# **“I feel it in My Heart.”**

Depression and Anxiety in Cardiovascular Disease

Megan Grech

School of Psychology

Faculty of Health and Medical Sciences

The University of Adelaide

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## Statement of Authorship

I certify that this manuscript does not contain material that has been accepted for the award of any other degree or diploma in any other institution., and that to the best of my knowledge, contains no material previously published or written by another person except where due reference is made.

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**Megan Grech**

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# LITERATURE REVIEW

An Emotional Heart:

Depression (and Anxiety!) in Cardiovascular Disease

## Abstract

Cardiovascular disease (CVD) and depression worldwide are societally and economically costly. The broader literature now recognises depression as a key risk factor in CVD populations, leading to the implementation of screening recommendations in this high-risk cohort. However, these guidelines did not include anxiety. A growing body of literature is now acknowledging an important role for anxiety as a potential CVD modifiable risk factor. Here we briefly summarise the supporting evidence in regards to the research on depression, anxiety and CVD and we discuss the forgotten notion of comorbidity and its potential influence on CVD risk and depression treatment outcomes. Lastly, we discuss the potential for psychiatric theory pertaining to anxiety and depression comorbidity to inform screening procedures in CVD patients. Lastly, we discuss the clinical implications in regards to the proposed method with specific recommendations for future research.


**Keywords:** depression, anxiety, cardiovascular disease, comorbidity, hierarchical theory, emotional disorders, internalising, screening

The statistics on cardiovascular disease (CVD) (e.g., coronary heart disease (CHD), heart failure (HF), coronary artery disease (CAD), Ischemic Heart Disease (IHD)) reflect opposing trends. On the one hand, the mortality rates from CVD in Australia have decreased from 20% of deaths in 2001 to 15% of deaths in 2011 (Australian Institute of Health and Welfare (AIHW), 2014). On the other hand, CVD affects one in six accounting for more than 4.2 million people Australia wide (Australian Bureau of Statistics (ABS), 2015). The number of CVD related hospital admissions has increased by 8% in 10 years (AIHW, 2016) and 1.4 million people are prevented from living a full life because of a CVD related disability (ABS, 2015). Thus, CVD still remains one of the world's leading health problems and one of the biggest burdens on our economy. With a rise in the average life expectancy and prevalence of cardiovascular risk factors (e.g. obesity), increases in economic and societal costs, and decreases in quality of life seem probable as CVD patients live longer (Pandya, Gaziano, Weinstein, & Cutler, 2013).

## DEPRESSION IN CARDIOVASCULAR DISEASE

Psychiatric disorders are particularly relevant to CVD (Correll et al., 2017). Major depression, a condition characterised by more than 2 weeks of depressed mood or loss of pleasure and multiple somatic symptoms (e.g., abnormalities in sleep, energy, concentration, appetite, and/or psychomotor functioning) (American Psychiatric Association, 2013), has received the most attention in CVD. Research popularity concerning depression in CVD is on the grounds that approximately 20% of CHD patients meet criteria for major depression after a heart attack, or, after undergoing coronary artery bypass graft surgery (Tully & Baker, 2012). Though, prevalence rates increase if milder forms of depression are considered. Given the high prevalence rates of depression in women than men in the general population, not surprisingly, self-reported symptom severity rates are somewhat higher in women (30.6%) than in men (19.8%) (Pogosova et al., 2017). Depending on the degree of functional

impairment, depression is also prevalent in roughly 20% of patients with chronic HF (Rutledge, Reis, Linke, Greenberg, & Mills, 2006). From a clinical perspective, it is now generally accepted that one in five patients with CHD, or, HF is depressed, a figure three times that found in the general population (Kessler et al., 2003).

## DEPRESSION AND RISK OF CARDIOVASCULAR DISEASE

A consistent body of literature now supports the view that depression is a risk factor for developing CVD. Rugulies (2002), and Wulsin and Singal (2003) reported that depressed patients had a 60% higher chance of developing CHD. Further, those with clinical depression tended to have a higher risk (relative risk=2.69; 95%; CI: 1.63-4.43) of developing heart disease than those with non-clinical depression (relative risk=1.49; CI: 1.16-1.92) demonstrating a dose-response relationship. Not surprisingly, depression in CHD has a population attributable risk (PAR) comparable to smoking, and higher than diabetes (PAR: 9.9%) and hypertension (PAR: 17.9%)(Yusuf et al., 2004). Rates as high as 80-90% were reported by Nabi et al. (2010); Nicholson, Kuper, and Hemingway (2006). Though, Nicholson et al. (2006) concluded that a failure to adjust for known CVD risk factors in many of the studies likely resulted in inflated estimates. For example, when adjusting for known cardiovascular risk factors (e.g., left ventricular function), the relative risk dropped by half (Nicholson et al., 2006). A recent meta-analysis reported more conservative findings, in that depression (i.e., meeting diagnostic criteria, or, achieving a higher questionnaire score), had roughly a 30% greater risk of heart attack and heart attack (Gan et al., 2014). Even when excluding angina and other non-definitive CHD outcomes, depression is associated with a 1.31 (95%CI, 1.09–1.57) and 1.36 (95%CI, 1.14–1.63) for heart attack and coronary death, respectively (Wu & Kling, 2016). While self-reported depression appears to increase the risk of incident CVD by four-fold when compared to other physically healthy people (Kyrou et al., 2017), the rates are still alarming when focusing on those with diagnosed severe mental

