Trajectories of Depressive Symptoms and Their Predictors among Jordanian Patients with Acute Coronary Syndrome

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Declaration

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Dedication

This thesis is dedicated to my Mom and Dad.

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List of Abbreviations

- ACS: Acute Coronary Syndrome
- AHA: American Heart Association
- ADL: Activities of daily living
- BDI: Beck Depression Inventory
- CDC: Centre for Disease Control and Prevention
- CES-D: Centre for Epidemiologic Studies Depression Scale
- CERQ: Cognitive Emotion Regulation Questionnaire
- CHD: Coronary Heart Disease
- CINAHL: Cumulative Index to Nursing and Allied Health Literature
- CCI: Charlson Comorbidity Index
- CFA : Confirmatory Factor Analysis
- CVD: Cardiovascular Diseases
- DALYs: Disability-Adjusted Life Years.
- DASS: Depression Anxiety Stress Scale
- DISH: Depression Interview and Structured Hamilton
- DS14: The 14-item Type D Personality Scale
- ESC: European Society of Cardiology
- GBD: Global Burden of Disease
- GBTM: Group-Based Trajectory Modelling
- GCM: Growth Curve Modelling
- GDS: Geriatric Depression Scale
- GMM: Growth Mixture Modelling
- GRACE: The Global Registry of Acute Coronary Events

- HADS: Hospital Anxiety Depression Scale
- HDRS: Hamilton Depression Rating scale
- LCGA: Latent Class Growth Analysis
- LVEF: Left Ventricular Ejection Fraction
- MACE: Major Adverse Cardiac Events
- MPSS: Multidimensional Perceived Social Support
- NSTE-ACS: Non-ST Segment Elevation Acute Coronary Syndrome.
- NSTEMI: Non-ST Segment Elevation Myocardial Infarction
- NYHA: New York Heart Association
- PCI: Percutaneous Coronary Interventions
- PHQ-9: Patients Health Questionnaire 9
- PHQ-LSD: Patient Heath Questionnaire for Lifetime Screening of Depression
- PRIME-MD: Primary Care Evaluation of Mental Disorders
- STEMI: ST Segment Elevation Myocardial Infarction
- UA: Unstable Angina
- WHO: World Health Organisation

Glossary of Terms

Acute Coronary Syndrome (ACS)	An umbrella term includes ST-segment elevation myocardial infarction (STEMI) and non-ST-segment elevation ACS (NSTE-ACS).
Cardiovascular Diseases (CVDs)	A group of disorders affecting the heart and blood vessels include coronary heart disease, cerebrovascular disease, heart failure, peripheral artery disease and other conditions.
Charlson Comorbidity Index (CCI)	A simple and valid tool for estimating mortality risk in individuals with comorbid diseases
Conceptual/Theoretical Framework	Narrative and geographical illustrations are used to clarify the study variables and how they are related.
Coronary Heart Disease (CHD)	A disease occurs when blood vessels supplying heart muscle become narrowed or blocked due to the accumulation of plaque in their walls (atherosclerosis).
Group-Based Trajectory Modelling (GBTM)	A set of analytical techniques allows the researcher to use information from repeated observations to make inferences about unobserved groups.
Growth Curve Model	A method of Analysis summarises the repeated measures for each individual using single set of growth parameters: Intercept (α) and slope (β)
Growth Mixture Modelling (GMM)	A method of analysis assumes that the entire population is heterogeneous and composed of subpopulations. It includes latent a categorical variable which is regressed on growth factors.
Left Ventricular Ejection Fraction (LVEF)	A cardiac severity test was measured using an echocardiogram. The value below 40% indicates low LVEF.

Prevalence	The number of patients who develop depression at a certain time point divided by the total number of patients at that time.
Incidence	The number of patients who had no history of depression but, who developed a new episode of depression divided by the number of patients at risk for depression.
Psychosocial Factors	Factors related to depression include Type D Personality, coping strategies, Perceived social support, and history of lifetime depression
The Global Registry of Acute Coronary Events (GRACE) score	A risk prediction tool to estimate six-month mortality following an ACS event

Thesis Summary

Background: Acute Coronary Syndrome (ACS) is an umbrella term that includes myocardial infarction and unstable angina. Depression is a common psychological response in patients with ACS and has been shown to be independently associated with increased mortality, cardiac events, and poor quality of life. Although the prevalence of depression after ACS tends to be stable over time, its trajectories are not, and little is known about the variation in depressive trajectories after an ACS event. Evidence suggests that trajectories of depressive symptoms are heterogenous; some patients experience minimal or no depressive symptoms while others experience transient, worsening, or persistent symptoms. Studies that have addressed this, identified two to five trajectories of depressive symptoms that vary in their stability and intensity. Therefore, it is important to understand the patterns of these trajectories in ACS patients and to identify the characteristics of different trajectory groups. To date, few studies have addressed trajectories of depressive symptoms and their predictors in patients with ACS. None of these studies were carried out in Jordan.

Aim: The aim of this study was to employ group-based trajectory modelling to identify the heterogeneous trajectories of depressive symptoms, and their predictors, following an ACS event.

Methods: This study was a prospective cohort study conducted across four hospitals in Jordan. Data were collected from ACS patients using structured interview and self-reporting questionnaires. At baseline, the following self-reported questionnaires were administered to all patients: (1) Patients Health Questionnaire (PHQ-9), (2) Multidimensional Perceived Social Support (MPSS), (4) Type D Personality (DS14), and (5) Brief COPE. Changes in depressive symptoms were evaluated by telephone at 1, 3 and 6 months using the PHQ-9. All questionnaires were in Arabic and required less than 25 minutes to complete. Nested logistic regression was used to identify predictors of in-hospital depressive symptoms. Trajectories of depressive symptoms were identified using growth curve and growth mixture modelling (GMM).

Multinomial logistic regression was used to identify predictors of trajectories of depressive symptoms over six months of ACS.

Results: A total of 434 patients participated in the study. The prevalence of depressive symptoms in patients with ACS was 23.5% (n=102), based on the PHQ-9 score ≥ 10. In the first nested model, monthly income (≤500 JOD), smoking, Type D personality, dysfunctional coping, low perceived social support, and history of depression were significant predictors of depressive symptoms. In the second nested model, Left Ventricular Ejection Fraction (LVEF<40), length of hospital stays, and the four aforementioned psychosocial variables were significant predictors of depressive symptoms. The Nagelkerke Pseudo R squared value for the demographics, and health-related behaviours model was 13.5%. Including psychosocial variables increased the R Squared to 33.7%. Likewise, adding the psychosocial variables into the clinical variables model increased the Nagelkerke Pseudo R squared value from 13.5% to 32.8%.

The prevalence of depressive symptoms at one, three and six months after ACS was 18% (n=75), 16.7% (n=67) and 15% (n=61), respectively. The cumulative incidence of depression over six months of ACS was 8.3%. Using GMM, four distinct depressive symptom trajectory groups were identified: minimal and decreasing (n=327, 75.4%), decreasing (n=39, 9.0%), increasing (n=31, 7.1%) and stable high (n=37, 8.5%). The final multivariate model explained 34.9% (Negelkerke R2) of the total variance in depressive symptom trajectory groups. The model showed that low (<500 JOD) monthly income (OR= 6.618, 95%CI, 1.630-26.876), having a history of depression (OR = 3.547, 95% CI, 1.379-9.123), Type D personality (OR= 2.544, 95%CI, 1.016-6.370), using dysfunctional coping (OR =1.073, 95% CI, 1.011-1.138), and having low perceived social support (OR =.910, 95% CI, .875-.946) were significant predictors of persistent depression compared to no depression. Further, current smoking status (OR= 4.635, 95%CI, 1.765-12.174) and problem-focused coping (OR =.874, 95%CI, .767-.996) were significant predictors of increased depression compared to no depression.

Conclusion: This is the first study in Jordan to address trajectories of depressive symptoms and their predictors after ACS. This is also the first study in Jordan to

examine the incidence of depressive symptoms following ACS. As depressive symptoms were found to be prevalent in hospitalised patients with ACS, screening for depression is highly recommended. This study also found that trajectories of depressive symptoms in patients with ACS are heterogenous and that a single trajectory does not represent the change over time. Therefore, screening of depressive symptoms in patients with ACS should not be limited to hospitalisation but should continue after discharge from the hospital.

Finally, the results of this study greatly inform the body of knowledge in this area of ACS care. They are particularly important for Jordanian healthcare professionals, policy makers as well as for patients themselves. Timely assessment and treatment of depression in the ACS cohort has the potential to optimise patient recovery, reduce mortality & morbidity whilst improving quality of life.

Chapter 1: Introduction

This thesis presents a Jordanian cohort study examining the heterogeneous trajectories of depressive symptoms following an acute coronary syndrome (ACS). Chapter 1 provides an overview and background to acute coronary syndrome in the context of cardiovascular disease. Following this, detail on the prevalence and incidence of depression in the ACS cohort is presented followed by the trajectories of depressive symptoms over 6 months of an ACS event. Finally, the predictors of trajectories of depressive symptoms after ACS are discussed and the rationale provided for examining depression amongst ACS patients in Jordan. The chapter concludes with the study aim and objectives and thesis overview.

1.1 Background to the Study

Cardiovascular diseases (CVDs) involve a group of conditions affecting the heart and blood vessels (Benjamin *et al*., 2018). These includes, for instance, coronary heart disease, cerebrovascular disease, heart failure, peripheral artery disease and other conditions (Lopez *et al*., 2021). The World Health Organisation (WHO) reported that CVDs are the main cause of death globally, accounting for 32% of all global deaths (World Health Organisation, 2019a). The Global Burden of Disease (GBD) study (2019) evaluated the burden of diseases in 204 countries from 1990 to 2019 and reported that the prevalence of CVDs globally has doubled from 271 million in 1990, to 523 million in 2019. Concurrently, the number of deaths related to CVDs increased significantly from 12.1 million to 18.6 million between 1990 and 2019 (Roth *et al*., 2020). More recently, the American Heart Association (AHA) estimated that around 19 million deaths globally were related to CVDs, which reflect an 18.7% increase on 2010 figures (Tsao *et al*., 2022).

According to the Centres for Disease Control and Prevention (CDC), each year in the United States (US), one in every four deaths are related to CVDs (CDC, 2019). In Europe, approximately 85 million individuals are living with CVDs with almost 3.9 million deaths attributed to CVDs annually (Wilkins *et al*., 2017). Similarly, CVDs are prevalent in the Middle Eastern region and are associated

with increased rates of morality (Tsao *et al*., 2022), which in 2015 accounted for 34% of all deaths (Narula, 2017). A recent systematic review and meta-analysis reported a pooled prevalence of CVDs in the Middle Eastern region of 10.1%, which is 6% higher than the global prevalence of 4% (Shehab and Bhagavathula, 2019).

CVDs are also a major cause of disability worldwide. The GBD study (2019) reported that disability-adjusted life years (DALYs), which is a measure of disease burden, increased globally from 17.7 to 34.4 million between 1990 and 2019 (Roth *et al*., 2020). Furthermore, DALYs attributed to CVDs were highest in low- and middle-income countries (Roth *et al*., 2020). IN addition, CVDs exert high economic burden on countries globally. For instance, in the US, CVDs cost the State about €363 billion each year in direct and indirect costs (CDC, 2019). Direct costs alone increased from $103 billion in 1996/1997 to $226.2 billion in 2017/2018 (Tsao *et al*., 2022). Meanwhile, in Europe, CVDs are estimated to cost the European Union about €210 billion each year (Wilkins *et al*., 2017).

Coronary heart disease (CHD) is the most common CVD and is considered the main cause of deaths worldwide (Khan *et al*., 2020). In 2019, CHD accounted for 8.9 million deaths worldwide, representing 16% of all global deaths (WHO, 2019b). Deaths from CHD represent almost half of CVD deaths globally (17.9 million deaths in 2019) (WHO, 2019a). The GBD (2019) study reported that 197 million individuals were living with CHD, and DALYs due to CHD increased globally from 120 to 182 million between 1990 and 2019 (Roth *et al*., 2020). The prevalence of CHD is increasing with prevalence rates estimated to increase further by 2030, from 1,655 to 1,845 per 100.000 population (Khan *et al*., 2020). According to Tsao *et al*. (2022), the highest prevalence and mortality rates worldwide due to CHD were observed in North Africa, the Middle East, and Eastern Europe.

CHD occurs when blood vessels supplying heart muscle (coronary arteries) and become narrowed or blocked due to accumulation of plaque in their walls (atherosclerosis). When coronary arteries become blocked, the heart muscle cannot get enough oxygen which may lead to myocardial ischemia and heart

muscle damage (Collet *et al*., 2021). CHD can be manifested though a group of life-threatening conditions referred to as Acute Coronary Syndrome.

1.2 Acute Coronary Syndrome

Acute Coronary Syndrome (ACS) is an umbrella term for ST-segment elevation myocardial infarction (STEMI), and non-ST-segment elevation ACS (NSTE-ACS). The latter can be further classified into non-ST segment elevation myocardial infarction (NSTEMI) and unstable angina (UA) (Collet *et al*., 2021). The cardinal symptom of ACS is chest discomfort. However, it may also include epigastric pain, dyspnoea, numbness or pain in the left arm and other symptoms. STEMI and NSTE-ACS can be differentiated through clinical assessment, electrocardiogram (ECG), and cardiac biomarkers (Kimura *et al*., 2019). STEMI is diagnosed with the presence of chest discomfort and persistent ST-segment elevation on ECG (> 20 minutes) while NSTE-ACS is diagnosed with the presence of chest discomfort without persistent ST segment elevation (Collet *et al*., 2021). Cardiac biomarkers, mainly, high sensitivity cardiac troponin T or I are evaluated to differentiate UA and NSTEMI (Kimura *et al*., 2019), with the latter generally showing an increase in biomarkers (Kimura *et al*., 2019, Collet *et al*., 2021).

ACS is the main cause of CHD-related deaths (Traina *et al*., 2017). ACS is a life-threatening condition that require immediate intervention by either percutaneous coronary interventions (PCI) or fibrinolytic therapy (Collet *et al*., 2021). It is estimated that more than 7 million individuals worldwide are diagnosed with ACS each year (Bhatt *et al*., 2022). The American Heart Association (AHA) estimates that in the US, someone suffers an MI every 42 seconds (Mozaffarian *et al*., 2016), while in the United Kingdom (UK), more than 80,000 individuals are hospitalised with ACS each year (Kotecha and Rakhit, 2016).

Data from the Australian Bureau of Statistics (2020) estimates that one Australian dies every 74 minutes as a result of ACS. Consequently, the economic burden of ACS is considered high. For instance, the total costs associated with ACS in Australia was around $4,830.9 million in 2017 and 2018 (Saunders,

2018), while in Europe and the US it is estimated to reach around $270 billion annually (Nichols *et al*., 2012, Mozaffarian *et al*., 2016).

Several international guidelines have been published on managing ACS and improving outcomes (Ibanez *et al*., 2018, Frost *et al*., 2019). Despite these, ACS remains a significant health problem associated with high rates of mortality, morbidity (Mozaffarian *et al*., 2016), and increased healthcare costs (Cowper *et al*., 2019). Psychological responses, specifically, depression may coexist with ACS and impose additional burdens on individuals, the economy and consequently on society (Kurdyak *et al*., 2008, Reese *et al*., 2011, Rodwin *et al*., 2013). Therefore, investigating depression among patients with ACS could be useful in reducing its negative impact at both individual and societal levels.

1.3 Depression

Depression, also referred to as "major depressive disorder or clinical depression" is a mental disorder that causes constant (1) feelings of sadness or (2) lack of interest in daily activities. It may also involve other symptoms including (3) feelings of worthlessness or excessive guilt, (4) disturbed sleep or (5) appetite, (6) psychomotor agitation or retardation, (7) lack of energy or fatigue, (8) poor concentration and (9) recurrent thoughts of suicide or death (American Psychiatric Association [APA], 2013). There are two widely used classification systems for diagnosing depression and other mental disorders: Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-4) (APA, 1994), and the tenth revision of the International Classification of Diseases (ICD-10) (WHO, 1992). While the DSM-4 is exclusively for diagnosing mental disorders, the ICD-10 consists of diagnostic codes for classifying medical and mental disorders (Tyrer, 2014). These classifications have been updated to DSM-5 (APA, 2013) and ICD-11 (WHO, 2019). The criteria of diagnosing depression in the DSM-5 has not changed from those in the DSM-4 (APA, 1994, 2013). According to DSM-5 criteria, depression is diagnosed when at least five of the nine aforementioned symptoms, including either depressed mood or loss of interest, are present, nearly every day, for at least two weeks (APA, 2013).

The threshold regarding the number of symptoms required for diagnosis of depression in the ICD-10 is slightly different to the DSM-5 criteria. Depression is diagnosed when four of ten symptoms are present, nearly every day, for at least two weeks, including at least two of the three core symptoms: depressed mood, loss of interest and lack of energy or fatigue (WHO, 1992). However, the ICD-11 is consistent with the DSM-5 with respect to the number of symptoms required for diagnosis of depression. According to the ICD-11, depression is diagnosed when five symptoms including either depressed mood or loss of interest, are present, nearly every day, for at least two weeks (WHO, 2019c). The difference between ICD-11 and DSM-5 is that the former includes 10 symptoms of depression while the latter includes 9 symptoms (Di Cerbo, 2021; First *et al*. 2021). The ten symptoms of depression in the ICD-11 criteria are similar to the aforementioned nine symptoms in the DSM-5 but also includes hopelessness about the future (Stein *et al.,* 2020; Di Cerbo, 2021).

According to a report released by the WHO (2017a), around 322 million individuals suffer from depression globally, constituting 4.4% of the global population. Prevalence of depression is high in sub-Saharan Africa, North Africa, and the Middle East. In the Middle East, prevalence of depression was reported as 4,349 cases per 100,000 (GBD 2019 Mental Disorders Collaborators, 2022). Depression is among the top leading causes of disability worldwide and in 2019, it accounted for 50 million DALYs (GBD 2019 Mental Disorders Collaborators, 2022). A recent Lancet commission report estimated the global costs of depression and anxiety to be around $1 trillion each year (The Lancet Global Health, 2020). Thus, depression continues to be a significant public health problem that requires screening, assessment, and treatment.

There is no single method for assessing depression. Depression can be assessed using structured clinical Interviews or self-reported questionnaires (Levis *et al*., 2019). Structured clinical interviews involve for example, the Composite International Diagnostic Interview (CIDI) (World Health Organization, 1990), the Structured Clinical Interview for DSM Disorders (SCID) (First *et al*., 1997; First, 2014) and the Depression Interview and Structured Hamilton (DISH) (Freedland *et al*., 2002). These structured clinical interviews are widely

considered the gold standard methods for screening depression. However, they are time consuming and require well-trained psychiatrists (Vaccarino *et al*., 2020). As a result, self-reported questionnaires were developed as cost and time efficient methods for assessing depressive symptoms. Several self-reported questionnaires are commonly used for assessment of depressive symptoms including the Centre for Epidemiologic Studies Depression Scale (CES-D) (Rodolff, 1977), the Hamilton Depression Rating Scale (HDRS) (Hamilton, 1960), the Beck Depression Inventory (BDI) (Beck *et al*., 1987), and the Patient Health Questionnaire-9 (PHQ-9) (Spitzer *et al*., 1999b). The PHQ-9 is a self-reported version of the Primary Care Evaluation of Mental Disorders (PRIME-MD), which is one of most commonly used questionnaires for assessing depression in primary care (Spitzer *et al*., 1999b; Levis *et al*., 2019). A PHQ-9 score ≥ 10 has shown high accuracy (85%) for detecting major depressive disorders against the clinician administered PRIME-MD (Spitzer *et al*., 1999b).

1.4 Depression in ACS

Depression is a common psychological response in patients with ACS, with prevalence rates ranging between 20% and 69% (Goudarzian *et al*., 2016, Allabadi *et al*., 2019). It is reported to be three to four times higher in patients with ACS than in the general public (Lichtman *et al*., 2014). A meta-analysis of seven studies found that the prevalence of depression in patients with ACS ranged from 20% to 35% (Khan *et al*., 2021). Another meta-analysis of 19 studies reported prevalence of depression in patients with MI ranged from 9.2% to 65.9%, with a pooled prevalence of 28.7% (Feng *et al*., 2019).

Depression has been shown to be independently associated with increased mortality (Smolderen *et al*., 2017; Worcester *et al*., 2019), cardiac events (Whooley *et al*., 2008; Ye *et al*., 2013) and worse quality of life (Beata *et al*., 2014; Mayer *et al*., 2020). For instance, Parker *et al*. (2019) found that depression following ACS (n=332) was associated with a three-fold increased risk of death or hospital readmission during the first month of ACS and associated with a 2.5 fold increased risk of death or hospital readmission within 12 month of ACS (Parker *et al*., 2019). Another study (Kim *et al*., 2021) (N=1152)

found that patients who developed depression after MI were 2.2 times more likely to develop Major Acute Cardiac Events (including death, recurrent MI, or emergent PCI) over 8.4 years follow-up compared to patients with no depression. In addition, a meta-analysis by Meijer *et al*. (2011) reported that the risk of one-year mortality, morbidity and new cardiac events was 1.6-2.7 times higher in patients who developed depression after ACS than in those with no depression. Another meta-analysis found that depression after MI was associated with a 22% increased risk of mortality and a 13% increased risk of recurrent cardiac events (Meijer *et al*., 2013). These findings are congruent with previous meta-analyses that reported twice the risk of adverse outcomes in patients who experienced depression after ACS, than those who did not (Barth *et al*., 2004; Spijkerman *et al*., 2006).

Several mechanisms have been suggested to explain the negative association between depression and patient outcomes, however the exact mechanism remains unknown (Smith *et al*., 2015; Vaccarino *et al*., 2020; Yang *et al*., 2021). It has been suggested that behavioural mechanisms such as smoking, medication non-adherence, alcohol use and physical inactivity make a large contribution (Ye *et al*., 2013). However, the association remains unexplained (Vaccarino *et al*., 2020). A position paper from the European Society of Cardiology (ESC) reported that mechanisms linking depression and ACS are complex and include multiple factors, for example, altered neurobiology, altered neuroendocrine, inflammation, disruption in the brain regulatory system, autonomic dysfunction, endothelial dysfunction, platelet activation and thrombosis, and genetic vulnerability (Vaccarino *et al*., 2020). In 2014, the AHA summarised the evidence and reported that depression after ACS to be an independent risk factor for poor outcomes (Lichtman *et al*., 2014). Recently, the American Academy of Family Physicians recommended that clinicians should screen for depression in patients with ACS using standardised depression assessment instruments (Frost *et al*., 2019). This is consistent with recommendations recently published by the ESC (Vaccarino *et al*., 2020).

1.5 Trajectories of depressive symptoms following an ACS event

Most studies that examined the prevalence of depressive symptoms in patients with ACS following discharge from hospital, reported depression to be stable at 3 months (Doering *et al*., 2010), 4 months (Lane *et al*., 2002), and 12 months (Kang *et al*., 2015; Lane *et al*., 2002). Although depressive symptoms appear to be stable over time, their trajectories may not be. Few studies have examined the trajectories of depressive symptoms, i.e. classifying individuals into different groups based on changes that occur to their symptoms of depression over time (Nagin, 1999; Muthén, 2004).

Studies that have addressed this, identified several trajectories of depressive symptoms that vary in their stability and intensity (Keegan *et al*., 2016; Martens *et al*., 2008; Kaptein *et al*., 2006). These studies employed different statistical methods to classify these trajectories into three (Doyle *et al*., 2011a; Murphy *et al*., 2008b; Keegan *et al*., 2016), four (Martens *et al*., 2008; Mittag *et al*., 2016) or five trajectory groups (Kaptein *et al*., 2006). For instance, Doyle *et al.* (2011) identified three groups of symptom trajectories: "non-depressed, subthreshold, and persistent". Another study identified four groups: "non-depressed, sustained remission, worsening, and persistent" (Mittag *et al*., 2016). Meanwhile, Kaptein *et al*. (2006) identified five groups: "non-depressed, mild, moderate and increasing, significant but decreasing, and significant and increasing symptoms".

Although all of these studies showed heterogeneity in the number and patterns of depressive trajectories, an increased risk of mortality or recurrent cardiac events was reported when baseline depressive symptoms worsened (Murphy *et al*., 2014a; Blumenthal *et al*., 2003), or persisted (Kaptein *et al*., 2006; Mittag *et al*., 2016; Keegan *et al*., 2016) over time. One study reported an association between trajectories of depressive symptoms and health related quality of life. This study showed poorer quality of life among those who had worsening or persistence in depressive symptoms over time.

It has been suggested that Group-Based Trajectory Modeling (GBTM) analysis might help in identifying the groups that are associated with an increased risk of poor outcomes (Musliner *et al*., 2016). These models empirically classify all patients into different groups, where each group shares the same pattern of symptoms over the follow-up period (Nagin, 2010). Therefore, understanding the differences in each groups' baseline characteristics, may help healthcare professionals recognise the characteristics of those patients with ACS, who are at risk for worsening or persistent depressive symptoms (Martens *et al*., 2008; Murphy *et al*., 2014a; Keegan *et al*., 2016).

1.6 Predictors of trajectories of depressive symptoms

While most studies focused on identifying patient groups that are associated with poorer outcomes, little is written about what predicts the course of depression and its trajectories following admission to hospital with ACS. Understanding these predictors, especially for the group whose depressive symptoms worsen or persist over time, may guide intervention development that improves poorer outcomes associated with this group (Martens *et al*., 2008; Murphy *et al*., 2014a). Most studies that investigated predictors of depression trajectories in patients with ACS were atheoretical and focused on health histories, demographics, or traditional characteristics. Psychosocial variables such as Coping (Kroemeke, 2016), Personality type D (Doyle *et al*., 2011a; Martens *et al*., 2008; Romppel *et al*., 2012; Keegan *et al*., 2016), and Perceived Social Support (Mittag *et al*., 2016) have been identified separately as predictors for trajectories of depressive symptoms. See Table 1 for conceptual definitions of these variables.

However, none of these studies evaluated the independent prediction of coping when present simultaneously with personality type D and social support. Further, history of depression has been suggested as a crucial factor for predicting trajectories of depressive symptoms after ACS (Kaptein *et al*., 2006; Martens *et al*., 2008) but most of previous studies did not include it (Doyle *et al*., 2011a; Romppel *et al*., 2012; Keegan *et al*., 2016; Kroemeke,

2016). Therefore, exploring history of depression, perceived social support, coping strategies, and personality type D in patients with ACS who experienced depression, may be useful in assessing their independent prediction of depressive symptom trajectory.

Table 1: Conceptual and operational definitions of the main study variables

Variables	Conceptual Definitions	Operational Definitions
Depression	"A common but serious mood disorder. It causes severe symptoms that affect how you feel, think, and handle daily activities, such as sleeping, eating, or working" (US Department of Health Human Services, 2019)	Depressive symptoms were measured using the Patient Health Questionnaire (PHQ-9) that was developed by Spitzer *et al*. (1999).
Incidence of Depression	Refers to "patients with a post-MI depressive episode who had not been depressed before the index MI" de Jonge *et al*. (2006, p 2205)	After excluding history of depression, incident depression was assessed at 1, 3, and 6 months after an ACS event using the Patient Health Questionnaire (PHQ-9) that was developed by Spitzer *et al*. (1999).
Perceived Social Support	"The individual's beliefs about the availability of varied types of support from network associates" (Gottlieb and Bergen, 2010, p.512)	Perceived Social Support was measured using the 12-item Multidimensional Perceived Social Support (MPSS) that was developed by Zimet *et al*. (1988).
Type D Personality	"A joint tendency toward negative affectivity (NA) and social inhibition (SI)" (Denollet, 2005, p.89)	Type D personality was measured using DS14 scale that was developed by Denollet (2005).
Coping	"Refers to the person's cognitive and behavioural efforts to manage (reduce, minimize, master, or tolerate) the internal and external demands of the person environment transaction that is appraised as taxing or exceeding the person's resources"(Folkman *et al*., 1986, p. 572)	Coping was measured using 28-item Brief COPE that was developed by Carver (1997)

1.7 Depression and ACS in Jordan

Jordan is one of the Middle Eastern countries located in Western Asia, on the east bank of the Jordan River. It is classified as a middle-income country (The World Bank, 2021). In line with global trends, CVDs are the leading cause of death In Jordan with most CVD deaths attributable to CHD (Jordanian Ministry of Health, 2021). CHD was responsible for 10.6% of all deaths in Jordan in 2017 (Jordanian Ministry of Health, 2021). People in the Middle Eastern region experience an ACS event 12 years younger than the median age in western countries (Gehani *et al*., 2014). There is also high prevalence of conventional risk factors for ACS, such as, smoking, diabetes, hypertension and sedentary and unhealthy lifestyle factors (Traina *et al*., 2017). A national stepwise Survey in 2019 reported almost half of the people in Jordan (n= 5713) were smokers; either tobacco (41%) or vaping (9.1%) (Jordanian Ministry of Health, 2020). Another study (N=358) reported that increased age, smoking, hypertension obesity and hyperlipidaemia were risk factors for CHD in Jordan (Raffee *et al*., 2020).

It has been suggested that Cardiac Rehabilitation (CR) programs might be helpful in improving outcomes after ACS (Kanazawa *et al*., 2020, Taylor *et al*., 2022). Despite this, the availability of these programs in Jordan is very limited. CR is a secondary prevention strategy that includes education, exercise, counselling and support (Cowie *et al*., 2019). It also helps patients to reduce their risk factors and modify behaviours, thereby improving their outcomes. Existing evidence shows that only 10 CR programs were found in 22 Eastern Mediterranean countries, compared with 125 programs in Canada alone yet no specific CR program has yet been developed in Jordan (Turk-Adawi *et al*., 2015, Turk-Adawi *et al*., 2019)

Jordan is a small country that has been largely affected by conflicts in the surrounding countries. It hosts more than four million refugees from Palestine, Syria and Iraq, making it the second largest refugee host country in the world (The UN Refugee Agency, 2019). This has put pressure on the country's infrastructure including health and mental health care. Jordan was classified by the WHO (2011) as a country that requires intense support for strengthening

their mental health system and thus was selected to implement the WHO's mental health action programme (mhGAP). Stigma towards mental illnesses in Jordan along with limited mental health services may prevent people from seeking the required treatment (Hasan & Musleh 2017, WHO, 2017b).

Culture plays an important role in how people view mental illness and their attitude towards seeking treatment (Bhugra *et al*., 2021). People in Arab countries, including Jordan, share a set of beliefs, values and norms which influence their perception of mental illness (Hasan and Musleh, 2017). In Jordan, mental illness is viewed as a source of shame, not only to individuals but also to their families. Therefore people who experience symptoms of mental illness tend to avoid being formally diagnosed with mental illness (Hasan and Musleh, 2017; Karnouk *et al*., 2019).

The cultural context may have an influence on estimated prevalence rates of depression across countries (Abdel Shafi and Abdel Shafi, 2014; De Vaus *et al*., 2018). Because of the stigma of depression, few people admit that they have symptoms of depression, which could mask the real prevalence rate (De Vaus *et al*., 2018). In addition, culture may influence how people describe their symptoms of depression and this would result in a cross-cultural variation in the presentation of depression (Abdel Shafi and Abdel Shafi, 2014). Research on cultural differences identified that people tend to describe symptoms of depression that are culturally appropriate to them (Vink *et al*., 2020). According to Dardas (2021), people in in the Arabic culture tend to express depression through somatic “physical” symptoms over psychological symptoms because they are socially acceptable. Thus, depression often goes undiagnosed in patients with physical illnesses because somatic symptoms of depression could be interpreted as symptoms related to the physical illness (Gold *et al*., 2020).

In Jordan, depressive symptoms are prevalent among patients with physical illnesses such as diabetes, cancer, rheumatoid arthritis and pulmonary diseases, with about 28% of patients found to have moderate to severe depressive symptoms (Hamdan-Mansour *et al*., 2014b). A study by Ghannam *et al*. (2014), carried out on 164 Jordanian patients diagnosed with stable CHD, showed that nearly half of them reported having depressive symptoms.

Another study was conducted in non-hospitalised individuals with CHD in Jordan and found that 17.5% had mild/moderate symptoms while 35.6% had severe depression (Al-Zaru *et al*., 2020). These findings are consistent with other studies in Jordan that were conducted in patients with diabetes (Al-Amer *et al*., 2011), cancer (Hamdan-Mansour *et al*., 2015), lung diseases (Hamdan-Mansour *et al*., 2014a), and renal failure (Khalil *et al*., 2011).

A limited number of studies were found to address depressive symptoms in patients with ACS in Jordan. One study examined depressive symptoms in 175 patients with MI and found that 69.7% (n=122) of patients had symptoms which ranged from mild to severe based on Beck Depression Inventory (BDI **≥**10) (AbuRuz *et al*., 2018). Another study conducted on older patients recruited from the Emergency Department with ACS reported prevalence of 65.7% using the Geriatric Depression Scale (GDS ≥7). However, none of these studies reported on the heterogenous changes that occur to depressive symptoms following discharge. All were cross-sectional and reported on demographics and clinical risk factors only (Hayajneh *et al*., 2021).

However, limited information has been found about depressive symptoms that occur among patients with ACS in Jordan, and the changes that occur to their symptoms following discharge. Furthermore, studies that have addressed depressive symptoms among patients with stable CHD were based on cross-sectional measures and did not address the heterogenous changes that occur to depressive symptoms after discharge. Accordingly, identifying trajectories of depressive symptoms might have important implications in understanding differences in the aetiology of depression and in identifying more homogenous depressive subgroups. A few studies have been found that evaluates trajectories of depressive symptoms in patients with ACS. This study intends to extend the aforementioned body of knowledge by examining psychosocial variables (coping, perceived social support, history of depression and personality type D) and investigating their association with trajectories of depressive symptoms.

1.8 Study Aim and objectives

Aim: The aim of this study is to employ group-based trajectory modeling to identify heterogenous trajectories of depressive symptoms after an ACS event.

Objectives

1. To estimate the prevalence of in-hospital depression among patients who have experienced an ACS event in Jordan.
2. To estimate the incidence of depression in these patients over a period of six-months post ACS.
3. To identify the trajectories of depressive symptoms during the six-months following an ACS event.
4. To determine what predicts trajectories of depressive symptoms after an ACS event: sociodemographic, cardiac disease severity or psychosocial factors.

1.9 Layout of the Thesis

The thesis contains seven chapters in total. Following on from this first chapter, Chapter two presents the international literature pertaining to depressive symptoms in patients with ACS. The influence of depression on patients' outcomes is discussed, including morbidity and mortality, and poor quality of life following ACS event. The chapter also reviews research studies that addressed trajectories of depressive symptoms in patients with ACS and the sociodemographic, clinical and psychosocial predictors of depressive symptoms trajectories.

Chapter three outlines the study methodology. The research paradigm is outlined and the conceptual framework guiding the study is presented. A conceptual model of relationships among psychosocial variables and trajectories of depressive symptoms is discussed and contextualised.

Chapter four provides detail about the study methods and research design choices, to show how the study aims and objectives were met. The chapter also describes the research site, population, sample, sampling technique, and instruments used in the study. Measures considered to ensure compliance with

ethical standards were also discussed in detail. Finally, the chapter concludes with information pertaining to techniques utilised in data collection and data management and data analysis. Rationale and choices for statistical approach is outlined here including the use of patients centred analyses. Much information is provided about the use of binary logistic regression, the analysis of longitudinal data, Latent Growth Curve Modelling and Group Based Trajectory Modelling.

In Chapter five, the results of the study are presented. Baseline data results are outlined in both narrative and graphic/tabular accounts. The chapter also presents the results of Growth Curve Modelling and Growth Mixture Modelling that have been used to identify trajectories of depressive symptoms after ACS. Factors related to distinct trajectories were identified using post hoc analysis and multinomial logistic regression. In addition, the chapter presents the prevalence at different time points and incidence of depressive symptoms at four time points.

