical, and psychosocial factors including depression (Edmondson et al., 2013). On the other hand, CVD events can be psychologically traumatic experiences given their sudden onset, unpredictable consequences and life-threatening nature: approximately 10·0-30·0% of people suffer from PTSD after a cardiac event such as a myocardial infarction

(MI) or cardiac arrest (Gander and von Kanel, 2006, Shemesh et al., 2001, Wiedemar et al., 2008).

Yet, evidence on whether and how the presence of PTSD in cardiac patients predicts the course of their disease and quality of life remains limited. The few existing studies suggest that PTSD in cardiac patients is associated with impaired psychosocial functioning, poor physical health (Ginzburg et al., 2003), decreased HRQL (Cohen et al., 2009), non-adherence to medication and treatment (Shemesh et al., 2001), as well as an increased risk of mortality, morbidity and recurrent cardiac events (Edmondson et al., 2011). These adverse associations of PTSD with HRQL may be partly mediated by other mental health symptoms (e.g. depression, anxiety or stress), also associated with heart disease patients' HRQL (AbuRuz, 2018, Stafford et al., 2007).

To the best of our knowledge, the longer-term impact of PTSD on HRQL among cardiac patients has not been conducted in the occupied Palestinian territories (oPt). The present study among a well-characterized cohort of cardiac patients in the Palestinian population a) investigates the independent predictive association of PTSD with HRQL over a one-year follow-up period, and b) assesses the mediating role of depression, anxiety and stress.

6.2 Methods

6.2.1 Study design and sample

A longitudinal design was used to explore the predictive association between PTSD and HRQL in hospitalized cardiac patients after a 12-month follow-up. This study followed cardiac patients consecutively admitted to cardiology units at four major hospitals in Nablus, Palestine. The recruitment and procedures of the study have been described in detail elsewhere (Allabadi et al., 2019). To be eligible for the study, patients were required to be between 30 to 80 years old and have clinically diagnosed CHD, MI, angina, heart failure, or any other cardiac disease.

Patients were recruited for the initial baseline assessment within one week of hospitalization (range one-seven days) between March, 2017 and November, 2017. With a participation rate of 96·0%, a total of 1053 patients were included in the study. Thirty four patients were excluded from the baseline analysis and follow-up due to incomplete data. A follow-up assessment was conducted approximately one year after enrollment in the study between June, 2018 and December, 2018 (Figure 6.1). Ethical approval for the study was obtained from the Ethics Committee of Nordwest-und Zentral Schweiz (EKNZ) in Basel, Switzerland, and the Institutional Review Board (IRB) committee at An-Najah National University in Nablus. All participants provided a written informed consent at baseline and follow-up.

Figure 6.1 Flowchart from baseline recruitment to longitudinal study sample

6.2.2 Procedures

Trained medical students from An-Najah University carried out in-person interviews using a structured questionnaire containing validated assessment tools. At follow-up, all assessed patients who provided consent at baseline were re-contacted by telephone and invited to attend an in-person interview at a medical facility in Nablus, Palestine. Patients refusing in-person interviews were asked to provide relevant information during a phone interview. In this current study, PTSD, depression, anxiety, stress, socio-demographic, clinical, psychosocial and lifestyle factors obtained from all participants at baseline assessment were the independent

variables of interest. HRQL was assessed as the study outcome at 12-month follow-up. An overview of the assessment tools has been described in detail previously (Allabadi et al., 2019).

6.2.3 Assessments

Predictor variable: Posttraumatic stress disorder (PTSD)

PTSD was assessed by the PTSD Checklist Specific (PCL-S), a 17-item questionnaire corresponding to PTSD symptoms based on the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV) criteria. Each item in the questionnaire is scored from 1 (not at all) to 5 (extremely), indicating the extent to which the patient has been bothered by the symptom during the previous month. A total PCL-S score is determined by summing up the scores of all items (range 17-85). In the present study, the total score was divided into two categories of PTSD symptom severity: "no-to-little symptoms" (PCL-S scores 17-29) and "moderate-to-high symptoms" (PCL-S scores ≥30; cutoff for clinically relevant PTSD) (Blanchard et al., 1996). In the current sample, the PCL-S demonstrated an internal consistency (Cronbach α) of 0·86 for all 17 items.

Mediating variables: Depression, anxiety and stress

Depression, anxiety and stress were measured using the Depression Anxiety Stress Scale-42 (DASS-42) by Lovibond & Lovibond (Lovibond SH, 1995). The questionnaire is divided into three scales (depression, anxiety and stress), with items scored on a four-point Likert scale ranging from 0 (did not apply to me at all) to 3 (applied to me very much) measuring the extent to which each state was experienced over the past week. Scores for each of the three scales are determined by summing up the scores and categorized into: depression 0-9 (normal), 10-20 (mild-moderate), ≥21 (severe-very severe); anxiety 0-7 (normal), 8-14 (mild-moderate), ≥15 (severe-very severe); stress 0-14 (normal); 15-25 (mild-moderate), ≥26 (severe-very severe)

(Lovibond SH, 1995). Cronbach α for the three scales in our sample was 0·92 (DASS-depression), 0·82 (DASS-anxiety), and 0·89 (DASS-stress), respectively.

Outcome variable: Health-related quality of life (HRQL)

HRQL was assessed using the HeartQoL questionnaire, a 14-item ischemic heart disease (IHD)-specific scale which measures overall quality of life. The global HeartQoL score indicates how the patient perceives being bothered by their heart disease (Oldridge et al., 2012). In this study the total score was determined by summing up the scores of all 14 items which were assessed on a four-point scale from 0 to 3 (0=poor and 3=good quality of life). The overall score range was 0-42, with higher scores indicating better HRQL. In the present study, Cronbach's α for HRQL was 0·91.

Other variables of interest

Socio-demographics factors----Age, gender, marital status, education, employment and residence were assessed by interview at baseline.

Clinical factors----Clinical data related to the cardiac disease including diagnosis, treatment procedure, comorbidities, duration of disease, medications at discharge and somatic symptoms, which were assessed using the Patient Health Questionnaire-15 (PHQ-15), were retrieved from medical records and by interview at baseline.

Lifestyle factors----Information on smoking status, body-mass index (weight (kg)/height $(m)^2$), and physical activity (e.g. the number of days of physical activity for at least 30 minutes per week) were obtained through in-person interviews at baseline.

6.2.4 Statistical methods

PTSD symptoms were analyzed as the dichotomous variable (presence/absence of moderate-high PTSD symptoms). To assess the relationship between PTSD at baseline and HRQL at follow-up involving potential mediators, we built a generalized structural equation model (GSEM), portrayed in figure 6.2. The model is based on the hypothesis that depression, anxiety and stress mediate the relationship between PTSD and HRQL. The analysis was adjusted for age, gender, occupation, education, residence, hospital, cardiac diagnosis, cardiac treatment, years with disease, somatic symptoms (PHQ-15), comorbidities, medications, body-mass index, physical activity, smoking status and duration of follow-up. We selected these covariates a priori, and based on evidence for association with PTSD as likely confounders of the association between PTSD and HRQL. All GSEM models were estimated using maximum likelihood in the STATA Statistical Software Release 15 (StataCorp., College Station, U.S.A.).

6.3 Results

6.3.1 Recruitment

Of the 1022 participants included at baseline, n=622 (61·0%) were reexamined at follow-up. The mean duration of the approximate one-year follow-up was 399 (SD= 93·7) days (range: 235-677 days). Among the patients whom we attempted to contact, 415 (40·6%) attended in-person interviews and 207 (20·2%) were interviewed by phone; while 351 patients (34·4%) were lost to follow-up (not reached after four telephone calls; phones disconnected). Telephone interviews were conducted with patients who were not able to attend in-person interviews due to (1) physical restrictions, (2) lack of means of transportation, or (3) no interest in attending the appointment. For deceased people (n=49, 4·8%), a telephone interview with the next of kin was used to ascertain or confirm the cause and date of death.

6.3.2 Sample characteristics at baseline

At baseline, among the 1022 patients, the mean age was 58·9±10·1 years (range 30-80 years). Of these participants, 73·4% were male, 90·6% were married, 37·0% were unemployed, and 58·7% did not have a high school diploma. With regard to clinical variables, 39·7% had an acute MI, 32.7% had established CHD, 15·9% had stable or unstable angina, and 11·7% had some other type of cardiac disease, including mitral or aortic valve stenosis, valve regurgitation, heart block and others. Among the category of other diagnoses, 29 (2·8%) patients had heart failure. There were no major socio-demographic or lifestyle differences at baseline among participants included vs excluded in the follow-up assessment. However, depression, complicated treatments, and number of medications were slightly more common among non-participants at follow-up (Table 6.S1).

6.1. Socio-demographic, clinical, psychosocial and lifestyle characteristics at baseline, by PTSD status, *n*=1022

	Moderate-to-high PTSD symptoms (PCL-S ≥30) ***(n=279)***	**No-to-low PTSD symptoms (PCL-S < 30)** ***(n=743)***
Socio-demographic factors		
Age	58·8±10·3	59·1±10·1
Gender		
Female	106 (39·0)	166 (61·0)
Male	173 (23·2)	571 (76·8)
Marital status		
Married	237 (25·7)	689 (74·3)
Not married	42 (43·7)	54 (56·3)
Residence		
City	115 (24·4)	356 (75·6)
Village	137 (29·0)	339 (71·0)
Camp	48 (64·0)	48 (64·0)
Education degree		
No high school diploma	180 (30·0)	420 (70·0)
High school diploma	64 (24·5)	197 (75·5)
College degree	35 (22·2)	126 (77·8)
Occupation		
Professional	51 (24·6)	156 (75·4)
Non-professional	62 (20·2)	245 (79·8)
Unemployed	125 (33·1)	256 (66·9)
Retired	22 (27·5)	58 (72·5)
House wife	19 (40·4)	28 (59·6)

Clinical Factors		
Cardiac diagnosis		
Coronary heart disease	116 (34·7)	218 (65·3)
Myocardial infarction	91 (22·5)	317 (77·5)
Angina	28 (17·5)	132 (82·5)
Other	44 (36·7)	76 (63·3)
Years with cardiac disease		
Less than one year	154 (24·6)	472 (75·4)
Two-nine years	79 (31·1)	178 (68·9)
10 or more years	46 (33·1)	93 (66·9)
Cardiac treatment (at admission)		
Catheterization/stent	127 (23·9)	405 (76·1)
Catheterization /coronary bypass artery graft	76 (31·8)	166 (68·2)
Catheterization/other & unknown	76 (30·6)	172 (69·4)
Co-morbidities		
None	62 (20·8)	236 (79·2)
One	80 (26·6)	224 (73·4)
Two or more	137 (32·6)	283 (67·4)
Medications		
None	33 (25·0)	99 (75·0)
One to two	39 (25·8)	112 (74·2)
Three to four	207 (28·1)	532 (71·9)
Somatic symptoms		
Minimal (PHQ ≤ 4)	17 (18·7)	74 (81·3)
Low (PHQ 5-9)	31 (13·0)	208 (87·0)
Medium (PHQ 10-14)	77 (24·5)	237 (75·5)
High (PHQ ≥ 15)	154 (41·1)	224 (58·9)
Psychosocial factors		
Depression		
Depressed (DASS-Depression ≥ 10)	213 (53·9)	185 (46·1)
Not depressed (DASS-Depression ≤ 9)	66 (10·6)	558 (89·4)
Anxiety		
Anxiety (DASS-anxiety ≥ 8)	236 (38·5)	380 (61·5)
No Anxiety (DASS-anxiety ≤ 7)	43 (10·6)	363 (89·4)
Stress		
Stress (DASS-stress ≥ 15)	258 (39·7)	395 (60·3)
No stress (DASS-stress ≤ 14)	21 (5·7)	348 (94·3)
Lifestyle factors		
Smoking status		
Never	125 (34·3)	239 (65·7)
Former	47 (27·6)	123 (72·4)
Current	107 (22·1)	381 (77·9)
Physical activity		
None	115 (34·3)	223 (65·7)
Not daily	53 (28·0)	136 (72·0)
Daily	111 (22·4)	384 (77·6)
Body-mass index		
Normal weight	56 (27·4)	148 (72·6)
Overweight	111 (25·7)	321 (74·3)
Obese	112 (29·2)	274 (72·8)

Data are mean (SD) or n (%). PTSD= Posttraumatic stress disorder, PCL-S= Posttraumatic stress disorder Checklist Specific, PHQ=Patient Health Questionnaire, DASS=Depression, Anxiety, Stress Scale. Physical activity defined as the number of days of physical activity for at least 30 minutes per week.