illnesses. For example, in a large scale meta-analysis major depressive disorder was significantly associated with CVD (odds ratio: 1.75, 95%CI: 1.36-2.26, $p = 0.001$) and CHD (odds ratio: 2.52, 95%CI: 1.81-3.52, $p < 0.001$) (Correll, 2017). Little attention has been paid to whether different subtypes of depression (i.e. melancholic, psychotic, atypical or undifferentiated) significantly moderate CVD risk, though, there is some evidence that those with atypical major depression or double depression (i.e., major depressive disorder and dysthymia) may be a subgroup that is particularly at high risk of new-onset CVD (Case, Sawhney, & Stewart, 2018). Further, those who have never been depressed before appear to have different risk factors and a more severe state of CVD as opposed to pre-existing or recurrent depression (de Jonge, van den Brink, Spijkerman, & Ormel, 2006; Goodman, Shimbo, Haas, Davidson, & Rieckmann, 2008; Grace et al., 2005; Spijkerman et al., 2005).

In addition to being a risk factor for the development of CVD, depression is also predictive of worse outcomes following cardiovascular events. Nancy Frasure-Smith, Lespérance, and Talajic (1993) were one of the first to document this relationship in patients following a heart attack where the six-month mortality of depressed patients was 17%, corresponding to almost 4 (95%CI: 2.25-4.63) times the increased risk compared to non-depressed patients. Since then a number of meta-analyses have evaluated all-cause, or, cardiac-related mortality after a heart attack, or, acute coronary syndrome (Barth, Schumacher, & Herrmann-Lingen, 2004; A Meijer et al., 2013; Meijer et al., 2011; Nicholson et al., 2006; Van Melle et al., 2004). All studies yielded comparative findings in that depression was predictive of all-cause mortality, cardiac-related mortality, and/or a combined endpoint of all-cause mortality and cardiac morbidity (Carney & Freedland, 2016). According to the largest of the meta-analysis, patients with post-heart attack depression have a nearly three-fold increased risk for cardiac mortality and nearly two-fold risk for new cardiac events (Meijer et al., 2011). This increased risk of mortality and secondary events is also true in HF (Rutledge et al., 2006). Even when

adjusting for known risk factors using the Global Registry of Acute Coronary Events (GRACE), a highly predictive measure of cardiac outcomes following a cardiac event (Fox, Eagle, Gore, Steg, & Anderson, 2010), depression still remained an independent predictor of all-cause mortality, and fatal and non-fatal cardiac events.

In a dose-response fashion, the severity of depression also appears to predict cardiovascular outcomes (Fiedorowicz, 2014; Wulsin et al., 2005). In a study reporting depression as a predictor of outcome following heart attack, compared to those with a Beck Depression Inventory (BDI) score lower than five, hazard ratios (HR) were highest for BDI scores exceeding 18 (HR. ) and lowest for scores between 5-9 (HR 1.4) (Lespérance, Frasure-Smith, Talajic, & Bourassa, 2002). Despite these findings, depression is a chronic, fluctuating condition and single measures do not provide sufficient information on the course of this condition over time (Freedland & Carney, 2013; Palacios, Khondoker, Mann, Tylee, & Hotopf, 2018). Further, evidence suggests clinicians should be aware of the aversive prognostic effects of somatic/affective depressive symptoms compared to cognitive/affective depressive symptoms (de Miranda Azevedo, Roest, Hoen, & De Jonge, 2014; Freak-Poli, Ikram, Franco, Hofman, & Tiemeier, 2018). In HF, worsening somatic symptoms, but not cognitive-affective symptoms, were found to be independently associated with increased mortality (Hwang, Moser, Pelter, Nesbitt, & Dracup, 2015).

Finally, in addition to the poor survival rate and increased risk of further CVD events, depression is also a significant predictor of decline in overall health status over time. In a study of 960 outpatients with CHD, depression predicted decline of health status across a five year period (Sin, Yaffe, & Whooley, 2015), while depressive symptoms have also been found to predict health care costs over time. Palacios et al. (2018) used Latent Class Growth Analysis (LCGA) to identify five distinct depression symptom trajectories ‘stable low’, ‘chronic high’, ‘improving’, ‘worsening’, and ‘fluctuating’ based on the Hospital Anxiety and

Depression Scale (HADS). CHD patients in the 'chronic high' class had average costs approximately double that of a patient in the 'stable low' class.

## MENTAL HEALTH SCREENING IN CARDIOVASCULAR DISEASE

Given the aforementioned, it is not surprising that routine screening for depression is now recommended by the American Heart Association (AHA)(Lichtman et al., 2008). The AHA recommends screening patients using the two-item Patient Health Questionnaire (PHQ-2) (Lichtman et al., 2008). A response of 'yes' to one of the two questions yields 90% sensitivity and 70% specificity for a diagnosis of depression (McManus, Pipkin, & Whooley, 2005). Following a score of one or higher on the PHQ-2, the AHA suggests that all nine items on the PHQ are administered to the patient. A score of above 10 showed a sensitivity and specificity of 88% for a diagnosis of major depression (Kroenke, Spitzer, & Williams, 2001).