Chapter six presents a discussion of the results of the study in relation to comparative international literature. Further, the contribution of the study to the advancement of knowledge with respect to trajectories of depressive symptoms and their predictors among patients with acute coronary syndrome is discussed. The chapter concludes with a consideration of the study's strengths and limitations.

Chapter seven provides a conclusion to the thesis along with several recommendations and implications for future clinical practice, research, and education. Finally, the thesis concludes with a plan for disseminating the results of this study.

Chapter 2: Literature Review

This chapter presents the literature regarding depressive symptoms in patients with ACS. The chapter discusses the concept of depression and its influence on patient outcomes including morbidity and mortality, following an ACS event. Following a systematic literature search, the chapter then reviews studies on the prevalence of depressive symptoms after ACS and the influence of sociodemographic, clinical, and psychosocial factors. Following this, the chapter reviews studies on the incidence of depression over time in patients with ACS. Finally, a further systematic search is conducted and a review of the evidence pertaining to trajectories of depressive symptoms in patients with ACS and their predictors is discussed.

2.1 The Impact of Depression on Patients' Outcomes following ACS

Depression is associated with an increased risk of arrhythmias and sudden death (Shi *et al*., 2017; AbuRuz *et al*., 2018). A meta-analysis of 17 studies which addressed this association found that depression was associated with 1.62 (95% CI, 1.37–1.92) times the risk of sudden cardiac death, 1.47 (95% CI, 1.23–1.76) times increased risk of ventricular arrhythmias, and 1.88 times increased risk of atrial fibrillation recurrence (95% CI, 1.54–2.30) compared to those with no depression (Shi *et al*., 2017). In the context of ACS, depression has been linked to adverse effects on patient outcomes during hospitalisation (AbuRuz *et al*., 2018) and after discharge. A Jordanian study by AbuRuz *et al*., (2018), enrolled 175 patients with MI and evaluated the association between in-hospital depression and in-hospital complications after MI. In-hospital complications were defined as the occurrence of any of the following events: recurrent ischemia, re-infarction, ventricular tachycardia, ventricular fibrillation, or death. The study found that patients who had increased depressive symptoms (BDI>10) were at 1.22 (95% CI, 1.14–1.30) times higher risk of in-hospital complications compared to those with minimal or no depressive symptoms (AbuRuz *et al*., 2018). Furthermore, depressive symptoms after MI were found to be associated with increased length of in-hospital stay.

A Chinese study of 644 patients with MI, evaluated the impact of depression on cardiac prognosis over 3 years after MI (Gu *et al*., 2019). The study found that depression after MI was independently associated with increased risk of mortality (HR=7.25; 95% CI, 4.74–11.10) and recurrent cardiac events (HR= 3.41; 95% CI, 2.49–4.67) (Gu *et al*., 2019). A Danish study (n = 97,793) found that ACS patients with new onset depression (HR = 1.66, 95% CI: 1.60, 1.72) and those with recurrent depression after ACS (HR = 1.62, 95% CI: 1.57, 1.67) were at higher risk of mortality over 12 years follow-up, compared to those with no depression (Osler *et al*., 2016).

Kim *et al*. (2021) evaluated the impact of depression on incidence of Major Adverse Cardiac Events (MACEs) over 8.4 years of ACS (n=1152) in Korea. They compared the incidence of MACEs among patients who screened positive for depression but were without a formal diagnosis of major depression and those who had screened positive for depression and who had a formal diagnosis of major depression. The study found that those who had positive screening for depression were 2.1 times more likely than those with no depression to develop MACEs over 8.4 years of ACS. However, there was no difference in risk of MACEs between those with and without a formal diagnosis of major depression (Kim *et al*., 2021). This was consistent with another Korean study which evaluated the impact of early (two weeks) and late (one year) depression on incidence of MACEs (all-cause death, MI, PCI) in 757 patients with ACS (Kim *et al*., 2020). Depression was assessed by Mini-International Neuropsychiatric Interview (MINI) and included both minor and major depression. The study found that both early and late depressive symptoms were significantly associated with increased risk of MACEs over 5 -12 years of ACS (Kim *et al*., 2020). A study by Pérez *et al*., (2020) included 145 patients hospitalised with CHD and evaluated the association between depression (3 months after discharge) and five-year cardiovascular events, including mortality or reinfection. The study found that depressive symptoms at 3 months after hospitalisation was associated with 3 times (95% CI 1.023–8.8) risk for subsequent cardiac events over 5-year follow-up (Pérez *et al*., 2020).

Several meta-analyses addressed the association between depression and poor prognosis after ACS. For instance, a meta-analysis (Meijer *et al*., 2011) which included 29 studies (n=16,889) from a 25 year search (1986 -2006) found that MI patients with depressive symptoms had 2.25 (95% CI, 1.73-2.93) times increased risk of all-cause of mortality, 2.71 (95% CI, 1.68–4.36) times increased risk of cardiac mortality and 1.59 (95% CI, 1.37-1.85) times increased risk of new cardiovascular events within 24 months of MI, compared to non-depressed patients (Meijer *et al*., 2011). This was consistent with another earlier meta-analysis that reviewed 22 studies (n=6367) between 1975 and 2003 and found that depression after MI was significantly associated with increased risk of all-cause mortality (OR= 2.38; 95% CI, 1.76 –3.22), cardiac mortality (OR= 2.59; 95% CI, 1.77–3.77), and new cardiovascular events (OR=1.95; 95% CI, 1.33–2.85) over an average of 13.7 months follow-up (Van Melle *et al*., 2004). Another meta-analysis of 16 studies found that depression after MI was independently associated with increased risk of all-cause mortality (HR= 1.32, 95% CI 1.26–1.38) and recurrent cardiac events (HR=1.19, 5% CI 1.14–1.24) (Meijer *et al*., 2013).

Although studies were inconsistent regarding which depression treatment was useful in improving cardiac prognosis after ACS, some studies showed that patients with untreated depression were at higher risk of mortality and cardiac events compared to those with treated depression or those who were not depressed. For example, a randomised controlled trial (RCT) by Zuidersma *et al*. (2013), enrolled 331 depressed patients with MI in the Netherlands. They evaluated the impact of several pharmacological and non-pharmacological antidepressant treatments on patients' outcomes, including cardiac mortality and cardiac events 8 years following MI. The study found that antidepressant treatment did not demonstrate an effect on 8-year mortality and subsequent cardiac events, compared to usual care (Zuidersma *et al*., 2013). However, patients who were treated for depression had significantly lower risk of all-cause mortality compared to those who were untreated for depression (HR= 0.52, 95% CI: 0.28–0.97).

These findings were consistent with a Translational Research Investigating Underlying Disparities in Acute Myocardial Infarction Patients (TRIUMPH) study (N=4,062) carried out in 24 hospitals in the United States (Smolderen *et al*., 2017). The study found that patients with untreated depression (n=528) after MI were associated with 1.9 times (95% CI, 1.39–2.62) increased risk of one-year mortality compared to non-depressed patients (n=3,303). However, no differences were found regarding one year mortality between patients with no depression (n=3,303) and those treated for depression (n=231).

However, some studies found that treatment of depression was suboptimal and not effective in reducing mortality and cardiac events after ACS. For instance, the Enhancing Recovery In Coronary Heart Disease Patients (ENRICHD) trial enrolled 2,481 MI patients with depression or low social support and investigated the impact of 6-month Cognitive-Behavioural Therapy (CBT) intervention on their outcomes. The study found that there was no difference in incidence of death or recurrent MI between those who were treated with CBT and those who received usual care at average follow-up of 29 months. However, the trial showed that CBT improved depression and social support (Enrichd Investigators, 2001). Similarly, the Sertraline Antidepressant Heart Attack Randomised Trial (SADHART) compared the impact of 6-month sertraline versus placebo treatment on 7-year mortality for 369 patients with a diagnosis of major depression. The study found that sertraline treatment did not predict mortality after MI (Glassman *et al*., 2002).

According to Davidson *et al*. (2013), fluctuations in depressive symptoms over time could provide an explanation for lack of effectiveness of interventions on patients' outcomes. Evidence suggests that a significant percentage of baseline depressive symptoms tend to spontaneously resolve over time and thus people who follow these trajectories do not require treatment (Murphy *et al*., 2014a). According to Mittag *et al*. (2016), one fifth of patients who experienced cardiac events in their study had transient symptoms that resolved 3 months after cardiac event and did not relapse. The ENRICHD investigators concluded that patients who display symptoms of depression following acute MI should be followed up and, if symptoms do not resolve then they should be considered

for treatment (Writing Committee for the ENRICHD Investigators, 2003). The SADHART trial (n=369) found no improvement in all-cause mortality following sertraline treatment. However, the trial did find that patients with persistent depression were 2 times more likely to die within an average of 7-year of MI. Therefore, recognising changes that occur in depressive symptoms after hospital discharge and understanding characteristics associated with different trajectories including persistent or transient symptoms of depression might guide treatment interventions on the appropriate time to implement treatment and who may benefit from treatment.

Mechanisms linking depression to poor outcomes after ACS

Mechanisms linking depression and poor outcomes after ACS are complex (Dhar and Barton, 2016). Several mechanisms have been suggested to explain the association between depression and poor outcomes in patients with ACS, yet it is not clearly understood (Vaccarino *et al*., 2020). One possible explanation is a neurobiological mechanism. Stress may increase stimulation of the sympathetic nervous system which increases heart rate and reduces heart variability, thus increasing the risk of developing arrhythmias (Harris *et al*., 2014; Granville Smith *et al*., 2015). Another suggested mechanism includes its association with increased inflammatory makers such as C-reactive protein or cytokines such as TNF- or IL-6 which worsen the progress of atherosclerosis (Mensour *et al*., 2022). Furthermore, depression is also linked to imbalance in neurotransmitters such as dopamine and serotonin, or increasing cortisol level, increasing platelet activation, and pro thrombotic factor activity, which in turn increase the risk of poorer outcomes after ACS (Stetler and Miller, 2011; Raič, 2017; Wilkowska *et al*., 2019).

Despite the well-known direct and indirect negative impact of depression on prognosis after ACS, it is often unrecognised and/or poorly treated (Tsu, 2012). Palacios *et al*. (2018) reported that information about depressive symptoms was available in the medical notes for only half of patients. Screening for depression is highly recommended according to international heart associations (Colquhoun *et al*., 2013; Lichtman *et al*., 2014; Frost *et al*., 2019). The AHA published a statement which highlighted the importance of assessing

depression routinely after ACS and should be considered as important as other traditional risk factors for poorer outcomes in patients with ACS (Lichtman *et al*., 2014). Accordingly, the American Academy of Family Physicians (AAFB) published a guideline on screening and treatment of depression after ACS. The AAFB recommended that clinicians should screen depression after ACS using a standardised screening tool. Although screening of depression is recommended after ACS, it should not be limited to hospitalisation and should be conducted during follow-up visits. According to AAFB, further assessments to confirm diagnosis of depression after discharge is a good practice point (Frost *et al*., 2019). This is consistent with another position statement from the National Heart Foundation of Australia which recommended screening hospitalised ACS patients for depression and a follow-up screening 2-3 months after the event and then on a yearly basis (Colquhoun *et al*., 2013). The following section examines the literature pertaining to the prevalence and incidence of depression in patients with ACS, and their predictors.

2.2 Prevalence and Predictors of Depression in Patients with ACS

2.2.1 Search strategy for Prevalence and Predictors of Depression

A systematic search of the literature was conducted to retrieve pertinent literature on prevalence and predictors of depression. Five electronic databases were employed, in addition to a manual search through google scholar. The databases included PubMed, Embase, CINAHL, MEDLINE, and PsycINFO. The researcher developed a search strategy based on three concepts: “Acute coronary syndrome” AND “depression” AND “prevalence or predictors”. To ensure a comprehensive search, both keywords and subject heading (MeSh) search were included. The search was limited to studies conducted in the last 10 years (2011-2021). A full search strategy is included in Appendix I. Cross-referencing was conducted by identifying relevant studies from the reference list of other full-text research studies and reviews.

Study Selection

Studies were included if they were (1) focused on prevalence or risk factors of depressive symptoms; (2) among ACS patients including MI or UA; (3) depression was measured using structured interview or standardized tools (4) published in English or Arabic languages. Studies were excluded if they were (1) cases studies or report; (2) lack of access to full text.

Search Results

Initially, out of 2511 records identified by the search, 1057 records were removed as duplicates and 1454 records were retained. After removing duplicates, 1400 records were excluded following title and abstract review as they were not related or did not evaluate the prevalence or predictors of depressive symptoms in patients with ACS. Fifty-four records were retrieved for full-text review while six additional records were identified from other sources. Accordingly, 60 studies were reviewed for full text, from which 38 were excluded for various reasons as detailed on Figure 1 below. Therefore, 22 studies were included in the current review (see Table 2).

Characteristics of Included Studies

From the 22 studies included in this review, 16 assessed depression using self-reported instruments, five studies used structured clinical interview and one study was based on hospital diagnosis. Of the five studies which used structured clinical interview, one study used the Diagnostic and Statistical Manual of Mental Disorders, fourth edition, text revision (DSMIV-TR) (Shafti, 2014), one study used the Mini International Neuropsychiatric Interview (MINI) to diagnose clinical depression and Hamilton Depression Rating Scale (HDRS) for severity of depressive symptoms (Kang *et al*., 2015); one study used Primary Care Evaluation of Mental Disorders (*PRIME-MD*) for depression diagnoses and Hospital Anxiety Depression Scale for assessing severity of depressive symptoms (Ossola *et al*., 2020). In addition, one study used International Classification of Diseases, 10th edition (ICD-10) for diagnosing depression and BDI for assessing severity of depressive symptoms (Makkar and Jiloha, 2019). Lastly one study used Structured Clinical Interview for the DSM-IV Axis I Disorders (SCID-I/P) (Figueiredo *et al*., 2017)

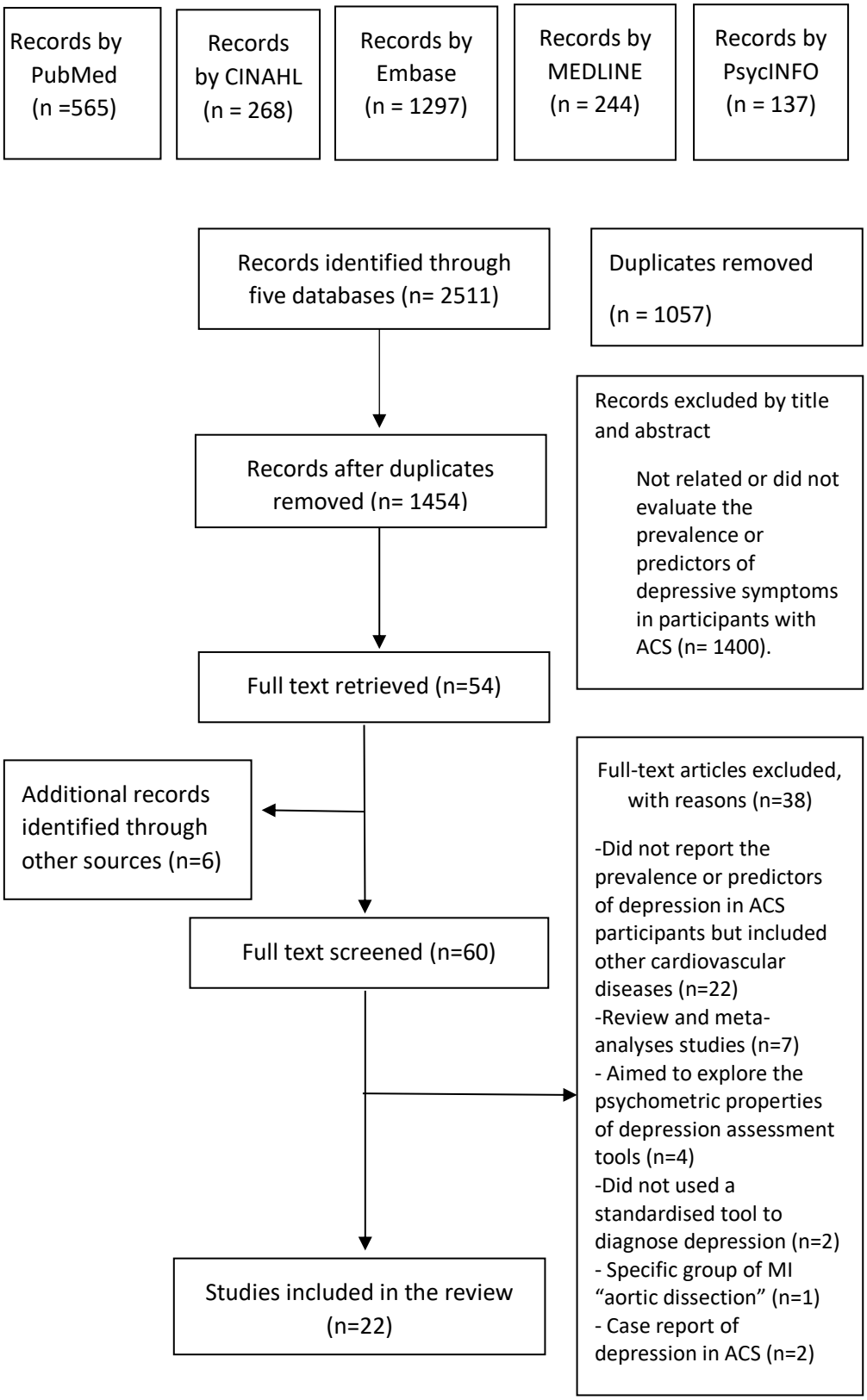
The most used self-reported instruments for assessing depressive symptoms were BDI. Five studies used BDI. Of these, two studies used BDI version II, and one study used BDI-Fast screen. Three studies used the Patient Health Questionnaire (PHQ-9), two studies used HADS, one study used PHQ-8, one study used the cardiac depression scale (CDS), one study used the Geriatric Depression Scale (GDS), one study used Depression Anxiety Stress Scale (DASS), one study used both the CDS and DASS, and one study used the HDRS (See Table 2).

Accordingly, this review identified eight different instruments used to assess depressive symptoms in patients with ACS. There was also variation in cut-off scores used to assess depressive symptoms among studies that used the same instrument. For instance, Maqsood *et al*. (2017) used HADS ≥ 11 to identify prevalence of significant depressive symptoms while another study (Murphy *et al*., 2020) used HADS ≥ 8. Similarly, Sanner *et al*. (2013) used BDI-II ≥ 14 to indicate significant depressive symptoms while George *et al*. (2021) used BDI-II>13. There was also variation in timing of depressive symptoms assessment.

For instance, some studies assessed depressive symptoms during hospitalisation (Doyle *et al*., 2011b; Allabadi *et al*., 2019; Hayajneh *et al*., 2021), some at 2 weeks after discharge (Kang *et al*., 2015; Makkar and Jiloha, 2019) and some others over longer period (Leong *et al*., 2021). These differences among studies may explain the wide variations in the prevalence rate of depression that has been reported in studies involving patients with ACS.

The review found that studies were conducted in 15 countries. Four studies were conducted in Pakistan, three in Malaysia, two in Ireland, two in Iran, one in China, one in Brazil, one in Italy, one in Poland, one in India, one in Korea, one in Palestine, one in Jordan, one in Australia, one in the United States, one in the United States, Australia and Spain. The review found that most of studies (N=21) were conducted with both men and women with ACS. One study was conducted among women only (Sanner *et al*., 2013). Among studies conducted on both men and women, nine studies (43%) enrolled men with more than 70% of the sample. However, one study had a higher proportion of women (67.1%) compared to men (32.9%) (Smolderen *et al*., 2015). Most of studies (n=20) were conducted among patients with ACS without focus on a specific age group. However, one study was conducted in only younger age patients (Median (IQR) =48 (44-52)), and one study was conducted among older adults with ACS (Mean (SD) = 70 (8.5).

Figure 1: Flow chart of studies selected for prevalence and predictors of depressive symptoms



2.2.2 Prevalence of Depression after ACS

Existing evidence shows that depression, including both elevated depressive symptoms and diagnosis of major depression, is prevalent among patients with ACS (Goudarzian *et al*., 2016, Allabadi *et al*., 2019; Hadi *et al*., 2020; Makkar and Jiloha, 2019)Studies which used clinical structured interview for identification of Depression after ACS found a prevalence ranging from 22.7% to 42.6%. For instance, a Brazilian study evaluated the prevalence of major depression for 356 ACS patients within 7 days of hospitalisation. Depression was assessed using Structured Clinical Interview of the DSM-IV Axis I Disorders and was present in 23% (n=82) of patients (Figueiredo *et al*., 2017). Similarly, a study was conducted in Korea (n=1152) and assessed clinical depression using the MINI at 2 weeks of ACS. The study reported that clinical depression was present in 38.7% of the sample (Kang *et al*., 2015).

Another study by Shafti (2014) included a structured clinical interview by a psychiatrist using DSMIV and assessed the presence of depressive symptoms in 101 patients with ACS (88.2%) and heart failure (11.8%). The study revealed that the prevalence of depressive disorder was 42.6% (n=43). Likewise, Makkar and Jiloha (2019) enrolled 75 patients with ACS and investigated the prevalence of depression 2-4 weeks after an ACS event. Depressive disorder was diagnosed by clinical interview using the International Classification of Diseases, 10th edition (ICD-10). BDI II was used to assess the severity of depressive symptoms. The study found that depression was present in 17 (22.7%) of patients (Makkar and Jiloha, 2019).

Several studies used self-reported instruments for identification of depression and found the prevalence of depressive symptoms ranged from 10.5% to 73.2%. For instance, a cross-sectional study in Pakistan included 153 patients with ACS and assessed depressive symptoms within one month of PCI (Mujtaba *et al*., 2020). Elevated depressive symptoms (BDI score >13) were found in 10.5% of the sample. Alvi and Ahmad (2016a) enrolled 180 patients hospitalised with ACS and assessed depressive symptoms using PHQ-9. Patients who had the PHQ-9 ≥10 were considered to have depression. The study found that 19.4% of patients reported high depressive symptoms. (Alvi and Ahmad,

2016b). A cross-sectional study by Maqsood *et al* (2017) enrolled 246 patients hospitalised with MI in Pakistan and assessed depressive symptoms using the depression subscale of HADS. A cut-off score of ≥11 was used to label depression. The prevalence of depression in the sample was 27.24%. Another cross-sectional study was conducted on 377 women hospitalised with ACS and assessed their depressive symptoms using BDI-II (Sanner *et al*., 2013). The BDI-II scores ≥ 14 were used as a cut-off score for elevated depressive symptoms. The study found that 31% (n=118) of the sample reported elevated depressive symptoms after ACS.

Furthermore, a Malaysian study on 95 patients with ACS, evaluated prevalence of depressive symptoms at baseline hospitalisation. PHQ-9 score ≥ 10 was used as a cut-off score for elevated depressive symptoms. Prevalence of depressive symptoms during hospitalisation was 46.3% (n=44)(Leong *et al*., 2021). Hadi *et al*. (2020) evaluated depressive symptoms using the Hamilton Depression Rating scale (HDRS) for 110 patients hospitalised with ACS in Pakistan. The study found that 69% of sample had elevated depressive symptoms. Of which, 18% (n=20), 15.5% (n=17) and 35.5% (n=39) had moderate, severe and very severe depressive symptoms, respectively (Hadi *et al*., 2020).

Similar findings of high level of depressive symptoms were found in a study conducted in Palestine which enrolled 1053 patients diagnosed with cardiac diseases including ACS and evaluated depressive symptoms using the Cardiac depression scale (Allabadi *et al*., 2019). The study found that 78.7% of patients reported elevated depressive symptoms. Regarding the severity of depressive symptoms, only 21.3% had no depressive symptoms while 25.2% and 53.5% of patients had mild to moderate, and severe to very severe depressive symptoms, respectively. Similarly, Goudarzian *et al*. (2016) enrolled 407 hospitalised patients with ACS in Iran and assessed depressive symptoms using the Cardiac depression Scale (CDS). The findings showed that 9.1% 17.7% and 73.2% of patients reported mild, moderate, and severe depressive symptoms, respectively.

There were also two recent meta-analyses and systematic reviews which addressed the prevalence of depressive symptoms in patients with ACS. Feng

and colleagues (2019) conducted a meta-analysis on 19 studies (n=12315) related to prevalence of depression after MI, and found that the pooled prevalence of depressive symptoms after MI was 28.7% (95% CI: 22.39–35.46%). The study reported that the prevalence of depressive symptoms in the reviewed studies ranged from 9.17% to 65.88% (Feng *et al*., 2019). Another meta- analysis reviewed 30 studies on risk factors for depression after ACS and reported that prevalence of depression in the reviewed studies ranged from 5% to 69.3% (Yuan *et al*., 2019). Finally, a systematic review on the prevalence of depression in patients with ACS identified seven studies with prevalence of depressive symptoms ranging from 20% to 35% (Khan *et al*., 2021). The previously mentioned systematic review and meta-analyses did not include all recent studies related to the prevalence and predictors of depressive symptoms in patients with ACS. Thus, the current review included all additional relevant studies that were conducted in the past ten years.

2.2.3 Prevalence of depressive symptoms after ACS in Jordan

Depressive symptoms among patients with ACS has been widely studied in western counties. However, few studies were found to evaluate depressive symptoms in patients with ACS in Jordan. Only three studies were found to address depressive symptoms following ACS in Jordan. The first study investigated the association between depressive symptoms and in-hospital complications (AbuRuz *et al*., 2018). The second study examined gender differences on this association (AbuRuz and Al-Dweik, 2018). The third study identified prevalence and predictors of depressive symptoms in older adults with ACS (60-98 years) (Hayajneh *et al*., 2021). The first study included 175 patients with MI and assessed depressive symptoms using BDI. Findings of the study showed that 30.3% (n=53) of patients had minimal depressive symptoms while 69.7% (n= 122) had depressive symptoms ranging from mild to severe (AbuRuz *et al*., 2018). The second study enrolled 230 patients with MI and assessed depressive symptoms using the depression subscale of HADS. However, this study did not provide information about the overall prevalence of depressive symptoms (AbuRuz and Al-Dweik, 2018). The third study was conducted on 300 older adults with ACS and assessed depressive symptoms

using the Geriatric Depression Scale (GDS). GDS score ≥ 7 indicated depression. The study found that the prevalence of depression in older age with ACS was 65.7% (Hayajneh *et al*., 2021)

Other studies which addressed depressive symptoms in the cohort in Jordan, were among patients with stable CHD (Ghannam *et al*., 2014; Al-Zaru *et al*., 2020; Rawashdeh *et al*., 2021). For instance, Rawashdeh *et al*. (2021) enrolled 335 patients with CHD after 10 days of PCI and assessed depressive symptoms using PHQ-9. The study found that high symptoms of depression (PHQ-9 score ≥ 10) were present in 34% (n=144) of patients. Regarding severity of depressive symptoms, about 20.9% (n=70) of patients had no depressive symptoms and 45.1% (n=151) had mild depressive symptoms. Moderate, moderately severe and severe depressive symptoms were present in 26.3% (n=88), 7.2% (n=24) and 0.6% (n=2) of patients, respectively.

Another study by Al-Zaru *et al*. (2020) used the Cardiac Depression Scale (CDS) to assess depressive symptoms in 174 patients with CHD. The findings showed that 53.4% (n=93) of patients had elevated depressive symptoms. Based on severity of depressive symptoms, 46.6% (n=81) of patients had no depression, 17.8% (n=31) had mild/moderate depression and 35.6% (n=62) had severe depressive symptoms. Ghannam *et al*. (2014) enrolled 164 patients diagnosed with CHD and assessed depressive symptoms using BDI. The study used 13 as a cut-off score to indicate depression. Findings showed that the mean score of depressive symptoms was 15.9 (10.6) with 50% of patients reporting symptoms higher than 15.

2.2.4 Prevalence of depressive symptoms across different time points

There were some studies which found similar prevalence rate of depressive symptoms at each assessment while some other studies did not. For instance, Mittag *et al*. (2016) assessed depressive symptoms over 12 months using Checklit-90-Revised at 3 time points: 1-3 weeks, 3 months and 12 months. The prevalence of depressive symptoms at baseline was 55%. Of these, 32% mild to moderate and 23% severe depressive symptoms. The study found that the prevalence rate of depressive symptoms was almost similar at all-time points. Likewise, a study by Kaptein *et al*. (2006) assessed depressive symptoms using

BDI at 4 time points. The prevalence of elevated depressive symptoms at baseline hospitalisation (22.7%), 2 months (23.8%), 6 months (25.5%) and 12 months (24.8%) were almost similar. Similar findings were reported by other studies (Lane *et al*., 2002; Schrader *et al*., 2004; Schrader *et al*., 2006; Martens *et al*., 2008)

In contrast, some studies found that the prevalence rate of depressive symptoms tended to decrease over time. For instance, a study was conducted in Australia and evaluated the prevalence of depressive symptoms over 12 months following a cardiac event (ACS, CABG, or/and PCI) (Murphy *et al*., 2020). Depressive symptoms were assessed for 911 patients during hospitalisation and at both early (2-4 months) and late periods (6-12 months) using the Hospital Anxiety Depression Scale. The prevalence of depressive symptoms was 22%, 17% and 15% at baseline, early and late phases, respectively (Murphy *et al*., 2020). Another study assessed depressive symptoms using PHQ-9 at both baseline and 3 months after ACS and found a prevalence of depressive symptoms (PHQ-9 ≥10) to be 20% and 11% at baseline and 3 months, respectively (Pérez *et al*., 2020).

In contrast, a study investigated depression in 79 patients with acute MI at five different time points including within 24 hours of PCI, prior to hospital discharge and then at 3, 6 and 12 months after discharge (Kala *et al*., 2016). The study found that the highest prevalence of depression was within 24 hours of PCI (21.5%), however, the prevalence of depression had significantly decreased prior to discharge (9.1%). In addition, the study found that prevalence of depressive symptoms after discharge tended to increase gradually over one year. The prevalence of depressive symptoms at 3, 6 and 12 months was 10.4%, 15.4% and 13.8% respectively (Kala *et al*., 2016).

To summarise, prior research has varied with regard to stability in prevalence rate across different points. Although some studies found a stable prevalence rate across time points, these studies have also reported fluctuations in depressive symptoms over time. Depressive symptoms are heterogenous. There is therefore a need to address interindividual differences in intraindividual changes in depressive symptoms. Studies using traditional

methods of analysing changes over time such as ANOVA are mainly looking at individuals within a time point, and this could mask fluctuations that occur in depressive symptoms. Instead, there is a need to look over time points within an individual in order to capture changes that occur in depressive symptoms over time. One of the aims of this study will be to assess the prevalence of in-hospital depression among patients who have experienced an ACS event in Jordan.

2.3 Risk factors for Depression after ACS

Numerous studies have identified several risk factors/predictors for depressive symptoms following ACS including sociodemographic, healthy/unhealthy behaviours, clinical and disease severity, and psychosocial factors.

2.3.1 Sociodemographic factors and unhealthy behaviours

Gender

Some studies identified that women who experience ACS were more likely to be depressed than men (Jankowska-Polańska *et al*., 2012; Kang *et al*., 2015; Alvi and Ahmad, 2016a; Figueiredo *et al*., 2017; Allabadi *et al*., 2019; Hadi *et al*., 2020; Wan Adnan *et al*., 2020; George *et al*., 2021; Leong *et al*., 2021). However, some studies found no significant association between gender and depression after ACS (Doyle *et al*., 2011b; Maqsood *et al*., 2017; Murphy *et al*., 2020; Mujtaba *et al*., 2020). Studies that evaluated gender differences in depression after ACS found a significant association between gender and depression. For instance, a cross-sectional study was conducted in Jordan by AbuRuz and Al-Dweik (2018) and evaluated the gender differences among 230 patients with MI in depressive symptoms and complications following MI. Depressive symptoms were assessed within 72 hours of hospitalisation using the depression subscale of HADS. The study found that depressive symptoms were more prevalent in women than in men and these symptoms in women were associated with 40% increased incidence of in-hospital complications compared to 30% for males ($p < .001$) (AbuRuz and Al-Dweik, 2018).

The variation in Recovery: Role of Gender on Outcomes of Young AMI Patients (VIRGO) study, enrolled 3572 younger age patients (18-55 years old) who were hospitalised with MI in the United States, Spain and Australia. The study evaluated gender differences in depressive symptoms following MI (Smolderen *et al*., 2015). The study used PHQ scores of ≥10 to categorise patients into depressed and non-depressed. Findings showed that 39% of females reported high depressive symptoms compared to 22% in males ($p<.0001$). The study also found that almost 48% of females reported a history of depression compared to 24% of males ($p<.0001$) (Smolderen *et al*., 2015).

Doyle and colleagues (2015) conducted a systematic review and meta-analysis to explore if sex differences affect depressive symptoms in patients with MI. Meta-analysis from the systematic review of 16 prospective studies of 10, 175 patients' diagnostic interviews or depressive symptoms questionnaires. This analysis showed that among the depressed individuals it was found that the prevalence of having depression in females (36%) was more likely than male (29%). Furthermore, this analysis reported that this gender differences in the prevalence of elevated depressive symptoms didn't vary with age, Body Mass Index (BMI), and smoking status (Doyle *et al*., 2015)

A more recent systematic review by Buckland *et al*. (2019) found that 5 out of 20 included studies assessed depression in both men and women and all reported higher depressive symptoms in women compared to men. The average prevalence of depressive symptoms for men was 23.46%, compared to 34.8% for women (Buckland *et al*., 2019). In addition, 8 out of 20 studies were conducted on women only. The average prevalence of depressive symptoms in women in these studies was 35.75% but tended to decrease to 27.8% and 22.7 in 3 weeks and 2 years after discharge, respectively.

Age

Evidence suggests that younger patients with ACS are more likely to be depressed than older patients (Sanner *et al*., 2013; Figueiredo *et al*., 2017; Murphy *et al*., 2020; George *et al*., 2021). However, some studies did not find significant association between age and depression after ACS (Maqsood *et al*., 2017; Allabadi *et al*., 2019; Hadi *et al*., 2020; Wan Adnan *et al*., 2020; Leong *et al*., 2021).

In contrast, two studies reported that being older was significantly associated with depression. The first study was conducted in Jordan on 300 older age adults with ACS (≥ 60 years old) and found that older age was a significant predictor of depressive symptoms after ACS (Hayajneh *et al*., 2021). The second study was conducted in Poland and evaluated gender differences in depressive symptoms after ACS. The study found being older (≥ 60 years old) was a significant predictor of depressive symptoms in women after ACS (Jankowska-Polańska *et al*., 2012).

Other demographics

Many studies have reported that a lower level of education to be associated with increased depressive symptoms after ACS (Smolderen *et al*., 2015; Allabadi *et al*., 2019; Hadi *et al*., 2020, Mujtaba *et al*., 2020; Kang *et al*., 2015). Being unmarried or widowed was also associated with increased depressive symptoms after ACS in many studies (Jankowska-Polańska *et al*., 2012; Murphy *et al*., 2020; Ossola *et al*., 2020; Hayajneh *et al*., 2021). Unemployment (Allabadi *et al*., 2019; Hayajneh *et al*., 2021), lack of health insurance (Smolderen *et al*., 2015), financial stress and low income (Jankowska-Polańska *et al*., 2012; Trick *et al*., 2019; Murphy *et al*., 2020) were also considered to be associated with depressive symptoms after ACS.