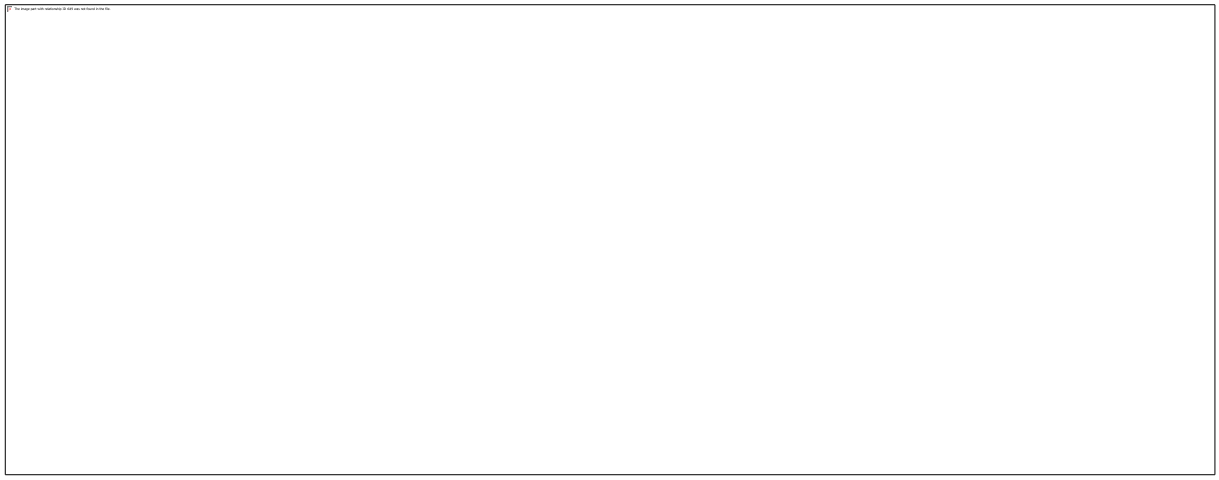
6.3.3 Distribution of socio-demographic, clinical, psychosocial and lifestyle characteristics according to PTSD status

The mean scores of PTSD symptoms at baseline and follow-up were 27·3 (SD = 9·5; range 17-71), and 23·5 (SD=11·0; range 17-80), respectively and the PTSD prevalence's were 27·0% and 21·2%, respectively. Characteristics of participants by PTSD status at baseline are shown in Table 6.1. Among our sample with PTSD symptoms, there were more females (39·0% vs 23·2%); there were more unmarried individuals (43·7% vs 25·7%); housewives [40·4% vs 24·6% (professional)]; individuals with severe cardiac diseases [36·7% vs 17·5% (angina)]; individuals diseased over 10 years [33·1% vs 24·6% (less than one year)]; patients who had a CABG [31·8% vs stent (23·9%)]; had two or more comorbidities [32·6% vs 20·8% (no comorbidities)]; and more individuals who scored high on the PHQ-15 [41·1% vs 13·0% (low somatic symptoms)]. Additionally, among those with PTSD symptoms, patients were more likely to be depressed [53·9% vs 10·6%]; stressed [39·7% vs 5·7%]; and anxious [38·5% vs 10·6%]; more likely to be never-smokers [34·3% vs 22·1% (current smoker)]; and physically inactive [34·3% vs 22·4% (daily)]. None of the patients confirmed when asked at baseline that in the context of their cardiac care they had ever been asked about their mental health well-being.

6.3.4 Mediation analyses: direct and indirect associations of PTSD with HRQL

The mean HRQL score at follow-up was 28·2 (SD=12·1). The mean HRQL score among those with PTSD at baseline was 24·6 (SD=12·8) compared to 30·0 (SD=11·4) among those without PTSD ($p < 0·001$).

Figure 6.2: GSEM: The estimation of the direct and indirect effects of PTSD on HRQL



Covariates additionally adjusted for: Age, gender, occupation, education, residence, hospital, cardiac diagnosis, cardiac treatment, years with disease, somatic symptoms (PHQ-15), comorbidities, medications, body mass index, physical activity, smoking status. Follow-up duration was also adjusted for with no differences in the results. Bolded lines indicate statistically significant effects and dashed lines indicate non-significant effects. Each line is labeled with the respective effect estimate and its 95%-confidence intervals. Note that because the scales of the three mediating variables are not the same, the effect sizes cannot be compared directly. Follow-up for HRQL: (n=619).
PTSD= Post-Traumatic Stress Disorder, PCL-S=Post-Traumatic Stress Disorder Checklist, DASS=Depression, Anxiety, Stress Scale, HRQL= Health-related quality of life, Questionnaire. *p<0·10, **p<0·05, ***p<0·001

Results from the mediation analyses (Figure 6.2) report the associations of PTSD with each potential mediating factor (depression, anxiety, stress) and between each potential mediator and HRQL, after adjusting for covariates. PTSD was a positive predictor of depression (β=10·3, p<0·001), anxiety (β=6·8, p<0·001) and stress (β=10·1, p<0·001). In turn, depression (β=-0·2, p=0·025) and anxiety (β=-0·2, p<0·068), but not stress predicted HRQL at follow-up, implying depression and anxiety to be mediators for the relationship between PTSD and HRQL. Furthermore, the direct effect of PTSD on HRQL was not statistically significant after controlling for covariates and mediators (β=-0·3, p=0·824), indicating the predictive association of PTSD with HRQL at one year follow-up was largely mediated by depression and anxiety. Our reference model further identified treating hospital, duration of disease, comorbidities and physical activity as independent predictors of HRQL. These factors neither modified the association of PTSD with depression or anxiety, nor the association of depression and anxiety with PTSD.

6.4 Discussion

This is the first study on the role of PTSD on the quality of life of cardiac patients in Palestine. Patients with moderate and high PTSD symptoms reported lower HRQL, approximately one year after baseline assessment. The PTSD and HRQL relationship was largely mediated by depressive and anxiety symptoms. The negative effect of PTSD remained evident after adjusting for relevant covariates. The careful control for confounding and the longitudinal nature of our study strengthens the belief that this relationship may be causal.

There has been extensive research on the relationship between PTSD and HRQL among war veterans and those with various chronic illnesses, but little on the relationship of PTSD and HRQL, specifically among CVD patients. Our results are consistent with similar studies of CHD patients, which found PTSD symptoms are associated with a lower quality of life (Cohen et al., 2009, Stoll et al., 2000). A further study which investigated HRQL among patients with PTSD following cardiac arrest reported more problems in overall quality of life and decreased HRQL scores compared to those without PTSD (Gamper et al., 2004).

To our knowledge, this is the first study to assess the specific mediating role of depression, anxiety and stress in the relationship between PTSD and HRQL among cardiac patients. Our findings are similar to those of a previous study conducted among a small sample of motor vehicle accident survivors, in which an indirect effect of PTSD on quality of life through depression and anxiety was also found (Gudmundsdottir et al., 2004). Numerous studies have also found that approximately half of people with PTSD had major depressive disorder (MDD) across different sub-samples (Rytwinski et al., 2013, Kessler et al., 1995), which is consistent with our analyses. Moreover, a body of literature has documented the independent associations of depression and anxiety with poor HRQL among CVD patients (AbuRuz, 2018, Stafford et al., 2007).

The prevalence of PTSD in our sample of cardiac patients was 27·0%, which is considerably higher than the PTSD rates reported in previous studies showing associations between PTSD and quality of life in different groups of patients. Cohen et al., who assessed for PTSD and HRQL among CHD patients found a prevalence of 9·0%.(Cohen et al., 2009) The prevalence of PSTD in our study exceeds PTSD rates found among patients with trauma (Danielsson et al., 2018), stroke (Goldfinger et al., 2014), and hematological malignancies (Liu et al., 2015).

One of the major strengths of the present study is its longitudinal design which allowed studying the predictive association of PTSD with HRQL in a clear temporal resolution. The detailed characterization of the study population limited residual confounding in studying the independent association of PTSD with HRQL. Moreover, previous research has focused on only one category of cardiac patients, rather than considering a sample of diverse cardiac diagnoses. Further strengths of this study are the high participation rate and the use of the HeartQoL questionnaire, which is specifically designed to assess quality of life in cardiac patients.

The findings in this present study should be interpreted taking into consideration several limitations. First, we cannot exclude the possibility that depression, anxiety and stress symptoms measured among those with PTSD pre-dated the traumatic event itself in some patients. Second, the baseline assessment was conducted shortly after admission following a cardiac event, when elevated stress and anxiety are to be expected, thus our estimates of the magnitude of effect may not be generalizable to a longer follow-up. Third, we did not assess HRQL at baseline. If HRQL at follow-up was correlated with HRQL at baseline, the association observed would suggest an association of PTSD with the persistence of decreased HRQL. Finally, individuals who died before the follow-up assessment, refused to participate in the follow-up, or could not be reached could in fact have had a very low quality of life. If

they were also more likely to exhibit PTSD symptoms, we may have underestimated the effect of PTSD on HRQL.

6.5 Conclusion

In the conflict-affected area of Palestine, high rates of PTSD as well as depression and anxiety are observed among cardiac patients (Allabadi et al., 2019). The current results suggest that individuals with a combination of PTSD and depression or anxiety are potentially faced with poor HRQL as a longer term outcome of their heart disease. Despite general recommendations for the integration of mental health care into cardiac rehabilitation, none of the patients in this study reported having been assessed for psychological problems. In Middle East settings such as Palestine, psychological disorders are often stigmatized, however integration of mental health care with cardiac care may offer a unique entry door for efficiently addressing psychological problems in a considerable part of the population. CVDs affect a high percentage of the population. Patients and their family members may be particularly receptive for mental health interventions in a period of life where faced with disability and death. Further studies need to assess the culturally acceptable and effective mental health interventions for improving quality of life in heart disease patients.

Contributors

HA conducted data collection, analyzed and interpreted data, and wrote the manuscript. AA supervised the data collection and the implementation of the study in Palestine and edited the manuscript. TZ, AA, AG, SH, and DA assisted in data collection. CS, MK and EZ participated in planning the data analysis. CS and MK supervised the statistical analysis. CS and MK contributed to the interpretation of the results. NPH designed the study, directed its

implementation, data analysis and result interpretation. She edited all versions of the manuscript. All authors read and approved the final manuscript.

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Competing interests

The authors declare that they have no competing interests.