Interestingly, anxiety was not considered in the AHA recommendations despite the fact that disorders of excessive fear and anxiety constitute the most prevalent psychiatric disorders in western countries, with the highest lifetime prevalence estimates ranging from 14%-29% (Kessler et al., 2005). Anxiety (i.e., the anticipation of future threat) is also highly prevalent in CVD populations. In a large European epidemiological study of 7589 patients who experienced a CHD event, approximately 1.4 years after the event, 26.3% of participants had symptoms of anxiety as measured by the Hospital Anxiety and Depression Scale-Anxiety subscale (HADS-A) (Pogosova et al., 2017). Other prevalence rates vary considerably depending on CVD subtype. For example, the pooled prevalence of anxiety symptoms is approximately 28% in HF patients (Easton, Coventry, Lovell, Carter, & Deaton, 2016), 27% following a heart attack, (Daniel et al., 2018), 20-40% following a cardioverter defibrillator implantation (Magyar-Russell et al., 2011), and 25% before coronary artery bypass graft surgery (Geulayov, Novikov, Dankner, & Dankner, 2018). Importantly, the prevalence of

anxiety remained consistent one year following the surgery. Similarly, three years following percutaneous coronary intervention anxiety symptoms were as high as 32%, after controlling for participant age and smoking habit ($p$ <0.001) (Olsen, Schirmer, Wilsgaard, Bønaa, & Hanssen, 2018). Lower estimates are reported by prospective studies using structured clinical interviews that provide psychiatric diagnoses. For example, the point prevalence rate of any anxiety disorder in CHD is approximately 16% in CHD (Tully, Cosh, & Baumeister, 2014) and 13% in HF(Easton et al., 2016). Thus, anxiety disorders are as common as a unipolar depressive disorder in CVD (Celano, Suarez, Mastromauro, Januzzi, & Huffman, 2013; Tully, Harrison, Cheung, & Cosh, 2016). Generalized Anxiety Disorder (GAD) is the most common anxiety disorder with an 11% point prevalence and 26% lifetime prevalence of GAD in CHD patients (Tully & Cosh, 2013). This is also consistent with prevalence rates of GAD in HF (Easton et al., 2016). Panic disorder is also common in CHD with one paper reporting prevalence rates up to 50% (Fleet, Lavoie, & Beitman, 2000). However, given that panic has been found to be significantly less common in post-acute coronary syndrome populations than GAD, and depression, lower estimates of 5-8% reported by Celano et al. (2013); Todaro, Shen, Raffa, Tilkemeier, and Niaura (2007) are likely more realistic. Importantly, anxiety disorder prevalence fluctuates depending on demographics, study design, and the setting (i.e. inpatient or outpatient) (Tully et al., 2014). Making an anxiety disorder diagnosis in chronic illnesses is not straightforward due to somatic symptom overlaps, such as those existing in panic disorder (e.g., chest pain and heart palpitations), and the clinical presentation of some CVDs, such as CHD (Tully et al., 2015). Taking this into consideration, it is not surprising that there is still considerable deliberation in regards to the strength of the relationship between panic disorder and CHD (Katerndahl, 2008). Notably, CHD and HF symptoms also significantly overlap with depression (Smolderen et al., 2009),

and therefore, depression is not exempt from the consequences of somatic symptoms confounding psychiatric disorder diagnoses.

Despite the high prevalence of anxiety disorders in CVD populations, anxiety screening is relatively uncommon, and as such it often goes undetected and untreated in cardiac populations (Cully, Jimenez, Ledoux, & Deswal, 2009; Hurley et al., 2017; Polikandrioti et al., 2015). For example, Huffman et al. (2006) reported that following admission for a heart attack health care providers failed to identify anxiety disorders in up to 50% of the patients and 69% with elevated symptoms of anxiety. Patients with anxiety symptoms are also rarely followed up. One study reported that a third of acute coronary patients with raised anxiety levels reported not being followed up by medical professionals in regards to these symptoms over 12 months (Grace, Abbey, Irvine, Shnek, & Stewart, 2004). Currently, if anxiety screening is performed, its recommend that patients are evaluated during a period of relative clinical stability to avoid false positive anxiety screens from those with subclinical symptoms of psychological distress that are often experienced in response to a cardiac event (Celano et al., 2015). More recently the AHA has recommended that more research needs to be published investigating whether anxiety disorders contribute independently to CHD prognosis (Lichtman et al., 2014).