A large Danish cohort study (Joergensen *et al*., 2016) enrolled 87, 118 patients who experienced first ACS between 2001 and 2009 and evaluated depression in early (<30 days) and late period (31 days to 2 years) after ACS and its association with different risk factors. Depression was assessed based on coding rather than a standardised tool for depression. However, the overall prevalence of depression was found to be 32%. The study found that as well as female gender, being divorced or widowed, and alcohol use were associated with a greater risk of depression in both early and late stages. A recent meta-analysis of 7 studies by Khan *et al*., (2021) reviewed factors associated with depressive symptoms after ACS and reported that the prevalence of depression was higher in patients who were living alone, those with a low level of education and those who were single or widowed.

Unhealthy behaviours

When examining the association between unhealthy behaviours and depression after ACS, several factors were investigated including smoking, physical inactivity and obesity. For instance, smoking was consistently associated with increased depressive symptoms in patients with ACS (Smolderen *et al*., 2015; Allabadi *et al*., 2019; Murphy *et al*., 2020). Analysis from the National Health and Nutrition Examination Survey (NHANES) in the United States (n=1509) found that active smoking was significantly and independently associated with depressive symptoms in patients with MI. A

study of 388 patients with MI in Denmark found that depressed patients with MI were more likely to continue smoking at one year of MI (Hald *et al*., 2016). A systematic review included 28 studies related to smoking in patients with stable CHD and ACS between 1990 and 2013 found that depression was associated with persistent smoking in patients with ACS (Doyle *et al*., 2014).

Sedentary lifestyle and physical inactivity were found to be associated with depressive symptoms after ACS (Figueiredo *et al*., 2017; Allabadi *et al*., 2019). In addition, overweight or obese patients were more likely than those with normal weight to be depressed after ACS (Sanner *et al*., 2013; Murphy *et al*., 2020; Ossola *et al*., 2020). A retrospective study on 20,483 older adults with MI in the United States evaluated the impact of depression on health behaviours after MI. The study found that depressed patients were more likely than non-depressed to be overweight, physically inactive and smokers (Nicholson *et al*., 2020).

A meta-analysis by Yang *et al* (2019) reviewed 30 studies on risk factors associated with depression after ACS. The study evaluated several risk factors including demographics, unhealthy behaviours, comorbidities, ACS severity, and treatment-related factors (Yang *et al*., 2019). Many risk factors for depression were identified in this review including being a current smoker and being obese.

2.3.2 Clinical Factors

Several clinical factors were found related to depression after ACS. For instance, several studies found that having diabetes was associated with increased depressive symptoms (Doyle *et al*., 2011b; Jankowska-Polańska *et al*., 2012; Smolderen *et al*., 2015; Murphy *et al*., 2020). However, only one study found that non diabetic patients were more likely than diabetic patients to have depression after ACS (Mujtaba *et al*., 2020). Jankowska-Polańska *et al*. (2012) in their Polish study, found that having hypertension was also associated with depression after ACS.

A study in Jordan (n=300) found that having positive troponin at the emergency department was a predictor of depression in patients with ACS (Hayajneh *et al*., 2021). However, another study found no difference between STEMI, NSTEMI and unstable Angina in the level of depression in 402 patients with ACS in Iran (Goudarzian *et al*., 2016). A study of 176 patients with MI found that lower left ventricular ejection fraction (LVEF) was associated with increased risk of depression at 3 months following ACS. A systematic review by Doyle *et al.* (2015) suggests that although women were at higher risk of elevated depressive symptoms, men had worsening cardiac prognosis and left ventricular ejection fraction, than women (Doyle *et al*., 2015).

A recent cross-sectional study conducted in Jordan revealed a positive association between elevated depressive symptoms and length of stay at hospital for patients with ACS (Hayajneh *et al*., 2021). This was consistent with another study in MI patients which found that depressive symptoms after MI was associated with longer stay at hospital (AbuRuz *et al*., 2018). The systematic review and met analysis by Yan *et al* (2019) suggest that patients with diabetes, hypertension, dyslipidaemia, previous MI, Chronic Obstructive Pulmonary Disease (COPD), angina, and Congestive Heart Failure (CHF) were more likely to be depressed. In addition, patients with history of depression or family history of depression had a higher risk of depression after ACS than those without a personal history or family history of depression. Lastly, patients who used calcium channel blockers and antidepressant medications were at higher risk of developing depression (Yuan *et al*., 2019). Similar findings of an association between comorbidities and depression were also reported in the systematic reviews of Kanno and Fukahori, (2016), Joergensen *et al*., (2016) and Khan *et al* (2021).

2.3.3 Psychosocial Factors

Depression is not simply caused by one factor but is multifactorial. In addition to demographics and clinical factors, prior studies identified that psychosocial factors were found to be associated with depression after ACS. A literature review by Doi-Kanno and Fukahori (2016) reported 21 predictors for depressive symptoms in patients with MI post PCI. From these predictors, the authors

recommend more attention be given to psychosocial predictors such as Type-D personality social support and previous history of lifetime depression.

ACS is a life threatening event, and patients who experience ACS usually experience high levels of stress (Xu *et al*., 2017). Evidence suggests that patients with ACS use non-effective coping strategies to deal with stressful events and thus patients tend to experience emotional distress including depression (Bafghi *et al*., 2018). Coping strategies were found be another important factor associated with depression after ACS (Charizopoulou *et al*., 2015).

History of Lifetime Depression

Assessment of a history of depression could predict current elevated depressive symptoms in patients with ACS (Doi-Kanno and Fukahori, 2016). Figueiredo and colleagues' study revealed that Major Depressive Disorders was predicted by a history of MDD. Similarly, an Indian study by Makkar and Jiloha (2019) found a history of depression was significantly higher in patients with depression compared to those with no depression. When considering gender, females were 3.5 times more likely to be depressed than males, while the prediction model was stronger when for female and having a history of depression in ACS patients (Figueiredo *et al*., 2017).

These findings were consistent with findings from the VIRGO study, which found that women had x4 reports of history of depression compared to men. In addition, a history of depression was significantly associated with increased depression at 12 months after MI (Smolderen *et al*., 2015). A study by Murphy *et al*. (2020) found that a history of depression was associated with increased depressive symptoms at both the early and late period after ACS. Similar findings were reported by a Danish study which found that a history of depression was associated with depression at both early (<30 days) and late periods (31 days to 2 years) after ACS (Joergensen *et al*., 2016).

Type D Personality

Type D personality is a general tendency to experience two traits: Negative affective and social inhibition (Denollet, 2005; Denollet *et al*., 2006). The negative affectivity is a tendency to experience emotion while social inhibition is a tendency to inhibit expression of emotion during social interaction (Denollet, 2005). Type D personality presents in 1 of every 4 patients with CHD (Kupper and Denollet, 2018). Type D personality is considered one of the psychological risk factors that affects prognosis following ACS (Bhartiya, 2021). Prior research found Type D personality to be associated with increased mortality and cardiac events (Bunevicius *et al*., 2014; Khoshamouz *et al*., 2022; Raykh *et al*., 2022; Wang *et al*., 2021; Mesa-Vieira *et al*., 2021). Type D personality is common in patients with MI with prevalence rate ranging from 24% to 76% (De Fazio et al. 2012; Pillai *et al*., 2019; Manoj *et al*., 2020).

A body of evidence shows that patients with Type D personality are often more depressed than those with non-Type D (Al-Qezweny *et al*., 2016; Yamaguchi *et al*., 2020; Wang *et al*., 2022). A study by Al-Qezweny *et al*., 2016, enrolled 534 patients with PCI and evaluated association between type D personality at 6 months after PCI and depression at both baseline (6 months) and 10 year following PCI. The study found that about 42%, and 31% of patients with Type D personality were reported as depressed at 6 months and 10 years of PCI, respectively. However, 9% and 13% of non-Type D personality patients were depressed using similar time points. The study reported that Type D personality had 3.69 times the odds of depression at 10 years following PCI compared to non-Type D (Al-Qezweny *et al*., 2016).

Another study by Yamaguchi and colleagues (2020) included 89 patients with CHD and reported a high prevalence of depression (55.1%) and Type D personality (44.9%) in the sample. The study found that Type D personality and low use of 'planning coping' predicted higher depressive symptoms in the cohort (Yamaguchi *et al*., 2020). Similar findings of high prevalence of depression among patients with Type D personality were reported by a recent study by Wang *et al*. (2022). The study found that depressive symptoms were

prevalent in 35.5% of patients with Type D personality compared to 14.6% for non-Type D patients (p<.001) (Wang *et al*., 2022)

A study conducted by Doyle and colleagues (2011b) evaluated factors predicting depression after ACS including demographics, clinical and psychological vulnerabilities. The vulnerabilities included Type D personality, cognitive distortions, interpersonal life events, and reinforcing events. The study found that all vulnerabilities were significant predictors of depressive symptoms and explained almost 22% of the variance in depressive symptoms compared to 7% and 1% for clinical and demographic factors, respectively (Doyle *et al*., 2011b). A study by Wang *et al.* (2021) suggests that patients (n=437) with both Type D personality and Depression after MI were at higher risk of major cardiac event over 2 years of MI than either alone. Accordingly, Type D personality seems to have a prognostic role in patients with ACS and thus it is important to evaluate its association with depression in patients with ACS (Lambertus *et al*., 2018).

Perceived Social Support

Perceived social support is referred to as an "individual's beliefs about the availability of varied types of support from network associates" (Gottlieb and Bergen, 2010). The international literature suggests that low social support is associated with worsening physical and mental health especially during a stressful event (Thoits, 2011; Bucholz *et al*., 2014). However, high social support can work as a buffer of the negative effects of stress on patient health outcomes (Wiesmaierova *et al*., 2019).

A study involving 176 patients with MI from Iran, found that low perceived social support was negatively associated with depression after ACS and predicted 48% of depressive symptoms (Mohsenipouya *et al*., 2021). Similarly, a Jordanian study of 164 patients with CHD found that perceived social support was the most significant predictor of depression (Ghannam *et al*., 2014). Analysis from the VIRIGO study in the United States found that 21.2% of patients (n=3432) had low perceived social support, and those with low perceived social support were at higher risk of worsening QoL. (Bucholz *et al*.,

2014). These results are supported by a prospective cohort study of 169 patients with ACS (Trick *et al.,* 2019b), which identified predictors of depressive symptoms within the last 6 months of ACS. The study revealed that perceived social support was a significant predictor of depressive symptoms over 6 months.

A Recent Randomized Control Trial by Kim *et al*. (2019b), included 217 patients with ACS, to assess if low social support moderated effects on depressive symptoms and cardiac outcome in patients with ACS. This study revealed that low social support during the acute phase of ACS significantly predicted higher depressive symptoms and worsening cardiac outcomes in 24 weeks treatment after ACS. Consequently, it is important to assess social support among depressed ACS patients in order to improve treatment outcomes (Kim *et al*., 2019).

Coping Strategies

Coping strategies are efforts made to manage demands that are exceeding individuals' resources (Lazarus and Folkman, 1984). Coping strategies are commonly classified into problem-focused coping and emotion-focused coping (Lazarus and Folkman, 1984). According to Lazarus and Folkman (1984), emotion-focused coping strategies aim to reduce emotional responses caused by the stressor through seeking emotional support, wishful thinking, distancing, emphasizing the positive, self-blame, tension-reduction, and self-isolation. However, problem-focused coping strategies aim to tackle the situation through the use of active coping and problem-solving strategies (Lazarus and Folkman, 1984; Lazarus, 1986).

Carver *et al*. (1989) expanded the work of Lazarus and Folkman's classification by adding another group of strategies called dysfunctional "less effective" strategies. In addition, Carver *et al*. (1989) suggested that some emotion-focused coping strategies can be effective while some others tend to be less effective. Accordingly, coping strategies including acceptance, emotional social support, humour, positive reframing and turning into religion are more likely to be effective emotion-focused coping strategies while denial and substance use,

venting of emotions and behavioural disengagement tend to be less effective or dysfunctional coping strategies (Carver *et al*., 1989). Endler and Parker (1990) developed the Coping Inventory for Stressful Situations (CISS) and classified coping strategies into emotion-oriented, task-oriented and avoidance coping. The authors reported that task-oriented coping was associated with low anxiety and depression while emotion-oriented coping was associated with increased level of anxiety and depression.

Coping is a complex construct with more than four hundred classifications (Skinner *et al*., 2003). There is, however, a general consensus in that using problem-focused coping is an effective or adaptive coping strategy as it reduces stress levels and associated emotional responses such as anxiety and depression (Carver *et al*., 1989; Endler and Parker, 1990a). According to Endler and Parker (1990a), emotion-oriented coping and avoidance coping tend to be less adaptive and have been linked to psychological distress. However, Carver *et al*. (1989) suggested that there is some emotion-focused coping strategies that could be effective while some others could be less effective coping strategies. This inconsistency in coping typology may explain the differences reported in literature regarding the impact of different coping strategies on psychological distress.

Patients with ACS experience high levels of stress following the event and tend to use various effective and non-effective coping strategies simultaneously to deal with the event (Bafghi *et al*., 2018). A case control study (including 220 patients with MI and 220 patients without MI) found that 53.6 % of patients with MI used emotion-oriented strategy (Bafghi *et al*., 2018). Another study found that dysfunctional coping strategies including self-blame denial and venting were the most commonly used strategies among patients with ACS (Rahman, 2013).

A study by Charizopoulou *et al*., (2015), evaluated the coping strategies in 100 males after MI. They used COPE to assess depressive symptoms using Profile of Moods states (POMS) The study found that seeking emotional support was negatively associated with depression while turning to religion and behavioural disengagement were positively related to depression after MI (Charizopoulou

et al., 2015). A study by Bennett *et al.* (1999) involving 37 patients with MI found that high levels of depression after MI were predicted by using denial and behavioural disengagement (Bennett *et al*., 1999). These findings are consistent with Chiavarino *et al*. (2012) who reported that when an individual faces a situation with potential life-threatening consequences, such as ACS, emotion-focused coping such as acceptance can be more relevant than problem-focused strategies (Chiavarino *et al*., 2012).

To summarise, the international literature suggests that that there are many sociodemographic risk factors associated with depression following ACS including female gender, low education level, unmarried status, living alone and unemployed status. Other risk factors include those pertaining to unhealthy behaviours, (such as sedentary lifestyle, inactivity, obesity and cigarette smoking) and clinical factors, such as other co-morbidities . It is important that clinical staff be mindful of patients with these associated risk factors and that assessment of depression is performed early in treatment and/or at the point of hospital admission. Particular attention should be paid to those with a history of depression, those with Type D personality, with low perceived social support and those displaying less adaptive coping strategies. Further research is required to ascertain the association of these risk factors with trajectories of depressive symptoms.

Table 2: Studies related to prevalence of and risk factors for/outcomes of depression following ACS

Authors (year) Country	**Sample (N)**	**Age (SD)**	**Gender[a] (Male %)**	**Instrument & Cut-off score**	**Prevalence**	**Risk Factors**
Wang *et al.* (2022) China	3009 (ACS)	48.20 (6.69)	72.4%	Clinical Diagnosis in-hospital	33.5% for patients with Type D versus 14.6% for non-type D	Type D personality
George *et al*. (2021) Malaysia	115 (ACS)	21-60 years	81.7%	BDI II >13	48.7 % 10.4 severe 17.4 moderate 20.4 mild	Younger age, female gender, unmarried (divorced, separated or widow), history of depression or anxiety
Hayajneh *et al*. (2021) Jordan	300 (ACS)	70 (8.5) Older adults ≥ 60	70.7%	GDS≥ 7	65.7%	Being widow, illiterate, unemployed, living in urban area, and stay longer in-hospital were associated with depressive symptoms. Older age, frailty, high Troponin, and high HBA1C were independent predictors of depressive symptoms.

Authors (year) Country	**Sample (N)**	**Age (SD)**	**Gender[a] (Male %)**	**Instrument & Cut-off score**	**Prevalence**	**Risk Factors**
Leong *et al*. (2021) Malaysia	95 (ACS)	60 (11.3)	72.6%	PHQ-9≥ 10	Baseline: 46.3% (n=44) using No (n=11, 11.6%) Minimal (n=17, 17.9%) Mild (n=3, 24.2%, Moderate (n= 12, 13.7%) Moderately severe (n=12, 12.6%) Severe depression (n= 19, 20%)	Predictors at 3 months: The study found that female gender, diabetes mellitus and being on dialysis and moderate to severe depressive symptoms at baseline.
Mujtaba *et al*. (2020) Pakistan	153 (ACS)	52.2 (10.6)	77.1%	BDI>13	10.5%	Non-diabetic and non- educated patients were at higher risk of depression.
(Murphy *et al*., 2020) Australia	911 (ACS and	n=257, 27.1% age <55	66.4%	HADS-D> 8	Baseline 22% Early (2-4 months) 17% Late (6-12 months) 15%	- Financial stress, low socioeconomic status**,** younger age, smoking, poor self-rated health and history of depression were associated with increased risk of

Authors (year) Country	**Sample (N)**	**Age (SD)**	**Gender[a] (Male %)**	**Instrument & Cut-off score**	**Prevalence**	**Risk Factors**
	elective CABG)	(n=654, 71.8%, age≥55				depressive symptoms at both early and late periods after cardiac event. - Obesity and diabetes were associated with depressive symptoms at early and late period but they were less significant than other factors. - Living alone and unmarried were associated with increased risk of late depressive symptoms only
Wan Adnan *et al*. (2020) Malaysia	400 (ACS)	60.4 (11.3)	Not reported	DASS-21≥ 10	Not reported	Female gender and having ischemic heart disease
Hadi *et al*. (2020) Pakistan	110 (ACS) 3-5 days	20-30 (1.8%) 31-40 (10.9%)	68.2%	HDRS <17 (mild) 18-24 (mild to moderate)	69% No (n=19, 17.4%) Mild (n=15, 13.6%) Moderate (n= 20, 18%)	Female and uneducated

Authors (year) Country	**Sample (N)**	**Age (SD)**	**Gender[a] (Male %)**	**Instrument & Cut-off score**	**Prevalence**	**Risk Factors**
		41-50 (24.5%) 51-60 (36.4%) 61-70 (12.7%) ≥70 (13.6%)		25-30 (moderate to severe)	Severe depression (n= 17, 15.5%) Very severe depression (n=39, 35.5%)	
Ossola *et al*. (2020) Italy	262 (ACS)	60.9 (11.1)	NA	- PRIME-MD - HADS to rate severity of symptoms	21.4%	Being widowed and having narcissistic personality trait.
Trick *et al*. (2019) Ireland	169 (ACS)	68 (16)	78%	PHQ-8 ≥ 10	14.4%	Younger age, living alone, smokers and lower socio-economic status. Had history of depression and lower social support.

Authors (year) Country	**Sample (N)**	**Age (SD)**	**Gender[a] (Male %)**	**Instrument & Cut-off score**	**Prevalence**	**Risk Factors**
Allabadi *et al*. (2019) Palestine	1053 (cardiac diseases including ACS	58.9 ± 10.1	73.4%	CDS >90 DASS-D ≥ 10	CDS = 78.7% - No symptoms (21.3%) - Mild to moderate (25.2%) - Severe to very severe (53.5%) DASS-D = 52.9% - No symptoms (47.1%) - Mild to moderate (33.4%) - Severe to very severe (19.5%)	CDS: Female and less educated Psychosocial: Low PCS and MCS scores, lower resilience, lower perceived social support, low self-esteem, and having symptoms of PTSD Health behaviours: Current smokers and being physically inactive Others: Being unemployed, and longer cardiac disease duration.

Authors (year) Country	**Sample (N)**	**Age (SD)**	**Gender[a] (Male %)**	**Instrument & Cut-off score**	**Prevalence**	**Risk Factors**
Makkar and Jiloha (2019) Delhi, India	75 (ACS)	49 (9)	84%	ICD-10 BDI-II to rate severity of symptoms	22.7%	History of current substance use, and history of past depressive episodes were significantly higher in depressed patients.
Figueiredo *et al*. (2017) Brazil	356 (ACS)	60 (11.42)	64.3%	SCID-I/P, version 2.0	23%	MDD history, female gender, sedentary lifestyle, and age ≤ 60 years
Alvi and Ahmad (2016b) Pakistan	188 (ACS)	54 (14)	67.8%	PHQ-9≥ 10	19.4%	Females had higher depressive than males
Goudarzian *et al*. (2016) Iran	402 (ACS)	63.72 (16.37)	55%	CDS used as continuous score	Mean score = 109.00 ± 16.49 Mild (n=37, 9.1%) Moderate (n=72, 17.7%) Severe (n=298, 73.2%)	No difference between UA, STEMI and NSTEMI

Authors (year) Country	**Sample (N)**	**Age (SD)**	**Gender[a] (Male %)**	**Instrument & Cut-off score**	**Prevalence**	**Risk Factors**
Maqsood *et al*. (2017) Pakistan	246 (MI)	56 +5.2	52.9%	HADS≥11	27.2%	Age and gender were not associated with depression
Kang *et al*. (2015) Korea	1152 (ACS)	38.7	NA	- MINI - HDRS to rate severity of symptoms	38.7%	Female gender, lower education Previous ACS, and high Heart rate
Smolderen *et al*. (2015) The United States, Australia and Spain	N=3572 (MI)	Median (IQR) 48 (44-52)	32.9%	PHQ-9≥ 10	39% in females 22% in males	Depressive symptoms were significantly associated low level of education, being uninsured, being smoker and having diabetes.
(Shafti, 2014) Iran	N=101 (ACS)	53 (7,4)	50.5%	Structured interview DSMIV-TR	42.6%	Female gender

Authors (year) Country	Sample (N)	Age (SD)	Gender[a] (Male %)	Instrument & Cut-off score	Prevalence	Risk Factors
Sanner *et al*. (2013) The United States	377 (ACS)	64 (13)	Females Only	BDI-II≥ 14	31%	Younger age patients and those who had higher BMI and previous history of CHD reported significantly higher depressive symptoms than other patients
Jankowska-Polańska *et al*. (2012) Poland	140 (ACS)	NA	50%	BDI ≥10	NA	Women: Older age>60 years, diabetes and arterial hypertension Men: Widower, having diabetes, and arterial hypertension.
(Doyle *et al*. (2011b) Ireland	N=408 (ACS)	61.7 (11)	86%	BDI-FS>3	BDI-FS	Psychological vulnerabilities (Type D personality, cognitive distortions, interpersonal events, and reinforcing events) Diabetes, younger age smoker

Legend : MADRS: Montgomery Asberg Depression Rating Scale; PRIM-MD Primary Care Evaluation of Mental Disorder; HADS : Hospital anxiety depression scale; BDI: Beck depression inventory ; PHQ-9 : Patient Health Questionnaire-9 ; SCID-I/P Structured Clinical Interview for the DSM-IV Axis I Disorders (Patient edition); CDS: Cardiac depression scale ; DAAS : Depression anxiety stress scale ; HDRS: Hamilton Depression rating scale ; BDI-SF , Beck depression inventory- fast screen; GDS: Geriatric Depression Scale; MINI : Mini International Neuropsychiatric Interview. a. The remaining percentage represents females.

2.4 Incident Depression in Patients with ACS

Patients who experience an ACS event have frequently reported incidence of depression during the first year of ACS (Halima *et al*., 2020). De Jong *et al.* (2006) suggest that Incident depression after MI is a depressive episode in patients who had not been previously depressed before the MI presentation. According to Indrayan (2013), incidence can be estimated by calculating the number of new cases of disease at a specific period of time divided by the population at risk for the disease during that period. A body of evidence suggests that incident depression is associated with increased mortality and morbidity after ACS (Ossola *et al*., 2018; Parker *et al*., 2020). However, the international literature shows variation among studies that evaluated the incidence of depression, with the reported incidence of depression ranging from 8% to 31% during the first year of ACS (Halima *et al*., 2020; Kang *et al*., 2018; Strik *et al*., 2004).

A study by Parker *et al*. (2008) assessed depression and history of depression for 489 patients following ACS using the Composite International Diagnostic Interview (CIDI). Depression was assessed at 1 month after MI using the DSMIV checklist for assessing depressive symptoms. The finding showed that 38.2% of patients reported a history of a previous episode of depression. A total of 25 patients developed post-ACS incident depression at 1 month (n=302), indicating a 1-month incidence of 8.3%. Using nearly the same timing period, a recent study by Halima *et al*. (2020) evaluated incidence of depression after ACS. Depression was assessed using HADS at hospital and on average 42 ± 8 days after discharge. The incidence of depression at baseline and follow-up was 19.1% and 6.2%, respectively. The cumulative incidence of depression was 25.3% (Halima *et al*., 2020).

A study was conducted by de Jonge *et al*. (2006) to evaluate incident and non-incident depression in 468 patients during the 12 months following MI. The findings showed that only incident depression was associated with increased risk of recurrent cardiac events (HR=1.65) in the 2.5 years after MI. Similarly, Dickens *et al*. (2008) evaluated 7 years mortality after MI in 3 groups of patients (n=440): depression-before MI, no depression (during 12-follow-up), and new-

onset depression. The study found that patients who developed new-onset depression in the 12 months after MI were 2 times more likely to die in the following 7 years. Similarly, a study was conducted on 489 patients with ACS to evaluate the relationship between depression and 1-year mortality (Parker *et al*., 2008). The findings indicated that only depression that occurred after ACS (incident) was strongly associated with increased mortality during the first year of ACS. The 489 patients were followed up for 5 years to assess the impact of depression on recurrent admissions and mortality (Parker *et al*., 2011). The study found only post-ACS depression was associated with poor outcomes over 5 years (Parker *et al*., 2011).

Similarly, a study by Ossola *et al.* (2018) enrolled 266 patients with no history of depression and evaluated the impact of new onset depression over 2 years of ACS on recurrent cardiac events. The study found that new onset depression was associated with X3 the risk of recurrent cardiac events over 2 years of ACS (Ossola *et al*., 2018). Recently, a study by Parker *et al*. (2020) has reviewed evidence related to depression in patients with ACS and found that incident depression appears to have a greater negative impact on ACS outcomes than non-incident depression.

A study by Kang *et al.* (2015) assessed 1152 patients with ACS for baseline depression after ACS using the Mini International Neuropsychiatric Interview (MINI). A total of 828 were assessed for depression using MINI 12 months later. Incident depression was defined as the absence of depression at baseline but present at 12 months. Depression at baseline was reported by 446 patients (38.7%). At one year follow-up, incident depression was reported in 66 out of 504 patients who had no depression at baseline. Thus, the one-year incidence of depression after ACS was 13.1%. A study by Dickens *et al*. (2008) assessed for depression and history of depression in 588 patients during their hospitalisation for MI. Dickens *et al.* (2008) used the schedule for clinical assessment in neuropsychiatry (SCAN), which is a structured interview based on ICD-10 criteria for depressive disorder. At 12 months, 440 patients were assessed for depression using HADS. Of the 440 patients, 96 patients had pre-

MI depression and 71 patients had incident depression. The one-year incidence of depression following MI was 20.6%.

Strik *et al*. (2004) evaluated one-year cumulative incidence of depression after first MI. A total of 206 patients were interviewed one month after MI using the Structured Clinical Interview of DSMIV and then depression was assessed using Beck Depression Inventory (BDI) and Hospital Anxiety Depression Scale (HADS) at 3, 6,9 and 12 months after MI. The findings showed that the one-year incidence of depression was 31% in patients with first MI. Ossola *et al*. (2015) assessed incident depression for 304 patients with first ACS. Patients were interviewed by a psychiatrist at baseline hospitalisation to evaluate the history of previous episodes of depression. After that, incident depression was assessed using Primary care evaluation for mental disorder (PRIME-MD) and HADS at 1, 2, 3, 6, and 12 months later. Patients were considered depressed if they fulfilled the criteria for major or minor depressive disorder. During the follow-up period, 13.1% of patients developed incident minor (8.2%) and major (4.9%) depression during the first year of ACS.

The studies above show that the incidence of depression after ACS varies largely between studies. This might be due to the differences in timing and method of assessing depression. Two studies estimated incidence of depression at one month after ACS while four studies were at 12 months after ACS. While 3 studies evaluated incidence at specific time points such as one month (Parker *et al*., 2008), 12 months (Dickens *et al*., 2008; Kang *et al*., 2015), other studies estimated cumulative incidence at more than one point (Halima *et al*., 2020; Ossola *et al*., 2015; Strik *et al*., 2004). Two studies did not measure a history of depression using a standardised method. The first study evaluated the history of depression using a general question (Halima *et al*., 2020). The second study did not explain how they evaluated the history of depression, however, authors in the second study defined incident depression as absence of depression at baseline but present at 12 months (Kang *et al*., 2015). Regarding the method of assessment, one study assessed depression using structured interviews at both baseline and follow-up (Kang *et al*., 2015). One study assessed depression using the self-reported instrument at both baseline

and follow-up (Halima *et al*., 2020). Other studies evaluated depression using structured interviews at baseline and self-reported instruments at follow-up (Dickens *et al*., 2008; Parker *et al*., 2008; Strik *et al*., 2004; Ossola *et al*., 2015).

To summarise, incident depression occurs in many patients after ACS and appears to be a distinct subtype of depression that has some prognostic features. Therefore, estimating the incidence of depression is necessary to give a better understanding of the extent of this distinctive subtype of depression in the ACS cohort. Although, the evidence pertaining to incident depression in ACS is growing, the majority of these studies was conducted in western countries. To our knowledge, no previous studies estimated the incidence rate of depression after ACS in Jordan. Therefore, one of the aims of this study will be to assess the incidence of depression in Jordanian patients over a period of six-months post ACS.

2.5 Trajectories of depressive symptoms after ACS

The international literature suggests that depressive symptoms can evolve over time in relation to type, intensity, frequency and length. The body of knowledge pertaining to these 'trajectories' of depressive symptoms is still emerging with many studies beginning to identify different numbers of trajectory groups and their associated socio-demographic, psychological and clinical factors. A systematic search of the literature pertaining to depressive symptom trajectories is outlined below followed by a discussion of retrieved studies.

2.5.1 Search strategy related to Trajectories of Depressive symptoms.

A systematic search of literature was conducted to retrieve literature pertaining to trajectories of depression in relation to ACS. Five databases were involved in retrieving literature for this search: PubMed, Medical Literature Analysis and Retrieval System Online (MEDLINE), Psychological Information (PsycINFO), Cumulative Index of Nursing and Allied Health Literature (CINAHL), and Excerpta Medica Database (EMBASE). These databases contain widespread literature from Medicine, Nursing, Allied health, and Psychology fields. Addressing all related literature in a systematic approach without bias is

essential to achieving a high-quality literature review (Polit & Beck 2010, p. 171).

To ensure effectiveness of search across these databases, the author addressed the following steps. (1) The search began using the Subject Headings (SH) for each concept in each database. (2) Suggested terms from using the SH were added to build up the Keywords. (3) The keywords for each concept were used consistently across all databases and combined by (OR) with the results of SH search in each database (See Appendix II). Three concepts were addressed in this search: The first concept was related to Acute Coronary Syndrome / Myocardial infarction/ Unstable Angina. The second was "Depression", while the last was related to "Trajectories". The search included Mesh terms in PubMed, CINAHL and MEDLINE, Emtree term in Embase and thesaurus terms in PsycINFO. To insure up to date literature, the search was restricted to full-text publications between 1990 and 2021 in both English and Arabic languages. The search was conducted with assistance from a librarian specialised in the field of Nursing and Midwifery. After completing the search, all references were exported into EndNote x9 reference manager (EndNote, 2018).

Inclusion Criteria

Studies were included in the literature review if they were conducted among ACS patients and fulfilled the following inclusion criteria (a) Published between 1999 and 2021 (b) Identified trajectories of "depressive symptoms" as variable of interest, (c) applied GBTM or clinical cut-off method to find out trajectories of depressive symptoms, (d) identified the baseline predictors or/and the outcomes that were associated with these trajectories, (e) had at least a sample size of 100 patients. The search was limited to full-text peer reviewed studies. Hence, abstracts, letters, reports and editorials were excluded. Only studies in English and Arabic languages were included in this analysis.

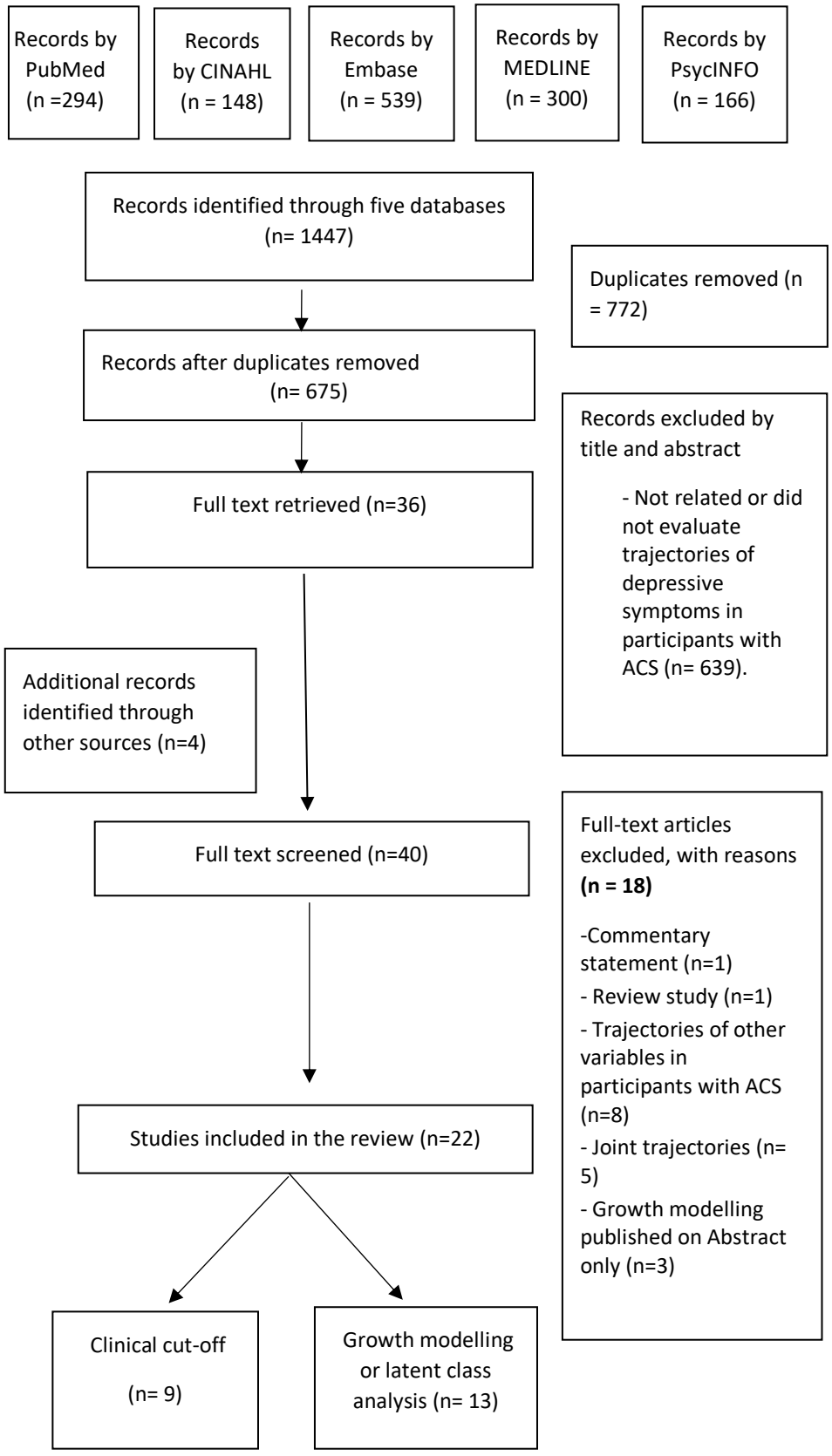
Selection and extraction

A total of 1147 studies were identified through the search of the five databases. Of these, 772 studies were removed because of duplicates. Of the remaining

(n=675) studies, 639 were excluded by titles and abstracts as they were not related or did not evaluate trajectories in depressive symptoms in patients with ACS. Thus, a total of 36 studies were eligible for full-text review. The researcher included another four studies for full-text review based on manual search in Google scholar. Of 41 studies reviewed in full text, 18 studies were excluded for the following reasons: one commentary statement, one review study linking arrhythmia to trajectories of depression after ACS (Sadlonova and Meyer, 2019), eight studies addressed trajectories of other variables in patients with ACS including such as trajectories of ACS symptoms (Knight *et al*., 2016, Tsai *et al*., 2019), perceived social support (Wang *et al*., 2019), Quality of life (Nobel *et al*., 2015; Nobel, 2017; Munyombwe *et al*., 2020), anxiety (Pedersen *et al*., 2008; Versteeg *et al*., 2015).