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6.6 Supplementary Material

Table S6.1: Sample characteristics among patients included vs excluded at follow-up

	Included at follow-up (n=622)	Excluded at follow-up (n=400)	*P* value
Socio-demographic factors			
Age	58·1±10·1	60·3±10·0	<0·001
Gender			
Female	152 (24·6)	120 (30·0)	
Male	470 (75·4)	280 (70·0)	**0·055**
Marital status			
Married	566 (91·4)	357 (89·2)	
Not married	56 (8·6)	43 (10·8)	0·243
Residence			
City	288 (46·5)	183 (45·7)	
Village	292 (46·7)	184 (46·0)	
Camp	42 (6·8)	33 (8·3)	0·682
Education degree			
No high school diploma	356 (57·5)	241 (60·2)	
High school diploma	169 (26·8)	97 (24·3)	
College degree	97 (15·7)	62 (15·5)	0·626
Occupation			
Professional	125 (20·2)	84 (21·0)	
Non-professional	206 (32·8)	103 (25·7)	
Unemployed	209 (33·8)	167 (41·8)	
Retired	51 (8·2)	30 (7·5)	
House wife	31 (5·0)	16 (4·0)	0·061
Clinical Factors			
Cardiac diagnosis			
Coronary heart disease	197 (31·8)	136 (34·0)	
Myocardial infarction	249 (40·2)	156 (39·0)	
Angina	104 (16·3)	60 (15·0)	
Other	72 (11·7)	48 (12·0)	0·864
Years with cardiac disease			
Less than one year	388 (62·7)	239 (59·7)	
Two-nine years	144 (22·8)	113 (28·3)	
10 or more years	90 (14·5)	48 (12·0)	0·110
Cardiac treatment (at admission)			
Catheterization/stent	340 (54·9)	192 (48·0)	
Catheterization/coronary artery bypass graft	149 (24·1)	91 (22·7)	
Catheterization/other & unknown	133 (21·0)	117 (29·3)	**0·010**
Co-morbidities			
None	193 (31·2)	105 (26·2)	
One	183 (29·5)	119 (29·8)	
Two or more	246 (39·3)	176 (44·0)	0·187
Medications			
None	94 (14·7)	40 (10·0)	
One-two	86 (13·9)	66 (16·5)	
Three-four	442 (71·4)	294 (73·5)	0·066
Somatic symptoms (PHQ-15)			
Minimal (PHQ ≤ 4)	52 (8·4)	38 (9·5)	
Low (PHQ 5-9)	148 (23·9)	92 (23·0)	
Medium (PHQ 10-14)	209 (33·3)	108 (27·0)	
High (PHQ ≥ 15)	213 (34·4)	162 (40·5)	0·113
Psychosocial factors			
PTSD (PTSD-PCL-S)			

Medium-high PTSD symptoms (PTSD ≥30)	197 (31·8)	119 (29·8)	
No-low PTSD symptoms (PTSD <30)	425 (68·2)	281 (70·2)	0·484
Depression			
Depressed (DASS-Depression ≥ 10)	229 (36·5)	169 (42·2)	
Not depressed (DASS-Depression ≤ 9)	393 (63·5)	231 (57·8)	0·066
Anxiety			
Anxiety (DASS-anxiety ≥8)	363 (58·2)	252 (63·0)	
No Anxiety (DASS-anxiety ≤7)	259 (41·8)	148 (37·0)	0·123
Stress			
Stress (DASS-stress ≥15)	395 (63·3)	259 (64·7)	
No stress (DASS-stress ≤14)	227 (36·7)	141 (35·3)	0·644
Lifestyle factors			
Smoking			
Never	217 (34·6)	149 (37·2)	
Former	100 (16.1)	70 (17·5)	
Current	305 (49·3)	181 (45·3)	0·454
Physical activity			
None	194 (30·9)	145 (36·2)	
Not daily	114 (18·4)	74 (18·5)	
Daily	314 (50·7)	181 (45·3)	0·162
Body-mass index			
Normal weight	124 (19·5)	82 (20·5)	
Overweight	263 (42·5)	167 (41·7)	
Obese	235 (38·0)	151 (37·8)	0·933

Data are mean (SD) or n (%). PTSD= Posttraumatic stress disorder, PCL-S= Posttraumatic stress disorder Checklist Specific, PHQ=Patient Health Questionnaire, DASS=Depression, Anxiety, Stress Scale. [†]=Independent *t*-test. Physical activity defined as the number of days of physical activity for at least 30 minutes per week; *P* values in bold are significant at p <0·05

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DISCUSSION

7.1 Summary of main findings

Although the co-morbidity of mental diseases and CVDs is well documented in literature and in western countries, there have been no studies to examine the relationship between mental and cardiac health in a non-western culture and setting such as Palestine. This thesis was guided by five primary goals to better understand the relationship between mental disorders and cardiac diseases among a well-characterized cohort of patients in conflict-affected Palestine and to provide local evidence for the need of integrating mental health treatment into cardiac care. The following sections will focus on the contributions of this PhD project to the aforementioned aim by addressing the following specific questions:

1) What is the prevalence of depression and anxiety among Palestinian cardiac patients?

2) What are the associated factors which put patients at higher risk of depression and anxiety?

3) Are women more likely to suffer from depression than men? What are socio-demographic, clinical psychosocial and lifestyle characteristics which mediate the relationship between gender and depression?

4) Is there a longitudinal association between PTSD and HRQL?

5) Are there mediating roles of depression, anxiety and stress in the relationship between PTSD and HRQL? Which combination of patient sub-groups is likely to benefit most from mental health screening and intervention?

7.1.1 Alarming rates of depression and anxiety among cardiac patients

The baseline cross-sectional study presented in Chapter 4 of this thesis documents for the first time the alarmingly high prevalence of depression and anxiety among cardiac patients in Palestine, with a prevalence rate of 53.5% and 33.9% for severe-to-very severe depressive and anxiety symptoms, respectively. The well characterized cardiac population at baseline provides evidence for important cross-sectional associations of depression and anxiety with socio-demographic, clinical, psychosocial and lifestyle characteristics. The presence of factors such as PTSD symptoms, low self-esteem, poor somatic symptoms, smoking, physical inactivity among cardiac patients should be a red flag for cardiologists to identify patients at higher risk of depression and anxiety. In perspective of mental health screening among cardiac patients, focus should be given to females and less educated patients. These results point to the potential need for integrating mental health care into cardiology practice for early diagnosis, prevention and treatment of these mental disorders. The outcomes of this study have implications for healthcare practice in hospital settings in Palestine, where physicians do not recognize or treat mental disorders, there are a lack of screening tools developed for the population in context as well as poor and untrained health professionals to treat for mental disorders among this patient population.

7.1.2 Women at greater risk of depression

Our second study brought to light new information regarding the high prevalence of severe depression among female patients with cardiac disease compared to male cardiac patients. In addition, our findings provide new evidence of the mediating factors of the association between

gender and depression among cardiac patients, in particular PTSD. The results emphasize the need for further research on potential mediating factors that could account for gender differences in depression and the need to provide support programs for female patients specifically in a setting such as Palestine as women are more prone to chronic and daily stressors and are underprivileged compared to men. As a part of CR programs, specific focus should be given to female patients with cardiac disease to improve their psychosocial wellbeing.

7.1.3 Influence of PTSD, depression, and anxiety on HRQL

The longitudinal study in Chapter 6 of the thesis and the first to assess the role of PTSD on HRQL in Palestine, while assessing the mediating roles of other mental disorders, found that the link between PTSD and HRQL was largely mediated by depression and anxiety over a one-year period (on average), even after adjusting for relevant socio-demographic, clinical and lifestyle covariates. The findings of this study also suggest that depression and anxiety strongly predicted poor HRQL and revealed that patients with higher levels of PTSD exhibited lower HRQL after one-year. Our study sample with PTSD have differences in health behaviours such as smoking and physical activity, which could also impact HRQL, thus PTSD could potentially directly and indirectly affect overall HRQL in cardiac patients. These results indicate the need to treat patients with a combination of PTSD, depression and anxiety as these are patients which are more likely to face disability and eventually death. These findings also hold strong implications for cardiologists and researchers which should be made aware of the long-term effect PTSD could have on HRQL as well as recurrent cardiac events and cardiac mortality (Edmondson and Cohen, 2013). Further studies need to be conducted to 1) better characterize the patients at higher risk 2) examine the mechanisms underlying the relationship between PTSD and poor HRQL among cardiac patients, 3) identify modifiable mechanisms for the

association of PTSD and cardiac disease (e.g. non-traditional risk factors) and 4) determine methods for decreasing PTSD, especially in medical settings.

7.2 Strengths and limitations

The specific strengths and limitations of each of the three studies have been reported in detail in the previous chapters. The strengths and limitations in the following paragraph are mainly related to the conclusions of the overall thesis. First, this thesis had several main strengths. The findings of the three thesis studies should be able to generalize well within a Palestinian context of cardiac and other chronic disease subgroups as well as other LMICs with similar health care systems and cultural settings. The potential generalizability our thesis findings present can also be attributed to the four study hospitals which provide cardiac care for a large percentage of the population in the West Bank. However, since Palestine is a conflict-affected country with poor economic resources, these findings might not generalize well to other countries, particularly in the United States and European countries. Additionally, all three studies were strengthened by the large sample size and high participation rate both at baseline and follow-up, resulting in 1) a strong statistical power to assess associations and 2) decreased the likelihood of selection bias. The designs of both the cross-sectional and longitudinal studies also enabled the consideration of a wide range of relevant socio-demographic, clinical, psychosocial and lifestyle covariates in the investigated associations.

There are also several limitations this thesis presents. In general, nonparticipation and loss to follow-up tend to be more evident among the physically unhealthy and less advantaged leading to cohort studies often being a relatively healthier sub-population. Thus, the loss to follow-up for the longitudinal study might have resulted in underestimation of those which still have high levels of depression, anxiety or PTSD and have poorer levels of HRQL. However,

several studies have demonstrated that this causes only minimal bias in some exposure-outcome associations.

Another shortcoming of this thesis was the short follow-up time, which could have also underestimated the true effect of PTSD on HRQL among cardiac patients, as cardiac diseases require longer latency periods for outcomes such as quality of life. Usually, longitudinal studies have longer follow-up times and thus allow for the occurrence of more events, and in the case of our longitudinal study, probably worse quality of life.

Although the assessment of depression, anxiety, PTSD and other clinical covariates were assessed at similar time points (one week within cardiac hospitalization), we presume there was an overestimation in the rates of these mental disorders, as patients are likely to be more depressed or anxious during the period right before or after their hospitalization.

Finally, it is important to point out that despite the use of screening instruments with excellent psychometric properties; our research lacked the use of clinical structural diagnostic interviews based on DSM-V criteria for these mental illnesses. Thus, our sample of cardiac patients were not diagnosed with these mental illnesses, rather they were screened and assessed for presence and severity of these mental-related symptoms within a specific period of time. Nonetheless, those who did score high on these screening instruments need to be further interviewed and assessed for clinical diagnostic confirmation of these mental illnesses.

7.3 Implications of findings

7.3.1 Weaknesses and challenges of the mental health care in Palestine

Given the impact of the war and the Israel occupation over the past 70 years in Palestine, and the vast extent of the mental health issues that Palestinians have been enduring, there is a strong need to integrate mental health within primary care services, raise awareness about the stigma

behind mental health and strengthen the mental health staff. There is a general lack of awareness of mental disorders and efforts should be made to tackle the misperceptions and stigmatization of health professionals as well as patients with mental diseases. The mental health system in Palestine needs to move toward multidisciplinary care at the primary and secondary health care levels such as public hospitals, where patients and families should be at the heart of interdisciplinary care. This will require the empowerment of nurses and social workers as there is a lack of psychiatrists in the country. The commitment of mental health professionals in Palestine and the international community will also help to develop quality mental health care services.

7.3.2 Significance of thesis findings for Palestine

Our thesis provides evidence for the first time of the extraordinarily high depression, anxiety and PTSD rates among Palestinian cardiac patients. This project has implemented already established screening instruments for mental disorders in clinical settings and provides evidence for the validity of the instruments in the Palestinian context. Additionally, the findings of this thesis help recognize socio-cultural and disease specific subgroups of CVD patients in particular need of future interventions. In light of this, a substantial percentage of the Palestinians of all ages can benefit from the evidence generated by this project. The results point to the potential need for integrating mental health care into cardiology practice and CR.