## ANXIETY AS A RISK FACTOR FOR CARDIOVASCULAR DISEASE

As per the AHA recommendations, there has been a rapidly growing number of empirical papers evaluating anxiety as a key risk factor in CVD (Janszky, Ahnve, Lundberg, & Hemmingsson, 2010; Nabi et al., 2010; Seldenrijk et al., 2015; Tully et al., 2015). Restricting their analysis to CHD only, Roest, Martens, de Jonge, and Denollet (2010) showed that in 250,000 patients, with follow up periods ranging from 2-20.9 years, the increased risk of CHD in people with anxiety was 26% and 48% for cardiac death. Despite these findings, multivariable analysis revealed that only 10 studies from a total of 20 demonstrated a

significant relationship between any anxiety disorder and CHD, highlighting limitations in regards to the heterogeneity of the findings concerning this relationship (Celano, Daunis, Lokko, Campbell, & Huffman, 2016). An extension of this work included a further 8 studies to also investigate the risk of any anxiety disorder with HF and cardiovascular mortality. Anxiety disorders were associated with a 41% increased risk of CHD and cardiovascular mortality, and a 35% increased risk of HF (Emdin et al., 2016). However, again, these findings are questionable given the lack of adjustment for confounding factors. Given the high rates of comorbidity (Kessler et al., 2008), adjusting for depression is crucial in order to ascertain whether anxiety is a true risk factor independent of depression. Taking this relationship into consideration, a recent meta-analysis with a total of 37 studies, with 1,565,699 participants found that anxiety (including both symptoms and disorders) was associated with a 52% increased risk of CVD incidence independent of traditional risk factors and depression (Batelaan, Seldenrijk, Bot, Van Balkom, & Penninx, 2016) . The researchers concluded that the effects of anxiety and depression are comparable and that the depression risk ratios reported by Nicholson et al., (2006) may be the result of a failure to adjust for anxiety as an important covariate.

Analysing anxiety disorder subtypes has uncovered differential associations with CVD. After adjusting for depression, Edmondson, Kronish, Shaffer, Falzon, and Burg (2013) found that people with PTSD had a 27% increased risk for incident CHD and cardiac-specific mortality, while household interviews conducted in 52 095 study participants in 19 countries found that diagnoses of depression, panic disorder, specific phobia, and posttraumatic stress disorder were all associated with self-reported heart disease onset (OR=1.3–1.6) (Scott et al., 2013). While GAD was not in these findings, the NEMESIS study based on 5149 persons at risk of cardiac diseases found that GAD was most strongly associated with the onset of non-fatal CVD in a three year follow up (Batelaan, ten Have, van Balkom, Tuithof, & de Graaf, 2014).

However, over a six year follow up, Seldenrijk et al. (2015) found that panic disorder was the only anxiety disorder associated with CVD incidence. Tully et al., (2015) conducted a meta-analysis to clarify the extent to which panic disorder offers risk in regards to the development of CHD. A total of 1,131,612 people with 58,111 cardiac events across 12 studies revealed that people with panic disorder were 47% more likely to have CHD, 36% more likely to suffer a heart attack, and 40% more likely to have a major adverse cardiac event (Tully et al., 2015). Panic disorder was also associated with other adverse cardiovascular events, including death from CAD, sudden cardiac death, and acute heart attack (fatal and non-fatal). Despite the robustness of the study, given that panic symptoms substantially overlap with those of cardiac disease, the researchers could not rule out whether panic symptoms were the result of an undetected cardiac illness. Collectively, the findings above demonstrate that it is still largely inconclusive exactly which anxiety subtypes are associated with incident CVD in previously non-diseased persons (Tully, 2017).

## ANXIETY IN ESTABLISHED CARDIOVASCULAR DISEASE

In addition to being a risk factor for the development of CVD, the extant literature suggests that anxiety predicts poorer prognosis in persons with already established cardiac disease. While controlling for disease severity, anxiety, but not depression, measured one month following hospital discharge was an independent predictor of recurrent heart attack or cardiac death in post-heart attack patients (Strik, Denollet, Lousberg, & Honig, 2003), while patients with elevated anxiety symptoms in the coronary care unit were also found to exhibit greater mortality within the first year after a heart attack (Wrenn, Mostofsky, Tofler, Muller, & Mittleman, 2013). Meta-analytic work has also confirmed that anxiety was associated with a 36% increased risk of adverse cardiac outcomes, 47% risk of all-cause mortality, 23% risk of cardiac mortality, and a 71% risk of new cardiac events after a heart attack (Roest, Martens,

Denollet, & De Jonge, 2010). However, it is not clear the extent to which the association was independent of depression.

Similar findings exist in stable heart disease where a 2-fold increased risk of adverse CVD events was reported in a rehabilitation sample (Rothenbacher, Hahmann, Wüsten, Koenig, & Brenner, 2007), and in patients with elevated anxiety during hospitalisation for cardiac catheterisation (Watkins et al., 2013), while patients with increasing anxiety at 12 months follow up had a significantly higher risk of poor cardiac outcomes when compared to patients with consistent anxiety over time (Shibeshi, Young-Xu, & Blatt, 2007). Anxiety also predicts hospitalisations in patients with chronic HF (Vongmany, Hickman, Lewis, Newton, & Phillips, 2016). Finally, in a meta-analysis of 44 studies, anxiety was associated with an increased risk of cardiac events and death in patients with established CAD. Despite these findings, the reported risk was attenuated when controlling for covariates leaving the researchers to conclude that the relationship is not as strong as depression (Celano et al., 2015).