Five studies were excluded as they assessed Joint Trajectories of depression with other variables, for instance, Joint trajectories of anxiety and depression after ACS (Tisminetzky *et al*., 2011), Joint trajectories of anxiety, depression and functional impairment (Tisminetzky *et al*., 2012) , Joint trajectories of anxiety, depression, neuroticism and phobia. Two studies were excluded as they assessed trajectories of distress emotional distress (anxiety and depression) using the total score of Hospital Anxiety Depression Scale (HADS) (Palacios *et al*., 2018; Chilcot *et al*., 2020). Three studies employed growth mixture modelling for depressive symptoms in ACS patients were excluded as these studies were published in Abstract only (Goble *et al*., 2006; Greco *et al*., 2016; Smith *et al*., 2019). The researcher tried to contact the authors of these studies by email to obtain the full-texts. Unfortunately, he did not received feedback from the authors of one study and the authors of other two studies confirmed that these studies were published on abstract only. Therefore, 22 studies were included in this review. Of these, 13 studies used growth modelling or latent class analysis to identify trajectories of depressive symptoms (Table 3) and 9 studies analysed trajectories of depressive symptoms using clinical cut-off score (Table 4).

Figure 2: Flow chart for studies selection for Trajectories of depressive symptoms



Study characteristics

Among studies using growth modelling, three studies were conducted in Australia, three in Netherlands, two in the United States, two in Ireland, two in Germany, and one in Poland. The sample size of the reviewed studies ranged from 160 to 2147 patients. Of the 13 studies, 10 studies (76.9%) had samples size of less than 500; 2 studies had a sample size of less than 2000 patients and one study had a sample size of more than 2000 patients. Regarding studies with a large sample size, 2 studies were analysed from Health and Retirement Study (HRS) study (1994-2008) (Galatzer-Levy and Bonanno, 2014) and (2006-2016) (Kong *et al*., 2022) in the United States. The third large study was an analysis from a study (1990-2000) in Germany (Peter *et al*., 2020). Of the remaining studies, three studies conducted in the Netherlands were analysis from Depression after MI (DepreMI) study (Kaptein *et al*., 2006; Martens *et al*., 2008; Roest *et al*., 2016). Two studies were conducted in Ireland one identified trajectories of depression (Doyle *et al*., 2011a) and the second extended work done by Doyle and colleagues by longitudinal modelling of predictors, trajectories of depression and outcomes (Keegan *et al*., 2016).

Studies included in this review were related to ACS or addressed cardiac conditions including ACS. Most of the included studies (n=12) were conducted on both male and females. One study included females only (Murphy *et al*., 2008b). Of the 12 studies that included both genders, 10 studies showed a higher proportion of males compared to females. However, one study showed almost equal proportions (Galatzer-Levy and Bonanno, 2014) and one study had higher proportion of females compared to males (Kong *et al*., 2022). Regarding instruments used for depression assessment, three different instruments were used: BDI, HADS, and Centre for Epidemiologic Studies Depression (CESD). BDI and HADS were the most commonly used instruments. Five studies used BDI, five studies used depression subscale of HADS, one study used both BDI and HADS, and two studies used CESD. Regarding number of depression assessments, six studies evaluated depression at 4 different times, three studies at 3 times, two studies at 6 times, one study at 5 times and one study at 2 times. Regarding follow-up period, 2 studies investigated trajectories

of depressive symptoms over 6 months, 6 studies over 12 months, 2 studies over 6 years, 2 studies over 10 years, and one study over 15 years.

The review also identified nine studies that used a clinical cut-off score rather than GBTM to identify trajectories of depression. Three of these studies were conducted in the United States, two in Australia, one in Canada, one in England, one in Germany, and study in Korea. Of the nine studies reviewed, four were carried out on patients with ACS, two on patients with MI and three on patients who experienced cardiac events including ACS. The sample size of the reviewed studies ranged from 172 to 1873 patients. Five of included studies (50%) had samples of less than 500; three studies had a sample size of less than 1000 but more than 500 patients; while two studies had a sample size of more than 1000 patients. Regarding studies with a large sample size, one study utilised data from Prospective Registry Evaluating outcomes after Myocardial Infarction: Events and Recovery [PREMIER] database, which was conducted in the United States (Parashar *et al*., 2006). The second study used data from the Korean DEPression in ACS registry (KDEPACS) (Kang *et al*., 2015).

All included studies were conducted in both male and female genders. However, the proportion of males in all included studies was higher than females. Almost 55.6% of studies (n=5) were conducted over 12 months follow-up, three studies over three months and one study over one month. Regarding assessment of depression, 66.7% of studies assessed depression at two time points (n=6) while 33.3% (n=4) assessed depression at three time points. BDI was the most commonly used instrument for assessing depression (n=4). Other instruments included CESD (n=2), SCL-90-R Symptom Checklist-90-Revised (n=1) and PHQ-9 (n=1). In addition, one study used the MINI to diagnose major and minor depression after ACS. Regarding the statistical methods used to analyse trajectories of depressive symptoms, four studies used LCA, and six studies used GMM. One study used parallel process latent class growth analysis and another used latent class mixture time to event modelling.

2.5.2 Patterns of Trajectories of Depressive Symptoms

The international literature suggests that variations exist regarding the number of identified trajectory classes and the pattern of depressive symptoms trajectories. Studies included in this review identified a range from two to five depressive symptoms trajectory classes. Most studies identified three (n=7) or four trajectory classes (n=4). The variations in the patterns were found in terms of stability and severity of depressive symptoms. Some studies found that stable trajectories differed in the level of severity (no, mild, moderate, severe) while other studies did not. Among studies that identified non-stable trajectories, some reported linear trajectories (increasing or decreasing) and others found quadratic or cubic trajectories (upturn or downturn).

For example, three studies identified 3-4 stable trajectories that differ in severity (Martens *et al*., 2008, Doyle *et al*., 2011a, Keegan *et al*., 2016). Martens *et al*. (2008) employed Latent Class Analysis (LCA) to identify 12-month trajectories of depressive symptoms following MI. A total of 287 Dutch patients completed BDI at baseline hospitalisation, 2 and 12 months after MI. The study found 4 stable trajectories of depressive symptoms varied in their severity including non-depressed (40%), mildly depressed (42%), moderately (14%) and severely depressed (4%). Similarly, Doyle and colleagues (2011a) enrolled 375 patients with ACS in Ireland and evaluated trajectories of depressive symptoms over 12 months. Patients completed both BDI and HADS-D at baseline hospitalisation and at 3, 6 and 12 months later. Using LCA, three stable trajectories were identified including: Never depressed (48%, n=180), sub-threshold (37%, n=138) and persistent trajectory (15%, n=57). This classification was found to be stable after including both psychological vulnerability (predictors) and distal outcomes (mortality and morbidity) in another Irish study by Keegan *et al*. (2016).

Alternatively, some studies identified trajectories of depressive symptoms with a linear trend. For instance, Depression after MI (DpreMI) study enrolled 475 patients who experienced MI in the Netherlands and assessed depressive symptoms using BDI at four times points: in-hospital, 3, 6 and 12 months after

MI. The study used Latent Class Analysis to identify trajectories of depressive symptoms. The study found that prevalence of depressive symptoms tended to be stable over time. However, its trajectories did not. A considerable fluctuation in depressive symptoms were found over 12 months of MI. The prevalence of depressive symptoms at baseline, 3, 6 and 12 months were 22.7%, 23.8%, 25.5, and 24.8%, respectively. However, the study identified five trajectory classes: no depressive symptoms (56.4%), mild depressive symptoms (25.7%), moderate but increasing depressive symptoms (9.3%), significant but decreasing (4.6%), and significant but increasing (4.0%).

Murphy *et al*. (2014a) employed Growth Mixture Modelling (GMM) to identify trajectories of depressive symptoms over 6 months following acute cardiac events in Australia (Murphy *et al*., 2014a). The study enrolled 160 patients with ACS including those who had undergone PCI or CAGB. Depressive symptoms were evaluated using HADS at baseline, 2 months and 6 months after discharge. The study found three trajectories of depressive symptoms: resolving (17%, n=27) worsening (29%, n=47) and no depressive symptoms (54%, n=86) (Murphy *et al*., 2014a). Similar findings of unstable (linear) trajectories of depressive symptoms were found in a German study with longer follow-up duration (6 years). Depressive symptoms were measured at two times: baseline hospitalisation and 6 years. The study used LCA to identify distinct trajectory classes of depressive symptoms among 679 cardiac patients including those with ACS. Depressive symptoms were assessed at both baseline and 6 years (2 times). Four latent classes were identified including stable low (60%, n=387), low increase (25.8%. n= 166), decrease (7.3% n=47) and high increase (6.9%, n=45).

Another study by Peter *et al* (2020), enrolled 1109 patients with CHD who participated in cardiac rehabilitation program between 1999 and 2000 in Germany and evaluated trajectories of depressive symptoms over 15 years. The baseline depressive symptoms were assessed during hospitalisation and the follow-up assessments were conducted via mailed questionnaires including HADS at 1, 3, 6-, 8-, 13- and 15-years follow-up. Trajectories of depressive symptoms were identified using joint latent class mixture time-to-event model.

The model identified four distinct trajectory classes including low-stable (69.6%), moderate stable (23.8%), increasing (3.3%), and high-stable (3.3%).

Two studies were conducted over a longer period and assessed trajectories of depressive symptoms before the onset of MI and then at different times after MI. Data used in these studies were from Health and retirement study in the United States. One study that utilised data from health and retirement study (2006-2017) evaluated gender-based trajectories of depressive symptoms following heart disease including ACS (Kong *et al*., 2022). The study used data from 1787 older adults (>50 years old) who reported no heart disease at baseline and then developed heart disease during the 6 times follow-up. Depressive symptoms were assessed at 6 time points, one before the onset of heart disease (2006-2007) and then, every two years for 10 years (5 times). Patients were included if they have at least 3 data points including (1) depression assessment before heart disease, (2) depression assessment at the onset of heart disease and (3) depression assessment after having heart disease.

Depressive symptoms were assessed using CES-D scale and trajectories of depressive symptoms were identified using GMM. The study identified three trajectories of depressive symptoms for both males and females. The females had three stable trajectories over time including persistent minimal depression (60.2%), moderate depression “sub-threshold” (29.7%) and chronic depression (10%). However, trajectories of depressive symptoms for males (n= 740) included persistent minimal depression (68.7%), moderate depression “sub-threshold” (18%) and emerging/increasing depression (13%). The study did not report quadratic changes over time in both males and females (Kong *et al*., 2022).

The second study utilised data from the Health and Retirement study (1994-2008) and enrolled 2147 older adults to identify trajectories of depressive symptoms over 10 years, of which 6 years were before they experienced the first MI and four years after MI (Galatzer-Levy and Bonanno, 2014). Depressive symptoms were assessed at five time points: Three times before MI and two

times after MI. Individuals were enrolled in the analysis if they had a minimum of three assessments of depressive symptoms including one assessment before having MI. Depressive symptoms were assessed using Centre for Epidemiologic Studies Depression (CES-D) scale and trajectories of depressive symptoms were identified using GMM. The findings reported four trajectories of depressive symptoms: Resilient (68.3%), chronic (14%), emergent (10.9%) and improved (6.8%).

Unlike earlier studies which reported some linear trajectories over time, this study identified quadratic changes in some classes. Regarding the pattern of the four trajectories, patients in the resilient group tended to have stable low trajectories from before MI and thus had no linear or quadratic changes after MI. In the chronic trajectory group, patients had high depressive symptoms before MI which persisted after MI. This class had also non-significant linear or quadratic change. In the emergent trajectory group, patients had low depressive symptoms before MI but increased after MI and then had some recovery (significant linear and quadratic change). Lastly, in the improved group, patients had low depressive symptoms before MI that increased over 6 years and then rapidly decreased after MI. This class also had significant linear and quadratic changes (Galatzer-Levy and Bonanno, 2014).

Similarly, another longitudinal study evaluated trajectories of depressive symptoms over 6 years following MI (Kroemeke, 2016). Depressive symptoms were assessed in 200 polish MI patients using Beck Depression Inventory (BDI) at four time points: hospitalisation, one month, 6 months and 6 years following MI. The study employed growth mixture modelling and identified three trajectories of depressive symptoms: rising (n=121, 55.7%), chronic (n= 49, 29.1%) and low (n=30, 15.2%). Findings showed that rising and chronic trajectories of depressive symptoms had a quadratic trend while low depressive symptom trajectories had a linear trend. The study found that almost half of the sample fell under a U shape trend (Rising trajectory). Patients in that class demonstrated moderate depressive symptoms at baseline and one month that decreased at 6 months and then increased at 6 years (Kroemeke, 2016). In chronic depressive symptoms trajectory, patients had high depressive

symptoms at baseline and one month, then increased at 6 months and slight decrease at 6 years. Trajectory of low depressive symptoms initiated with low depressive symptoms at both baseline and one month after AMI and then further decreased at 6 months and then stabilised at 6 years.

There were two studies which conducted shorter follow-up periods (6 months and 12 months) and reported non-linear trajectories of depressive symptoms. For example, a study by Murphy *et al*. (2008b) investigated trajectories of depressive symptoms for 226 Australian women following MI or CABG. Depressive symptoms were evaluated using HADS at four time points: 4-8 days of cardiac event and at 2, 4 and 12 months later. Growth curve and growth Mixture modelling were used to identify trajectories of depressive symptoms over 12 months. The study identified two trajectory groups with Log10 trend: Worsening (N=25, 11%) and improving (n= 201, 89%). Patients in the worsening group began with high depressive symptoms that worsened over time while patients in the improving group begin with low depressive symptoms that improved over time.

Another Australian study by Murphy and colleagues (2008a) evaluated depressive symptoms for 184 patients before Coronary Artery Bypass Graft (CABG), and then at 2 and 6 months after CABG. The study identified 3 different trajectories of depressive symptoms using cube root GMM: remitted minor depression, partially remitted major depression and worsening minor depression. Most patients (n=132, 72%) were in remitted minor depression group as they started with low depressive symptoms that improved over time. In partially remitted major depression group, patients started with high level of depression but then improved over time (n-=26, 14%). Lastly, 14% of patients (n=26) had low level of depression that worsened over 6 months after CABG and these were in the worsening minor depression group (Murphy *et al*., 2008a).

Lastly, there is some evidence that there are subtypes of depressive symptoms which tend to be more toxic than others and thus associated with poorer outcomes after ACS. For instance, somatic symptoms of depression (i.e., loss of

energy, fatigue, and sleep disturbances) but not cognitive symptoms (i.e., loss of interest and feeling of worthlessness) were linked to increased risk of mortality and recurrent cardiac events after ACS (Smolderen *et al*., 2009; Roest *et al*., 2011). Accordingly, Roest *et al*. (2016) investigated trajectories of depressive symptoms based on subtypes of depressive symptoms (somatic versus cognitive). Depressive symptoms were assessed using BDI-I at baseline, 3, 6 and 12 months after ACS and trajectories were identified using parallel processes latent class growth analysis. The study identified three groups of trajectories: low severity (69.1%, n=316), somatic persistence (24.1%, n=110) and overall persistence (6.8%, n=31**).** Patients in the low severity group tended to have relatively stable low somatic and low cognitive scores over time. In somatic persistence, patients tended to have stable low cognitive symptoms of depression but high stable somatic symptoms over time. Lastly, patients in the overall persistence group were likely to have higher and increasing somatic and cognitive symptoms over time (Roest *et al*., 2016).

Thus far, the reviewed literature has identified that depressive symptoms after ACS are heterogenous and vary in both their stability and severity. The review identified 13 studies which employed growth modelling or latent class analysis to identify trajectories of depressive symptoms. Four of these studies had long-term follow-up (>6 years) and nine studies had follow-up of 12 months or less. The review identified distinct trajectories ranging from two to five in number. The most commonly identified number of classes were from three to four (in 11 out 13 studies). Despite the variations among studies regarding the pattern of depressive symptom trajectories, classes of no depression, or low remitted depression comprised the largest proportion of patients (40%-80%). However, there is a small proportion of patients whose trajectories were associated with worsening (4.6%-14%) or a persistence in depressive symptoms (10%-15%) over time. Yet, some studies found the proportion of patients in these groups as high as 29% and 24.5% for worsening (Murphy *et al*., 2014a) or persistent symptoms (Kroemeke, 2016), respectively. The following section will discuss trajectories of depressive symptoms using clinical cut-off score (Table 4).

2.5.3 Trajectories of depressive symptoms using clinical cut-off score

A German study by Mittag *et al*. (2016) involved 252 patients following a cardiac event and assessed depressive symptoms using Check List-90-Revised at three times: baseline (1-3 weeks), 3 months, and 12 months after cardiac event. The study classified depressive symptoms after first cardiac event including ACS and Coronary Artery Bypass Graft (CABG) using clinical cut-off points rather than growth modelling technique. The study dichotomised depressive symptoms into no depressive symptoms versus mild to moderate/ severe depressive symptoms and then evaluated fluctuations between these classes at 3 and 12 months after cardiac event. At baseline, about 54.7% (n=138) reported mild to moderate/severe depressive symptoms. A similar proportion of depressive symptoms were found both at baseline and during the follow-up. However, almost 40% of patients changed from one class to another over 12 months. The study found 4 trajectories of depressive symptoms over 12 months following the cardiac event: no symptoms (n=66, 26.2%), worsening symptoms (n=23, 9.1%), sustained remission (n=23, 9.1%), and persistent symptoms (n=87, 34.5%) (Mittag *et al*., 2016).

These findings were consistent with two other studies which evaluated changes in depressive symptoms in cardiac hospitalised patients in Australia. For example, Schrader and colleagues (2006) assessed depressive symptoms at baseline, 3 and 12 months for 739 hospitalised cardiac patients, including ACS. Depressive symptoms were measured using the Centre for Epidemiological Studies Depression (CES-D) at baseline, 3 months and 6 months after cardiac event. The study found that 60.9% (n=451) of patients had no depressive symptoms at baseline while 22.5% (n=168), and 16.4% (n=120) of patients had mild, moderate to severe depression, respectively. These proportions of depressive symptoms were similar at both 3 months and 12 months after cardiac event. However, the study found that half of those (n=60/120) who had moderate depression at baseline remained depressed at 12 months. In addition, one quarter (n= 43/168) of those with mild depression switched to moderate to severe depression group at 12 months after the event. In addition, about 5% (21/451) of those who were not depressed at baseline moved to

moderate to severe depression group over 12 months following the cardiac event. About 10% (12/120) of patients with moderate to severe depression at baseline had transient symptoms that resolved at 3 months and did not relapse at 12 months. Regarding those with no depression at baseline, nearly 65% (294/451) of patients with no depression at baseline remained non-depressed at 3 and 12 months of cardiac event.

Another study by Schrader (2004) enrolled 833 hospitalised cardiac patients, including ACS and evaluated trajectories of depressive symptoms from baseline hospitalisation to 3 months after discharge using CES-D. The study found that 58.5% (n=487) of patients had no depressive symptoms at baseline while 23.9% (n=199), and 17.5% (n=149) of patients had mild, and moderate to severe depression, respectively. The study found that almost similar proportions of patients were classified into mild, moderate to severe depressive at both baseline and at three months after discharge. Despite that, significant fluctuations in depressive symptoms were found. Findings showed that the majority of patients (n=372/487, 76.4%) who were non-depressed at baseline remained non-depressed at 3 months. About 59.6% (n=87/156) of patients with moderate to severe depressive symptoms at baseline remained highly depressed at 3 months while 30.1% (n=44/156) and 10.3% (n=15/156) of those with moderate depression at baseline become with mild and no depression, respectively. Furthermore, about 15.1% (n=30/199) of those who had mild depression at baseline developed moderate to severe depression at 3 months. About 5.7% (n=28/487) of those who were non-depressed at baseline developed moderate to severe depression at 3 months. Consistent with findings reported by Mittag *et al*. (2016), the study found that more than one third of the sample switched between classes of depressive symptoms during 3 months following the cardiac event.

A study by Lane *et al*. (2002) enrolled 288 patients in England between the 2nd and 15th day following an MI and assessed depressive symptoms using BDI at baseline, 4 months and 12 months of MI. The prevalence of depressive symptoms at baseline, 4 months and 12 months were 30.9% (n=89), 37.7% (n=75) and 37.2% (n=67), respectively. Of 288 patients included at baseline, 165

patients completed three assessments of depressive symptoms. The study found that 12.7% (n=21) of patients who were non-depressed at baseline developed depression at both 4 and 12 months. Nearly 6.7% of patients (n=11) had depression at baseline but remitted later. Lastly, 14.6% of patients (n=24) were depressed at baseline and remained depressed at 12 months.

Five studies assessed depression at baseline and one other time point such as 1 month (Parashar *et al*., 2006), 3 months (Kronish *et al*., 2006; Rieckmann *et al*., 2006b) and 12 months after ACS (Thombs *et al*., 2008; Kang *et al*., 2015). For example, a Prospective Registry Evaluating Outcomes after MI: Event and Recovery (PREMIER) study was conducted by Parashar *et al.* (2006) in the United States and assessed depressive symptoms in 1873 patients with MI at two different time-points: baseline and one month after MI using the Patient Health questionnaire (PHQ-9). Depressive symptoms were classified using clinical cut-off into three trajectories: Transient (baseline only), new (one month follow-up only) and persistent depressive symptoms (both baseline and one-month follow-up). The prevalence of depressive symptoms was 20.6% during hospitalisation and 13.1% at one month after discharge. The study found that 6% (n=112) of patients had new depressive symptoms, 7.1% (n=134) had persistent depressive symptoms, 13.5% (n=253) had transient depressive symptoms and 73.5% (n=1382) had no depressive symptoms.

Another American study of 172 patients with ACS (Rieckmann *et al*., 2006b), used BDI to assess depressive symptoms at 2 time points: hospitalisation and 3 months. The study identified four groups of depressive symptoms including no depression (50%, n = 86), new (4.1%, n =7), remitted (23.3%, n = 41), and persistent (22.1%, n = 38) (Rieckmann *et al*., 2006b). A Canadian study of 425 patients used BDI to assess depressive symptoms at 2 time points: baseline hospitalisation and 12 months after ACS (Thombs *et al*., 2008). The study identified 4 groups of depressive symptoms that were similar to those identified by previous studies and included: no depression (66.1%, n = 281), new (4.9%, n = 21), transit (8.9%, n = 38) and persistent (20%, n = 85). Another study was conducted in the United States on 482 patients with ACS and assessed depressive symptoms using BDI within 7 days of hospitalisation and

after 3 months of ACS. The study identified 3 trajectories of depressive symptoms: no depression (52 %, n=256), remitted depression (22.8%, n=112) and persistent depression (22%, n=108) (Kronish *et al*., 2006).

A Korean randomised control trial (K-DEPACS) examined depression in 1152 patients to assess effectiveness of escitalopram on depression after ACS. The two-week prevalence and one-year persistence of depression were assessed by trained psychiatrists, using the Mini-International Neuropsychiatric Interview (MINI). Of 1152 patients, 446 (38.7%) were found depressed within 2 weeks of ACS. Of these, 300 patients were randomised into escitalopram or placebo treatment and 146 patients refused to take part and thus received the usual medical treatment. At 12 months, persistent depressive symptoms were found in 150 (46.3%) of 324 patients who were depressed at baseline and completed follow-up at 12 months. The study identified three groups of depressive symptoms including no depression (63.6%), improving (25.8%), and worsening (10.5%).

To summarise, studies that used clinical cut-off scores to identify trajectory classes of depressive symptoms also found fluctuations in depressive symptoms in patients with ACS. Although most of these studies found a similar proportion of depressive symptoms at different time points, significant number of patients tended to switch from one class to another over time. Most studies identified three to four classes of depression. The classes included: no depression, improved, and persistent depression. However, some studies found additional classes such as new or worsening depression classes. The majority of the patients (52% to 76.4%) followed a trajectory of no depression. Only one study reported a much lower proportion of patients (26.2%) in the no depression class (Mittag *et al*., 2016). There are variations among studies regarding the proportion of patients in persistent (7.1% and 46.3%) and improving (6.7% to 25.8%) depression classes. However, only a small number of patients tend to develop new depression over time (4.9% to 6%). The following sections will discuss predictors of trajectory classes of depressive symptoms and patient outcomes in studies using growth modelling or latent class analysis.

2.5.4 Predictors of Trajectory Classes of Depressive Symptoms

Of the 13 reviewed studies using growth modelling or latent class analysis, seven studies identified predictors of trajectories of depressive symptoms only (Martens *et al*., 2008, Murphy *et al*., 2008a; Murphy *et al*., 2008b; Doyle *et al*., 2011a; Romppel *et al*., 2012; Murphy *et al*., 2014a; Kroemeke, 2016), four studies identified both predictors and outcomes associated with trajectory classes (Galatzer-Levy and Bonanno, 2014; Roest *et al*., 2016; Keegan *et al*., 2016; Kong *et al*., 2022), and two studies identified only outcomes associated with trajectory classes (Kaptein *et al*., 2006; Peter *et al*., 2020).

For example, Murphy *et al*. (2008c) identified 2 trajectory groups including (a) worsening (n=25, 11%) and (b) improving (n= 201, 89%) and found that patients who spoke languages other than English, those who feel loneliness and those with diabetes were more likely to be in the worsening trajectory group. Another study by Murphy and colleagues (2008a) identified 3 trajectories of depressive symptoms including (a) remitted minor depression, (b) partially remitted major depression and (c) worsening minor depression. The study found that older age was associated with remitted minor trajectories. On the other hand, patients who followed the partially remitted major depression trajectory were found to be un-partnered, smokers, to have high anxiety (before CABG), high cholesterol, angina and previous CABGS. The worsening minor depression was more likely among patients with low left ventricular ejection fraction and high New York Heart Association classification (NYHA) (Murphy *et al*., 2008a).

Romppel *et al*. (2012) identified four trajectory groups including (a) stable low, (b) low increase, (c) decrease, and (d) high increase. The study found that Type D personality was a significant predictor of the high increase group compared to remaining three groups. Furthermore, being female was a significant predictor of the decrease group compared to low increase and high increase (Romppel *et al*., 2012). A study by Doyle and colleagues (2011a) found 3 trajectories including (a) never depressed, (b) sub-threshold, and (c) persistent symptom trajectory. The study found that psychological vulnerabilities including reinforcing events, interpersonal life events, cognitive distortions,

and Type D personality predicted depression at both persistent and sub-threshold level compared to never depressed, with effect size higher for persistent depression than sub-threshold even after controlling baseline depression scores (Doyle *et al*., 2011a).

Martens *et al*. (2008) identified 4 trajectories including (a) non-depressed, (b) mildly depressed, (c) moderately and (d) severely depressed and found that a history of cardiac disease, history of depression and Type D personality were significant predictors of persistent moderate and severe depressive symptoms over 12 months of MI (Martens *et al*., 2008). Kroemeke (2016) identified 3 trajectories of depressive symptoms: (a) rising, (b) chronic and (c) low. Patients who had low depressive trajectories were more likely than those in chronic or rising depressive trajectory groups to be younger, more educated, employed, with better socioeconomic status, with less symptoms of heart failure as measured by NYHA and less likely to use antidepressant medications. Regarding coping factors, patients with chronic depressive symptom trajectories showed a higher level of negative appraisal and emotion-focused coping than those in the rising or low depressive symptoms trajectory class. In addition, patients in the rising trajectory class were more likely than those in the low trajectory class to have higher level of emotion-focused coping strategies (Kroemeke, 2016).

Kong *et al*. (2022) identified 3 trajectories of depressive symptoms for both males and females. Trajectories of depressive symptoms for males included (a) persistent minimal depression, (b) moderate depression and (c) emerging depression. However, for females it included (a) persistent minimal depression, (b) moderate depression and (c) chronic depression (Kong *et al*., 2022). The study found that male patients with a low level of education predicted increased risk of moderate depression compared to those with minimal depression. Younger age males and those reported ADL limitations were at increased risk of emerging depression compared to minimal depression. Regarding female gender, patients with low income and more ADL limitations were at increased risk of having moderate depression compared to minimal depression. In addition, younger age patients, having more ADL limitations, and

chronic health condition were at higher risk of chronic depression compared to minimal depression (Kong *et al*., 2022).

Galatzer-Levy and Bonanno (2014) reported 4 trajectories of depressive symptoms: (a) resilient, (b) chronic, (c) emergent and (d) improved. The study found that patients in the resilient group had significantly higher optimism compared to all other groups. A study by Roest *et al*. (2016) identified three group of trajectories based on subtypes of depressive symptoms (somatic versus cognitive): low severity, somatic persistence, and overall persistence. The study found that being female, older age, living alone, and having higher GRACE score were significantly associated with somatic persistence trajectories compared to other classes.

Table 3: Studies related to trajectories of depressive symptoms after ACS

Authors (year) /country	Sample(N) Male (%)	Diagnosis Follow-up period	Time of assessments	Instrument	Model	Number of classes	Predictors /Outcomes
Kong *et al*. (2022) The United States (USA)	1787 (41.4%)	Older adults (>=50) who had no heart disease at baseline but reporting cardiac event over 10 years follow-up	Six times: Baseline: before onset heart disease (2006-2007). Then, followed up every two years for 10 years (5 times) Patients included if they have at least 3 data points: 1. Depression assessment before heart disease. 2. Depression assessment at the onset of heart disease.	CES-D	GMM	Male gender (n= 740) 3 classes - Persistent minimal depression (68.7%) - Moderate depression (18%) - Emerging depression (13%) Female (n= 1047) 3 classes - Persistent minimal depression (60.2%) - Moderate depression (29.7% - Chronic depression (10%)	- Examined trajectories of depressive symptoms after onset of heart disease & Separately in males and females. Predictors: Males with low education level predicted increased risk of moderate depression compared to those with minimal depression. Younger age males and those with ADL limitations were at increased risk of emerging depression compared to minimal depression. Predictors: Females with low income and more ADL limitations were at increased risk of moderate depression compared to minimal depression. Younger

Authors (year) /country	Sample(N) Male (%)	Diagnosis Follow-up period	Time of assessments	Instrument	Model	Number of classes	Predictors /Outcomes
			3. Depression assessment after heart disease			Note: Moderate depression (i.e., subclinical depression)	age with more ADL limitations, and chronic health condition were at higher risk of chronic depression compared to minimal depression. Outcomes: Disability and Mortality - Moderate and chronic (emergent) depression were associated with more disability in both genders compared to minimal depression. Emergent depression trajectories were associated with increased risk of mortality in males. No association between moderate depression and mortality. No difference between classes in mortality of female patients
Peter *et al*. (2020) Germany	1109 (84.6%)	CHD 15 years	Six times 1, 3, 6, 8, 13 and 15 years	HADS-D	Latent class mixture time-	Four: - Low-stable (69.6%), - Moderate stable (23.8%),	Compared to patients in low stable class, those following moderate stable, increasing and high stable trajectories were

Authors (year) /country	Sample(N) Male (%)	Diagnosis Follow-up period	Time of assessments	Instrument	Model	Number of classes	Predictors /Outcomes
					to-event model	- increasing (3.3%) - High-stable (3.3%).	significantly at higher risk of cardiovascular events and non-CV mortality over 15 years Predictors: Older age patients were more likely to be increasing class compared to low stable.
Kroemeke (2016) Poland	200 (70.5%)	MI 6 years	Four times H, 1 month,6 months and 6 years	BDI	GMM	Three classes Rising: (Moderate: decrease then increase, 60.5%) Chronic: High (increasing then decreasing; 24.5%). - Low: (Low: decreasing then stabilising; 15%)	Chronic depressive trajectories were associated with negative appraisal and emotion-focused coping
Keegan *et al*. (2016) Ireland	375 (79%)	ACS 12 months	Four times H, 3, 6 and 12 months	BDI-Fs	LCA	Three classes Never depressed (48%) Subthreshold (37%) Persistent (15%)	Cognitive vulnerabilities (interpersonal life event, reinforcing events, cognitive distortions, and type D personality) predicted course of

Authors (year) /country	Sample(N) Male (%)	Diagnosis Follow-up period	Time of assessments	Instrument	Model	Number of classes	Predictors /Outcomes
							depressive symptoms which in turn predict outcomes.
Roest *et al*. (2016) The Netherlands	457 (81.2%)	MI 12 months	Four times H, 3, 6, and 12 months later	BDI	PP-LCGA	Three classes Low severity (69.1%) Somatic persistence (24.1%) Overall persistence (6.8%)	Being female, older age, living alone, and having higher GRACE score were significantly associated with somatic persistence trajectories compared to other classes.
Galatzer-Levy and Bonanno, (2014) USA	2147 (48.6%)	MI From 6 years before MI to 4 years after MI	Five times 3 times before MI and 2 times after MI	CES-D	GMM	Four classes Resilient class (68.3%) Chronic depression (14%) Emerging depression (10.9%) Depressed improved class (6.8%)	Emerging depression was associated with higher risk of mortality. Optimisms predicted course of depressive symptoms and mortality.
Murphy *et al*. (2014a) Australia	160 (68%)	Acute cardiac event (80% ACS) 6 months	Three times H,2, and 6 months	HADS-D	GMM	Three classes No depression (54%) Worsening depression (29%) Resolving depression (17%)	Mental health history, younger age, smoking, financial stress, poor self-rated health, were predictors of worsening depression

Authors (year) /country	**Sample(N) Male (%)**	**Diagnosis Follow-up period**	**Time of assessments**	**Instrument**	**Model**	**Number of classes**	**Predictors /Outcomes**
Doyle *et al*. (2011a) Ireland	374 (79%)	ACS 12 months	Four times H, 3, 6 and 12 months Patients completed in-hospital and at least one time	HADS-D BDI-FS	LCA	Three classes Never depressed (48%) Subthreshold (37%) - Persistent (15%)	Depressive vulnerabilities included: Type D personality, cognitive distortion, stressful life event, and reinforcing events. Depressive vulnerabilities predicted both sub-threshold and persistent depressive symptoms where the higher effect size for persistent depressive symptoms.
Romppel et al. (2011) Germany	679	Cardiac diseases including ACS	Two times Baseline and 6 years	HADS-D	LCA GMM	Four Classes: - Decrease (7.3%) -Low (60%) Low increase (25.8%) -High increase (6.9%)	Type D personality independently predicted "high increase class" Note: 47.5% of the females tend to be in "decrease" class
Martens *et al*. (2008) The Netherlands	287 (81%)	MI 12 months	Three times H,2,12 months	BDI	LCA	Non-depressed (40%) Mildly depressed (42%) Moderately depressed (14%) Severely depressed (4%)	Cardiac history, history of depression, and Type D personality were associated with persistence of depressive symptoms

Authors (year) /country	**Sample(N) Male (%)**	**Diagnosis Follow-up period**	**Time of assessments**	**Instrument**	**Model**	**Number of classes**	**Predictors /Outcomes**
Murphy *et al*. (2008a) Australia	184 (79%)	CABG 6 months	Three times Before CABG, 2, and 6 months later	HADS-D	GMM	Three classes - Remitted minor depression (72%) - Partially remitted major depression (14%) - Worsening minor depression (14%).	Smokers, unpartnered, anxiety before CABG, high cholesterol, angina, severe cardiac disease, or repeated CABG
Murphy *et al*. (2008b) Australia	226 (0%)	Cardiac event (MI or CABG) 12 months	Four times H, 2,4,12 months later	HADS--D	GCM, GMM	Two classes - Low level of depression at baseline and improved overtime (89%) - High level of depression that worsened overtime (11%)	Loneliness, first language non-English, and diabetes are associated with worsening group.
Kaptein *et al*. (2006)	475 (81.1%)	MI 12 months	Four times H,3,6, and 12 months	BDI	LCA	Five classes No depressive symptoms (56.4%) Mild (25.7%)	Patients who follow significant and increasing class are at risk for recurrent cardiac events

Authors (year) /country	Sample(N) Male (%)	Diagnosis Follow-up period	Time of assessments	Instrument	Model	Number of classes	Predictors /Outcomes
The Netherlands						Moderate and increasing (9.3%) Significant but decreasing (4.6%) Significant and increasing (4.0%)	

Legend: HADS-D: Hospital Anxiety Depression scale- Depression subscale; BDI: Beck depression inventory; BDI-SF: Beck depression inventory- fast screen; CES-D: Center for Epidemiologic Studies Depression Scale; LCA: Latent Class Analysis; GCM: Growth curve modelling; GMM: Growth Mixture modelling; PP-LCGA: Parallel Process Latent class Growth Analysis

2.5.5 Outcomes Associated with Trajectory Classes of Depressive Symptoms

Seven studies evaluated outcomes associated with trajectories of depressive symptoms and these outcomes were related to mortality and morbidity. For instance, Kaptein *et al*. (2006) identified five trajectory groups: (a) no depressive symptoms, (b) mild depressive symptoms, (c) moderate but increasing depressive symptoms, (d) significant but decreasing, and (e) significant but increasing. Compared to no depression, patients in the significant but increasing group (HR =2.73, 95% CI, 1.27; 5.87) had a higher risk of developing cardiac events over 12 months of MI. Keegan *et al*. (2016) examined the associations between psychological vulnerabilities (reinforcing events, interpersonal life events, cognitive distortions, and Type D personality), 12-month trajectories of depressive symptoms and clinical outcomes including one year morbidity and 7 years mortality. The study found that all psychological vulnerabilities predicted both sub-threshold and persistent depression classes which in turn predicted mortality and morbidity compared to never depressed class (Keegan *et al*., 2016)

Peter *et al.* (2020) identified four trajectories of depressive symptoms including (a) low-stable class, (b) moderate stable class, (c) increasing and (d) high-stable. The study evaluated incidence of CV events and non-CV mortality over the 15 years and found that all classes of depression had higher risk of subsequent CV events and non-CV mortality compared to low stable trajectory class. The study found that patients following moderate-stable depression trajectories were at higher risk for CV events (HR= 1.18 95% CI, 0.34; 4.07) and for non-CV mortality (HR =1.94, 95% CI, 0.21; 17.5) compared to those in stable low trajectories. Furthermore, patients following the increasing trajectory class were at 1.65 (95% CI, 0.44; 6.15) higher risk of CV events and 2.76 (95% CI, 0.31; 27.7) higher risk of non-CV mortality compared to those in low-stable trajectory class. Lastly, high stable trajectory was associated with 2.47 higher risk of CV events (95% CI, 1.35; 4.54) and non-CV mortality (95% CI, 0.77; 6.65) compared with low stable trajectory class. Regarding characteristics associated with these trajectories, the study found that older patients were more likely to be in the increasing class compared to the low stable class (Peter *et al*., 2020)

Galatzer-Levy and Bonanno (2014) reported four trajectories of depressive symptoms: (a) resilient, (b) chronic, (c) emergent and (d) improved. The study found that patients in the emergent-depression class were at a higher risk of mortality during the four years following MI compared to those in resilient class (HR=1.88, 95%CI, 1.03; 3.43). However, no differences existed in risk of mortality between patients who were in the improved or chronic depression classes and those in the resilient class. Another study by Roest *et al*. (2016) investigated trajectories of depressive symptoms based on subtypes of depressive symptoms (somatic versus cognitive) and investigated whether somatic subtypes of depression had prognostic effects in patients with ACS. The study identified three trajectory classes: (a) low severity, (b) somatic persistence, and (c) overall persistence. The findings showed that only somatic persistence (HR= 1.86, 95% CI, 1.18; 2.94) predicted increased 12-month mortality after ACS compared to low severity. However, overall persistence did not (Roest *et al*., 2016)

Kong *et al*. (2022) identified three trajectories of depressive symptoms for both males and females. Trajectories of depressive symptoms for males included (a) persistent minimal depression, (b) moderate depression and (c) emerging depression. However, for females it included (a) persistent minimal depression, (b) moderate depression and (c) chronic depression (Kong *et al*., 2022). The outcomes in the study were related to disability and mortality over 8 years. The study found that moderate and chronic /emergent depression were associated with more disability in both genders compared to persistent minimal depression. The study found that only emergent depression trajectories were associated with increased risk of mortality in males (HR=2.0, 95%CI, 1.36; 3.04). However, no association was found between moderate depression and mortality. Regarding female patients, there was no difference between trajectories classes with regards to mortality (Kong *et al*., 2022). The following sections will discuss predictors of trajectory classes of depressive symptoms and patient outcomes in studies using clinical cut-off score.