Evidence has shown that CHD also imposes significant physical, psychological and social burden eliciting anxiety and stress on patient's family members as well. Mental intervention during CR may be an entry door for addressing mental health issues in a broader family and societal context. The patient's family commonly also experiences major distress as a result of comorbid CHD and psychological disorders among their loved ones. Research on depression and anxiety among family members has not been conducted as extensively as for the patient;

however it has been suggested that levels of these mental health symptoms can be as high among the patient's partner/family member as the patient's themselves. It has also been recommended that the patient and partner/family member should be involved in the care and recovery process after a cardiac event (Reid et al., 2013).

Systematic reviews evaluating the effectiveness of psychological interventions for patients with chronic diseases including CHD and their partner or family member show potential benefits for both the patient and partner. (Hartmann et al., 2010, Martire et al., 2010, M Martire et al., 2004) Potential benefits of psychological interventions for patients include improvement in mental health, cardiac-related health, mortality and quality of life, while benefits for the partner/family member include improvements in mental health and quality of life. Additionally, the intervention may prevent healthy family members from also developing cardiac disease. There is mounting evidence emphasizing the adverse effect of psychological disorders on the onset of heart disease, even in family members. Individuals with depression are twice as likely to develop MI than the general population (Chaddha et al., 2016). In order to determine which psychological interventions are most effective, it would be best if a psychological intervention trial would be tests on patients alone and on patients and their partner or family member.

It therefore seems pivotal to integrate mental health services and interventions into cardiac care for both, patients and their family members, addressing in particular stress and psychosocial factors (i.e. lack of social support) (Lichtman et al., 2014b).

7.3.3 Implications for interventions: evidence from psychosocial intervention studies

There is a growing interest on the influence of psychosocial interventions on CVD outcomes. It is known after a cardiac event, it remains challenging for healthcare providers to identify and treat patients with depression and anxiety. Epidemiological studies suggest that treatment of

mental disorders, specifically depression and anxiety as well as other psychosocial factors may improve CVD related symptoms and decrease adverse outcomes, hospitalizations, and overall quality of life in patients suffering from cardiac disease. The most effective time to screen for psychological problems has been either before hospital discharge or during the first sessions of a CR program. The European Society of Cardiology (ESC) has established a comprehensive CR program which includes core components such as patient assessment, physical activity counseling, dietary counseling, management of risk factors (e.g. hypertension, lipid profile, and diabetes), patient education, psychosocial management and vocational advice. Patients and families may be offered a range of psychological therapies including stress management, relaxation therapies, treatments for psychological and mood disorders, coping strategies, enhancing disease adjustment and specific cardiac-related rehabilitation such as diet and lifestyle advice, or exercise. Systematic reviews have documented CR programs which address medical and lifestyle factors have shown to have positive effects on behavioral changes and reducing the risk of recurrent cardiac events, mortality depressed mood and social isolation (Oldridge et al., 1988).

The Ischemic Heart Disease study, a unique home-based stress reduction program has shown that treatment has been associated with reduction in cardiac events. Among patients attending CR programs, a study by Dusseldorp et al. found reduction in mortality and recurrent MI following interventions for reduction in psychological stress (Olafiranye et al., 2011). In a meta-analysis of 23 randomized controlled trials that evaluated the impact of adding psychosocial interventions to standard cardiac rehabilitation regimens, Gellis et al. observed that lack of psychosocial intervention was associated with greater rates of mortality and recurrent MI after a two year follow-up (Gellis and Kang-Yi, 2012).

The first study to investigate the effectiveness of collaborative mental care for patients with diabetes or heart disease in the context of the primary care setting in the UK was recently

published. In the COINCIDE cluster-randomized trial, where patients could choose between different psychological and pharmacological treatments, there was a decrease in symptoms of depression over a four-month follow-up, however there was no improvement in quality of life or social support (Coventry et al., 2015). These results point to the need for additional research into the long-term effectiveness of collaborative mental care approaches in the setting of CVD patients. These types of interventions and CR programs will enable patients to receive the appropriate treatment to improve their cardiac health and their mental well-being.

7.4 Public health relevance and implications

Considering this project is a large population-based study, this will set the basis for mental health policies among cardiac populations across the West Bank, and ultimately in the Gaza Strip. Further, in terms of Palestine, to address the population at need, integrated mental health services should be implemented at the primary healthcare level. This step will provide easier access to health services, and will reduce the stigma associated with mental issues (Afana et al, 2004). The evidence presented in this thesis points to the importance of identifying and treating depression, anxiety and PTSD among the cardiac population, in particular as they impact individual's quality of life. As many physicians overlook depressive and anxiety symptoms in cardiac patients mistaking them for cardiac-related somatic symptoms as well as the high prevalence of depression and anxiety in cardiac populations, the AHA recommends the screening of all cardiac patients for depression (Lichtman et al., 2008). This could identify those with higher risk of morbidity, mortality and HRQL and help in reducing associated risks. These recommendations have implications for clinical practice on which best ways to treat comorbid mental disease and cardiac disease.

The comprehensive, representative and predetermined patient data obtained throughout the study period including health status, socio-demographics, mental health status, and other variables will help in the establishment of a heart disease registry with authentic and of good

quality data to monitor quality of care, record management and outcomes of cardiac diseases, and encourage further epidemiological research.

In Palestine, the results from the study will provide health policy and medical agencies with the needed evidence base to justify integrating mental health care into cardiac care and rehabilitation. Evidence abroad points to a beneficial cost-effectiveness of treating heart disease patients for their mental problems. Mental intervention during CR may be an entry door for addressing mental health issues in a broader family and societal context.

The rationale for integration of mental health care into other health care platforms includes improving access to mental health care; providing patient-centred care; avoiding fragmentation of health services; reducing stigma; optimising both mental health and physical health outcomes; and overall health system strengthening. Mental health interventions for CVD patients are the most promising for integration (Patel, 2013). There are at least two advantages to integrate treatment of common mental health problems during cardiovascular routine care. First, integrated treatment programs in which medical providers are supported to treat common mental health problems offer a better chance to treat 'the whole patient', as a patient-centred approach, which is recommended worldwide. Second, integrated care programs that can address patients' mental health needs in the context of general or other specialized health care settings are often more attractive to patients and family members who are concerned about the stigma that is still associated with mental health and the treatment settings that specialize on caring for individuals with severe mental disorders.

7.5 Conclusion and future work

In conclusion, the prevalence of anxiety and depression among cardiac patients was alarmingly high. One of the key outcomes of this thesis is the need to consider the different characteristics between men and women in the relationship between depression and cardiac disease. Future research should focus on the importance of gender-specific research when examining the

effects and role of depression on the onset, prognosis and recovery of heart diseases. The crucial prognostic influence of PTSD, depression and anxiety on overall HRQL among this cardiac population also calls for concern. Early diagnosis of predictors associated with depression, anxiety and PTSD is necessary to promote patient adherence and compliance. In addition, the identification and treatment of patients with these mental disorders in particular is an important goal for clinical practice, in both cardiac populations and the general population. Collaborative team work between healthcare providers and patients is needed to prevent worse disease outcomes. More research needs to be conducted on a national level to develop strategies for the prevention and control of psychological distress among patients with chronic diseases in Palestine.

Our findings in this thesis can be considered as first steps to the translational approach of innovation, validation and application, where we can use the current cardiac sample as an entry door to pursue family members of diseased patients whom also could be at risk of onset and progression of cardiac diseases. This could potentially lead to a national mental health program that could be generalizable to similar health care systems in the Middle East region.

To embark on this aim, the current PhD project will take the findings one step further from the observational setting (innovation) to the validation setting by developing a psychological intervention and evaluating its effectiveness in the Palestinian context. Going further, the intervention will integrate a strong family focus, as patient's families commonly also experience major distress as a result of comorbid CHD and psychological disorders among their loved ones.

To date, no programs exist in CR that focus on comprehensive psychological interventions for cardiac patients and their partner/family member in Palestine. The efficacy of intervention on psychological and psychosocial outcomes in cardiac patients and their family members

remains unknown. Therefore, we intend to implement a comprehensive psychosocial intervention program to evaluate the effects of a comprehensive psychological intervention on the one-year course of mental health and well-being, coping and social support of the cardiac patients included in this thesis as well as their one partner/family member. The major components of the intervention will be 1) assessment and evaluation of risk factors, and indicators of need for further specific psychological intervention, and 2) psychosocial intervention that focuses on lifestyle/behavioral changes; support, coping strategies with anxiety, affect dysregulation and or depression; psychological support with life stressors and stressors of surgery and treatment; stress management training, and emotional as well as social support for families and care givers (See Appendix IV).

In brief, the study will enroll (n=250) patients with a previously diagnosed CHD and at least moderate depression reported at the 12-month follow-up. The study will also enroll n=250 family members identified by the patient as the family member most likely to provide emotional and physical support. For ethical reasons all these patients with symptoms of depression and their family members must obtain a psychological intervention at baseline.

Two additional repeat psychological interventions during a one-year follow-up at month 3 and month 6 after the baseline intervention will be randomly assigned to half of the patients and their family members, while the other 50% of the patients and family members will just receive the intervention at baseline. To test the efficacy of the repeat intervention, all participants will undergo detailed interviews on mental health, well-being, social support, behavior and clinical characteristics at baseline before the intervention, at three months before the intervention, at six months before the intervention, and at 12 months to test the efficacy of the intervention.

The primary outcomes for patients/family members will include: 1) psychological well-being (depression & anxiety & stress, 2) quality of life, and 3) satisfaction with life. Secondary

outcomes for patients/family members will include: social support/coping, knowledge of disease and treatment, satisfaction with treatment and care, lifestyle (diet; physical activity; smoking; weight change), treatment adherence (in patients only), attitude towards mental health problems, health resource use.

We hypothesize that this type of intervention will lead to better psychological outcomes, improve coping, lifestyle behaviors and reduce stress among cardiac patients and their partner/family member at one end as well as improve medical outcomes, treatment compliant behavior and overall quality of life. Ultimately, if the intervention is found to be effective, it can be scaled up to a national CR policy.

The longer-term goal of this proposed project in the future is to develop clinical guidelines and national policies for strengthening mental health services overall and in CR, in particular. With regard to the cardiac setting, the population-based studies offer the potential for the future setup of population-based heart disease registries. According registries could make an important contribution to the evaluation and promotion of effectiveness of cardiac and mental health care in the region.

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Appendices

I. Screening Instruments

1. Heart Quality of Life (Heart QoL) Questionnaire

	How much has your heart problem bothered you and how have you been feeling **during the last 4 weeks.**	No (3)	A little (2)	Some (1)	A lot (0)
First, in the last 4 weeks, have you been bothered by having to:					
1	Walking indoors on level ground?				
2	Garden, vacuum, or carry groceries?				
3	Climb a hill or flight of stairs without shopping?				
4	Walk more than 100 yards at a brisk pace?				
5	Lift or move heavy objects?				
Now, in the last 4 weeks, have you been bothered by:					
6	Feeling short of breath?				
7	Being physically				
8	Feeling tired, fatigued, low on energy?				
9	Not feeling relaxed and free of tension?				
10	Feeling depressed?				
11	Being frustrated?				
12	Being worried?				
13	Being limited in doing sports or exercise?				
14	Working around the house or yard?				