In regards to specific anxiety disorder diagnoses, evidence suggests that GAD increases the risk for major cardiac events (Frasure-Smith & Lespérance, 2008; Martens et al., 2010; Tully et al., 2011). In Martens et al. (2010), after adjustment for demographic characteristics, comorbid conditions (including major depressive disorder), cardiac disease severity, and medication use, GAD remained associated with a 62% higher rate of cardiovascular events (hazard ratios: 1.62; 95%CI: 1.11-2.37; $p = .01$). Similarly, over a 10 year follow up period, Roest, Zuidersma, and de Jonge (2012) reported that GAD was associated with an increased rate of cardiac events independent of depression and disease severity, while patients meeting criteria for GAD (not panic disorder), prior to CABG surgery had an increased risk of cardiovascular and cerebrovascular outcomes five years later (Tully et al., 2015). Interestingly, some studies reported no association of GAD in established CVD (Versteeg et

al., 2013), while some even report GAD as a protective factor (Parker, Hyett, Hadzi-Pavlovic, Brotchie, & Walsh, 2011). Collectively, there is a paucity of studies evaluating anxiety subtypes in CHD suggesting more high-quality studies are needed (Tully, Cosh, & Baumeister).

## COMORBIDITY OF ANXIETY AND DEPRESSION

There are several issues to consider in understanding the relationship between anxiety and CVD, including that anxiety rarely exists in isolation. While there appears to be an independent association of depression and anxiety in CVD, many of the studies did not take into consideration comorbidity, despite the likelihood of many depressed persons having a comorbid anxiety disorder (Kessler et al., 2008). GAD and major depression are considered the most common type of anxiety-mood comorbidity (Gorwood, 2004). Research in CVD yields comparative findings. For example, in established CHD, up to half of the patients were considered to have comorbid depression and anxiety (Tully et al., 2014), while Denollet and colleagues (2006) report that mixed anxiety and depressive symptom profiles are much more common after a heart attack than depression alone. In 4,256 participants from the Vietnam Experience Study, 55% of those with major depression also had GAD (Phillips et al., 2009). Similarly, in 2,315 participants in the Netherlands Study of Depression and Anxiety, approximately 40% had comorbid depression and anxiety disorders (Vogelzangs et al., 2010).

While some studies do not agree (Frasure-Smith & Lespérance, 2008), there is now building evidence to suggest that the combined impact of depression and anxiety in cardiac populations results in poorer outcomes in CVD. For example, in the Vietnam Experience Study, veterans with comorbid major depression and GAD were at a substantially greater risk of mortality than the veterans who reported either condition alone (Phillips et al., 2009). The co-occurrence of anxiety and depression also increased the risk of hospitalisations when compared to either alternate disorder (Chamberlain, 2011), while in stable heart disease

patients the combined presence of anxious and depressive symptoms contributed significantly to mortality, whereas, anxiety and depression alone did not (OR 2.35, 95% CI 1.23–4.47, p=.010) (Doering et al., 2010). Further, the findings of Watkins et al. (2013) reported a three-fold increased risk of mortality in patients with comorbid anxiety and depression in CHD, higher than that revealed for either factor alone, while the same was reported for the combined effects of anxiety and depressive symptoms on the mortality rate of adults with HF (Alhurani et al., 2015).

Recently it was reported that patients with depressive symptoms in HFare at a high risk for experiencing anxiety symptoms, also, and therefore, they encourage clinicians to assess patients for comorbidity (Easton et al., 2016). Particularly since, in groups of depressed populations without co-occurring medical illnesses, the presence of anxiety is associated with a slower response to antidepressants (Altamura, Montresor, Salvadori, & Mundo, 2004), less symptom reduction over time (Altamura et al., 2004), non-adherence to treatment, and a poorer overall response to intervention (Howland et al., 2008; Rush et al., 2008). In a CVD population higher levels of anxiety symptoms as measured by the HADS-A were found to be associated with less improvement of depressive symptoms from baseline and increased odds of depression persistence at 6 months, independent of functional status, baseline depression severity, and history of depressive episodes (Celano et al., 2012). Similarly, anxiety evaluated within 2 weeks of an acute coronary syndrome was significantly associated with a depressive disorder at follow up and less improvement in depressive symptoms over 1 year (Kim et al., 2017). Collectively, these findings highlight the importance of identification and management of anxiety as a way of optimising depression interventions and decreasing the patient's overall risk of adverse CVD outcomes.

## HIERARCHICAL THEORY OF COMORBIDITY

Psychiatric theory has attempted to provide explanations for the high rates of anxiety and depression comorbidity. Such theoretical observations have the potential to provide ways in which comorbid disorders could be detected more effectively in high risk CVD populations. For example, factor analytic work focused on understanding relationships among mental disorders has shown that the most common psychological disorders can be explained in a hierarchical fashion with an overarching general factor (i.e., a predisposition to experience negative affect, such as sadness, anger, disgust, or fear; Watson, 2005) and two sub-domains: 'internalising' and 'externalising' (see *Figure 1*), where, notably, depression and anxiety disorders load onto the 'internalising' domain (Kotov et al., 2017; Krueger & Markon, 2006). This two-factor structure has been found to be robust and various studies continue to support this idea (Kotov et al., 2017). For example, in comorbidity studies the two domains have been found to match comorbidity patterns observed across an individual's lifetime (Kessler, Petukhova, & Zaslavsky, 2011). In addition, the two major dimensions have also been accounted for in genetic studies (Kendler et al., 2011). The two-factor structure is also considered to be structurally stable across countries (de Jonge et al., 2018).