2.5.6 Predictors of Trajectory classes of depressive symptoms based on clinical cut-off score

Seven out of the nine reviewed studies which used clinical cut-off score, evaluated characteristics associated with trajectory classes of depressive symptoms. For instance, Kronish *et al*. (2006) found that patients with persistent depression over 3 months were less likely to (quit smoking, adhere to medications or exercise regimen and to attend cardiac rehabilitation) compared to non-depressed. No differences were found between no depression and remitted depression. A study by Rieckmann *et al*. (2006b) found that adherence to aspirin was significantly lower in patients with persistent depression compared to those with remitted depression or no depression. No differences were found regarding adherence to aspirin between remitted depression and no depression.

Schrader *et al*. (2004) evaluated fluctuations in depressive symptoms over three months of cardiac event and found that depression at three months of cardiac event was predicted by level of depression at baseline, history of anxiety, depression or stress, history of cardiac illnesses, younger age and smoker. Schrader *et al*. (2006) evaluated changes in depressive symptoms over 12 months of cardiac events and found that depression at 12 months of ACS was associated with elevated baseline depression, history of anxiety, depression or stress, and being a current smoker. Kang *et al*. (2015) found that persistent depression at 12 months was predicted by baseline Hamilton depression rating (HAMD) scale and being in placebo or medical treatment group. However, the prevalent depressive symptoms at 2 weeks of ACS were predicted by being female, having low socioeconomic status (rented house), having low level of education, having high heart rate and having a history of prior ACS.

A study by Mittag *et al*. (2016) identified four trajectory classes including no symptoms, worsening, sustained remission and persistent symptoms of depression. The study found that patients with persistent depressive symptoms were more likely than those with no depressive symptoms to have high baseline

depressive symptoms scores and low perceived social support. Compared with persistent depressive symptoms, patients with sustained remission depressive symptoms were more likely to be female, admitted for CABG and using low depressive coping style. Another study by Parashar *et al*. (2006) identified four trajectory classes including no new, transient and persistent symptoms of depression. The study found that patients with transient, new or persistent depressive symptoms, as compared to no depression, were more likely to be female, younger age, unemployed, unmarried and African American. In addition, they were more likely to have hypertension, diabetes, chronic obstructive pulmonary disease, and chronic heart failure. Furthermore, patients in these groups were more likely to be smokers and to have a history of depression compared to patients with no depressive symptoms.

2.5.7 Outcomes associated with Trajectory classes based on clinical cut-off score

Three out of the nine reviewed studies which used clinical cut-off score, evaluated association between classes of depression and outcomes. A study by Thombs *et al*. (2008) classified courses of depressive symptoms over 12 months of ACS into four classes: no depression, new, transit and persistent and found that only persistent symptoms of depression were associated with poorer physical component score (PCS) of SF12 at 12 months of ACS.

Parashar *et al*. (2006) identified classes of depressive symptoms similar to those identified by Thombs and colleagues (2008) and found that all new, transient, and persistent depressive symptoms were associated with increased rate of re-hospitalisation, mortality and poorer HRQoL at 6 months compared with no depression. A study by Mittag *et al*. (2016) identified four trajectory classes including no symptoms, worsening, sustained remission and persistent symptoms of depression. The study found that patients follow worsening depressive symptoms had significantly more frequent MACEs compared to those with sustained remission.

Table 4: Studies that used clinical cut-off scores to classify trajectories of depressive symptoms

Authors (year) / country	N (Male %)	DX	Age M (SD) Follow-up	No of Assessments	Instrument and cut-off score	Number of classes	Predictors /notes
Mittag *et al*. (2016) Germany	252 (67.1%)	Cardiac event including ACS	58.15 (9.7) 12 months	Three: 1-3 weeks, 3 months, 12 months	SCL-90-R *T* score ≥ 60	Off-on/on-off (n=53). Four trajectories: No symptoms (n=66, 26.2%) Worsening symptoms (n=23, 9.1%) Sustained remission (n=23, 9.1%), Persistent symptoms (n=87, 34.5%).	- Patients with persistent depressive symptoms were more likely than those with no depressive symptoms to have high baseline depressive symptoms score and low perceived social support. - Compared with persistent depressive symptoms, patients with sustained remission depressive symptoms were more likely to be female, have CABG and use low depressive coping style. Patients with worsening depressive symptoms had significantly more frequent MACEs compared to those with sustained remission.
Kang *et al.* (2015) Korea	1152 (71.4%)	ACS	12 months (n=828)	Two: Two weeks one year	- MINI - HDRS for rating severity of depression	No depression (63.6%) Improving (25.8%) Worsening (10.5%)	Two-week prevalence: 38.7% One year incidence: 13.1% One year persistence: 46.3% Prevalent depressive symptoms were predicted by being female, having low

Authors (year) / country	N (Male %)	DX	Age M (SD) Follow-up	No of Assessments	Instrument and cut-off score	Number of classes	Predictors /notes
							socioeconomic status (rented house), low level of education, high heart rate and history of prior ACS. Persistent depression was predicted by: -Baseline Hamilton depression rating (HAMD) scale and being in placebo or medical treatment group. -HAMD, family history of depression, unemployment, left ventricular ejection fraction.
Thombs *et al*. (2008) Canada	425 (65%)	ACS	61.89(12.0) 12 months	Two: Hospital 12 months	BDI≥ 10	No depression (66.1%, n = 281) New (4.9%, n = 21) Transit (8.9%, n = 38) Persistent (20%, n = 85)	Only persistent symptoms of depression were associated with poorer PCS-SF12 at 12 months
Kronish *et al*. (2006) The United States	492 (58.9%)	ACS	60.6 (12.2) 3months	Two: Within 7 days of ACS 3 months	BDI ≥10	Non-depressed (52 %, n=256) Remitted depressed (22.8%, n=112)	Compared to non-depressed, patients with persistent depression were less likely to quit smoking, adhere to medications, exercise, and attend cardiac rehabilitation. No differences

Authors (year) / country	N (Male %)	DX	Age M (SD) Follow-up	No of Assessments	Instrument and cut-off score	Number of classes	Predictors /notes
						Persistent depressed (22%, n=108)	between no depression and remitted depression.
Rieckmann *et al*. (2006b) The United States	172 (62.8%)	ACS	59.8 (11.5) 3 months	Two: Hospital 3 months	BDI≥ 10	No depression (50%, n New (4.1%, n =7) Remitted (23.3%, n = 41) Persistent (22.1%, n = 38)	Adherence to aspirin was significantly lower in patients with persistent depression compared to those with remitted depression or no depression. No difference regarding adherence to aspirin between remitted depression and no depression. New depression were excluded from analysis
Schrader *et al*. (2006) Australia	739 (68%)	Cardiac diseases including ACS	Not reported 12 months	Three: 2-3 days of hospitalisation, 3 months 12 months	CES-D >16	- Moderate to severe at baseline Remained depressed at 12 months (n=60/120) - Mild depression at baseline developed moderate to severe at 12 months (43/168). - Moderate depression at baseline resolved at 3	Depression at 12 months was predicted by baseline depression, history of anxiety, depression or stress, and current smoking.

Authors (year) / country	N (Male %)	DX	Age M (SD) Follow-up	No of Assessments	Instrument and cut-off score	Number of classes	Predictors /notes
						months no relapse at 12 months (n= 12/120). -No depression at baseline but developed moderate to severe over 12 months (n=21/451) - No symptoms of depression at baseline and remained non-depressed at 3 and 12 months (294/451)	
Parashar *et al*. (2006) The United States	1873 (67%)	MI 62.5 (14)	One month	Two: Hospital 1 month	PHQ-9 ≥ 10	Four classes: No depression (73.5%, n=1382) Transient (13.5%, n=253) New depression (6%, n=112) Persistent (7.1%, n=134)	**Prevalence** 20.6% (n=387) and 13.1% at one month 6 -month: Compared to non-depressed, patients in transient, new depression and persistent depression had higher risk mortality, rehospitalisation and poorer HRQoL during 6 months of MI.

Authors (year) / country	N (Male %)	DX	Age M (SD) Follow-up	No of Assessments	Instrument and cut-off score	Number of classes	Predictors /notes
							Predictors: Compared with those who had no depressive symptoms, patients with transient, new and persistent depressive symptoms were more likely to be female, younger, unemployed, unmarried and African American. Also, more likely to have Hypertension, Diabetes, Chronic Obstructive pulmonary disease, heart failure and previous MI compared with those with no depressive symptoms. Also, people in these groups were more likely to smoke and have history of depression compared to patients with no depressive symptoms.
Schrader *et al*. (2004) Australia	833 68%	Cardiac diseases including ACS	3 months	Two: 2-3 days of hospitalisation, 3 months	CES-D >16	**Baseline:** Non-depressed (n= 487, 58.5%) Mild (n= 199, 23.9%) Moderate to severe (n=146, 17.5%)	Five predictors of persistent depression at 3 months of ACS including younger age, being smoker, having history of cardiac condition, having moderate to severe baseline depressive symptoms

Authors (year) / country	N (Male %)	DX	Age M (SD) Follow-up	No of Assessments	Instrument and cut-off score	Number of classes	Predictors /notes
						3 months: Non-depressed (n= 481, 57.7%) Mild (n=206, 24.7%) Moderate to severe (n=145, 17.4%) 59.6% (n=87/156) of patients with moderate and severe depressive symptoms at baseline remained highly depressed at 3months. 30.1% (n=44/156) and 10.3% (n=15/156) of those with moderate depression at baseline became with mild and no depression, respectively. 5.7% (n=28/487) of those non-depressed at	and having history of depression, anxiety or stress.

Authors (year) / country	N (Male %)	DX	Age M (SD) Follow-up	No of Assessments	Instrument and cut-off score	Number of classes	Predictors /notes
						baseline developed moderate to severe at 3 months. 15.1% (n=30/199) with mild depression at baseline developed moderate to severe at 3 months. 76.4% (n=372/487) of non-depressed at baseline remained non-depressed at 3 months	
Lane *et al*. (2002) England	288 (74.4%)	MI	62.7 (11.5) 12 months	Three: 2-15 days of MI, 4 months 12 months)	BDI≥ 10	3 assessments (n=165) - Non-depressed baseline but depressed at both 4 and 12 months (12.7%, n=21) - Depressed baseline but remit later (6.7%, n=11)	Baseline prevalence (n=89, 30.9%) Prevalence at 4 months (n=75, 37.7%) Prevalence at 12 months (n=67, 37.2%,

Authors (year) / country	N (Male %)	DX	Age M (SD) Follow-up	No of Assessments	Instrument and cut-off score	Number of classes	Predictors /notes
						- Depressed at baseline and remain depressed at 4 and 12 months (n=24, 14.6%)	

Legend: DX: Diagnosis; M (SD): Mean (Standard deviation); SCL-90-R: Symptoms Check List-90-Revised; MINI: Mini-International Neuropsychiatric Interview; PHQ-9: Patient Health Questionnaire; BDI: Beck depression inventory; CES-D: Center for Epidemiologic Studies Depression Scale.

2.6 Conclusion

This large chapter has presented the literature regarding depressive symptoms in patients with ACS. It reviewed the concept of depression and the associated negative impact on many patient outcomes following ACS. The literature on prevalence and incidence of depression suggests that varying estimates are evident in the literature however it is clear that early identification of depression and an understanding of the risk factors/predictors of depression are of huge importance to patient care and future policy development. The chapter concludes with a discussion about depressive symptom trajectories, and it is evident that the evidence is still emerging in this field. Many different types and numbers of groups/classes of trajectory exist. Many of these trajectories have discrete predictors and are associated with specific impacts on patient outcomes. It is clear that further research is needed on depressive symptom trajectories, to inform the growing body of knowledge in this important area of care. One of the main aims of this study is to identify the trajectories of depressive symptoms in Jordanian patients during the six months following an ACS event. The study will also determine the predictors of these depressive trajectories after an ACS event and examine sociodemographic, cardiac disease severity and psychosocial factors. The following chapter will outline the study methodology and methods used to meet the study aims and objectives.

Chapter 3: Methodology

In this chapter the methodology underpinning this study is discussed. The study aim and objectives are reiterated and the paradigm outlined, within which the proposed research study is located. This is discussed from an ontological, epistemological, and methodological perspective. The study design is outlined along with an explanation as to why a prospective cohort design was considered appropriate. Following this, the conceptual framework guiding the study is presented and contextualises a conceptual model of relationships among psychosocial variables and trajectories of depressive symptoms. This model is conceptually threaded throughout the remainder of the thesis.

3.1 Study Aim and objectives

Aim: The aim of this study is to employ group-based trajectory modeling to identify heterogenous trajectories of depressive symptoms after an ACS event.

Objectives

1. To estimate the prevalence of in-hospital depression among patients who have experienced an ACS event in Jordan.
2. To estimate the incidence of depression in these patients over a period of six-months post ACS.
3. To identify the trajectories of depressive symptoms during the six months following an ACS event.
4. To determine what predicts trajectories of depressive symptoms after an ACS event: sociodemographic, cardiac disease severity or psychosocial factors.

3.2 Philosophical perspectives

The way in which research is conducted is generally influenced by the research paradigm (Tombs and Pugsley, 2020), which is the framework that guides researchers towards the design and methodology that fits their study (Mackenzie and Knipe, 2006). McGregor and Murnane (2010, p. 419) define a

paradigm as “a set of assumptions, concepts, values and practices that constitutes a way of viewing reality”. Similarly, (Kamal, 2019, p.1389) describe it as the “researchers’ beliefs and values about the world, the way they define the world and the way they work within the world”. According to Mackenzie and Knipe (2006), paradigms influence what information should be studied and how the results should be interpreted. Consequently, aligning the paradigm with the research aim/question in the early stages of a study provides a basis for choosing the appropriate methodology, study design and data analysis techniques (Kivunja and Kuyini, 2017).

Two main paradigms are commonly used to generate knowledge about a topic of research: Positivist/postpositivist and interpretivist. Both paradigms can be determined based on the interaction between the nature of (1) reality (ontology), (2) knowledge (epistemology), and (3) research (methodology) (Guba 1990). Ontology is related to the question “what is the nature of reality?” (Guba & Lincoln, 1989, p.83). With the positivist paradigm, a single fixed reality is generally assumed, whilst with the interpretivist paradigm, reality is multiple, socially created and can be changed through an individuals’ interpretation (Bunniss & Kelly 2010; Gray 2021). With positivism, reality consists of pre-existing patterns and can be generalised (Aliyu *et al*., 2015), while reality within the interpretivist paradigm is context based and is mainly subjective (Gray, 2021).

Positivist researchers conduct research in a structural and controlled approach without the influence of their beliefs. Knowledge within a positivist philosophy is mainly generated through observation and measurement (Objectivism), whereas in interpretivism, knowledge is created by an individuals’ subjective interpretations (Constructivism) (Guba, 1990; Gray, 2021). From a methodological perspective, positivists tend to use deductive-quantitative research approaches (Park *et al*., 2020), while inductive-qualitative approaches are commonly used by interpretivists (Cooper and White, 2011).

More recently, there has been a move from positivism to post positivism (Allmendinger, 2002; Onwuegbuzie *et al*., 2009). Post positivism is similar to

positivism in that both are based on reality and objectivism, but to different extents (Mackenzie and Knipe, 2006). The assumptions of post positivism are based on the fact that all observations and measurement have the potential for error, therefore the reality (ontological assumption) is viewed as relative rather than a fixed absolute reality (Laudan, 1996). Creswell (2009) views post positivism as an extension of positivism but challenges its true objectivism. Both positivists and post positivists use quantitative approaches in data collection and analysis (Mackenzie and Knipe (2006).

This study assessed depressive symptoms at different time points based on valid and reliable self-reported measures. Following this, trajectories of depressive symptoms were analysed using a person-centred approach to analysis called group-based modelling. This type of analysis classifies individuals into different groups based on similarities in their trajectories over time. Given that the current study aimed to assess depressive symptoms using self-reported instruments and assess the association between variables using a quantitative approach, the epistemological perspective of the study is rooted in objectivism rather than constructivism. However, the researcher acknowledges the absence of true objectivism in the assessment of depressive symptoms which were measured using self-reported instruments. Therefore, this study is grounded in the postpositivist philosophical perspective.

3.3 Research Design

The research design refers to the strategies that are implemented by researchers to answer the research question (Polit and Beck, 2018). It is a plan on how to conduct the study and organise its components in a logical way (Cohen *et al*., 2018). There are three forms of quantitative research designs: experimental, quasi-experimental and non-experimental designs (Polit and Beck, 2018, Boswell and Cannon, 2018). Experimental and quasi-experimental designs examine cause and effect relationships between independent and non-independent variables. Non-experimental designs describe relationships between variables as they naturally occur, without making causal inferences (LoBiondo-Wood and Haber, 2017).

In experimental designs, the researcher introduces an intervention to manipulate the independent variables and randomly assigns patients into control or treatment groups (Nieswiadomy and Bailey, 2018). In quasi-experimental designs, the researcher introduces an intervention, but may not include a control group or randomly assign patients into groups (Boswell and Cannon, 2018). The choice of appropriate design is directed by the study aim(s) and objectives (LoBiondo-Wood and Haber, 2017).

A non-experimental design was deemed appropriate for the aims and objectives of this study as the researcher did not introduce an intervention, manipulate independent variables, or randomise patients into groups. Further, non-experimental designs are appropriate for descriptive, comparative and correlational research. Boswell & Cannon (2018) viewed comparative and correlational research as subtypes of descriptive designs. Descriptive research aims to observe, describe and document the situation as it stands without manipulation (Polit and Beck, 2018). In descriptive-comparative designs, researchers compare two or more groups to one or more variables without manipulation, control or randomisation (Boswell and Cannon, 2018). Likewise, in descriptive-correlational designs, researchers assess relationships between variables and seek to explain those relationships without interference (LoBiondo-Wood and Haber, 2017). The strength of the relationship between correlated variables indicates how the change in one variable is related to another variable but does not conclude causal effect relationships (LoBiondo-Wood and Haber, 2017; Polit and Beck, 2018). To this end, this study used a descriptive design to estimate the prevalence of depressive symptoms at baseline and used a descriptive-correlational design to describe the relationships between sociodemographic, clinical and psychosocial variables and depressive symptoms.

The non-experimental research design can also be classified based on their time dimension into cross-sectional or longitudinal designs (Polit and Beck, 2018; LoBiondo-Wood and Haber, 2017). In cross-sectional designs, data are collected

from patients at one particular point in time (LoBiondo-Wood and Haber, 2017). Researchers use cross-sectional designs to describe the phenomenon of interest, explore relationships, or test differences between variables on one occasion, while longitudinal designs are used to gather data over an extended period (Polit and Beck, 2018). Cohort designs, which are a type of longitudinal study design, follow patients who share the same characteristics or experiences over time to evaluate the occurrence of an outcome of interest or report changes that occur to the phenomenon under investigation (Cohen *et al*., 2018). In this study, a prospective cohort design was deemed most appropriate to achieve the study aims and objectives.

Cohort designs can be retrospective or prospective (Polit and Beck, 2018; Wang and Kattan, 2020). With prospective cohort designs, researchers collect data prospectively from the same patients at two or more timepoints, but patients do not have an outcome of interest at the time of entry into the study (Wang and Kattan, 2020). Instead, the researcher classifies patients based on their exposure status; exposed and unexposed. Patients are then followed over time to evaluate the occurrence of the outcome of interest (Cohen *et al*., 2018; Wang and Kattan, 2020). Thus, prospective cohort designs collect valuable information regarding exposure and outcomes (Setia, 2016; Wang and Kattan, 2020).

With retrospective cohort designs, researchers initiate the study after the outcome of interest has already occurred (Setia, 2016; Polit and Beck, 2018) and use pre-existing data, usually from records. The researcher assesses an individual's exposure status at a point in time and evaluates whether or not they subsequently developed the outcome of interest (Setia, 2016; Cohen *et al*., 2018). Retrospective cohort designs require less time to be conducted and are less expensive than prospective cohort designs (Polit and Beck, 2018). However, they are less accurate than prospective designs as data in records are often incomplete or were not specifically devised to answer a particular question (Cohen *et al*., 2018; Wang and Kattan, 2020). To maximise the quality

and accuracy of data used in this study, data were collected prospectively from patients over time, rather than retrospectively from records. As such, a prospective cohort design was deemed most relevant for the current study.

3.4 Justification for choosing the study research design

A quantitative research approach with a prospective cohort design was therefore used to achieve the aims of this study, which were concerned with (a) estimating the incidence of depressive symptoms at one, three and six months following an ACS event, (b) identifying trajectories of depressive symptoms over 6 months following ACS, and (c) understanding the predictors associated with trajectories of depressive symptoms. According to LoBiondo-Wood & Haber (2017, p. 200), prospective cohort designs are considered appropriate for studies that aim to assess the incidence and cumulative incidence of certain conditions over a period of time. In addition, it also enables researchers to address changes that occur in certain phenomena and to examine their patterns with great accuracy (Setia, 2016).

The ability of cohort designs to address individual patterns of change over time is one of the main strengths of this design. Unlike cross sectional studies which focus on group-level analysis, cohort designs allow researchers to use advanced analytical techniques to address changes at the individual-level (Cohen *et al*., 2018). According to Polit & Beck (2018), a prospective cohort design is considered the strongest design for informing aetiology and outcomes in situations when randomisation is not practical or ethical. The strength of the cohort design comes from the design's ability to establish sequencing of a phenomenon, which helps the researcher in determining causality (Polit and Beck, 2018). This type of design allows researchers to collect information about confounders that may be related to the occurrence of the outcome and to then control for them (Setia, 2016; LoBiondo-Wood and Haber, 2017).

With prospective cohort designs, researchers can collect a larger number of variables than with cross sectional designs, which enables examination of a greater number of relationships and differences between variables (LoBiondo-

Wood and Haber, 2017). However, prospective cohort designs have several disadvantages such as (a) being more costly than cross-sectional designs, and (b) requiring a longer time frame for data to be collected (LoBiondo-Wood and Haber, 2017). The main issue affecting cohort designs is patient attrition following the collection of baseline data, which may be due to death or unwillingness to participate (Boswell and Cannon, 2018; Cohen *et al*., 2018). A significant loss of patients from studies (≥ 30% of the sample) can introduce bias (Setia, 2016), pose threats to validity and limit the generalisability of the study (Polit and Beck, 2018). Having an awareness of potential disadvantages allows the researcher to make every effort to avoid them as much as possible.

3.5 Conceptual/Theoretical Framework

A conceptual framework is an illustration used to clarify the study variables and how they are related. It can be a narrative or graphical illustration that links variables to make the study results more meaningful and generalisable. A conceptual framework helps researchers to integrate all aspects of the research so that it is easier for the reader to understand why the study is important. In addition, it allows researchers to determine if the chosen methodology is appropriate for the research question. Some researchers use the term 'conceptual framework' interchangeably with 'theoretical framework', while others consider them to be different concepts (Grant and Osanloo, 2016; Adom *et al*., 2018).

Grant and Osanloo (2014 p. 12) consider a theoretical framework to be a 'blueprint for your house'. It is a conceptualisation based on an existing theory, which guides researchers to organise the structure of their study, to clarify concepts and how they relate to each other and to the research problem. In addition, a theoretical framework guides researchers when choosing an appropriate philosophy and methodology suited to their research purpose. The same authors viewed a conceptual framework as "a logical structure of connected concepts that helps provide a picture or visual display of how ideas in a study relate to one another within the theoretical framework" (Grant and Osanloo, 2016, p. 17). According to Polit and Beck (2017), a conceptual

framework has less formal structure than a theoretical framework due to the absence of propositions between related concepts but when it is included in quantitative research the significance of the findings is increased.

Conversely, Ravitch and Riggan (2016) purport that a conceptual framework is composed of three components: personal experience, literature and theory. The researcher's interest in investigating certain phenomenon may drive them to conduct the study. However, a conceptual framework cannot be developed on personal experience alone, thus exploring the literature is an integral component in determining the extent of the problem and identifying the gap in knowledge about certain phenomenon. The theoretical framework is the final component of the conceptual framework which researchers use to test a theory or to organise the study structure (Ravitch and Riggan, 2016).

In reviewing the literature pertaining to this study, a body of evidence indicates that depressive symptoms in patients with ACS are prevalent and persist over time, while certain psychosocial factors are related to/or influence these symptoms, it was considered that psychosocial variables would impact depressive symptoms and their trajectories over time. The main concepts considered in this study included Type D personality, perceived social support, coping and depressive symptoms, all of which are examined below.

3.6 Type D personality in patients with ACS

Personality traits have been found to influence the development of negative emotions (Rusting, 1998). High neuroticism and low extraversion have been linked to increased depression and poorer outcomes (Kim *et al*., 2016). Type D personality is common in patients with MI, with prevalence rates ranging from 24% (Pillai *et al*., 2019) to 76% (De Fazio *et al*., 2012). Pillai *et al*. (2019) reported that 24% (n=200) of MI patients in their study had Type D personality, while Annagür *et al*. (2017) and Ogińska-Bulik (2014) reported prevalence rates of 38.2% and 46.5% (n=86) respectively, in their studies a similar cohort of patients. A case control study which compared the prevalence of type D personality in patients with MI (n= 150) to individuals from the general

population (n=150), found that more people with MI had Type D personality (50.7%), than the general population (33.3%) (Manoj *et al*., 2020).

With respect to the presence of Type D personality across countries, Kupper *et al*., (2013) carried out cross cultural analysis on 6,222 patients with angina (33%), MI (37%) and heart failure (30%) from 22 countries. Variations in the prevalence of Type D personality across countries were as follows; 37% and 35% of patients had Type D personality in southern and eastern Europe respectively, with lower rates reported in northern Europe (24%) western Europe (27%) and in English speaking countries (27%) such as the United States, Canada, Australia, Ireland and the United Kingdom (Kupper *et al*., 2013). In Italy, De Fazio *et al*. (2012) reported prevalence of Type D personality to be the highest at 76%.

A review of the literature showed Type D personality to be associated with poor prognosis in cardiac patients, including those with ACS. Denollet *et al*. (2006) evaluated Type D personality in 875 patients with CHD after PCI and found that Type D personality was independently associated with increased mortality and major cardiac events. Similarly, Martens *et al*. (2010) reported that MI patients with Type D personality were at double the risk of mortality and recurrent MI over 1.8 years, compared to those without Type D personality. Likewise, Denollet and Pedersen (2008), who included 337 patients with MI in their study, found that patients with Type D personality had three times the risk of a five-year major cardiac event after MI compared to patients without Type D personality. These findings are consistent with Du *et al*. (2016) who found Type D personality to be an independent predictor of cardiac events five years after PCI, in patients with angina and NSTEMI.

Type D personality and depressive symptoms

Type D personality was also found to have a negative impact on emotional states after ACS, especially depression. De Fazio *et al*. (2012) evaluated the association between Type D personality and depressive symptoms in 70 patients after ACS and reported Type D personality to be a significant predictor of depressive symptoms after ACS. Similarly, Al-Qezweny *et al*., (2016), found

that baseline Type D personality had a 3.7 times increased risk of depression after 10 years, following PCI. Consistent with these findings, a large multicentre study conducted on 6,222 patients with heart disease (70% MI or angina, 30% heart failure) from 22 countries, found Type D personality to be associated with increased risk of depression in all groups with heart disease (Kupper *et al*., 2013).

Likewise, Annagür *et al*. (2017), evaluated the impact of Type D personality on depression (N=131), 2 to 6 months after MI. Depression, which was measured using the Structured Clinical Interview for DSMIV (SCID-I), was found in 19.1% (n=25) of patients and was significantly higher in patients with Type D personality compared to those without Type D personality.

Studies that addressed trajectories of depressive symptoms over time found that Type D personality was associated with persistent depressive symptoms over time. For instance Martens *et al*. (2008) who evaluated 1-year trajectories of depressive symptoms after MI (N=287), found that Type D personality was an independent risk factor for persistence of depressive symptoms during the first year of MI. Similarly, Romppel *et al*. (2012) evaluated the association between Type D personality and 6-year trajectories of depressive symptoms in cardiac patients and found that Type D personality independently predicted class membership in 'significant and increasing trajectory classes' of depression. Likewise, a study by Doyle *et al*. (2011a) evaluated 1-year trajectories of depressive symptoms for 375 patients with ACS and found that Type D personality independently predicted persistence of depressive symptoms after ACS. Keegan *et al*. (2016) extended the work carried out by Doyle and colleagues and used path analysis to evaluate the association between theoretical vulnerabilities, including Type D personality, and 7 year-mortality and 1-year morbidity. The study found that Type D personality predicted trajectories of depressive symptoms, which in turn predicted poor outcomes after ACS.

Conclusion of Type D Personality

In conclusion, type D personality was found to be independently associated with increased depressive symptoms at baseline and one year after ACS. Type D personality was also associated with persistence of depressive symptoms in patients with ACS. In light of the link between type D personality and depression, the researcher included this variable in the conceptual model.

3.7 Perceived social support in patients with ACS

There are two forms of social support: perceived and received social support (Eagle *et al*., 2019)**.** The concept of perceived social support encapsulates how people view friends, family, and others as resources that may offer them psychological, emotional, financial, and overall support when they are in need (loannou *et al*., 2019). Eagle *et al*. (2019) purport that perceived social support is strongly associated with depressive symptoms and is more useful in predicting depressive symptoms than received social support. This is consistent with Wethington and Kessler (1986) who report that perceived social support is more important for individuals when facing stressful situation than received social support.

Low perceived social support was found to be associated with poorer clinical and health outcomes after ACS. For instance, Burg *et al*. (2005) examined the impact of low perceived social support on 1,503 patients enrolled in the Recovery in Coronary Heart Disease (ENRICHD) clinical trial and found that low perceived social support predicted mortality and recurrent MI during an average of 29 months. Similarly, a systematic review and meta-analysis study found that low perceived social support was associated with increased cardiac and all-cause mortality after MI (Barth *et al*., 2010). More recently, Weiss-Faratci *et al*. (2016) found that low perceived social support was significantly associated with increased mortality at baseline and again 10-13 years after a first MI.

Perceived social support and depressive symptoms

A body of evidence showed that low perceived social support is associated with increased negative emotions, such as depression. Murphy *et al*. (2013) reported that low perceived social support, which was measured by the Enriched Social Support Inventory (ESSI), independently predicted depressive symptoms after a cardiac event (MI, PCI, CABG). Similar findings emerged from a prospective cohort study which used data from the Prospective Registry Evaluating Myocardial Infarction: Events and Recovery (PREMIER) database of 2,498 patients with MI across 19 centres in the USA. The researchers (Leifheit-Limson *et al*., 2010) reported that low perceived social support, as measured by the ESSI at baseline, was independently associated with more depressive symptoms (as measured by the PHQ-9) over the first year of MI. They also found that there was no change in this association at four time points (baseline, 1, 6, and 12 months) after MI.