2. Cardiac Depression Scale (CDS-26)

This questionnaire consists of a number of statements about the way you feel at present. Next to each statement there is a rating scale from 1 to 7 for you to indicate how much you agree or disagree with the statement. Please circle one of the numbers on the scale:

Strongly disagree 1 2 3 4 5 6 7 Strongly agree

1	I have dropped many of interests and activities…	1 2 3 4 5 6 7 None dropped All dropped
2	My concentration is as good as it ever was…	1 2 3 4 5 6 7 Very poor concentration Excellent concentration
3	I can't be bothered doing anything much…	1 2 3 4 5 6 7 Keen to do things Can't be bothered
4	I get pleasure from life at present…	1 2 3 4 5 6 7 No pleasure Great Pleasure
5	I am concerned about the uncertainty of my health…	1 2 3 4 5 6 7 Not concerned Very concerned
6	I may not recover completely...	1 2 3 4 5 6 7 Will recover completely Will not recover

7	My sleep is restless and disturbed…	1 2 3 4 5 6 7 Not restless Very restless
8	I am not the person I used to be…	1 2 3 4 5 6 7 Just the same Completely different
9	I wake up in the early hours of the morning and cannot get back to sleep...	1 2 3 4 5 6 7 Never wake Always wake
10	I feel like I am living on borrowed time...	1 2 3 4 5 6 7 Unlimited time Very much on borrowed time
11	Dying is the best solution for me...	1 2 3 4 5 6 7 No solution Best solution
12	I feel in good spirits…	1 2 3 4 5 6 7 Very poor spirits Excellent spirits
13	The possibility of sudden death worries me...	1 2 3 4 5 6 7 Not at all Very worried
14	There is only misery in the future for me...	1 2 3 4 5 6 7 No misery Only misery
15	My mind is as fast and alert as always...	1 2 3 4 5 6 7 Slow and inattentive Very fast and alert
16	I get hardly anything done...	1 2 3 4 5 6 7 Everything done Nothing done
17	My problems are not yet over...	1 2 3 4 5 6 7 All problems over Still major problems
18	Things which I regret about my life are bothering me...	1 2 3 4 5 6 7 Absolutely no regrets Great regrets
19	I gain just as much pleasure from my leisure activities as I used to...	1 2 3 4 5 6 7 No pleasure at all Very great pleasure
20	My memory is as good as it always was...	1 2 3 4 5 6 7 Very poor memory Excellent memory
21	I become tearful more easily than before…	1 2 3 4 5 6 7 Not at all tearful Very easily tearful
22	I seem to get more easily irritated by others than before...	1 2 3 4 5 6 7 Never irritated Very easily irritated
23	I feel independent and in control of my life...	1 2 3 4 5 6 7 No independence Completely Independent
24	I lose my temper more easily nowadays...	1 2 3 4 5 6 7 Never lose temper Lose it very easily
25	I feel frustrated...	1 2 3 4 5 6 7 Not at all frustrated Extremely frustrated
26	I am concerned about my capacity for sexual activity...	1 2 3 4 5 6 7 No concern At all Grave concern

3. Depression Anxiety Stress Scale (DASS-42)

Please read each statement and select a number 0, 1, 2 or 3 which indicates how much the statement applied to you over the past week. This assessment is not intended to be a diagnosis.

0= Did not apply to me at all; 1= Applied to me to some degree or for some of the time; 2= Applied to me to a considerable degree or for 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 could not seem to experience any positive feelings at all	0	1	2	3
4	I experienced breathing difficult (e.g. breathlessness or excessively rapid breathing in the absence of physical exertion	0	1	2	3
5	I just could not seem to get going	0	1	2	3
6	I tend to over-react to situations	0	1	2	3
7	I had a feeling of shakiness (e.g. 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 (e.g. 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 was not 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 (e.g. 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
21	I felt that life wasn't worthwhile	0	1	2	3
22	I found it hard to wind down	0	1	2	3
23	I had difficulty in swallowing	0	1	2	3
24	I could not seem to get any enjoyment out of things I did	0	1	2	3
25	I was aware of the action of my heart in the absence of physical exertion (e.g. 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 by 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 what I was doing	0	1	2	3
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 (e.g. in the hands)	0	1	2	3
42	I found it difficult to work up the initiative to do things	0	1	2	3

Depression Score_____

Anxiety Score_____

Stress Score_____

4. Patient Health Questionnaire (PHQ-15)- (Somatic Symptoms)

	During the last four weeks, how much have you been bothered by any of the following problems?	Not bothered (0)	Bothered a little (1)	Bothered a lot (2)
1	Stomach pain			
2	Back pain			
3	Pain in your arms, legs, or joints			
4	Feeling tired or having little energy			
5	Trouble falling or staying asleep, or sleeping too much			
6	For women: menstrual cramps or other problems with your period			
7	Pain or problems during sexual intercourse			
8	Headaches			
9	Chest Pain			
10	Dizziness			
11	Fainting spells			
12	Feeling your heart pound or race			
13	Shortness of breathe			
14	Constipation, loose bowel, or diarrhea			
15	Nausea, gas, or indigestion			

PHQ-15 Score=

_____+_____

5. ENRICHED Social Support Instrument (ESSI)

Please read the following questions and circle the response that most closely describes your current situation.

1	Is there someone available to you whom you can count on to listen to you when you need to talk?	None of the time 1	A little of the time 2	Some of the time 3	Most of the time 4	All the time 5
2	Is there someone available to give you good advice about a problem?	None of the time 1	A little of the time 2	Some of the time 3	Most of the time 4	All the time 5
3	Is there someone available to you who shows you love and affection?	None of the time 1	A little of the time 2	Some of the time 3	Most of the time 4	All the time 5
4	Is there someone available to help you with daily chores?	None of the time 1	A little of the time 2	Some of the time 3	Most of the time 4	All the time 5
5	Can you count on anyone to provide you with emotional support (talking over problems or helping you make a difficult decision?)	None of the time 1	A little of the time 2	Some of the time 3	Most of the time 4	All the time 5

6	Do you have as much contact as you would like with someone you feel close to, someone in whom you can trust and confide in?	None of the time 1 A little of the time 2 Some of the time 3 Most of the time 4 All the time 5
7	Are you currently married or living with a partner?	None of the time 1 A little of the time 2 Some of the time 3 Most of the time 4 All the time 5

6. Resilience Scale (RS-14)

Please read the following statements. Please circle the number which best indicates your feelings about the statement. The numbers range from "1" (strongly disagree) to "7" (strongly agree).

1	I usually manage one way or another	1	2	3	4	5	6	7
2	I feel proud that I have accomplished things in life	1	2	3	4	5	6	7
3	I usually take things in stride	1	2	3	4	5	6	7
4	I am friends with myself	1	2	3	4	5	6	7
5	I feel that I can handle many things at a time	1	2	3	4	5	6	7
6	I am determined	1	2	3	4	5	6	7
7	I can get through difficult times because I have experienced difficulty before	1	2	3	4	5	6	7
8	I have self-discipline	1	2	3	4	5	6	7
9	I keep interested in things	1	2	3	4	5	6	7
10	I can usually find something to laugh about	1	2	3	4	5	6	7
11	My belief in myself gets me through hard times	1	2	3	4	5	6	7
12	In an emergency, I am someone people can generally rely on	1	2	3	4	5	6	7
13	My life has meaning	1	2	3	4	5	6	7
14	When I am in a difficult situation, I can usually find my way out of it	1	2	3	4	5	6	7
	Total							

7. Single-item Self-Esteem Scale (SISE)

I have high Self-esteem.

1 2 3 4 5 6 7
Not very true — Very true of me

8. Short-Form Health Survey (SF-12)

This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities. Answer each question by choosing just one answer. If you are unsure how to answer a question, please give the best answer you can.

1. In general, would you say your health is:

Excellent Very good Good Fair Poor

2. Does your health limit you in moderate activities such as moving a table, pushing a vacuum cleaner, bowling, or playing golf?

Yes, limited a lot Yes, limited a little No, not limited at all

3. Does your health limit you in climbing several flights of stairs? Yes, limited a lot Yes, limited a little No, not limited at all
4. During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of your physical health? Accomplished less than you would like YES NO
5. During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of your physical health? Were limited in the kind of work or other activities. YES NO
6. During the past four weeks, have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)? Accomplished less than you would like? YES NO
7. Did work or activities less carefully than usual? YES NO
8. During the past four weeks, how much did pain interfere with your normal work (including work outside the home and housework)? Not at all A little bit Moderately Quite a bit Extremely
These questions are about how you have been feeling during the past four weeks. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the past 4 weeks… All of the time / Most of the time / A good bit of time / Some of the time / A little bit of time / None of the time 9. Have you felt calm and peaceful? 10. Did you have a lot of energy? 11. Have you felt down-hearted And blue?
12. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting friends, relatives, etc.)? All of the time / Most of the time / A good bit of time / Some of the time / A little bit of time / None of the time

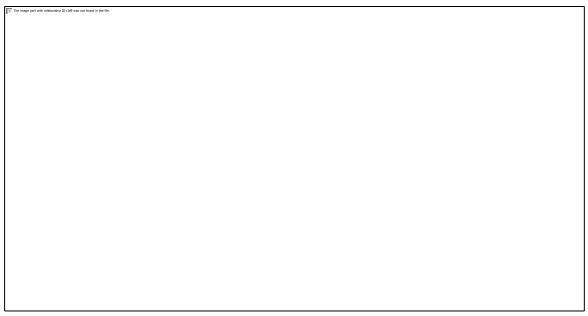
9. Posttraumatic Stress Disorder- Checklist Specific Version [PTSD-CL-S]

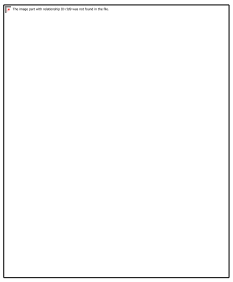
Below is a list of problems and complaints that individuals sometimes have in response to stressful life experiences. Please read each one carefully, put an "X" in the box to indicate how much you have been bothered by that problem *in the last month*.

No.	Response	Not at all (1)	A little bit (2)	Moderately (3)	Quite a bit (4)	Extremely (5)
1	Repeated, disturbing *memories, thoughts, or images* of a stressful experience from the past?					
2	Repeated, disturbing *dreams* of a stressful experience from the past?					

3	Suddenly *acting* or *feeling* as if a stressful experience *were happening* again (as if you were reliving it)?					
4	Feeling *very upset* when *something reminded* you of a stressful experience from the past?					
5	Having *physical reactions* (e.g., heart pounding, trouble breathing, or sweating) when *something reminded* you of a stressful experience from the past?					
6	Avoid *thinking about* or *talking about* a stressful experience from the past or avoid *having feelings* related to it?					
7	Avoid *activities* or *situations* because they *remind you* of a stressful experience from the past?					
8	Trouble *remembering important parts* of a stressful experience from the past?					
9	Loss of *interest in things that you used to enjoy?*					
10	Feeling *distant* or *cut* off from other people?					
11	Feeling *emotionally numb* or being unable to have loving feelings for those close to you?					
12	Feeling as if your *future* will somehow be *cut short*?					
13	Trouble *falling* or *staying asleep*?					
14	Feeling *irritable* or having *angry outbursts*?					
15	Having *difficulty concentrating*?					
16	Being *"super alert"* or watchful on guard?					
17	Feeling *jumpy* or easily startled?					

II. Questionnaires





CARMEN I: Baseline Questionnaire

Mental disorders among Cardiac Patients

I. PERSONAL INFORMATION

All questions contained in this questionnaire are optional and will be kept strictly confidential.

PERSONAL/BACKGROUND INFORMATION			
Patient ID no.:	(Baseline/Follow-up; hospital; department; Last three digits of ID)		**Date of Birth:** (dd/mm/yy)
Fieldworker name:			
Place of Residence: ☐ City ☐ Village ☐ Camp			**Sex:** ☐ M ☐ F
Date of arrival (at treatment facility): (dd/mm/yy)			
Marital status:	☐Single ☐Married ☐Separated ☐Divorced ☐Widowed		**Department:** ☐Cardiac Surgery ☐Outpatient Clinic ☐Cardiology
Hospital:	☐ An-Najah National University Hospital ☐ Nablus Hospital	☐ Arab-Specialized Hospital ☐ Al-Watani Hospital	
Weight:	**Height:**		**Number of years of education completed:**
What is your profession?			**Highest degree of education completed:** ☐Less than high school ☐High school graduate ☐Some college, no degree ☐2-year Diploma ☐Bachelor's ☐Masters ☐Ph.D. ☐Graduate or professional degree

	What is your monthly income? ☐<1000 ILS ☐1000-2000 ILS ☐2000-3000ILS ☐3000-4000ILS ☐4000-5000ILS ☐5000+ ILS

II. DIAGNOSIS INFORMATION

Current Diagnosis/condition:	☐ Coronary Artery Disease	☐ Heart Failure	
	☐ Angina	☐ Atrial Fibrillation	
	☐ Myocardial Infarction		
Previous Reported Diagnosis:	☐ Coronary Artery Disease ☐ Angina ☐ Atrial Fibrillation ☐ Myocardial Infarction ☐ Heart Failure		Year of first heart problem?