However, as further structural analytic work reveals, the two-factor structure is more complex with the existence of multiple sub diversions (Kotov et al., 2017). For example, disorders under the 'internalising' domain tend to cluster together forming lower order groups, two of which are, 'anxious-misery' (i.e., major depressive disorder, dysthymia, generalised anxiety disorder and post-traumatic stress disorder), and 'fear' (i.e., panic disorder, agoraphobia, specific phobia, social anxiety disorder and obsessive-compulsive disorder (OCD)) (Kotov et al., 2017; Krueger, 1999). Notably, GAD is considered more strongly related to the unipolar disorders than to the other anxiety disorders since it shares more of the general factor variance (i.e., trait disposition towards negative affectivity). While there is some debate regarding the structure of the lower order, the two-factor structure is considered robust

(Kotov et al., 2017), and is a partial explanation for the substantial interrelation of anxiety and depression across the lifespan (de Jonge et al., 2018).

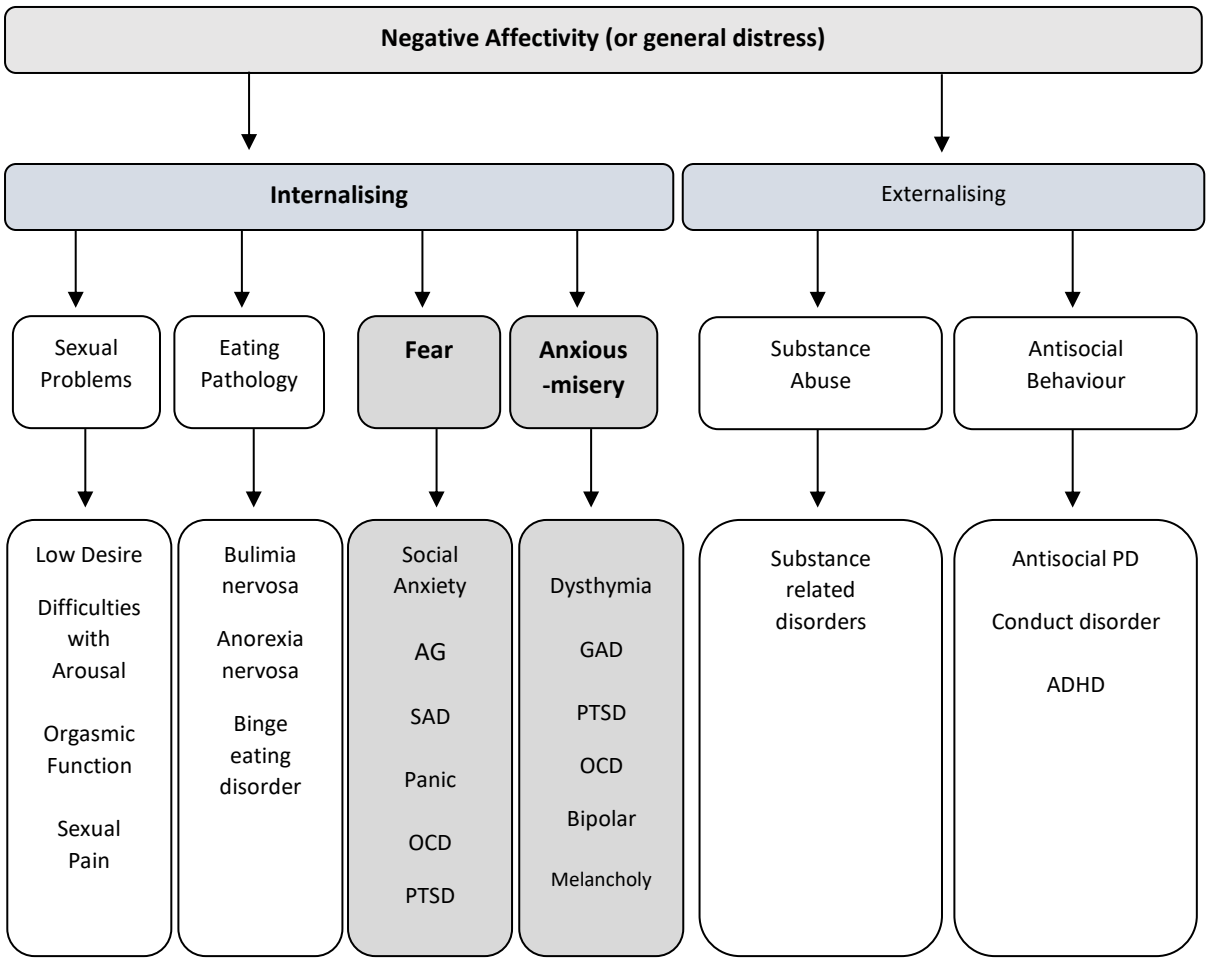


*Figure 1*. Flowchart of the Hierarchical Taxonomy of Psychopathology. Adapted from Kotov et al., (2017). AG = Agoraphobia; SAD = Social Anxiety Disorder; Panic = Panic Disorder; OCD = Obsessive-Compulsive Disorder; PTSD; Post-traumatic Stress Disorder; GAD = Generalized Anxiety Disorder; ADHD = Attention Deficit Hyperactivity Disorder; PD = Personality Disorder