Using data from the Variation in Recovery: Role of Gender on Outcomes of Young AMI Patients (VIRGO), a prospective multicentre American and Spanish study, evaluated the impact of perceived social support on depressive symptoms (Bucholz *et al*., 2014). The study used the ENRICHD Social Support Inventory to assess perceived social support and the PHQ-9 to assess depressive symptoms. The researchers reported that 22.1% of the sample (n=3432) had low perceived social support and that low perceived social support was associated with high depressive symptoms at 12 months after MI (Bucholz *et al*., 2014).

Some studies found that perceived social support was associated with worsening of and persistence in depressive symptoms over time, after a cardiac event. For instance, Hammond *et al*. (2008) enrolled 191 patients after cardiac event (about 50% were MI or angina) and evaluated depressive symptoms at baseline and at one month (n=155) after a cardiac event. They found that low perceived social support, as measured by a subjective social support scale, was associated with increased risk of persistent depressive symptoms after 1 month. Likewise, Murphy *et al*. (2014a) evaluated trajectories of depressive

symptoms at hospitalisation and 2 and 6 months after an acute cardiac event (n=160) using HADS. They also evaluated social support based on the following one item from the Social Adjustment Scale 'Do you have a close friend or confidant – that is, someone with whom you can discuss your personal and private feelings?' Lack of a close friend or confidant was found to be a significant predictor of worsening depressive symptoms over 6 months of the acute event (Murphy *et al*., 2014a).

Conclusion of perceived social support

In conclusion, perceived social support was found to be related to depressive symptoms following ACS (Leifheit-Limson *et al*., 2010; Bucholz *et al*., 2014). Some studies showed that perceived social support predicted persistence of or worsening in depressive symptoms over time (Hammond *et al*., 2008; Murphy *et al*., 2014a). Accordingly, it was considered that perceived social support would have an association with depressive symptoms in this current study, and this variable was also included in the conceptual model.

3.8 History of depression in patients with ACS

Evidence suggests that a history of depression is an essential factor for predicting depressive symptoms after ACS (Makkar and Jiloha, 2019; George *et al*., 2021). A study of 115 patients with ACS in Malaysia found that a history of depression was associated with increased depressive symptoms after MI (George *et al*., 2021). These findings were consistent with findings from an Indian study which included 75 patients with ACS and found that a history of depression was significantly associated with an increased risk of depression after ACS (Makkar and Jiloha, 2019). Similarly, a study in Ireland included 169 ACS patients and found that a history of depression was a significant risk factor for depression (Trick *et al*., 2019).

These findings were congruent with other longitudinal studies that found the history of depression was independently associated with worsening or persistence in depressive symptoms over time (Martens *et al*., 2008; Murphy

et al., 2014a). For instance, Murphy *et al*. (2020) studied 911 patients with ACS in Australia. They found that a history of depression was associated with an increased risk of depression in the early and late periods after ACS. Another study by Murphy *et al*. (2014a) found that a history of depression was a predictor of worsening depressive symptoms over six months of an acute cardiac event. Similarly, Schrader *et al*. (2006) found that a history of depression predicted depression 12 months after a cardiac event.

Martens *et al*. (2008) enrolled 287 MI patients in the Netherlands and found that a history of depression was associated with the persistence of depressive symptoms over 12 months of ACS. These findings were consistent with Schrader *et al*. (2004), who enrolled 833 cardiac patients in Australia and found that a history of depression was significantly associated with persistent depressive symptoms 3 months after hospitalisation.

Conclusion of history of depression

In conclusion, history of depression was found to be related to depressive symptoms following ACS (Trick *et al*., 2019; Makkar and Jiloha, 2019). Some studies showed that history of depression predicted persistence of or worsening in depressive symptoms over time (Martens *et al*., 2008; Murphy *et al*., 2014a). In light of the link between history of depression and post-ACS depression, the researcher included this variable in the conceptual model.

3.9 Coping strategies

Lazarus and Folkman (1984), two of the pioneers of the coping theory, define coping as "constantly changing cognitive and behavioural efforts to manage specific internal and/or external demands that are taxing or exceeding the resources of the person" (Lazarus and Folkman, 1984, p. 141). According to their 'Transactional Theory of Stress and Coping', the process of coping includes (1) primary appraisal (a perception that the threat is challenging), (2) secondary appraisal (a realisation that the threat exceeds available resources) and (3) coping responses (identifying ways to deal with the threat) (Lazarus and

Folkman, 1984). Coping responses or strategies include two major dimensions: Problem-focused coping and emotion-focused coping. Problem-focused coping aims at managing or altering the problem causing the distress while emotion-focused coping tries to regulate the emotional responses to the problem (Lazarus and Folkman, 1984, p. 150). Accordingly, Lazarus and Folkman developed a 'Ways of Coping Scale' in order to measure the dimensions of coping strategies (Folkman and Lazarus, 1980; Folkman and Lazarus, 1985).

Some researchers have criticised Lazarus and Folkman's classification of problem-focused and emotion-focused coping (Carver *et al*., 1989; Endler and Parker, 1990b; Compas *et al*., 2001). For instance, Compas *et al*. (2001) argued that emotion-focused coping is too broad and includes a variety of coping strategies. Endler and Parker (1990b) argued that the classification is insufficient and consequently they expanded on the previous work by adding another coping dimension. The three coping dimensions as suggested by Endler and Parker (1990b) is measured using the Coping Inventory for Stressful Situation (CISS) scale and includes: Task-oriented, emotion-oriented and avoidance-coping strategies. Other distinctions used in the literature include: adaptive versus maladaptive coping, engagement versus disengagement, accommodative coping and meaning focused coping and proactive coping approaches (Carver and Connor-Smith, 2010).

Carver *et al*. (1989) found that the classification adopted by Lazarus and Folkman did not provide a clear distinction between useful and less-useful strategies. Accordingly, they developed the COPE inventory which is based on the transactional model of stress and coping and the behavioural self-regulation model (Carver *et al*., 1989). Carver *et al*. (1989) made a distinction between the three coping strategies using the COPE inventory: Problem-focused coping and emotion-focused coping and dysfunctional strategies. In order to reduce the response burden, an abbreviated version of the COPE inventory (Brief COPE) was developed and consists of 28 items and the following 14 coping strategies (Carver, 1997): "active coping, planning, denial, venting of emotion, acceptance, substance use, humour, positive reframing,

use of emotional support, use of instrumental support, turning to religion, self-blame, self-distraction and behavioural disengagement" (Carver, 1997, p.94).

However, Carver (1997) did not report any distinction between the broader dimensions of coping strategies in the Brief COPE and those reported in the original COPE inventory. Instead, Carver suggests that those interested in the broader domains of coping should conduct a factor analysis. Accordingly, some researchers took each of the 14 scales and assessed their relationship to other variables (Carver *et al*., 1999; Charizopoulou *et al*., 2015). Others conducted factor analysis and used the identified higher domains of coping (Bose *et al*., 2015; Sanjuan *et al*., 2016) while some others adopted classifications reported by other researchers without doing their own factor analysis (Cooper *et al*., 2008a; Chiavarino *et al*., 2012).

For instance, Carver *et al*. (1999) looked at each of the 14 strategies and assessed their relationship with distress in patients with breast cancer. They reported that acceptance and humour predicted lower distress while denial and behavioural disengagement predicted higher distress. Dev *et al*. (2021) found that venting of emotions and self-distraction was associated with increased depressive symptoms in cancer patients. Nipp *et al*. (2016) reported that greater use of emotional support and acceptance coping was associated with lower depressive symptoms, while denial and self-blame were associated with higher depressive symptoms in patients with lung or gastrointestinal cancer. Another study by Nipp *et al*. (2017) found that positive reframing, and active coping were related to less depressive symptoms in patients with cancer.

Similarly, Gourounti *et al*. (2013), who conducted a study on women from the general population reported that those who used acceptance coping strategies had fewer depressive symptoms than those who did not. However, women who used denial, self-blame and behavioural disengagement were found to have increased depressive symptoms. Similar findings were reported by Almeida *et al*. (2021) (N=313), who found that self-blame, denial, self-distraction, disengagement, and substance use were associated with increased depressive symptoms. In a study of university students, Rashid *et al*. (2021)

found that using religious strategies was negatively associated with depressive symptoms.

In the context of cardiac illnesses and patients with heart failure, it was reported that using self-distraction, venting, denial and behavioural disengagement were associated with increased depressive symptoms while greater use of acceptance, planning, humour, emotional support was associated with less depressive symptoms (Trivedi *et al*., 2009). This was consistent with Klein *et al*. (2007) who reported denial, self-blame, and self-distraction to be negatively associated with depressive symptoms in patients with heart failure. A review of the literature on heart failure found active coping, planning and acceptance were associated with low depressive symptoms while denial and behavioural disengagement were associated with higher depressive symptoms (Allman *et al*., 2009). Similarly, Giammanco and Gitto, (2016) reported that using positive reappraisal and growth (positive reframing) was significantly associated with lower depressive symptoms in hospitalised cardiac patients (N=200).

Iqbal *et al*. (2021) conducted a study on 240 patients experiencing cardiac surgery and found that self-blame, behavioural disengagement and substance use were negatively associated with physical, psychological, social and environmental domains of the WHOQOL-BREF (Iqbal *et al*., 2021). Likewise, following their pilot study of 37 patients with MI, Bennett *et al*. (1999) found that denial, venting emotion, and behavioural disengagement were associated with depressive symptoms in this cohort. Another study by Charizopoulou *et al*. (2015) enrolled 100 male patients with MI and their findings were consistent with previous studies in that using behavioural disengagement and self-distraction were associated with increased depressive symptoms (Charizopoulou *et al*., 2015). However, the researchers also found that using religious coping was associated with increased depressive symptoms. This latter finding is consistent with Park and Dornelas (2012) who assessed the relationship between religious coping using the Brief Multidimensional Measure of Religion and Spirituality (BMMRS) and depressive symptoms using the Centre for Epidemiological Studies-Depression (CES-D) scale. The study

results showed that using religious coping was associated with increased depressive symptoms one month following MI.

Broader domains of coping

Coping strategies have been measured in patients with ACS using several instruments. These instruments vary in the way coping is conceptualised. According to Skinner (2003), the conceptualisation of coping is complex with more than 100 classifications of coping in the literature. CISS is one of the instruments commonly used to assess coping strategies in patients with ACS (De Fazio *et al*., 2012; Messerli-Bürgy *et al*., 2015; Svensson *et al*., 2016; Bafghi *et al*., 2018). Endler and Parker (1990) expanded upon the previous classification of Lazarus and Folkman and proposed three coping strategies: task-oriented coping, emotion-oriented coping and avoidance coping. Bafghi *et al*. (2018) used CISS to evaluate the coping strategies of 220 patients with MI and 220 patients without MI or history of MI. They found that MI patients tended to have higher levels of stress compared to those without MI. In addition, more than half of MI patients (n=118) used emotion-oriented coping strategies, 97 (82.2%) of whom reported high perceived stress. Also using CISS, Messerli-Bürgy *et al*. (2015) evaluated the association between task-oriented coping and event free survival in 158 ACS patients. The researchers reported that patients in the upper half of the distribution of 'task-oriented coping' were associated with 73% lower hazard of major cardiac events over an average of 5 years of ACS compared to those in the lower half of the distribution.

Similarly using CISS, Svensson *et al*. (2016), found avoidance coping to be associated with increased IHD-related mortality in patients with hypertension. Using a sample of 70 ACS patients, De Fazio *et al*. (2012) reported high emotion-oriented coping, high avoidance coping and low task-oriented coping to be significantly associated with higher depressive symptoms following ACS. One study by Kroemeke, (2016) evaluated trajectories of depressive symptoms over 6 years following MI and found that patients with chronic depression reported increased use of emotion-oriented coping.

Another study used the New Italian Version of COPE Inventory (COPE-NVI-25) to assess coping strategies in women who had experienced MI and those without MI (Fuochi and Foà, 2018). The COPE-NIV-25 includes five dimensions: avoidance, religion, acceptance, social support and problem-oriented coping. Fuochi and Foà (2018) found that problem-oriented coping was positively correlated with all the physical, psychological, social and environmental domains of WHOQoL while avoidance coping was negatively correlated with the physical, psychological and environmental domains of WHOQoL.

Some studies used the Jalowiec Coping scale (JCS) to assess coping strategies in patients with ACS (Bagherian-Sararoudi *et al*., 2011; Bagherian *et al*., 2011; Panthee *et al*., 2011). The JCS consists of 60 items and was developed based on the classification of Lazarus and Folkman (Jalowiec, 1988). It comprises 8 subscales that measures problem-focused coping (confrontational, optimistic, supportive and self-reliant) and emotion-focused coping (emotive, evasive, palliative, and fatalistic) (Jalowiec *et al*., 1984, Jalowiec, 1988). Using the JCS, Bagherian Sararoudi *et al*. (2011) found that confronting and supportive coping strategies were associated with lower depressive symptoms in patients with MI, while Bagherian *et al*. (2011) found that optimistic and supportive coping strategies were associated with lower depressive symptoms in patients with MI.

The Cognitive Emotion Regulation Questionnaire (CERQ) was developed by Garnefski *et al*. (2001), to assess the cognitive aspects of coping strategies and is used in patients with ACS. Garnefski *et al*. (2001) criticised Lazarus and Folkman's classification in that both problem-focused and emotion-focused strategies include a mixture of cognitive and behavioural coping strategies. The CERQ is composed of 8 coping strategies that can be classified theoretically into adaptive and maladaptive coping. Adaptive coping includes planning, acceptance, positive reappraisal, and positive refocusing while maladaptive coping includes rumination, catastrophising, self-blame and blame others (Garnefski *et al*., 2001).

Garnefski *et al*. (2009) tested the relationship between cognitive-coping strategies and depressive symptoms of 139 patients, 3 to 12 months following first MI. The study used three subscales of CERQ: rumination, catastrophising and positive refocusing. Rumination relates to obsessive thinking about threatening or stressful situations while positive refocusing involves thinking about joyful events rather than the stressful situation. Catastrophising involves exaggerating the negative impact of the stressful situation and jumping to the worst possible conclusion (Garnefski *et al*., 2001). In their study, Garnefski *et al*. (2009) found that rumination and catastrophising coping strategies were positively correlated with depressive symptoms, while positive refocusing was negatively correlated with depressive symptoms after MI.

Following on from this, Garnefski and Kraaji (2010) assessed the relationship between cognitive coping strategies and depressive symptoms on 88 patients between 3-12 months after MI and again 12 months following enrolment. The researchers reported that using rumination and catastrophising coping strategies predicted higher depressive symptoms at both time points. Conversely, using positive refocusing strategies was a predictor of lower depressive symptoms at baseline and again 12 months later (Garnefski and Kraaji, 2010).

Broader domains of coping using Brief COPE

There is no consistency in the literature regarding the factor structure of the Brief COPE (Krägeloh, 2011). Most studies conducted factor analysis and identified different factors ranging from 2 (Sanjuan *et al*., 2016) to 11 (Tang *et al*., 2016). Other studies supported the 14 factor structure of Brief COPE (Monzani *et al*., 2015; García *et al*., 2018). In the context of cardiac illnesses, Sanjuan *et al*. (2016) enrolled 153 patients after a cardiac event and evaluated the association between coping strategies and depressive symptoms using the Brief COPE and the Depressive Symptoms Subscale of Symptoms Check List Revised (SCL-90-R) respectively. The study conducted Exploratory Factor Analysis (EFA) and distinguished between 2 broader coping strategies: effective and non-effective. Effective coping strategies included active coping, planning, self-distraction, acceptance, positive reappraisal, instrumental social support and humour. Non-effective coping strategies included behavioural disengagement, substance abuse, denial, self-blame, emotional social support, venting and religion. The study found that effective coping strategies were negatively correlated with depressive symptoms after a cardiac event. On the other hand, Bean *et al*. (2009) enrolled 100 patients with heart failure and evaluated the association between coping strategies (using Brief COPE) and depressive symptoms (using HADS). Using EFA, two coping strategies were identified: (1) active coping which included acceptance, use of instrumental support, emotional support, religion, active coping, planning, and positive reframing (2) avoidant coping which included self-blame, humour, substance use, self-distraction, behavioural disengagement, venting and denial. Bean *et al*. (2009) found that avoidant coping was significantly associated with increased depressive symptoms in patients with heart failure.

As shown above, Sanjuan *et al*. (2016) identified ineffective coping strategies as religion and emotional social support while Bean *et al* (2009) identified these same coping strategies (religion and emotional social support) as active coping strategies. Sanjuan *et al*. (2016) identified self-distraction as an effective coping strategy while it was identified as avoidance coping strategy by Bean *et al*. (2009). Inconsistencies in the factor structure of the Brief COPE might have

attributed to the differences reported, owing to the statistical methods used such as EFA or CFA and/or the use of item level analysis or scale level analysis (Krägeloh, 2011).

On the other hand, Cooper *et al*. (2008a) used the Brief COPE in carers of patients with dementia without conducting a factor analysis and operationalised the classification of the COPE inventory as reported by Carver (1989). The 3-factor classification involved problem-focused coping, emotion-focused coping and dysfunctional coping. Cooper *et al*. (2008a) found that this classification of the brief COPE showed construct validity, good internal consistency and adequate one year stability. Chiavarino *et al*. (2012) used the Brief COPE as operationalised by Cooper *et al*. (2008) in patients with ACS and found that emotion-focused strategies predicted cardiac disease severity (as measured by LVEF) three months after ACS. The researchers also found that patients who reported using higher emotion-focused strategies were found to have higher LVEF at three months (Chiavarino *et al*. 2012).

Carver and colleagues (1989) developed the COPE inventory to assess three distinct dimensions of coping: problem-focused coping, emotion-focused coping and dysfunctional coping. The authors conducted exploratory factor analysis of the COPE inventory and found that both the seeking emotional and instrumental social support subscales were loaded together into a single factor. Likewise, Carver (1997) conducted exploratory factor analysis of the 14-scales of the Brief COPE in order to identify higher-order structure of coping. The author identified nine factors where both the seeking instrumental and emotional social support subscales loaded on a single factor reflected social coping. In the current study, the researcher evaluated the factor structure of the Arabic version of the Brief COPE by comparing several models based on theory and previous research. The researcher found that the four-factor model, which included problem-focused, emotion-focused, dysfunctional and social coping provided the best fit to the data (Appendix VI).

Conclusion of Coping Strategies

In conclusion, the above studies suggest that the evidence pertaining to coping is continuously moving forward with the view of coping as a multifaceted concept. The reviewed literature suggests that people usually use a variety of coping strategies during stressful situation (Carver *et al*., 1989; Lazarus, 1993). Problem-focused coping can be an effective strategy when the threat is perceived as manageable, while emotion-focused strategies works best when the threat cannot be changed (Lazarus, 1993; Cooper *et al*., 2008a). Using problem-focused coping strategies was found to be associated with lower depressive symptoms, while using emotion-focused coping strategies may be considered useful in some situations and associated with fewer depressive symptoms. In other situations, emotion-focused coping might be less useful "dysfunctional" and associated with increased depressive symptoms.

In the current study, the researcher identified four factors of coping strategies that match with the theoretical classification of coping as suggested by Carver *et al*. (1989). This classification includes problem-focused coping, emotion-focused coping, dysfunctional coping and social coping. The classification was similar to that operationalised by Cooper *et al*. (2008a) except that instrumental and emotional coping were included together in the social coping scale. This was congruent with second order factor analysis conducted by Carver *et al*. (1989) and Carver (1997). Accordingly, it was considered that problem-focused coping, emotion-focused coping, dysfunctional coping and social coping would have an association with depressive symptoms in this current study, and these variables were also included in the conceptual model

3.10 Depressive symptoms in patients with ACS

As mentioned previously, depressive symptoms are common in patients with ACS. A recent meta-analysis that reviewed the prevalence of depressive symptoms in patients with MI in 19 studies reported that prevalence ranged from 9.2% to 65.9%, with a pooled prevalence of 28.7% (95% CI: 22.4-35.5%) (Feng *et al*., 2019). The prevalence of clinical depression was found to be

around 20% in patients with ACS (Annagür *et al*., 2017). Depressive symptoms were found to be associated with increased mortality and cardiac events after ACS. A meta-analysis investigating the association between depression after MI and clinical prognosis found that depression after MI was associated with a 1.6-times increased risk of cardiac events, 2.3-times increased risk of all-cause mortality, and 2.7-times increased risk of cardiac mortality (Meijer *et al*., 2011). Whang *et al*. (2010) found that depressive symptoms was associated with 2-times increased all-cause mortality 42 months after unstable angina. Likewise, Larsen *et al*. (2013) found that MI patients with depressive symptoms had 2 times increased risk of mortality compared to patients with no depressive symptoms.

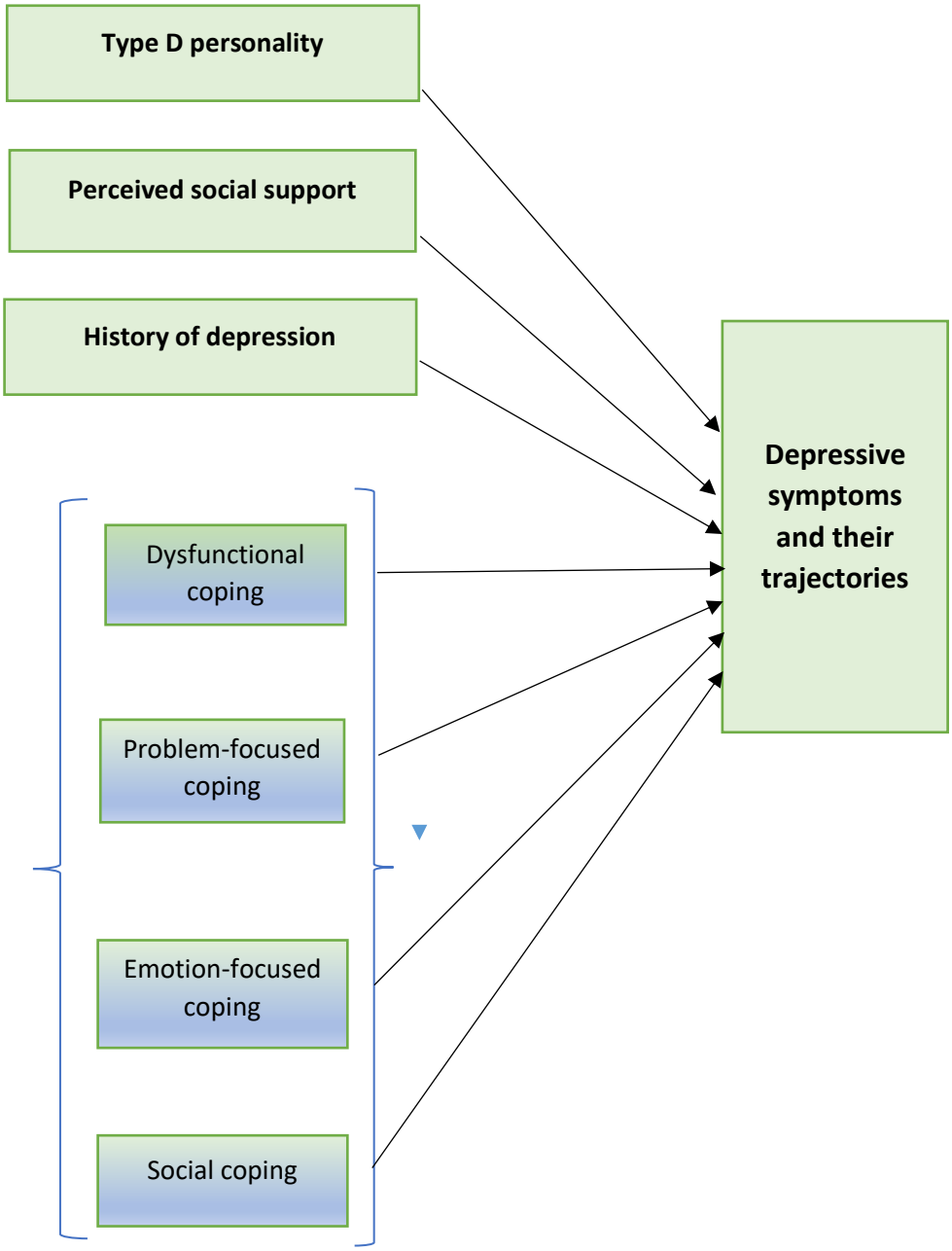
In addition, depressive symptoms in patients with MI were associated with increased hospital readmission and reduced their adherence to cardiac rehabilitation programs (Myers *et al*., 2012). Furthermore, a systematic review and meta-analysis showed that ACS patients with depressive symptoms were 2 times more likely to be non-adherent to medications compared to those without depressive symptoms (Crawshaw *et al*., 2016). Accordingly, the AHA conducted a systematic review to evaluate the impact of depression on ACS prognosis and they concluded that depression is a risk factor for poor outcomes in patients with ACS (Lichtman *et al*., 2014). Accordingly, the AHA and the ESC have recommended routine screening for depressive symptoms after ACS (Lichtman *et al*., 2014; Piepoli *et al*., 2016). As such, depression is considered the main variable of interest in this study and the dominant concept in the conceptual model.

3.11 The conceptual model of relationships

The international literature reviewed above has indicated that history of depression, personality type D, coping and perceived social support are associated with depressive symptoms. As such, these concepts became the main variables for consideration in this study, as demonstrated in the conceptual model below (Figure 3). It was considered that type D personality along with perceived social support and coping strategies, would have a direct

effect on trajectories of depressive symptoms at 6-months. Coping was described according to Carver's conceptualisation in the context of Lazarus and Folkman's theory of stress and coping. The direction of arrows indicates the considered influence of psychosocial variables on trajectories of depressive symptoms at 6 months of ACS. Other variables such as age, gender, comorbidities, and LVEF were treated as covariates and were controlled for in the analysis.

Figure 3: The conceptual model of relationships



In conclusion, this chapter has presented the methodology underpinning the study, from an ontological, epistemological, and methodological perspective. The conceptual model guiding the study was also discussed and contextualised. This model suggests that a relationship exists between psychosocial variables and trajectories of depressive symptoms. The following chapter outlines the methods used to address the research aim and objectives.

Chapter 4: Methods

Introduction

This longitudinal study examines trajectories of depressive symptoms among Jordanian patients with an ACS event, and their relationship with psychosocial variables. Specifically, it describes prevalence, incidence, and trajectories of depressive symptoms after an ACS event; and identifies predictors of these trajectories. This chapter discusses the research methods that were used in the study. The chapter also describes the research site, population, sample, sampling technique, and instruments used in the study. Measures considered to ensure compliance with ethical standards are also discussed in detail. Finally, the chapter describes the techniques utilised in data collection, data management and analysis.

4.1 Research Sites

Jordan is an Arab country located in western Asia, on the east bank of the Jordan River. According to the Department of Statistics (DOS) in Jordan, it has a population of around 10 million (DOS, 2017). Approximately 30% of the population in Jordan are refugees from neighbouring countries such as Palestine, Syria, and Iraq (Overseas Development Institute, 2018). Jordan consists of twelve governorates in three regions: northern, central, and southern regions (Hadidi, 2017). The majority of the population in Jordan (64%) live in the central region (DOS, 2017) which includes four governorates: Amman, Zarqa, Madaba and Balqa. Amman is the capital of Jordan and most people (nearly 42%) live there (Hadidi, 2017). The health care system in Jordan is comprised of public and private sectors, and some non-profit organisations/charitable clinics (Hadidi, 2017). According to the Ministry of Health, public and private sectors in Jordan include 116 hospitals with 14,779 beds (MOH, 2017), of which approximately 66% and 34% of hospital beds are in public and private hospitals respectively (DOS, 2017). The majority (70.1%) of hospital beds are available in the central region of Jordan (DOS, 2017; MOH, 2017). Accordingly, the central region of Jordan was chosen as the location for

selecting hospitals as it covers most of the Jordanian population and has the largest number of hospital beds. In addition, the central region of Jordan includes the largest hospitals, which usually receive referrals from smaller hospitals in the northern and southern regions.

Four large hospitals were selected from the private and public sectors. Eligibility for selecting hospitals included (a) the largest hospitals based on the number of beds and (b) having cardiology wards and coronary care units. The rationale for choosing hospitals with coronary care units (CCU) and cardiology wards is because they are the most common sites for recruiting ACS patients (O'Neill *et al*., 2017). The non-profit organisations were not included in the hospital selection process as they mainly focus on providing primary care services in Jordan and do not provide treatment for acute cardiac cases (Hadidi, 2017).

Details of the four selected hospitals are as follows: Hospital A is a public hospital in Jordan, comprising 1101 beds, including 18 CCU beds and has approximately 100,000 admissions per year. Hospital B is another public university hospital with 599 beds, including 68 in the intensive care unit (ICU) and CCU. Hospital C is a public hospital with 442 beds, including 17 in CCU and 46 in the cardiac surgery unit. Hospital D is a large private hospital in Jordan with 273 beds, including 11 in the CCU (Table 5).

Table 5: Summary of the participating hospitals in Jordan

Hospital	Number of beds	Other details
Hospital A	1101	18 CCU beds
Hospital B	442	17 CCU beds and 46 cardiac surgery unit
Hospital C	599	69 beds for both ICU and CCU
Hospital D	273	11 CCU beds

4.2 Research Population

The research population refers to a set of individuals or elements with common features that suits the researchers' interest (Nieswiadomy and Bailey, 2018). The target population is the population about which the researcher is

interested in drawing conclusion and making generalisations (Nieswiadomy and Bailey, 2018). The accessible population is a subset of the target population, that is accessible to the researcher, and from which the sample can be drawn (Polit and Beck, 2018; Boswell and Cannon, 2018). In this study, the target population includes all patients in Jordan who experienced an ACS event. The accessible population includes patients who experienced an ACS event and were admitted to any of the four participating hospitals in Jordan between 1st August 2017 and 28th February 2018.

4.3 Sample and Sampling

The sample is a group of individuals or objects taken from the accessible population through a defined sampling method to draw conclusions about the target population (Boswell and Cannon, 2018). The method used for selecting the sample can determine the extent to which the sample is representative of the target population (Nieswiadomy and Bailey, 2018). A non-probability convenience method of sampling was used to recruit patients from the four chosen hospitals. In non-probability sampling, the researcher selects patients in a non-random way (Cohen *et al*., 2018; Polit and Beck, 2018). Convenience sampling is a type of non-probability sampling methods that allows the researcher to include patients based on availability or accessibility (LoBiondo-Wood and Haber, 2017). This sampling method was chosen because it provides easy access to patients using a simple method, and less expensive way compared to other methods (LoBiondo-Wood and Haber, 2017; Polit and Beck, 2018). However, given the selection of patients in this type of sampling is non-random it may increase the risk of selection bias, and decrease the generalisability of the results (Cohen *et al*., 2018).

4.3.1 Inclusion and exclusion criteria

Selecting appropriate inclusion and exclusion criteria is an essential measure to enhance the validity of a study's results (Boswell and Cannon, 2018; Patino and Ferreira, 2018). Including variables that are unrelated to the study aims or objectives or excluding variables that do not make a difference to the outcome,

could result in potential bias, and impact the external validity of the study (Patino and Ferreira, 2018). Polit and Beck (2018, p. 550) define inclusion criteria as the "criteria designating the specific attributes of the target population, by which people are selected for inclusion in a study". In other words, inclusion criteria are those characteristics that potential patients should have in order to be included in the study (Patino and Ferreira, 2018). Accordingly, patients were considered eligible to participate in the study if they:

a. were admitted to one of the four participating hospitals in Jordan with a diagnosis of ACS and were aged over 18 years.
b. were able to read, understand and speak the Arabic language.
c. had access to a telephone.
d. had ability to give consent.
e. were haemodynamically stable (as assessed by the gatekeeper).
f. were resident in Jordan.

According to Boswell & Cannon (2018, p.226), exclusion criteria "are not the polar opposite of the inclusion criteria; rather, they are characteristics that, if present, would make persons ineligible to be in the sample, even though they might meet all of the inclusion criteria". Patino & Ferreira, (2018) contend that using the same criterion in both inclusion and exclusion is one of the common errors that could lead to excluding variables that are related to the study. Hence, the following exclusion criteria were selected, and patients were excluded from this study if they:

a. were too ill to participate, as determined by the gatekeeper.
b. had a major or uncorrected hearing loss.
c. were unwilling to participate in the follow-up at 1, 3 and 6 months.
d. had a terminal illness as determined by actively receiving end of life care.
e. had a current diagnosis of substance dependence.

Rationale for inclusion and exclusion criteria

Patients were included in this study if they had a diagnosis of ACS as this was the population of interest. Patients were required to be aged over 18 due to the low incidence of primary ACS in those younger than 18 (Kondo *et al*., 2021). Being able to read, understand and speak the Arabic language was required in order that the patient could understand the details of study, provide informed consent, and complete the questionnaires. Given that some questionnaires would be completed over the telephone, access to a telephone was important. Patients were required to be resident in Jordan as many refugees temporarily reside in Jordan and could potentially leave at any time during the study period. Including patients who might leave Jordan during the follow-up period could increase the number of those lost to follow-up, thus reducing the generalisability of the study's results.

Patients were excluded from this study if they were unstable (too ill) as this could affect their ability to provide informed consent in addition to affecting their ability to complete the questionnaires. Further, they may have multiple comorbidities, which might confound the study results. Likewise, terminally ill patients actively receiving end of life care were excluded due to their potential inability to follow-up. As the nature of this study is longitudinal and attrition is one of its main concerns, those unwilling to participate in the follow-up were excluded. Patients who had major hearing loss were excluded as questionnaires at 1, 3 and 6 months were conducted by telephone. Finally, patients with a current diagnosis of substance dependence were excluded due to its potential impact on the assessment of depressive symptoms (Weatherford, 2012).

4.3.2 Sample Size

This study aimed to evaluate depressive symptoms over time to determine changes that occur in depressive symptoms following discharge. Therefore, sample size was estimated for Trajectory analysis. Different factors were considered when estimating the sample size. The prevalence of depressive symptoms was evaluated during hospitalisation. However, incidence of depressive symptoms was evaluated at 1, 3 and 6 months. Therefore, the

sample size was estimated for both prevalence and incidence. Factors related to depressive symptoms at baseline were also evaluated. This kind of analysis was conducted to provide insight into which factors might predict different trajectories of depressive symptoms over time. Consequently, sample size was estimated for using logistic regression. This study also included Type D personality and coping strategies as psychological predictors of depressive symptoms and their trajectories. In order to use the Type D personality scale (DS14) in subsequent analyses, it was necessary to check if the items and subscales were measuring what was intended to be measured using CFA. This was necessary because the DS14 scale had been translated into Arabic and had never been used in Jordan. Likewise, with the Brief COPE scale which consists of 28 items and 14 subscales, it was not practical (need a large sample size) to include the 14 subscales as predictor variables for depressive symptoms and their trajectories. Therefore, CFA was used to generate a higher order factor structure to use the new generated scales as predictor variables. Accordingly, the sample size was estimated using CFA for the DS14 and Brief COPE.

The following statistical considerations/tests influenced the sample size.

(1) Prevalence rate. The sample size for assessing prevalence of depressive symptoms was estimated using the following formula: $N=4p(1-p)/L^2$, where N= sample size, p= prevalence from previous studies, and L=allowable error (Singh and Masuku, 2014). According to a recent meta-analysis on prevalence of depressive symptoms in 10 countries, the prevalence of depressive symptoms in patients with ACS ranged from 9.2% to 65.9% while the pooled prevalence was 28.7% (Feng *et al*., 2019). Accordingly, assuming a prevalence of depressive symptoms in previous studies of 29%, and allowing an error of 5%, the required sample size for this study was calculated as 329 patients.