Other Medical History [Check all that apply]:

☐ Anemia ☐ Cancer ☐ Embolism ☐ Diabetes ☐Chronic liver disease ☐Chronic lung disease ☐Chronic kidney disease

☐ Hypertension ☐High blood lipids ☐ Thyroid problems ☐Chronic pain

☐Mental disorders, specify:_____

☐ Other chronic conditions, specify:_____

Surgeries (related to cardiovascular health):

Year	Procedure	Hospital

Other hospitalizations (related to cardiovascular health):

Year	Reason	Hospital

Current Medications (including contraceptives or hormones for treatment of menopause symtoms):

Drug	**Dosage**	**Frequency**

WOMENS HEALTH

No. of pregnancies:	**What year of last menses?**
Last menses at least a year ag o? ☐Yes ☐No	**Bleeding became more irregular?** ☐Yes ☐No

FAMILY HISTORY

	CARDIOVASCULAR DISEASE		IF DECEASED, CAUSE OF DEATH	
	DIAGNOSIS	**AGE AT DIAGNOSIS**	**CAUSE OF DEATH**	**AGE AT DEATH**
MOTHER				
FATHER				
BROTHERS				
SISTERS				
OTHERS				

HEALTH HABITS

(Think about a normal week)

Exercise

How many days of the week are you physically active for at least 30 minutes?

☐ 0 (never)
☐ 1 day
☐ 2 days
☐ 3 days
☐ 4 days
☐ 5 days
☐ 6 days
☐ 7 days

HOW MUCH TIME DO YOU SPEND SITTING ON A TYPICAL WEEKDAY (HOURS/MINUTES)
HOW MUCH TIME DO YOU SPEND SITTING ON A TYPICAL WEEKEND? (HOURS/MINUTES)

Diet	Are you dieting?			☐ Yes	☐ No
	Rank salt intake	☐ Hi	☐ Med	☐ Low	
	Rank fat intake	☐ Hi	☐ Med	☐ Low	
	Rank of fruit/vegetable intake	☐ Hi	☐ Med	☐ Low	
How many caffeinated drinks do you drink daily?	☐ Never	☐ not daily	☐ 1-2	☐ 2-3	☐ 5+

Smoking

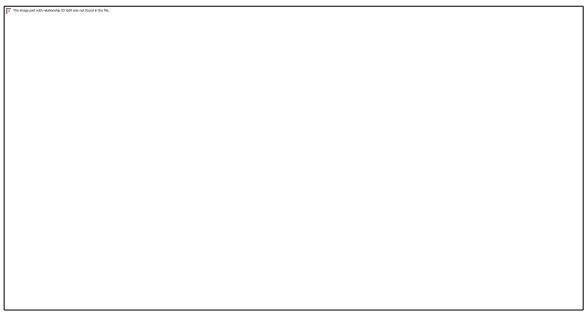
Have you ever smoked regularly for at least one year?

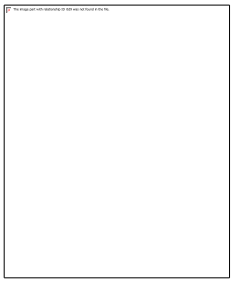
☐Yes
☐Never smoked

Are you a current smoker?

☐Yes

	☐No If yes, what do you smoke? ☐Cigarettes ☐Shisha ☐Other, specify:_____ If yes, how many cigarettes do you smoke a day? _____ How often do you smoke shisha? What age did you start smoking? _____ If you quit, what age did you stop smoking? _____
Alcohol	Do you drink alcohol? ☐Yes ☐No How often do you drink alcohol? ☐none of the time ☐a little bit of the time ☐some of the time ☐a good bit of time ☐most of the time ☐all of the time





CARMEN II: Follow-up Questionnaire

One-year follow-up of participants in the CARMEN baseline assessment

I. PERSONAL INFORMATION

All questions contained in this questionnaire are optional and will be kept strictly confidential.

PERSONAL/BACKGROUND INFORMATION			
Patient ID no.:		**Fieldworker name:**	
Date of interview: (dd/mm/yy)		**Residence:**	☐camp ☐village ☐city
Marital status:	☐Single ☐Married ☐Separated ☐Divorced ☐Widowed		
What is your profession?	☐Professional ☐Non-professional ☐Retired ☐Housewife ☐Unemployed		

II. CLINICAL INFORMATION

Current Diagnosis:	☐Coronary artery disease ☐Angina ☐Myocardial infarction ☐Atrial fibrillation ☐Heart Failure ☐None ☐Other_____
Previous diagnosis:	☐Coronary artery disease ☐Angina ☐Myocardial infarction ☐Atrial fibrillation ☐Heart Failure ☐None ☐Other_____
Last time you visited a physician or were treated for your heart condition	**Date:** **Place:** **Name of treating physician:**

Doctor's visits related to cardiovascular health since the last interview		
Reason of visit	**Date of visit**	**Physicians name and hospital**

Hospitalizations as in-patient related to cardiovascular health since the last interview				
Reason/diagnosis	**Procedures performed**	**Date of stay**	**Duration of stay**	**Hospital**
Surgeries (related to cardiovascular health) in the last year:				

Procedure	Duration of stay ; date of stay	Hospital

Current Medications		
Name of the Medication	**Dosage**	**At what times do you take the medication; How many tablets to you take at each time?**
Medications taken since last interview, but no longer taking		

Medication	Dosage	At what times do you take the medication; How many tablets to you take at each time?

FAMILY HISTORY

	CARDIOVASCULAR DISEASE		IF DECEASED, CAUSE OF DEATH	
	DIAGNOSIS	**AGE AT DIAGNOSIS**	**CAUSE OF DEATH**	**AGE AT DEATH**
MOTHER				
FATHER				
BROTHERS				
SISTERS				
OTHERS				

HEALTH HABITS
(Think about a normal week)

Exercise	How many days of the week are you physically active for at least 30 minutes? ☐ 0 (never) ☐ 1 day ☐ 2 days ☐ 3 days ☐ 4 days ☐ 5 days ☐ 6 days ☐ 7 days Have you increased your physical activity since the last interview? ☐ yes ☐ no Have you ever received medical advice to increase your level of physical activity? ☐ yes ☐ no

Diet	Are you dieting?			☐ Yes	☐ No
	Rank salt intake	☐ Hi	☐ Med	☐ Low	
	Rank sugar intake	☐ Hi	☐ Med	☐ Low	
	Rank fat intake	☐ Hi	☐ Med	☐ Low	
	Rank of fruit/vegetable intake	☐ Hi	☐ Med	☐ Low	

Since the last interview

1) Have you decreased your salt consumption?

   ☐ yes☐ no

2) Have you ever received medical advice to decrease your salt consumption?

   ☐ yes ☐ no

3) Have you increased your fruit and vegetable consumption?

   ☐ yes ☐ no

4) Have you ever received medical advise to increase your fruit/vegetable consumption?

   ☐ yes ☐ no

5) Have you decreased your sugar consumption?

   ☐ yes ☐ no

6) Have you ever received medical advise to decrease your sugar consumption?

   ☐ yes ☐ no

How many caffeinated drinks do you drink daily?	☐ Never	☐ not daily	☐ 1-2	☐ 2-3	☐ 5+
Snoring	Do you Snore Loudly (loud enough to be heard through closed doors or your bed-partner elbows you for snoring at night) ☐ yes ☐ no				
Sleep	How many hours of sleep do you get a night?				
	Do you often feel Tired, Fatigued, or Sleepy during the daytime (such as falling asleep during driving or talking to someone)? ☐ yes ☐ no				
	Has anyone Observed you Stop Breathing or Choking/Gasping during your sleep ? ☐ yes ☐ no				
Smoking	Have you ever smoked regularly for at least one year? ☐Yes ☐Never smoked				

	Are you a current smoker? ☐Yes ☐No If yes, what do you smoke? ☐Cigarettes ☐Shisha ☐Other, specify:_____ If yes, how many cigarettes do you smoke a day? _____ How often do you smoke shisha? What age did you start smoking? _____ If you quit, what age did you stop smoking? _____ Do you smoke less since the last interview? ☐ yes ☐ no ☐ N/A Have you ever received medical advise to no smoke or smoke less? ☐ yes ☐ no ☐ N/A
Alcohol	Do you drink alcohol? ☐Yes ☐No How often do you drink alcohol? ☐none of the time ☐a little bit of the time ☐some of the time ☐a good bit of time ☐most of the time ☐all of the time Have you consumed less alcohol since the last interview? ☐ yes ☐ no ☐ N/A Have you ever received medical advise to drink less alcohol? ☐ yes ☐ no ☐ N/A
Psychosocial	
	Have you experienced one or more events in your family and social environment in the last 12 months that were very stressful for you, in addition to any events mentioned on your personal health? ☐ yes ☐ no If yes please explain:

III. Article I (Publication)

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BMC Public Health

RESEARCH ARTICLE Open Access

Depression and anxiety symptoms in cardiac patients: a cross-sectional hospital-based study in a Palestinian population

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Abstract

Background: Mental health problems have an adverse effect on the course of cardiac disease. The integration of their diagnosis and treatment into cardiology care is generally poor. It is particularly challenging in cultural environments where mental health problems are stigmatized. The objective of the current study was to investigate the proportion of cardiac patients with depression and anxiety as well as factors associated with the presence of these symptoms in a Palestinian population.

Methods: This cross-sectional hospital-based study was conducted on patients consecutively admitted with a new or existing cardiac diagnosis to one of the four main hospitals in Nablus, Palestine over an eight-month period. Data was obtained from hospital medical charts and an in-person interview, using a structured questionnaire with a sequence of validated instruments. All subjects were screened for depression and anxiety using the Cardiac Depression Scale (CDS) and the Depression Anxiety Stress Scale (DASS-42). Multivariate ordered logistic regression analyses were performed to identify factors among four categories (socio-demographic, clinical, psychosocial, lifestyle) independently associated with depression and anxiety.

Results: In total, 1053 patients with a confirmed cardiac diagnosis were included in the study with a participation rate of 96%. Based on the CDS and DASS-42, 54% met the criteria for severe depression (CDS > 100) and 19.2% for severe-to-very severe anxiety (DASS-anxiety > 15), respectively. Symptoms of depression and anxiety were more prevalent among females and less educated patients. Factors independently associated with both depressive and anxiety symptoms were post-traumatic stress disorder symptoms, low level of self-esteem, high somatic symptoms, low physical and mental health component scores, active smoking, physical inactivity, and longer disease duration. Patients with depressive and anxiety symptoms also reported poor social support and lower resilience.

Conclusion: There was a high level of depression and anxiety in this sample of cardiac patients. The results point to characteristics of patients in particular need for mental health screening and suggest possible targets for intervention such as strengthening of social support and of physical activity. The integration of mental health services into cardiac rehabilitation in Palestine and comparable cultural settings is warranted from the time of first diagnosis and onward.