Inopportunely, such observations that inform psychiatric and psychological nomenclature are rarely employed in the screening of mental health in CVD. Anxiety disorders, as single constructs, are only just beginning to attract attention in screening studies and very few studies have discussed recommendations for the screening of anxiety and depression contemporaneously (Bunevicius et al., 2013; Celano et al., 2013). Bunevicius and colleagues

reported on three self-report measures to detect anxiety disorders in a CAD sample. A notable finding was that depression screening omitted a substantial number of persons suffering from an anxiety disorder, demonstrating that disorder-specific screening is invaluable in CVD populations where there is high risk and comorbidity is likely to exist. The researchers recommended further investigation into the inclusion of anxiety screening as a compliment to depression screening. Celano et al. (2013) also concluded that the screening of both depression and GAD (but not panic disorder) is justified in CVD, given the high prevalence rates of major depression and anxiety (GAD) in their sample (20.5% and 18.5%, respectively). The researchers advocated for the use of the amalgamation of the Patient Health Questionnaire – two item and the Generalized Anxiety Disorder – two-item scales given they could be performed in a timely matter. However, a confirmation diagnosis would need to be completed via the PHQ-9 and GAD-7 items, in a two-step process. Although this recommendation takes into consideration two highly comorbid and prevalent disorders in CVD, there is potential for other disorders to coexist that may not be captured by this method. Though this is yet to be empirically tested in a CVD population, the theoretical 'clusters' may solve the comorbidity quandary by targeting the common factors (i.e., 'anxious-misery' or 'fear') that contribute to the emotional disorders. Given that a psychometrically sound instrument could be tested and employed to target 'anxious-misery' and 'fear' clusters, this would also simplify the screening process and the need for multiple screening measures recommended by Bunevicius et al. (2013) and Celano et al. (2013).

## CLINICAL IMPLICATIONS AND FUTURE RESEARCH

Detecting psychological distress in patients with CVD is only the first step in coordinating the best care of such patients, and screening that is not interlinked with a treatment plan is likely not efficacious for the patient. Indeed, the recommendation from the AHA in regards to the screening of depression in CHD has since been challenged as there remains a paucity of

studies demonstrating that it is useful and cost-effective in improving outcomes for heart disease patients (Hasnain, Vieweg, Lesnefsky, & Pandurangi, 2011; Thombs et al., 2008; Thombs et al., 2013; Ziegelstein & Thombs, 2011). A review concluded that treatments that are deemed suitable for this cohort are only considered modestly effective (Carney & Freeland, 2017). The lack of encouraging outcomes in treatment studies has led some to question whether, therapeutically, depression is a suitable target in CVD, indicating the need to search beyond the realms of depression to improve outcomes for patients. There is evidence to suggest that potential therapeutic efficacy may lie within transdiagnostic methods that target the core processes common to the emotional disorders. A study that examined the specific effect of treatment on comorbid anxiety and mood diagnoses, found that after using a transdiagnostic method, 66.7% of the participants with comorbidity at baseline did not meet criteria for a comorbid diagnosis compared to 48.5% where only the main diagnosis was targeted (Norton et al., 2013). In CVD, the use of collaborative care programs, and interdisciplinary treatment approaches are also yielding promising results (Bradley & Rumsfeld, 2015). The following findings indicate that cluster based screening can also be linked to treatment plans that may increase treatment efficacy for depression and anxiety in this population. However, to date, there is a paucity of empirical research suggesting that the theoretical ‘clusters’ could inform screening procedures in CVD populations (Tully & Penninx, 2012), and thus further research is warranted.

## SUMMARY AND CONCLUSIONS

The prevalence and risk of depression in CVD are fairly established in the broader literature leading to the recommendation that depression should be screened in this high-risk cohort. While it may have been slow to start, there is now a growing body of evidence to indicate that anxiety is also associated with some increased risk of incident CVD and also, in those with already established conditions. Despite evidence for their independent roles, anxiety and

depression rarely exist in isolation. As such, there are apparent limitations to screening depression as a lone construct, including implications for CVD related risk and the efficacy of interventions. The theoretical ‘clusters’ may provide an answer to the comorbidity quandary, as well as facilitate a shift from disorder-specific interventions to include transdiagnostic methods that may also increase treatment efficacy in CVD. However, the paucity of studies evaluating this novel approach to screening suggests this warrants further empirical support before such a method could be considered.