(2) Logistic regression. The research aims and objectives required that logistic regression would be necessitated for data analysis. The sample size for logistic regression was calculated based on Peduzzi and colleagues (1996) formula: $N=10k/p$, where K is the number of independent variables, and p is the proportion of patients with who are depressed in the sample. Assuming the

proportion of patients with elevated depressive symptoms is *p*=0.29, then the required sample size for 10 independent variables would be 345 patients.

(3) **Incidence.** This refers to risk in terms of events per individual per time (Lemeshow *et al*., 1990). The incidence of depressive symptoms over a period of six months was estimated to be within 10% of the true value (ε=0.10), with a 95% confidence interval, using the following formula: $N=(Z_{1-\alpha/2}/\varepsilon)^2$, where $Z_{1-\alpha/2}=1.96$ and ε=0.10 (Lemeshow *et al*., 1990). Accordingly, a sample of 385 patients was required to estimate incidence.

(5) Factor analysis. Guidelines for sample size required for factor analysis varies, but there is some consensus that 10 observations per item is required (Bentler and Chou, 1987), with a minimum of 200 observations (Comrey and Lee, 1992). The DS14 and Brief COPE scales consist of 14 and 28 items, respectively. Therefore, a sample size of around 280 would be adequate.

(6) Trajectory analysis. In trajectory-based modelling and subsequent examination of covariates of trajectory classes, no formal power calculation can be meaningfully applied. The ability to infer classes is dependent on the proportion of patients in each class, which is impossible to know in advance (Nagin, 2010). This sort of exploratory analysis has been carried out in the past, in cohorts (ACS & Depression) ranging from 100 subjects upwards (Tisminetzky *et al*., 2011; Murphy *et al*., 2014a). Curran *et al*. (2010) recommends a sample of at least 100 patients for group-based modelling. Some evidence suggests that a sample of 200 subjects is preferred when identifying trajectories (Diallo and Morin, 2015). However, a target sample size of 200 was increased based on likely attrition during the follow-up period. An estimate of 20% (200*1.25= N=250) was considered reasonable to address this issue.

However, for model stability, one would require 10 to 20 observations per predictor variable in a linear model (Harrell, 2001), and so to fit a model with 3 dummy variables for categorical time would require at minimum 20 patients with complete longitudinal data. In latent class methods, to infer groups of patients, one might conservatively speculate that a subgroup consists of 5% of the patients, and that one would require 20 patients in that group. Therefore,

a total of 400 patients was required. Based on the above, the minimum sample size to address all these issues was estimated to be 400 patients.

4.4 The Research Instruments

A total of 6 questionnaires were used to collect data that would address the study aims and objectives (Appendix III). Two of these were researcher administered with some patient reporting and included:

1) The previously validated Patient Heath Questionnaire for Lifetime Screening of Depression (PHQ-LSD)
2) A questionnaire devised by the researcher detailing the patients' sociodemographic details, medical history, and clinical characteristics.

The remaining previously validated questionnaires were self-reported (Table 6), took less than 25 minutes to complete and included:

3) Patient Health Questionnaire (PHQ9).
4) Multidimensional Scale of Perceived Social Support (MSPSS).
5) Brief COPE.
6) Type D Personality Scale (DS-14).

Permission was obtained to use all validated questionnaires. Some were freely available in the public domain; therefore, permission was not required to use them in this study. The authors who translated the Brief COPE, and MSPSS into the Arabic language, granted the researcher permission to use them in this study (Appendix IV).

4.4.1 Patient Health Questionnaire for Lifetime Screening of Depression (PHQ-LSD)

The PHQ-LSD is a researcher-administered version of the PHQ-9, that was validated to measure history of lifetime depression (Cannon *et al*., 2007). Patients who reported having a history of depression were asked about their symptoms of depression using the following question "For the 2 weeks in your life that you were the most blue, sad, or depressed, how often were you bothered by any of the following problems?" (Cannon *et al*., 2007, p 249) Those

who reported having any five depressive symptoms nearly every day were considered as having a lifetime history of depression. Internal consistency (Cronbach's α) for this instrument was deemed excellent at 0.94 (Cannon *et al*., 2007).

PHQ-LSD data were collected at baseline during hospitalisation to evaluate patients as having a history of depression or not. History of depression was found to be associated with increased depressive symptoms during hospitalisation and with persistence of these symptoms after discharge (Martens, *et al*. 2008). Patients who reported no history of depression were evaluated at 1, 3, and 6-months using Patient Health Questionnaire 9 (PHQ-9) to estimate the incidence of depressive symptoms over 6 months of ACS.

4.4.2 Sociodemographic details, medical history, and clinical characteristics

Patients (assisted by the research nurse where required) recorded their age, gender, marital status, educational level, income, medical insurance, employment status, living status, current smoking status and family history of depression on the personal details section of the questionnaire. The research nurse assisted patients to complete this information when required and retrieved data pertaining to medical history and clinical characteristics from the medical notes. Data included medical diagnosis, length of hospital stay, total cholesterol level, body mass index and measures of ACS severity and comorbidities. These included the following measures:

I. Left Ventricular Ejection Fraction (LVEF):

Following ACS, patients' LVEF is routinely measured using echocardiogram. Results below 40% indicates low LVEF and is the cut-off score used in most studies that evaluates ACS severity following an event (Meurs *et al*., 2013; Keegan *et al*., 2016; Roest *et al*., 2016). Previous studies showed that low LVEF was associated with increased depressive symptoms (Jonge *et al*. 2006; Roest, *et al*. 2011) and poor HRQoL following an ACS event (Dzubur *et al*. 2016; Kang, *et al*. 2018).

II. **The Global Registry of Acute Coronary Events (GRACE)**: This is a risk scoring instrument commonly used to estimate six-month mortality among patients

following an ACS event (Abu-Assi *et al*., 2010; Fox *et al*., 2010). It was used by Meurs *et al.* (2013) when examining factors associated with depressive symptoms amongst this cohort. The instrument was originally developed and validated by Eagle *et al*. (2004). Its validity for predicting mortality was reported in a study conducted with more than 100,000 patients across 30 countries (Fox *et al*., 2010). These findings are congruent with other large studies carried out in six Arabic countries, where good validity of the GRACE instrument in predicting six-month (Yusufali *et al*., 2011) and one-year mortality following ACS events was reported (Thalib *et al*., 2016). GRACE scores can be calculated by adding points for each of the following variables: age, heart rate, creatinine level, systolic blood pressure, history of congestive heart failure, history of MI, elevated cardiac troponin, ST segment depression, and in-hospital percutaneous coronary intervention (Eagle *et al*., 2004). GRACE scores range from 1 to 263, with higher scores indicating higher risk of mortality (Eagle *et al*., 2004).

III. **Charlson Comorbidity Index (CCI):** The CCI is a simple and valid tool used for estimating mortality risk in individuals with comorbid diseases (Charlson *et al*., 1987). It has also been widely used as a prognostic indicator of poor outcomes in a variety of clinical populations, including critically ill patients (Barnes, *et al.* 2013). The CCI contains 17 comorbidities, with each one classified from 1 to 6 for mortality risk. Scores are calculated to form a total CCI score, which if more than 5, is associated with greatest risk of one-year mortality (Charlson *et al*., 1987). The CCI is a valid tool for predicting in-hospital and one-year mortality in patients with ACS (Radovanovic *et al*., 2014). Recent evidence shows that using both CCI and GRACE after an ACS event, predicts mortality better than using either on their own (Erickson *et al*., 2014).

4.4.3 Self-Reported Questionnaires

Patient Health Questionnaire (PHQ-9)

The nine-item PHQ is a brief self-reported questionnaire that was developed by Spitzer *et al*. (1999a) to replace the interviewer-administrated Primary Care Evaluation for Mental Disorders (PRIME-MD) questionnaire. The PHQ-9 was

designed to measure depression and its severity according to the nine criterion symptoms of the Diagnostic Statistical Manual of mental disorders (DSM-IV) (Kroenke and Spitzer, 2002; Kroenke *et al*., 2001). Each symptom is rated from 0 to 3 using a 4-point Likert scale, with total scores ranging from 0 to 27. The higher the total score, the more severe the depressive symptoms, based on the following cut-off scores: 5 (mild), 10 (moderate), 15 (moderately severe) and 20 (severe) (Kroenke *et al*., 2001).

Early validation studies of the PHQ-9 reported good sensitivity (88%) and specificity (88%) in detecting clinical depression at a cut-off score of 10 (Kroenke and Spitzer, 2002; Kroenke *et al*., 2001). This score has been validated to measure depression among clinical (Gilbody *et al*., 2007, Moriarty *et al*., 2015) and non-clinical populations (Martin *et al*., 2006; Manea *et al*., 2012). The PHQ-9 has been commonly used to identify symptoms of depression in a variety of medical conditions (van Steenbergen-Weijenburg *et al*., 2010; Rathore *et al*., 2014) including CHD (Stafford *et al*., 2007; Haddad *et al*., 2013). Internal consistency (Cronbach's α) of the PHQ-9 in patients with CHD was reported as excellent (0.85) (Haddad *et al*., 2013) and was consistent with that reported in the original studies (0.86) (Kroenke and Spitzer, 2002; Kroenke *et al*., 2001). The original English version has been translated into several languages, including Arabic (Pfizer, n.d.) The Arabic version has shown a criterion validity against clinical interviews with 431 patients in Saudi Arabia (Becker *et al*., 2002). In addition, the PHQ-9 has shown good reliability (Cronbach's $\alpha = 0.82$), when administered by telephone (Pinto-Meza *et al*., 2005b).

Multidimensional Scale of Perceived Social Support (MSPSS)

The MSPSS was originally developed by Zimet *et al*. (1988) to measure perceived social support among undergraduate students using three subscales: family, friends and significant others. The scale contains 12 items with response options ranging from 1 to 7 and total scores ranging from 12 to 84. Higher scores indicate greater perception of social support. The MSPSS has good psychometric properties in both clinical (Pedersen *et al*., 2009; Bagherian-

Sararoudi *et al*., 2013) and non-clinical populations (Wongpakaran *et al*., 2011; Merhi and Kazarian, 2012).

Construct validity of the original scale has been examined using correlations with anxiety and depressive symptoms and showed moderate levels. Internal consistency and test-retest reliability of the scale were 0.88 and 0.85, respectively (Zimet *et al*., 1988). In cardiac patients, the MSPSS showed high structural and construct validity and high internal consistency (Cronbach's α = 0.94) (Pedersen *et al*., 2009). Similarly, an Iranian study conducted in patients post MI showed good internal consistency (Cronbach's α = 0.84) and stable two-month test-retest reliability (*r* = 0.84) (Bagherian-Sararoudi *et al*., 2013). The Arabic version of the MPSS that was used among Jordanian patients with CHD, reported Cronbach's α for "family", "friends", and "significant others" subscales of 0.85, 0.79, and 0.75, respectively (Ghannam *et al*., 2014).

Type D Personality Scale (DS-14)

The 14-item Personality Type D scale comprises 7 items (2,4,5,7,9,12,13) for Negative Affectivity (NA) and 7-items (1,3,6,8,10,11,14) for Social Inhibition (SI) (Denollet, 2005). Each item in the NA and SI subscales is rated on a 5-point Likert scale (0–4); the SI subscale contains two reversed items (1,3). The total score for each subscale ranges from 0 to 28. Respondents who obtain scores of 10 or more in the NA and SI subscales are referred to as Type D (Denollet, 2005).

The original scale was validated against the Neo five factor inventory scale (NFO-FFI) and demonstrated construct and structural validity. Reliability of the DS14 was good with Cronbach's α of 0.88 and 0.86 and test-retest reliability of 0.72 and 0.82 for the NA and SI subscales, respectively (Denollet, 2005). The DS14 has been commonly used in ACS patients (Marchesi *et al*., 2014; Arslan *et al*., 2016) and showed cross-cultural equivalence among cardiac patients (including ACS), across 22 countries (Kupper *et al*., 2013). To my knowledge, there is no previous translated and validated Arabic version of DS14 in Jordan. Thus, the researcher translated the original English version of DS14 into the

Arabic language and evaluated its psychometric properties. Complete details of these processes can be found in Appendix V. Permission to translate the DS14 into the Arabic language was sought and obtained from the developer of the questionnaire (Appendix IV).

Validity and reliability of Type D personality scale

The structural validity of the AR-DS14-was tested using Confirmatory Factor Analysis (CFA). Confirmatory factor analysis was conducted using Weighted Least Squares Mean and Variance Adjusted (WLSMV) as a model estimator. The WLSMV estimator was chosen because items of DS14 measured on a five-point ordinal scale. Proitsi and colleagues (2009) reported that WLSMV method of estimation would be the best choice when the data are ordinal. One factor solution was compared to the two-factor solution based on several model fit indices. In one-factor model, all items of DS14 were loaded into a single factor. In the two-factor model, 7 items (2,4,5,7,9,12,13) were specified for one factor (Negative affectivity) and 7 items (1,3,6,8,10,11,14) for another factor (Social inhibition). Five model fit indices were considered to estimate model fit such as (1) Chi-squared statistics ($\chi 2$); (2) Root Mean Square Error of Approximation (RMSEA); (3) Comparative fit indices (CFI); (4) Tuker-Lewis index (TLI) and (5) Standardized Root Mean Square Residual (SRMR). Kline (2005) suggested using several indices simultaneously to indicate a goodness of model fit. The model was considered a good fit based on the following cut-off points. The *p*-value for $\chi 2$ test was not significant (>.05) and the ratio of $\chi 2$ value to the degree of freedom (df) equal to three or less. Regarding RMSEA and SRMR indices, values below a cut-off point of.08 and.05, respectively suggested a good model fit. For CFI and TLI indices, values above .90 indicated reasonable fit and values above .95 suggest a good model fit (Kline, 2005).

The construct validity was confirmed by examining the relationship between Type D and other constructs such as depressive symptoms, coping and perceived social support. The internal consistency reliability of the DS14 was evaluated using Cronbach's Alpha and Corrected Item- Total Correlation (CITC).

Brief Coping Orientation to Problems Experienced (Brief COPE)

The Brief COPE is a short version of the 60-item COPE Inventory (Carver, 1997). It consists of 28 items that measure the following 14 coping strategies: (1) acceptance, (2) emotional support, (3) humour, (4) positive reframing, (5) religion, (6) active coping, (7) instrumental support, (8) planning, (9) behavioural disengagement, (10) denial, (11) self-distraction, (12) self-blame, (13) substance abuse, and (14) venting (Carver, 1997). Each of these strategies are rated on a 4-point Likert scale ranging from 1 to 4. Coolidge *et al*. (2000) classified the strategies into three main scales: emotion-focused (1-5), problem-focused (6-8) and dysfunctional coping strategies (9-14). The reliability of the three subscales of Brief COPE have been reported in caregivers of individuals with Alzheimer's disease (Cooper *et al*., 2008b). Cronbach's α for the problem-focused coping scale was good at .84, while the emotion-focused and dysfunctional coping scales were adequate at.72, and.75, respectively (Cooper *et al*., 2008b). The classification operationalised by Coolidge and colleagues (2000) was based on adopting the same subscales of the original COPE inventory. However, Carver (1997), reported that there is no specific instruction on how to combine the 14 scales of Brief COPE into two or three aggregates. The author suggested using each scale separately to evaluate its relationship with the other variables. Alternatively, the author recommended that the researcher use their own data to determine the higher order factor structure and to generate higher domains of coping (https://local.psy.miami.edu/faculty/ccarver/sclBrCOPE.phtml).

In Jordan, the Brief COPE has been translated and used in different clinical populations such as CHD (Ghannam *et al*., 2014), lung disease (Hamdan-Mansour *et al*., 2014a), cancer (Hamdan-Mansour *et al*., 2015) and other chronic diseases (Al Abeiat *et al*., 2014). Cronbach's α in patients with stable CHD was 0.73 for the whole scale (Ghannam *et al*., 2014). Although the Brief COPE has been used in Jordan across many populations, the factor structure has not yet been evaluated. Including the 14 scales of the Brief COPE (and other

baseline variables) to predict trajectories of depressive symptoms requires a huge sample size.

The author who developed the Brief COPE suggested creating a higher order factor structure in order to reduce the number of scales, and then to use the reduced scales as predictors for other variables. Accordingly, the current study used the CFA technique to identify higher order structure of the Brief COPE.

Validity and Reliability of the Brief COPE

Internal consistency reliability of the Brief COPE was assessed through Cronbach's α. The first order CFA of the original 14-factor structure of Brief COPE was evaluated. Then, CFA was used to examine the higher factor structure by comparing five models based on previous theories and research. The process of validation of the Arabic version of the Brief COPE scale can be found in Appendix VI.

Table 6: Summary of the self-reported questionnaires

Scale	No. of items	Rating scale	Subscale/ related items	Scores	Time to complete	Interpretation
PHQ-9	9 items	4-point Likert scale (0-3)	One scale	0-27	2-3 minutes	PHQ-9 score greater than or equal to 10 indicates depressive symptoms
MSPSS	12 items	7-point Likert (1-7)	Total scale - Family (3,4,8,11) - Friends (6,7, 9,12) - Significant others (1,2,5,10)	12-84	<5min	The higher total score indicates higher perceived social support.
DS14	14 items	5-point Likert (0-4)	Negative affectivity: (2,4,5,7,9,12,13) Social inhibition: (I,3,6,8,10,11,1)	0-28 0-28	5 minutes	Scores ≥ 10 in both negative affectivity and inhibition subscales indicate Type D personality.
Brief COPE	28 items	4-point Likert (1-4)	- Problem-focused (2,7,14,25) - Emotion-focused (12,17,18, 20,22,24, 27,28) - Social coping (5,10,15,23) -Dysfunctional coping (1,3,4,6,8,9,11,13 ,16, 19, 21,26)	4-16 8-32 4-16 12-48	10 minutes	The higher score in any group represents the higher use of these coping strategies.

Legend: PHQ-9: Patient Heath Questionnaire; MSPSS: Multidimensional Scale of Perceived Social Support; DS14:Type D Personality Scale

The Research Team

The research team comprised the researcher and three research nurses, each of whom had experience in cardiovascular nursing and had very good communication and interpersonal skills. The researcher provided training to the research nurses with respect to the study aims and objectives, recruitment, data collection procedures and data management. This included training in conducting the structured/telephone interview. Following training, the research nurses' skills were evaluated through questioning and practicing scenarios of structured /telephone interviews to ensure consistency of data collection across the four research sites. The researcher recruited and collected baseline and follow-up data from patients at one research site. Additionally, the researcher supervised the process of data collection in the other three sites to ensure consistency of data collection and procedures across all sites.

Gaining patient access

Following receipt of ethical approval from the Faculty of Health Sciences Research Ethics Committee, Trinity College Dublin (Appendix VII) and the ethics committees of each of the four participating hospitals at Jordan (Appendix VIII), a letter was sent to the Directors of Nursing at each research site, seeking permission to access and recruit patients from the CCUs and cardiology wards. The researcher also requested each Director of Nursing to nominate a gatekeeper, such as a charge nurse working in the area where potential patients were being cared for, but who were not directly involved in the provision of patient care yet were capable of screening for eligibility and determining patient stability.

Access was granted to the four research sites and gatekeepers were appointed. Prior to the commencement of the study, the researcher met with the gatekeepers and presented an overview of the study as well as a detailed description about their role in providing patient access.

Patient recruitment

Patients were recruited to the study from the CCUs and cardiology wards at each of the research sites. Gatekeepers (1) identified eligible patients for recruitment (2) provided patients with a Patient Information Leaflet (PIL) (Appendix IX) to peruse (3) ascertained which patients were interested in the study versus those who were not. When doing so, the gatekeeper informed the patient that they were not part of the research team and that they had no vested interest in the study and (4) they then provided the research nurse with a list of the names of eligible patients who were potentially interested in participating in the study.

Following receipt of the names of potentially eligible, interested, haemodynamically stable patients, the research nurse visited these patients in the CCUs or cardiology wards. He or she (1) provided the patients with additional information about the study (2) re-assessed their eligibility and (3) clarified any queries or questions that the patient may have had. When the research nurse was satisfied that the patient was fully informed about the study, written informed consent (Appendix X) was obtained.

Recruitment for most patients occurred from the third day of hospitalisation onwards but could take place anytime from the day following admission. The justification for selecting a period of reflection for participation of less than seven days is that patients who were admitted with unstable angina or uncomplicated myocardial infarction may be discharged before the third day of their admission. Obtaining consent after this period could potentially exclude several patients who may have been willing to participate in this study. Furthermore, data collection between two-and five-day post ACS event is consistent with other research studies carried out in this cohort (Grewal *et al*., 2010, Mooney *et al*., 2014).

Written consent was only obtained from patients after first ensuring that they: (1) fulfilled the inclusion and exclusion criteria, (2) understood all study details including the purpose of the study, the procedure involved, the benefits and possible risks, (3) were aware of the measures that would be taken to maintain confidentiality and (4) were aware of their right to refuse to participate in the

study or to withdraw from the study at any time, without coercion or impact on the quality of care they received. The consent form contained a clear statement outlining that the patient understood all aspects of the study including the fact that their medical records would be accessed to obtain specific clinical data. Both the patient and the research nurse signed and dated three copies of the consent form.

4.5 Baseline data collection

Baseline data collection commenced on 1st August 2017 and was completed in late February 2018. Data were collected using structured interview and self-reporting questionnaires in the patients' room in the hospital or in a private office/room allocated by the gatekeeper. The structured interview commenced with a general 'yes' or 'no' question "Have you ever been diagnosed with or have a history of depression for a period of two weeks or more?" Patients who answered 'No' were not considered to have a history of depression. Patients who answered 'Yes' were evaluated using the PHQ-LSD. Patients who were hesitant to say yes or no were also evaluated using PHQ-LSD. All patients were then invited to complete the following self-reported questionnaires:

1) Sociodemographic and Clinical Characteristics.
2) Multidimensional Perceived Social Support.
3) Patient Health Questionnaire.
4) Type D Personality Scale.
5) Brief COPE.

Patients were asked to read the questionnaires and to ensure their completeness before returning them to the research nurse. All questionnaires were in Arabic and required less than 30 minutes to complete. Questionnaires were coded before being handed to patients, and each code included identifiers for the hospital and the patient. The research nurses obtained the required data related to sociodemographic and clinical characteristics from the patients' records. The researcher and research nurses received the questionnaires from patients after checking that all items were completed and ensured that there were no missing data. After that, the research nurses asked

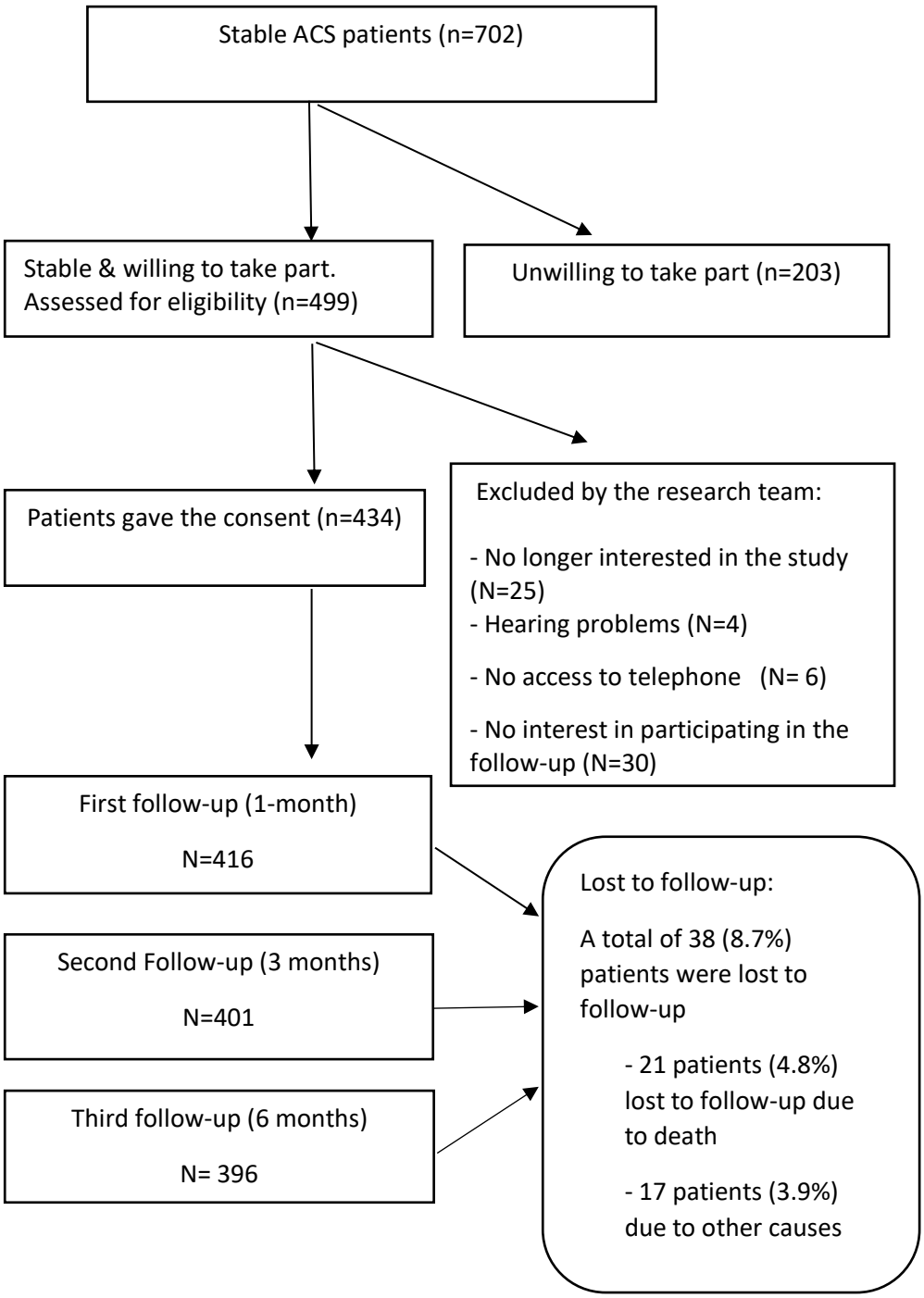
the patient to put the completed questionnaires in an envelope and hand it to them.

4.6 Follow-up data collection

Follow-up data collection commenced in September 2017 and continued until the end of August 2018. Patients who completed baseline questionnaires (n= 434) were followed up for a period of 6 months. Changes in depressive symptoms were evaluated by telephone at 1, 3 and 6 months using the PHQ-9. During the process of data collection, 38 (8.7%) patients were lost to follow-up due to death (4.8%, n=21) or other causes (3.9%, n=17). A flow diagram of patient recruitment and follow-up is presented in Figure 4.

It was decided that follow-up data collection would be conducted by telephone for the following reasons: (a) the PHQ-9 has been used over telephone in several studies on patients with ACS (Goulart *et al*., 2013; O'Neil *et al*., 2015); (b) when the PhQ-9 was administered over the telephone, it showed procedural validity and comparable reliability with the self-reported version (Pinto-Meza *et al*., 2005a); (c) telephone assessment is a more cost effective and time efficient method of data collection compared to face-to-face interview (Block and Erskine, 2012); (d) it allows flexibility for patients to choose a time suitable to them (Cohen *et al*., 2018); and (e) it helps to minimise attrition and improve the response rate (Teague *et al*., 2018).

Figure 4: Flow chart of data collection



Patient Retention Strategies

This study used a person-centred approach for data collection and analysis. The high retention rate in this study (91.3%) was achieved by adopting elements from a conceptual model of patient-centred recruitment and retention (Chhatre *et al*., 2018). The model includes four concepts: trust, attitude, expectations, and communication. A variety of strategies were used for trust building. Firstly, the researcher provided the patients with all details related to the study including the benefits of participating. Secondly, patients were informed about the voluntary nature of this study and that they could leave at any time with no negative impact on the quality of care received. Thirdly, patients were informed about privacy/confidentiality measures and ways of protecting their information. Another concept for optimising recruitment and retention was understanding patients' attitudes towards participation in the study.

Regarding patients' expectations, the researcher adopted a clear consented process, in which patients involved in the study fully understood the nature of the longitudinal study, and therefore nothing was unusual or unexpected during their participation. Clear communication was another strategy used to maximise patient engagement in the study. The research nurses had competent interpersonal skills and provided patients with up-to-date information regarding the progress and outcomes of the study to maintain their interest. The same research team member who recruited the patient at baseline, continued their follow-up to ensure consistent communication.

Patients were asked to provide comprehensive contact information, including full name and address, along with a fixed line telephone number. If a fixed-line number was not available, then patients were asked to provide the research nurse with the phone number of another contact person. The research team used text messages and phone call reminders a few days prior to follow-up to remind patients about the upcoming assessment *(study reminder).* If a patient did not respond to a phone call, the researcher contacted them on one

additional occasion. If there was no response to the repeated attempt, the patient was considered lost to follow-up.

Additional strategies used to maintain patient engagement in this study were informed by systematic reviews on retention strategies (Booker *et al*., 2011; Abshire *et al*., 2017; Teague *et al*., 2018). A 2018 meta-analysis and systematic review study that evaluated the retention strategies used in 143 cohort studies found that flexibility in data collection was the most effective retention strategy (Teague *et al*., 2018). Flexibility can be achieved by offering alternative options for questionnaire completion (Abshire *et al*., 2017). A systematic review found that offering a telephone survey option was associated with highest retention rates in comparison to other methods, such as email or post (Booker *et al*., 2011). Telephone surveys make it easier for patients to complete questionnaires at their convenience and thus maintain their research participation (Cohen *et al*., 2018).

Abshire *et al*. (2017) in their systematic review reported that: study reminders, focusing on study benefits, and a well-functioning/organised research team were among the most used strategies in cohort studies with high retention. The research team in this study was organised and consistent. The research nurses were educated on how to improve data collection practices and implement retention strategies. Regular meetings were held to evaluate data collection and to review retention rates. The research team regularly reviewed the retention strategies used in this study and tailored designs to those that best suited patients.

Piloting study

A pilot study is a small study, which is conducted to assess the feasibility of methods to be used in a larger study (Polit and Beck, 2018). By conducting the pilot study, the researcher can assess whether the study is feasible and if research instruments are easy to administer and to understand (Cohen *et al*., 2018). It also helps in assessing the clarity of the instruments and required time

to their completion (Gray *et al*., 2017). Results from the pilot study allow for the refining of content, wording, or length of instruments (Cohen *et al*., 2018). Piloting can reduce the potential for unanticipated problems to occur in the main study as it provides an opportunity to refine them earlier (Gray *et al*., 2017; Cohen *et al*., 2018). A pilot study can also provide the researcher with anticipation about response rates in the main study (Cohen *et al*., 2018) and subsequently inform strategies to ensure patient engagement in the study.

According to Sousa and Rojjanasrirat (2011), a sample of 10 to 40 patients is adequate for a pilot study. A sample of 25 patients were therefore enrolled in this pilot study. The pilot patients were recruited from the four participating hospitals over a period of two weeks. The response rate was 71%. Guidelines for optimal response rates vary but there is consensus suggesting response rates of 50-60% is generally acceptable (Story and Tait, 2019; Cohen *et al*., 2018). The researcher invited the patients to evaluate the clarity and understandability of study instruments (instructions, items, and the response format) and other documents such as the PIL and consent form. Patients reported that the study instruments, PIL and consent form were clear and understandable. Therefore, no modifications on the study methods or instruments were required. However, the researcher gleaned important insight into how long it takes to recruit patients and to collect data. All patients in the pilot study completed the questionnaire within 30 minutes. Given that there were no modifications required, patients in the pilot study were included in the main study.

Pilot testing of DS14 scale.

The DS14 scale was translated from English to Arabic. Following this, the scale was piloted with 25 patients who experience ACS before testing its psychometric properties. Pilot testing was conducted to ensure that each item of the translated scale had a conceptual and content equivalence to the original version (Sousa and Rojjanasrirat, 2011). In other words, the researcher evaluated whether phrases in the translated version was understood in the same way to those used in the original scale. Patients were asked to provide

feedback on the clarity of each item, and if they had difficulties in understanding some words. There was agreement among the patients on the clarity of the scale, instructions, response formats and there was lack of any ambiguities or difficulty in understanding the scale items.

In addition, the conceptual and content equivalence of the translated version of DS14 was evaluated by a panel of six experts, as recommended by Sousa & Rojjanasrirat (2011). Four of the experts were academic researchers in general nursing and two were clinical nurse specialists in mental health nursing. The experts were asked to evaluate each item for relevance and clarity. The rating scale for each of relevance and clarity was a four-point Likert scale ranging from 1-4. The relevance scale included (1=Not relevant, 2=Unable to assess the relevance 3=Relevant but needs minor alterations, 4=Very relevant and succinct), and the clarity scale included (1=Item is not clear, 2=Item needs major revision to be clear, 3=Item needs minor revision to be clear, 4=Item is clear) (Lynn, 1986).

The content validity of the DS14 was evaluated by calculating the Content Validity Index (CVI). The CVI is a quantitative method to determine the degree to which items are relevant or representative of the content of the domain that is being measured (LoBiondo-Wood and Haber, 2017). There are two forms of CVI: Item level (I-CVI) and Scale level (S-CVI). The I-CVI for each item was calculated based on a number of experts rating “very relevant and succinct” divided by the total number of experts (Lynn, 1986). The I-CVI scores range from 0 to 1. Items with an I-CVI of 0.78 or higher is considered excellent in terms of content validity (Polit and Beck, 2017). In this study, the I-CVI of the DS14 items ranged from 0.83 to 0.1, with 5 items scoring 0.83 and 9 items scoring 1.00. The results showed excellent content validity. According to Polit and Beck (2017), the preferred method for calculating S-CVI is to divide the sum of I-CVI by the total number of items (S-CVI/Ave). The S-CVI/Ave of 0.90 or above indicates excellent content validity (Polit and Beck, 2017). The average S-CVI for the DS14 was 0.94, suggesting an excellent content validity.

4.7 Ethical considerations

Researchers who conduct a study on people should address ethical issues. A Code of ethics has been developed in order to protect people when participating in research. This study was founded on ethical principles from two international ethical standards: the Belmont Report (1979), and the Declaration of Helsinki (1965, 2013). The Belmont report was developed by the National Commission for the Protection of Human Subjects of Biomedical and Behavioural Research in 1979. The Declaration of Helsinki was developed by World Medical Association in 1965 and revised in 2013. The ethical standards of research were based on three main principles: (a) respect for person (b) beneficence, and (c) Justice.

4.7.1 Respect for Person

Right to self-determination, self-disclosure, and autonomy

The right to self-determination is a fundamental ethical principle of respect for the person, which suggests that individuals are allowed to make their own decisions without external control (LoBiondo-Wood and Haber, 2017). As such, individuals should have the freedom to determine whether to participate in a study or not (Gray *et al*., 2017). Researchers can violate the right to self-determination when using deception, concealment or coercion (Gray *et al*., 2017). Deception involves providing individuals who are willing to participate with false or incomplete information about the study (Polit and Beck, 2018). With concealment, individuals are involved in research without knowing that they are part of that research (Cohen *et al*., 2018). Another aspect of violating the right to self-determination is to coerce individuals to be part of a study. Coercion is a threat of harm, visible or hidden, if an individual declines to participate in the study (Polit and Beck, 2018). Coercion may also occur when the researcher provides individuals with inappropriate or extreme rewards to participate in a study (Gray *et al*., 2017; Polit and Beck, 2018).

The right to full disclosure is another principle of respect for persons. In this principle, individuals have the right to receive complete information about a study before making a decision about participation (Polit and Beck, 2018). Autonomy can be achieved when the researcher provides potential patients with full information about the study and then allows them to freely choose whether to participate in the study or not (Boswell and Cannon, 2018).