Keywords: Depression, Anxiety, Cardiovascular diseases, Predictors, Prevalence, Cardiac rehabilitation

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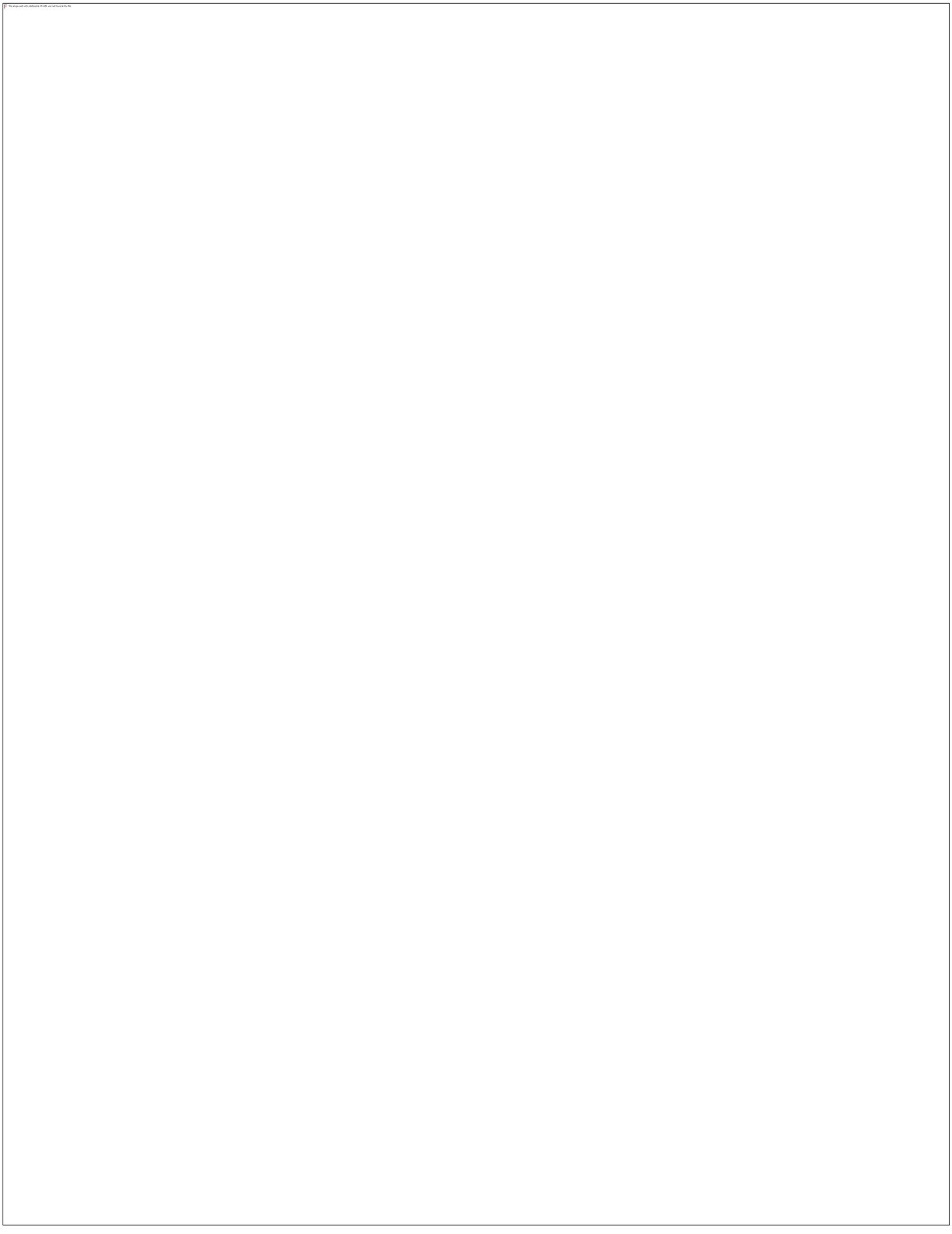
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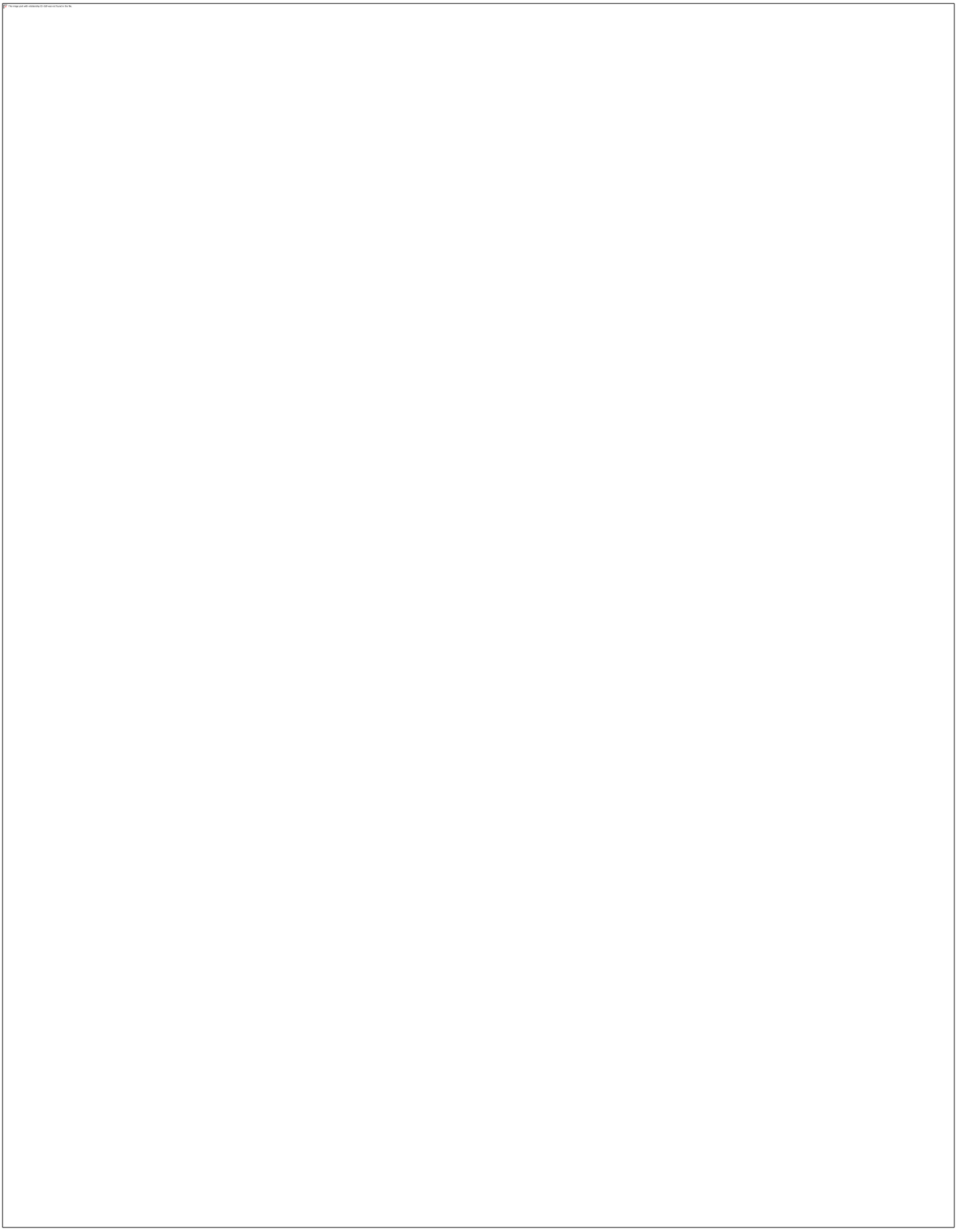
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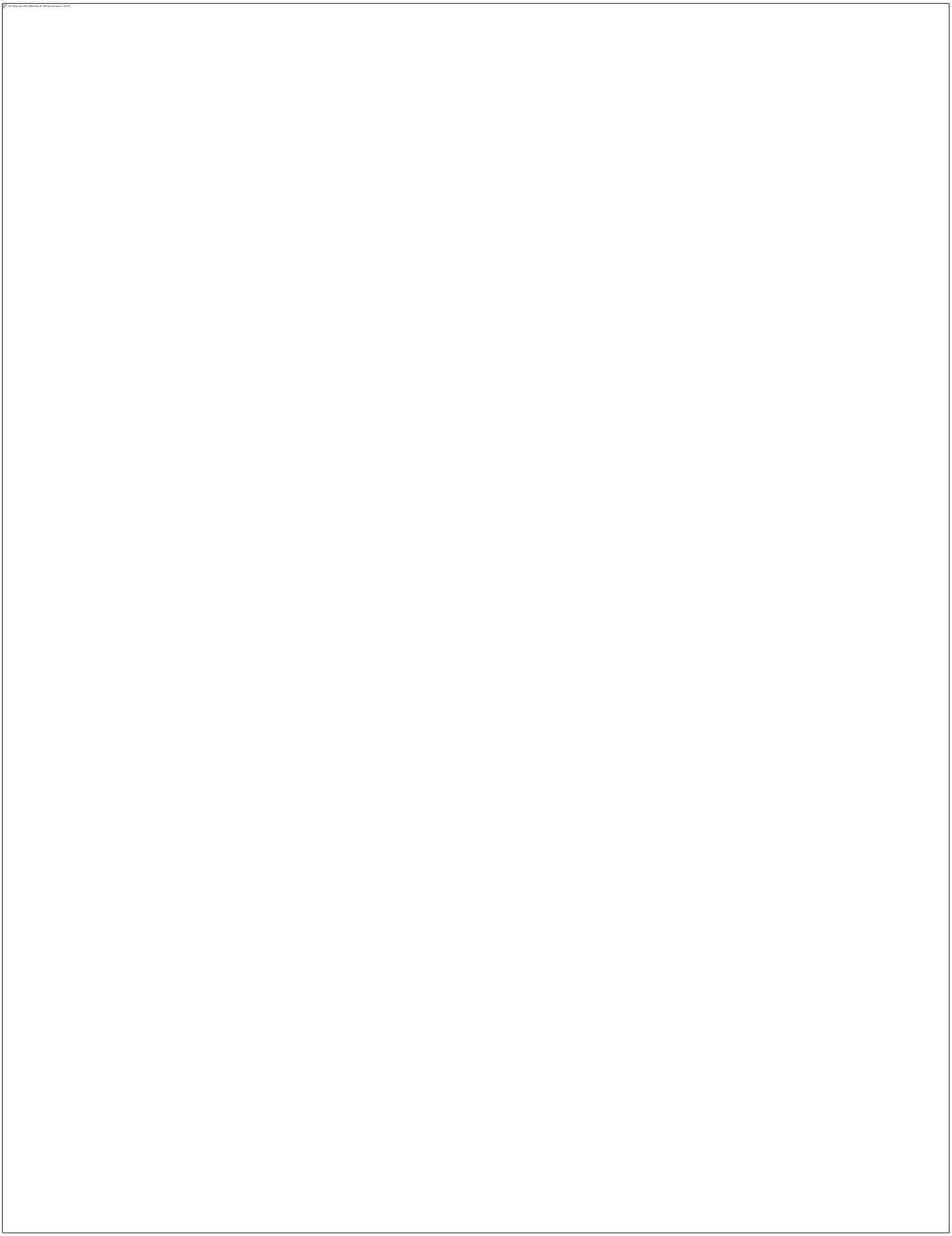
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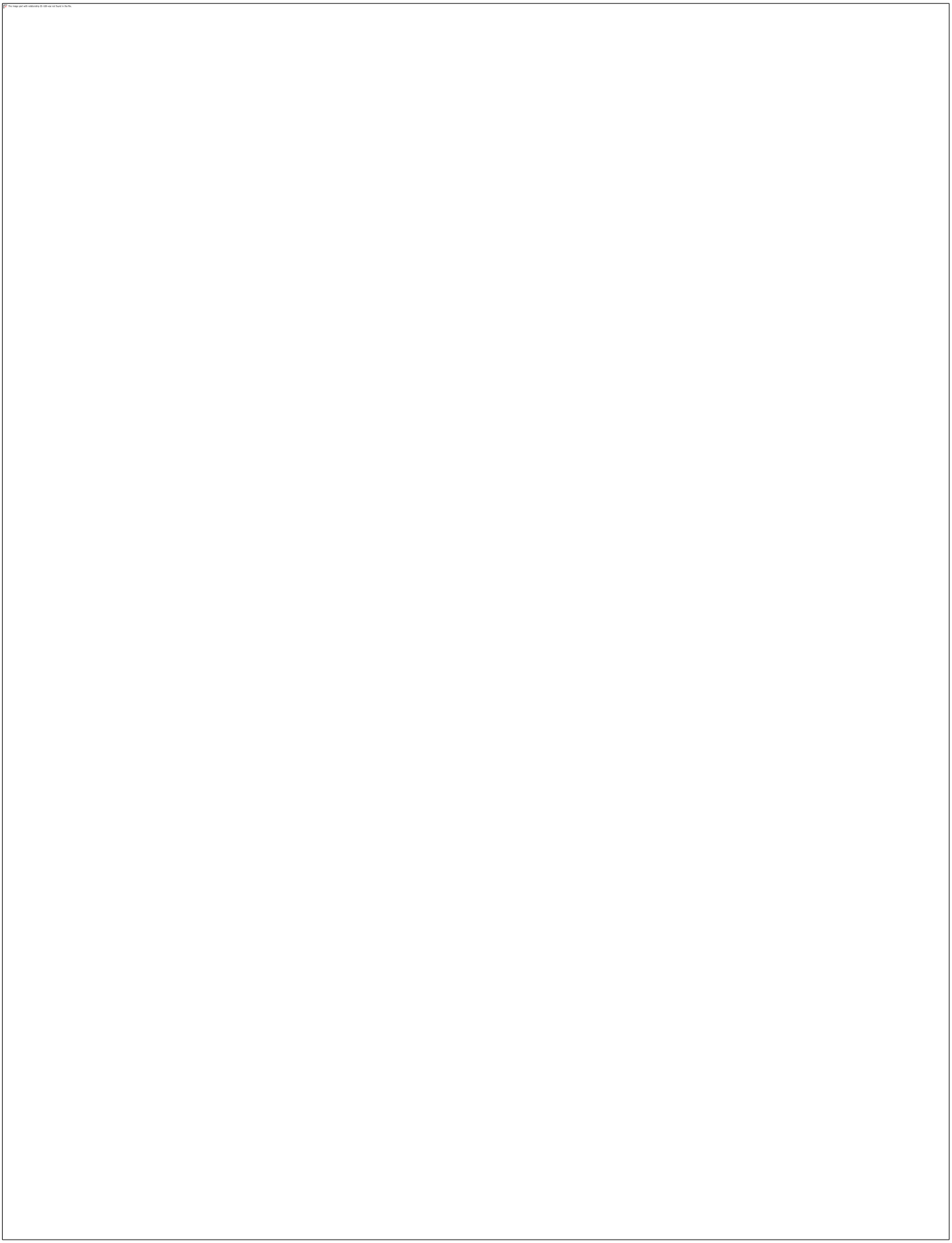
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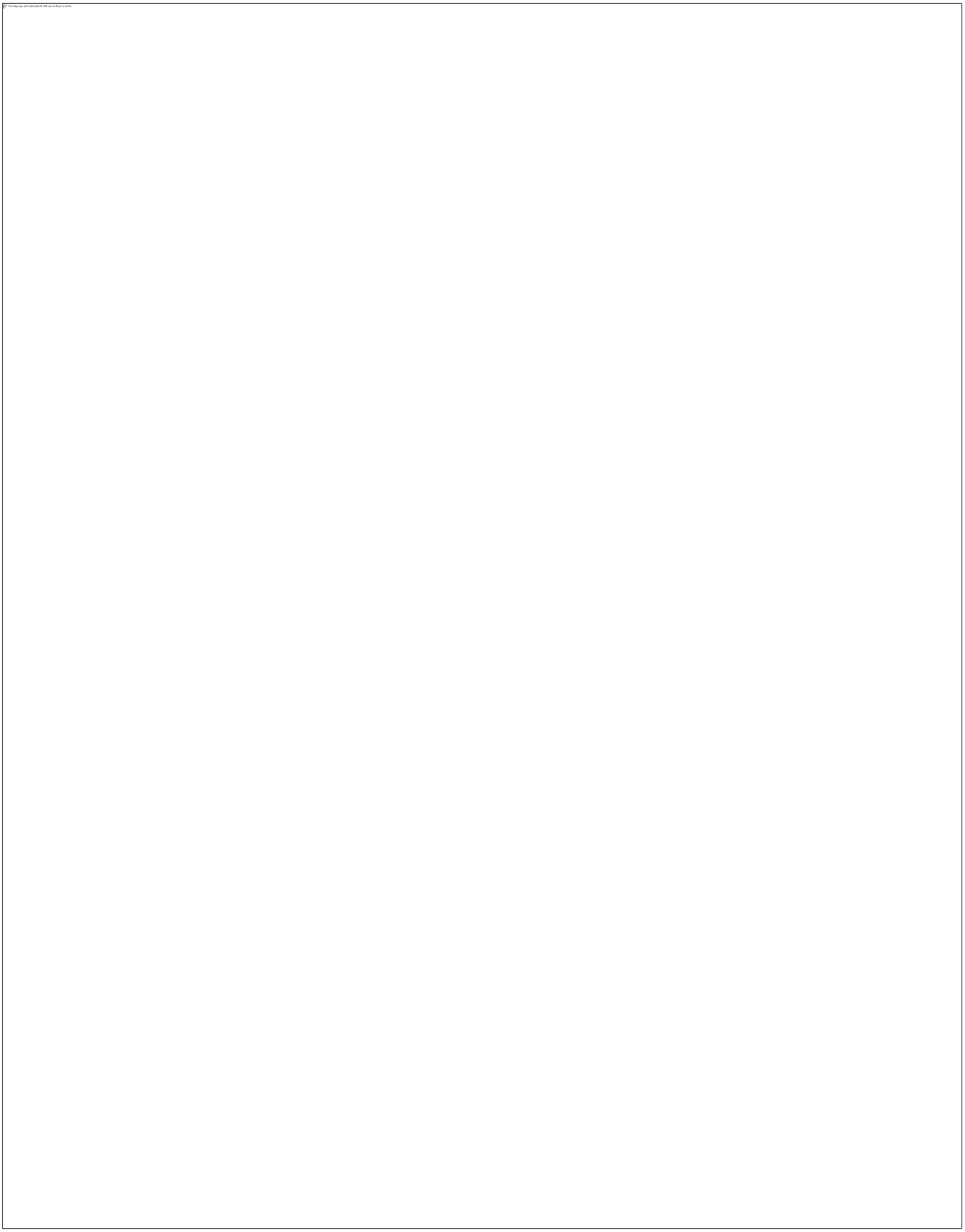
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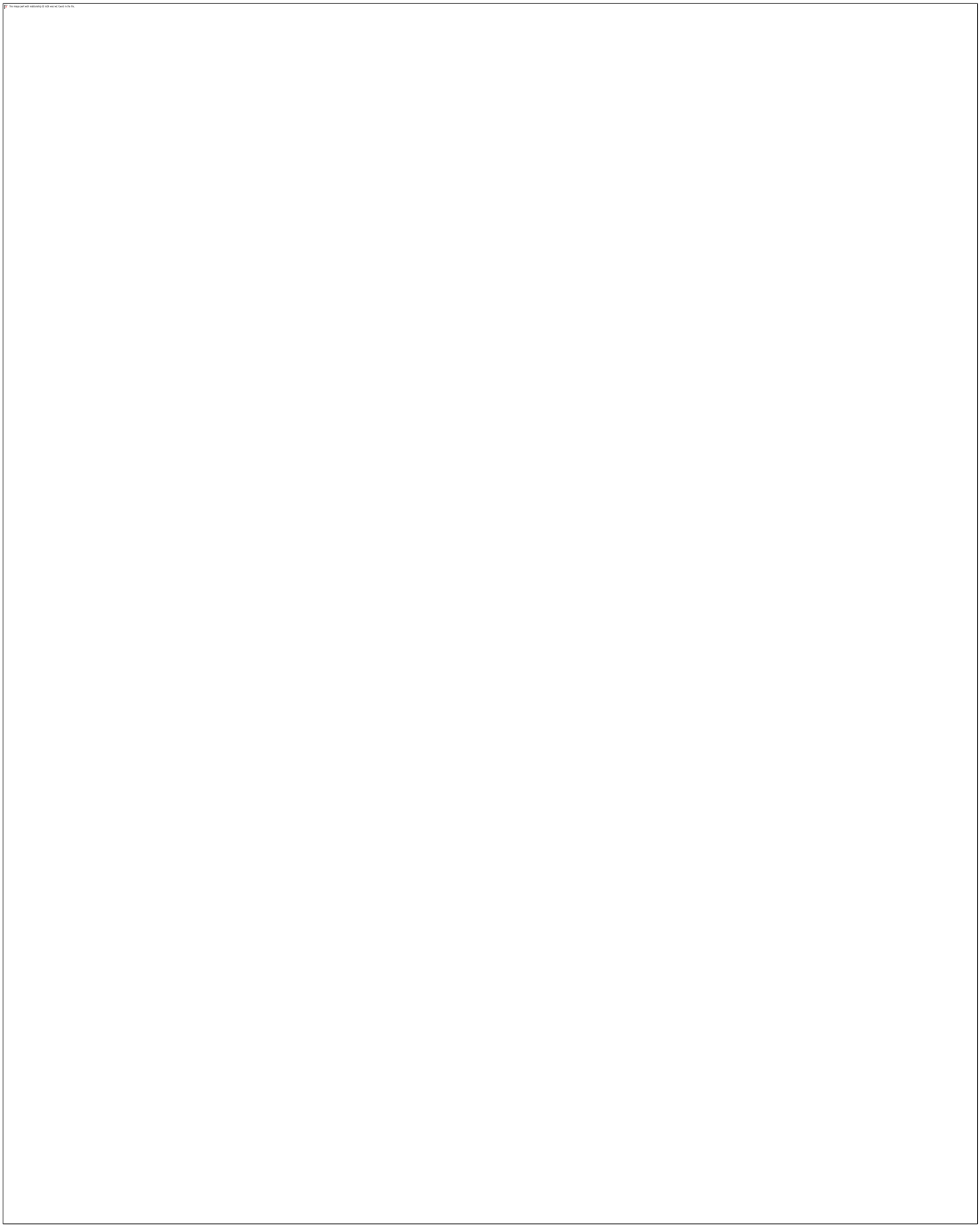
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IV. Description of psychosocial intervention