To uphold the principle of respect for the person, patients were given freedom to decide whether to participate in the study without coercion or external pressure. This was achieved in the followings ways: (1) they were approached by a gatekeeper, a charge nurse, not involved in their direct care; (2) the gatekeepers informed the patient that they were not part of the research team but rather served as advocate for them; (3) the researcher received a list of names of only interested patients from the gatekeepers; (4) the gatekeepers informed patients that if they were not interested in participating then the quality of care they received would not be affected in any way.

4.7.2 Informed Consent

Obtaining valid consent is an essential requirement for conducting ethical research (Boswell and Cannon, 2018, Cohen *et al*., 2018).Ensuring that patients are fully informed to sign this consent incorporates the right to full-disclosure, the right to self-determination and the right to autonomy (Polit and Beck, 2018). Informed consent is a process in which a researcher provides potential patients with full information about the study, and then seeks voluntary participation based on that (Polit and Beck, 2018). Obtaining valid informed consent does not rely only on the information provided by the researcher but also on the patients' competency to make the decision as well as his/her ability to comprehend the information received (Gray *et al*., 2017; Polit and Beck, 2018).

To ensure full disclosure during this study, potential patients received a comprehensive PIL, which included an overview of the study aims, procedure, benefits, possible risks, adverse outcomes, privacy and confidentiality

measures, voluntary participation and right to withdraw (Appendix VIII). Along with this, the researcher visited potential patients who were interested in taking part in the study and explained the study information in detail. Potential patients were encouraged to ask questions if they felt that anything was unclear. The researcher's mobile number was available to patients for any queries.

In order to ensure that the information provided by the researcher was clearly understood by patients, the researcher used simple and clear language in both verbal and written information. The PIL was designed according to the guidelines of the Faculty of Health Sciences Research Ethics Committee, Trinity College Dublin. The researcher gave attention to the content and appearance of the information in the leaflet, to ensure that it was accurate, and the font/font size was appropriate to the reader. The readability and understandability of the PIL and consent form were also evaluated in the pilot study. Patients were asked to read these documents and to report if they found any words unclear or confusing. Patients reported that the information in the leaflet and consent form were easily understood and clear & easy to read.

Informed consent was obtained from patients before data collection commenced. The research nurse obtained written consent from patients only after first ensuring that they (1) fulfilled the inclusion and exclusion criteria (2) understood all study details including the purpose of the study, the procedure involved, the benefits, and possible risks (3) were aware of all measures that would be taken to maintain confidentiality (4) were aware of their right to refuse to participate in the study or to withdraw from the study at any time, without coercion or impact on the quality of care they received. When the research nurse was satisfied with the aforementioned, they invited the patient to sign the consent form (see Appendix X). Both the patient and the researcher signed and dated three copies of the consent form; one was given to the patient so that they have a copy of what they had signed, one was placed in the patients' medical notes, and one was retained by the research nurse in a locked

cabinet in the researcher's office in a separate location to the completed questionnaires.

4.7.3 The Principle of Beneficence

The principle of beneficence is the obligation of the researcher to act for the benefit of the patients. It supports actions by the researcher to do good for the patient (beneficence) and to avoid harm (non-maleficence) (LoBiondo-Wood and Haber, 2017; Boswell and Cannon, 2018). The principle suggests that patients should have the right to be free from harm or discomfort when participating in a study (Gray *et al*., 2017). As such, the researcher must balance between study benefits and risks for patients (Gray *et al*., 2017) and not expose them to unnecessary risks (Polit and Beck, 2018). Harm and discomfort are not limited to physical, but can be emotional, social or even financial (Gray *et al*., 2017).

Although there was no direct benefit to the individual patient for taking part in this study, it was hoped that the study findings would inform the body of knowledge in this area of care. The study findings have the potential to improve knowledge about the changes that occur in depressive symptoms following discharge and this knowledge will be important in identifying patients who are at risk of developing persistent or worsening depressive symptoms in the six months after their ACS event. The findings will also assist healthcare professionals to identify characteristics of ACS patients who are at risk of developing distinct depressive trajectories that are associated with poor outcomes after ACS. This is important in planning immediate and follow-up care for patients who experience an ACS event. However, in keeping with the principle of beneficence, and with the patient's permission, their cardiac physician was notified if persistent elevation in depressive symptoms occurred for the patient during the study. It was hoped that this would be helpful in directing appropriate referral or further psychological support for the patient.

Although it was anticipated that no physical harm would come to patients as a result participating in the study, it was acknowledged that completing the

questionnaires, might cause some psychological distress. To this end, patients were offered immediate support by the research team member if they became tired or upset when completing the questionnaires at baseline. Patients were advised that the completion of questionnaires would be suspended or stopped completely. A clinical psychologist was available in each of the hospitals as a support to patients of this study. Patients were also provided with the contact details of this psychologist at the outset of the study and encouraged to make contact if they needed this support. This was also noted in the PIL. In addition, and with the patient's permission, the researcher offered to contact to the clinical psychologist on their behalf.

4.7.4 The Principle of Justice.

This ethical principle involves fairness in the selection and treatment of patients. It also includes protection of privacy and confidentiality. Patient selection should be fair in order to ensure an equal distribution of the risks and benefits of the study (LoBiondo-Wood and Haber, 2017). Polit and Beck (2018) suggest that the selection of patients in the study should be based on the research needs rather than an individuals' vulnerability. The researcher should treat patients fairly and respect all agreements with them (Gray *et al*., 2017). In this study, the researcher followed specific inclusion and exclusion criteria to ensure that patients had equal opportunity to take part. Patient selection was explicit and based on the study requirement. The study was conducted as agreed with patients. The research team showed respect to patients who withdrew from the study and treated them fairly and without prejudice.

4.7.5 Protection of privacy and confidentiality

Privacy is the right of a patient to keep their personal information protected. The right to privacy is an element of the ethical principle of Justice (Polit and Beck, 2018). Confidentially refers to procedures considered by the researcher to protect the patient's private information (Boswell and Cannon, 2018, Cohen *et al*., 2018). A breach of confidentiality can occur when private information from a patient is disclosed to unauthorised person without consent (Gray *et al*., 2017).

To maintain privacy and confidentiality in this study, baseline questionnaires were completed in the patients' room in the hospital, if they had a single room. Otherwise, it took place in a private office/room, allocated by the gatekeeper. Data collection at one month, three months and six months took place over the telephone, at a time convenient for the patient. Prior to data collection, each research nurse signed a confidentiality form. Patients were reassured that all information would remain confidential. None of the questionnaires contained any patient identifying details. Each patient was given a unique identification number (ID), and the linking document to his/her responses was available only to the research team. When the research team received the questionnaires from patients, they ensured their completeness. The questionnaire was then given to the researcher and if there was any identifying data, it was removed. The document linking the patient's details with his/her responses was kept by the researcher with the consent forms in a locked cabinet within a locked office belonging to the researcher.

All data collected were stored in a locked cabinet in the researcher's office. The linking documents were kept in a separate locked cabinet within this office also. Only the researcher had access to the locked cabinets. The researcher received data collected from the research nurses on a weekly basis. Data were inputted by the researcher and stored on a password-protected computer. Non-anonymised data will be retained for five years in line with the Data Protection Act 2003 and will be destroyed thereafter by the researcher.

In conclusion, there were no ethical issues or problems arising from participation in this study. The study posed no physical risk to patients as it necessitated the completion of questionnaires only. The individuals had the choice to be involved in the study, without coercion from others, and they were able to gauge their own ability to participate. However, because follow-up data were collected on three occasions post discharge, it caused inconvenience to some patients, even though they agreed to do so. Ongoing consent was

confirmed at the beginning of each follow-up phone call (patients were asked if they were still happy to take part in the study and if they wanted, they could leave without any impact). Some patients expressed that the follow-up calls were inconvenient to them, and they decided to withdraw from the study and their decision were respected. No adverse events occurred during the study. A copy of the study results was made available to all patients on request.

4.8 Data Management

4.8.1 Data entry and cleaning

To reduce any missing data, the research team checked all questionnaires before receiving them from the patients. Data were then coded and entered into SPSS software version 25. All entered data were doubled checked against the questionnaire to ensure accurate entry at each time point. Following this, the data were cleaned to evaluate any missing values and outliers by exploring the frequencies, minimum and maximum, and using measures of central tendency for each variable.

4.8.2 Dealing with missing data

The percentage and pattern of missing data were screened. The number of missing values was minimal and found in less than 3% of all questionnaires. However, 16.1% (n= 70) of the recruited sample had no cholesterol values in their records. Missing values can be classified into the following categories: Completely Missing At Random (CAMR), Missing At Random (MAR), and Missing Not at Random (MNAR). The missing values in the cholesterol variable were considered MAR. MAR assumes that missing values in any variable can be predicted based on the available information from other variables (Rubin *et al*., 1987). Missing values in the cholesterol variable were handled using the multiple imputation technique, which replaces the missing values by imputed values (Papageorgiou *et al*., 2018). This technique creates different imputed datasets based on a Bayesian approach and then combines the results from each imputed set to estimate the missing values (Sterne *et al*., 2009).

Using the default setting of imputation in SPSS, five imputed datasets were generated to replace the missing values in the cholesterol variable. The five imputed datasets were then averaged into one set that was used in the subsequent analysis. This method is considered a robust method for handling missing values and reducing the variance in the dataset (Sterne *et al*., 2009; Papageorgiou *et al*., 2018). Barzi and Woodward (2004) evaluated several techniques for handling the missing data of cholesterol in 28 CHD studies. The authors suggested that the multiple imputations technique is a good choice when 10 % to 60% of the values are missing. Similarly, a recent Monte Carlo study compared different missing data handling techniques for logistic regression and found that multiple imputations work well when the data is MAR (Meeyai *et al*. 2016). The authors recommended using multiple imputations when the percentage of missing values is 20% or less (Meeyai *et al*. 2016).

4.9 Data analysis

The aim of data analysis in quantitative research is to summarise and organise the collected data using statistics (LoBiondo-Wood and Haber, 2017). There are two forms of statistical analysis: descriptive and inferential. Descriptive statistics can be used to describe one variable at a time, and is usually referred to as univariate descriptive statistics (Polit and Beck, 2018). In univariate descriptive statistics, the researcher describes central tendency measures such as the mean, median and mode, and dispersion measures such as range, variance, and standard deviation (LoBiondo-Wood and Haber, 2017). Univariate data are also presented in frequency tables, bar charts, or pie charts. Bivariate descriptive statistics, such as cross-tabulations and correlations, are used to describe the relationships between two variables (Polit and Beck, 2018). Descriptive statistics are limited in so far as they are usually used to describe and summarise (LoBiondo-Wood and Haber, 2017). Inferential statistics however, can make inferences about the population based on the sample data (Gray *et al*., 2017). Logistic regression is an inferential method to identify strength of association between the dependent variable and covariates

when all covariates are included together in the model (LoBiondo-Wood and Haber, 2017; Wilcox, 2019)

4.9.1 Descriptive analysis

Descriptive statistics were conducted to summarise the sample and clinical characteristics, as well as scores of psychosocial measures. In this study, categorical variables are presented in frequencies and percentages, while continuous variables are presented in means and standard deviations. To estimate the prevalence of depressive symptoms, patients were categorised into depressed (PHQ ≥10) or non-depressed (PHQ<10). The prevalence of depressive symptoms at baseline and follow-up was estimated, and the 95% confidence interval was calculated using a Binomial test. Incidence of depressive symptoms was calculated based on the formula: Incidence rate = "Number of new cases with the condition or disease over a given time period divided by Number in the population at risk of being a case (free of condition at the outset" (Polit and Beck, 2017, p.305). The result of this equation was multiplied by 100 in order to estimate the rate per 100 individuals (Polit and Beck, 2017). Data were analysed using the Statistical Package for Social Sciences (SPSS) version 25 (IBM Corp, 2017) for descriptive statistics and logistic regression. Mplus software version 8.1 (Muthén and Muthén, (1998-2017)) was used to conduct Confirmatory Factor Analysis (CFA), Growth Curve Modelling (GCM) and Growth Mixture modelling (GMM).

4.9.2 Binary logistic regression

Binary logistic regression was used to identify predictors of in-hospital depressive symptoms in patients with ACS. Binary logistic regression can be used when the dependent variable is dichotomous and the independent variables are nominal, ordinal, or even scale (Hair *et al*., 2013). Univariate binary logistic regression is a simple form of logistic regression in which only one independent variable predicts the dichotomous outcome (Polit and Beck, 2013). In multivariate binary logistic regression, there are, however, two or more independent variables predicting the dichotomous outcome (Polit and Beck, 2013). Logistic regression is a widely used technique of analysis as it does

not require meeting the stringent assumptions of linearity, normality, or homogeneity of variance when these assumptions are violated (Hair *et al*., 2013).

Logistic regression fits the purpose of this study for the following reasons: First, Shapiro-Wilk's test of normality for the depressive symptoms was significant (p<.0001), indicating a violation of the normality assumption. Second, depressive symptoms were measured using the PHQ-9, which is a validated measure used to assess depressive symptoms based on a predetermined cut-off point (Kroenke *et al*. 2001). Thus, depressive symptoms can be classified into a binary response (depressed and non-depressed). Third, logistic regression has been widely used to examine predictors of depressive symptoms in this cohort, and this would facilitate comparing the results with those from other studies. Although logistic regression does not require the stringent assumptions of linear regression, it does require the following four assumptions to be met.

Lack of multicollinearity between the independent variables.

Multicollinearity refers to the presence of a high correlation (r=0.8 or more) between any two independent variables in a model (Hair *et al*., 2013; Tabachnick and Fidell, 2012). According to Hair and colleagues (2013), when two variables are highly correlated, it is difficult to know how much variation in the dependent variable is explained by each of the independent variables. This, however, makes the regression coefficients non-significant because of the large standard errors of both variables (Tabachnick & Fidell, 2012). This assumption was tested by evaluating the collinearity statistics: Variance Inflation Factor (VIF) and the Tolerance Statistic (Field, 2013). A VIF value greater than 10 or a tolerance value of less than 0.1 indicates an extreme collinearity problem (Field, 2013; Hair *et al.,* 2013).

Linearity of the logit

Logistic regression assumes that there is a linear relationship between the continuous independent variables and the logit of the binary dependent

variable (Field, 2013; Josephat and Ame, 2018). This assumption was checked through the box-Tidwell procedure, which suggests including the interaction between each continuous independent variable and its natural logarithm in the logistic regression analysis (Hosmer and Lemeshow, 1989). This test is specified only for the purpose of testing the linearity assumption (Field, 2013). All interactions should achieve *p* values greater than 0.05 in order to meet this assumption (Field, 2013; Hosmer and Lemeshow, 1989).

The expected cell frequency.

The expected cell frequency should be more than five and no more than 20% of the cells should end up with expected frequencies of less than five (Field, 2013). This assumption was tested using the cross-tabulation table.

Independence of residuals

This assumption was examined after fitting the nested models to check whether the residuals in the logistic regression models were independent of each other. Residuals can be estimated by calculating the difference between the observed and the expected values in the regression equation (Schreiber-Gregor, 2018). When the observed variance is greater than the expected variance for the model, an overdispersion problem will take place, leading to a small standard error, narrow confidence interval and high chance of a Type 1 error (Field, 2013; Tabachnick and Fidell, 2012). Residuals were examined to detect outliers and to check observations that had an influence on the fitted regression models (Tabachnick and Fidell, 2012). Standardised residuals, which refer to residuals divided by the standard error of the estimate, were explored to detect outliers (Schreiber-Gregor, & Jackson, 2018). Influential observations were checked through Cook's distance and DFBeta values (Field, 2013; Tabachnick and Fidell, 2013). Observations with standardised residual values greater than 3.0 (or less than -3.00) might indicate an outlier (Field 2013; Tabachnick and Fidell, 2013). Furthermore, observations that have Cook's distance and/ or DFBeta values greater than one indicates influence on the regression model (Cook and Weisberg, 1982, Field, 2013).

After testing the assumption of logistic regression, all variables were initially evaluated using univariate binary logistic regression and those significant at $p \leq .15$ in the univariate logistic regression were included in the multivariate logistic model. Two nested logistic regression models were evaluated. The first nested model included the demographics and health-related behaviours in block 1 and the psychological variables in block 2. The second nested model included significant clinical and cardiac disease severity in block 1 and the psychosocial variables in block 2.

4.9.3 Growth Mixture Modelling

Overview of analysing longitudinal data

Longitudinal data analysis can provide researchers with information about changes that occur in an outcome of interest over time. Understanding changes in depressive symptoms after discharge from hospital is necessary for designing treatment interventions for those with worsening or persistent depressive symptoms (Keegan *et al*., 2016). There are several approaches to analysing changes over time. The raw change score is one of the common approaches for analysing average change between two-time points (Fu and Holmer, 2015). This method of analysis estimates the mean difference of an outcome variable between two adjacent time points (Time 2 score – Time 1 score). Several statistical tests use raw change scores as a method of analysis such as the Student's t-test, Analysis of Variance (ANOVA) and Multivariate Analysis of Variance (MANOVA) (Clifton and Clifton, 2019). While the t-test is used to evaluate the change in the mean score between two-time points, both ANOVA and MANOVA estimate changes in the mean score at more than two-time points (Mishra *et al*., 2019). Although ANOVA and MANOVA analyse changes at more than two time points, they still focus on a series of two-point comparisons (Mishra *et al*., 2019).

Regression analysis can also be used for analysing change (Castro-Schilo and Grimm, 2018). This can be achieved (a) through examining the Time 1 score as a covariate and Time 2 score as a dependent variable or (b) by calculating

residualised change (Dalecki and Willits, 1991, Castro-Schilo and Grimm, 2018). However, these statistical approaches are variable-centred and do not consider individual differences over time (Howard and Hoffman, 2018). Instead, these approaches try to pool individual scores within a specific time point and then estimate the average change or calculate the residualised change (Howard and Hoffman, 2018). These methods are fixed-effect methods of analysis, which consider individual differences in change over time as variance errors (sampling error) (Dettori *et al*., 2022).

These methods have been extended into random-effect models (i.e., random-effects ANOVA, and linear hierarchical models), which capture individual differences in change over time by random coefficients. According to Muthén and Curran (1997, p372) "The random coefficient approach in these models, however, has been limited to a single response variable that does not accommodate the general analysis needs of developmental theories"

There is increasing interest in using the random coefficients approach within a latent variable framework and this is termed a 'latent variable approach' (Berlin *et al*., 2014). This approach is a form of structural equation modelling that uses information from the repeated measures of an outcome of interest to make inferences about the latent variables (Muthén, 2004). The latent variable approach allows for more flexibility in (1) modelling the change over time, (2) handling the random missing data, (3) modelling unequally spaced time points, and (4) nonlinear trajectories compared to the traditional methods of analysis (Muthén and Shedden, 1999; Curran *et al*., 2010). Furthermore, given that this approach has been developed within the structural equation modelling (SEM) context, (5) it allows for including covariates and/or distal outcomes in the model (Ram and Grimm, 2009)

Latent Class Analysis (LCA) is a latent variable approach that uses a finite mixture modelling to capture unobserved heterogeneity in cross-sectional categorical outcomes (Nylund-Gibson and Choi., 2018; Nguefack *et al*., 2020). Finite mixture modelling assumes that there is unobserved "latent" groups present within the heterogeneous population (Muthén and Shedden, 1999;

Chen, 2017). Repeated measures LCA is a latent class model that is not related to growth models, but it allows us to identify the latent patterns of categorical outcomes over time (longitudinal) (Feldman *et al*., 2009).

Growth Curve Modelling (GCM)

Growth Curve Modelling (GCM) is the conventional method for analysing longitudinal data within the latent variable framework (Jung and Wickrama, 2008). This model summarises repeated measures (i.e., depressive symptoms) for every individual using two pieces of information: Intercept (α) and Slope (β): The intercept is the starting point of an outcome of interest when time is equal to zero (Curran *et al*., 2010). The slope is the trend or rate of change over time (Geiser, 2012). The intercept and slope for every individual can capture within-individual change over time (Curran *et al*., 2010). In GCM, this information can be used to estimate a single set of growth factors (intercept (μ α) and slope (μ β)) for the entire population. Both of these intercepts and slopes have means, variances and covariances (Duncan and Duncan, 2009). The mean of the intercept refers to the average starting level when the time is equal to zero. The mean of the slope parameter refers to the average rate of change over time. The variance refers to the individual variability around means of intercept and slope growth factors (Geiser, 2012). In LGCM, the mean of the intercept and slope are represented by fixed effects because the model estimates the entire population using a single set of growth factors. However, the variance around the mean of these growth factors is assumed to be a random effect (Murphy *et al*., 2014b). This random-effect variance allows for capturing information regarding the interindividual differences over time (Curran *et al*., 2010). Researchers commonly use this approach to "capture the interindividual differences in intraindividual change" (Curran and Wirth, 2004, p.219). A general diagram of the linear Growth Curve Model (GCM) used in the study is shown in Figure 5.

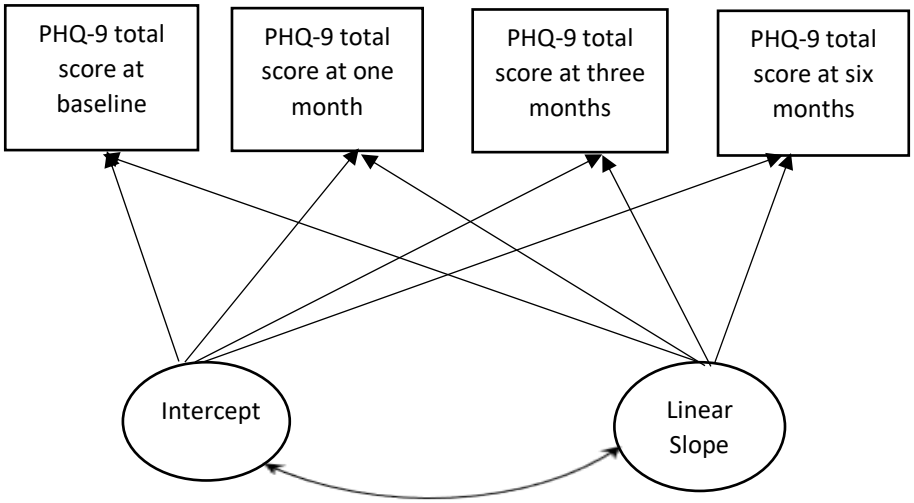


Figure 5. A general linear Growth Curve Model (GCM) for an outcome variable (PHQ-9) measured at four time points.

Group Based Trajectory Modelling (GBTM)

Group-Based Trajectory Modelling (GBTM) is a latent variable method of analysis that allow the researcher to use information from repeated observations to make inferences about unobserved or latent groups (Ram and Grimm, 2009; Nagin, 2010). Unlike methods of analysis such as regression and ANOVA, which are variable-centred approaches, GBTM stems from a person-centred approach, which focuses on identifying differences between individuals rather than on examining relationships between variables. Unlike GCM, GBTM does not assume that a single set of growth factors (intercept and slope) can estimate the trajectories over time (Curran *et al*., 2010), GBTM assumes that the population is heterogeneous and composed of different latent subgroups (Nylund *et al*., 2007; Muthén and Asparouhov, 2008; Berlin *et al*., 2014). More specifically, GBTM includes a latent categorical variable (C) that is regressed on the growth factors. This allows different growth trajectories to vary across different means (Muthén and Shedden, 1999; Muthén, 2004; Jung and Wickrama., 2008). Accordingly, GBTM is assumed to identify interindividual

differences in intraindividual changes better than GCM (Jung and Wickrama., 2008).

GBTM includes Latent Class Growth Analysis (LCGA) and Growth Mixture Modelling (GMM). Both approaches are conceptually similar but have some technical differences (Nagin and Odgers, 2010). The similarity between LCGA and GMM is that both are finite mixture models. These models are known to be powerful for "analysing outcomes from a population that contains a finite number of homogenous subpopulations or for approximating unknown distributions" (Nagin and Odgers, 2010, p.115). The difference between them is that LCGA does not estimate within-class variance because it assumes that individuals within-class are homogenous in their trajectories. However, the GMM does freely estimate them in order to capture more homogenous groups within the heterogeneous population (Muthén and Asparouhov, 2008; van der Nest *et al*., 2020).

Accordingly, GMM consists of intercept and slope growth factors in addition to a latent categorical variable (C), which is regressed on both intercept and slope. In order to run GMM, repeated measures of at least three-time points are required to capture linear change (Geiser, 2012). The curvilinear changes can be estimated by including the quadratic growth parameter in the model. The quadratic parameter reflects upward or downward changes in the growth trajectories over time and requires at least four-time points to be estimated (Geiser, 2012). Figure 6 shows the general diagram of linear GMM used in the current study.

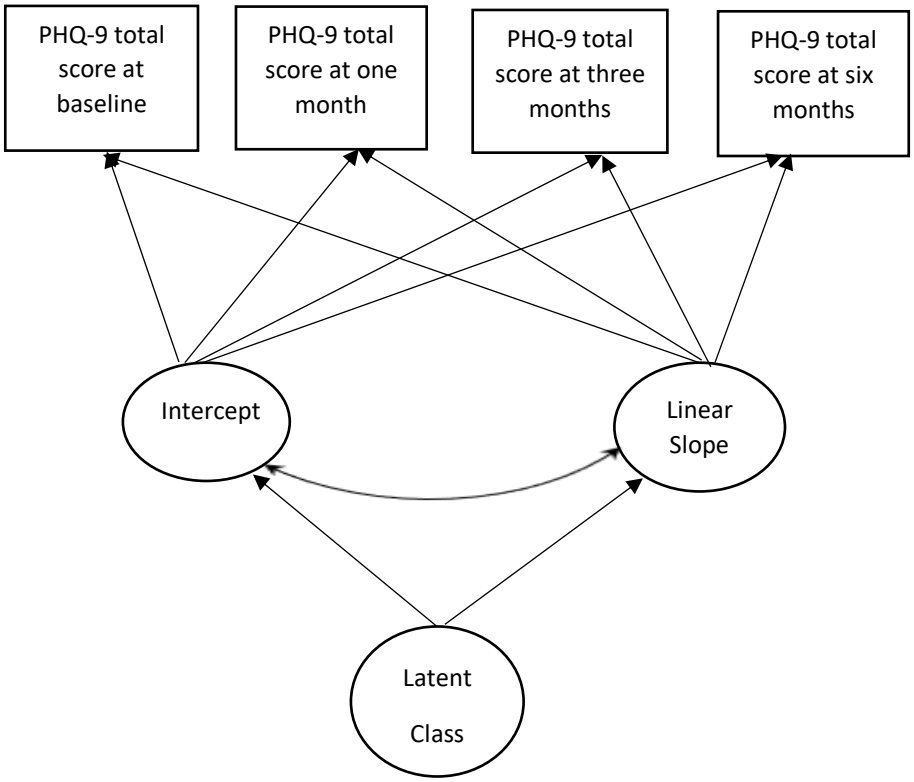


Figure 6. Linear Growth Mixture Model (GMM) for an outcome variable (PHQ-9) measured at four time points.

Rationale for choosing GMM as a method of analysing trajectories of depressive symptoms

GMM was chosen over traditional methods of analysis such as ANOVA or regression as it was considered most appropriate to achieving the study aim. As previously mentioned, these methods of analyses assume that individuals belong to a single population and change can be analysed based on the average score for the entire population. However, evidence shows that depressive symptoms are heterogenous (Keegan *et al*., 2016; Peter *et al*., 2020). Accordingly, trajectories of depressive symptoms tend to be different from one person to the next and it is unlikely that all individuals follow a single trajectory of depressive symptoms over time. Therefore, it is necessary to use a method

of analysis (i.e., GMM) that would capture the heterogeneity within and between groups.

On the other hand, using a person-centred approach is congruent with the Transactional Theory of Stress and Coping by Lazarus and Folkman (1984), which assumes that individuals vary in their way of coping and adapting to a stressful event. It can be expected that patients follow distinct trajectories of depressive symptoms such as worsening or persistent symptoms based on whether they are using specific coping strategies (i.e., dysfunctional coping strategies). According to Lazarus and Folkman (1984), if someone has the recourses to cope with the stressor of including social resources (i.e., perceived social support), he or she will appraise the stressor as less challenging. Lack of perceived social support has been found to be associated with depressive symptoms (Ghannam *et al*., 2014). It would be expected that patients who experience low perceived social support would follow different trajectories of depressive symptoms than those with high perceived social support. Similarly, Carver and Connor-Smith (2010) indicated that coping and personality traits play an independent and interactive role in affecting both physical and mental health. It is also expected that patients experience distinct trajectories of depressive symptoms depending on having Type D personality. Thus, using GMM as a person-centred method of analysis in this study is consistent with the study's theoretical background.

GMM was chosen over other growth models (i.e., GCM) or mixture techniques (i.e., LLCA) for the following reasons. First, GCM is a single-class growth model that assumes a single set of growth parameters (intercept and slope) represents the entire population. However, GMM is a combination of a finite mixture and a growth model which assumes an unknown number of latent classes within the population, each of which has growth parameters. This study examined GCM as an initial step before conducting GMM to see which growth parameters (Intercept-only, linear or quadratic) provided a better fit to the data. While LLCA requires the outcome variables to be categorical, this study used the continuous score of PHQ-9. The researcher believes that using continuous scores would provide rich information about heterogeneity in

depressive symptoms and would represent the data better than relying on the dichotomous classification of depressed and non-depressed. According to Kaptein *et al*. (2006), using the dichotomous classification of depressed and non-depressed would estimate the prevalence rates over time rather than examining the pattern of depressive symptoms over time. Therefore, using the total score of PHQ-9 and employing GMM for analysing trajectories of depressive symptoms in this study might address limitations of previous studies

Statistical analysis for GMM

GMM was conducted using Mplus version 8.1. The model was estimated using the Maximum Likelihood (ML) method. The choice of estimator can be affected when variables are extremely non-normal. Strongly non-normally distributed data may result in over-extraction of trajectory classes in GMM (Bauer and Curran, 2003). Skewness and Kurtosis are commonly used statistics to evaluate the normality of the data (Sheard, 2018). Skewness and kurtosis values between -2 and +2 are considered within the acceptable range for normality (George and Mallery, 2010; Sheard, 2018). Muthén and Muthén (2017, p, 668) recommend the use of MLR estimator for GMM when continuous data are non-normal and with missing values. The MLR uses the standard ML estimator, but it corrects standard errors with a robust sandwich estimator approach (Yuan and Bentler, 2000; Yuan *et al*., 2012). The MLR estimator can be requested on Mplus by adding "ESTIMATOR= MLR" in the analysis command (Asparouhov, 2002). The MLR applies similar ML approaches for handling missing data, which is a Full Information Maximum Likelihood (FIML). Given that both Skewness and Kurtosis values for the repeated measures of depressive symptoms in this study were within the acceptable range (>1), an ML estimator was used. To ensure that the final solution was identified correctly, the four-class model was also estimated using the robust ML (MLR). The results indicate that the loglikelihood and information criteria (AIC, BIC, and ASBIC) values for both estimators were similar, indicating that ML was an appropriate estimator for the data.

The missing values were handled using the FIML technique. The FIML uses a maximum likelihood (ML) estimation under the assumption of Missing at

Random (MAR) (Cham *et al*., 2017) . This is a default technique for handling the missing values in Mplus 8.1 (Muthén and Muthen, 2017). FIML is an advanced technique for handling missing data and is more superior than listwise deletion or multiple amputations when data are missing at random, as it produces unbiased parameters, low standard error and reduces Type I errors (Enders and Bandalos, 2001; Larsen, 2011). This technique has been commonly used for handling missing vales in longitudinal studies (Gomez *et al*., 2017; Clark, 2019).

GMM was conducted using three steps. Initially, three unconditional growth curve models (GCM) were specified to determine the functional form of change over time. Given that depressive symptom data were collected at four-time points, three functional forms were evaluated: intercept, linear and quadratic. In the next step, unconditional growth mixture models were compared from 2 to 5 classes. Many fit indices have been suggested in the literature to determine the optimal number of classes (Jung and Wickrama., 2008). The most commonly used fit indices include the information criteria and likelihood ratio tests (Nylund-Gibson and Choi., 2018). Information criteria include Bayesian Information Criteria (BIC), Adjusted Bayesian Information criteria (ABIC) and Akaike Information Criterion (AIC). Lower BIC, ABIC, AIC values indicate the better class solution. The likelihood ratio tests include Mendell and Rubin Likelihood Ratio Test (MLR-LRT) and Bootstrap Likelihood Ratio Test (BLRT). The BLRT and MLR-LRT compare the model fit between the K (i.e., 4 classes) and the k-1 (i.e. 3 classes) classes. The significant *p* values ($p<0.05$) for BLRT and MLR-LRT indicate that the addition of one class significantly improves the fit compared to a model containing one class less (K-1). However, the non-significant *p* values for BLRT and MLR-LRT indicate that there was no significant improvement in the K class model fit compared to the K-1 class model; thus a model with one less class is preferred (Jung and Wickrama., 2008).

The quality of the classification for the classes was evaluated using entropy. Values of entropy close to one indicate a better distinction between the latent classes (Celeux and Soromenho, 1996). A simulation study by Nylund and colleagues (2007) found that BLRT was the best indicator of model fit followed

by BIC and ABIC fit indices (Nylund *et al*., 2007). The above-mentioned fit indices were specified in Mplus software using TECH11 and TECH14 (Asparouhov and Muthén, 2012).

For every solution, the researcher ensured that the best loglikelihood for model was replicated at least twice. In case that the best loglikelihood value was not replicated, the number of random start values were increased until it was replicated. After successful replication, two seed values from the best loglikelihood were evaluated using the OPTSEED option to ensure that the resulted solution was not a local solution (Asparouhov and Muthén, 2014).

Once classes were identified, posterior probabilities and class assignments were saved into an output text file. After that, class assignments were exported into SPSS version 25 to conduct multinomial logistic regression (STEP3). All variables were initially evaluated using univariate multinomial logistic regression and those significant at $p \leq .05$ in the univariate multinomial logistic regression were included in the multivariate model. Three multivariate models were investigated to assess the independent prediction of each group of variables when present together in one model. The models included (a) demographics and health-related behaviours, (b) clinical and cardiac disease severity, and (c) psychosocial factors. After that, a final multinomial logistic model was investigated.

4.10 Conclusion

Data were analysed using the Statistical Package for Social Sciences (SPSS) version 25 (IBM Corp, 2017) for descriptive statistics and logistic regression. Mplus software version 8.1 (Muthén and Muthén, (1998-2017)) was used to conduct Confirmatory Factor Analysis (CFA), Growth Curve Modelling (GCM) and Growth Mixture modelling (GMM). Descriptive statistics were presented in frequencies and percentages for categorical variables, and as means and standard deviations for continuous variables. The prevalence of depressive symptoms at baseline and over six months were estimated by dividing the number of patients who scored 10 or more on the PHQ-9 at each time point by

the number of all patients at that time. The incidence of depression was estimated by dividing the number of new cases of depression at each time point divided by the number of patients at risk of new depression at that time. Binary logistic regression was conducted to identify predictors of in-hospital depression. Prior to binary logistic regression, assumptions of multicollinearity, expected cell frequency, linearity of logit and independence of residuals were tested. A univariate binary logistic regression was conducted for all variables and those that were significant at $p<.15$ were included in multivariate analysis. GMM was estimated using maximum likelihood method. FIML was used to handle the missing data. Three steps were used to estimate GMM and to identify predictors of different trajectories of depressive symptoms. Initially, unconditional growth curve models were examined to evaluate the functional forms. Three functional forms were evaluated including intercept-only linear and quadratic forms. After that, different GMMs were estimated. After that, posterior probabilities and class assignments were exported into SPSS version 25 to conduct multinomial logistic regression. Finally, Univariate, and multivariate multinomial logistic regressions were used to identify predictors of different trajectories of depressive symptoms.