Target	Intervention	Methodology
Behavioral risk (diet, physical activity, medication adherence)	Psycho-education Behavioral change/ modification	− In groups − On pairs (patient/ partner) − Simulation , role play, charts and check lists, illustrative handouts
Coping skills	Psycho-education Behavioral change/modification Hands on training	− In groups − On pairs (patient/ partner) − Simulation , role play, life style analysis and practicing
Depression	Assessment Psycho-education Daily life routine and activation behaviors Family and social support Pharmacological intervention when needed	− In groups − On pairs (patient/ partner) − Group therapy sessions − Monitoring daily life activities − Activation behaviors − Referral for psychiatric/ medical support when needed
Anxiety	Assessment Psycho-education Managing physical symptoms Cognitive intervention Pharmacological intervention when needed	− In groups − On pairs (patient/ partner) − Simulation , role play, negative/ anxious thinking patterns modification, relaxation training, daily life settings modification − Referral for psychiatric/ medical intervention when needed
Stress	Psycho-education Stress management skills training Life style assessment and modification Nutrition and exercise	− In groups − On pairs (patient/ partner) − Simulation , role play − Social support − Breathing − Nutrition and exercise − Daily life supportive activities
Affect dysregulation Anger management	Psycho-education Assessment of personality patterns and attitudes towards illness and life Anger management skills training Affect regulation training	− In groups − On pairs (patient/ partner) − Simulation , role play, charts and check lists, illustrative handouts − Mood and behaviors monitoring − Behavior change − Breathing and biofeedback