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# RESEARCH REPORT

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# Utilising the Theoretical 'Clusters' to Inform Screening Procedures in Cardiovascular Disease

Grech, Megan[1] BAPsych(Hons); Turnbull, Deborah[2] BAPsych(Hons), MPsych(Clin), PhD(Psych); Tully, Phillip[3] B.Hsc(Hons), MPsych(Clin), PhD(Psych)

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[1] School of Psychology, Faculty of Health and Medical Sciences, The University of Adelaide, North Terrace, Adelaide, South Australia, 5005, Australia
[2] School of Psychology, Faculty of Health and Medical Sciences, The University of Adelaide, North Terrace, Adelaide, South Australia, 5005, Australia
[3]Adelaide Medical School, Faculty of Health and Medical Sciences, The University of Adelaide, North Terrace, Adelaide, South Australia, 5005, Australia

## Abstract

To examine the utility and diagnostic detection of common anxiety and depression instruments for the screening of internalising 'clusters' (i.e., anxious-misery and fear) in a cardiovascular population. The participants, patients with a hospital administration for cardiovascular disease (CVD) (*n* = 85, 59 (69.4%) were male), underwent a structured clinical interview with the MINI- International Neuropsychiatric Interview. The participants also completed the Patient Health Questionnaire (PHQ) 9 item scale, Generalized Anxiety Disorder (GAD) 7 item scale, Overall Anxiety Severity Impairment Scale (OASIS), and the stress subscale of the Depression Anxiety Stress Scale (DASS). The PHQ-9 (sensitivity, 85.71%, specificity 82.94%), and the GAD-7 (sensitivity 85.71%, specificity 82.81%) yielded appropriate screening properties for the 'anxious-misery' cluster. The GAD-7 was the only instrument to display favourable screening properties for the 'fear' cluster (sensitivity 81.25%, specificity 76.81%). The PHQ-9 and the GAD-7 can be implemented to reliably screen emotional disorder 'clusters' in a CVD population.


**Keywords:** depression, anxiety, internalising disorders, clusters, receiver operating characteristics, cardiovascular disease

Depression and anxiety (e.g., collectively named the emotional disorders) are highly prevalent (29% anxiety disorders; 19% depressive disorders) and disabling resulting in substantial individual, societal and economic cost worldwide (Chisholm et al., 2016). Their coexistence is also common and alarming, both in clinical and community samples, and concurrently and across the lifespan (Brown, Campbell, Lehman, Grisham, & Mancill, 2001; Hasin & Kilcoyne, 2012; Kessler, Chiu, Demler, & Walters, 2005; Teesson, Slade, & Mills, 2009). Some scholars implicate the current diagnostic classification system in the high rates of comorbidity between depression and anxiety (Zbozinek et al., 2012), other evidence is found in twin studies where genetic risk factors for depression and anxiety substantially overlap in men and women (Kendler, Gardner, Gatz, & Pedersen, 2007; Kendler, Neale, Kessler, Heath, & Eaves, 1992), while some have suggested that depression and anxiety share underlying metacognitive processes and beliefs (Hendriks et al., 2014; Rector, Szacun-Shimizu, & Leybman, 2007; Wells & Matthews, 1994). Although, this is yet to be empirically tested. Other evidence exists in intervention studies where treatments for one disorder effectively reduce symptoms in the other, such as psychotherapy (Weitz, Kleiboer, van Straten, & Cuijpers, 2018), or, antidepressant intervention (Andrews et al., 2009).

Structural modelling research suggest that a common ‘negative affectivity’ component, a general dimension of subjective distress including negative emotional states such as fear, anger, sadness, guilt, and disgust (Watson, 2005)), is an etiological factor partially responsible the high rates of comorbidity (Kotov, Gamez, Schmidt, & Watson, 2010). Though ‘negative affectivity’ is considered to be common to all emotional disorders, its disposition failed to account for heterogeneity across disorders, and the broader literature now supports a structure that is far more complex (Kotov et al., 2017). For example, supporting a ‘clustering’ approach, structural modelling suggests that common mental disorders tend to band together under broader domains. In particular, the emotional disorders

were found to cluster under the ‘internalising’ domain, which is distinct from the ‘externalising’ domain reflecting the antisocial and substance use disorders (Kotov et al., 2017; Krueger & Markon, 2006). Subsequent research suggested that the ‘internalising’ domain can bifurcate into lower order groups characterised by ‘anxious-misery’ (e.g., Major Depressive Disorder, Dysthymia, Generalized Anxiety Disorder (GAD), and Post Traumatic Stress Disorder (PTSD)), or, by ‘fear’ (e.g., Panic Disorder, Agoraphobia, Specific Phobia, Social Anxiety Disorder, and OCD) (de Jonge et al., 2018; Eaton et al., 2013; Kotov et al., 2017; Krueger, Caspi, Moffitt, & Silva, 1998; Slade & Watson, 2006; Vollebergh et al., 2001). Notably, GAD is considered to be a part of the ‘anxious-misery’ cluster since it shares a more substantial portion of the general factor ‘negative affectivity’ variance compared to the other anxiety disorders, which are generally characterised by phobias and somatic arousal (Watson, 2005). Besides the fact that there are ongoing debates regarding the optimal placement of disorders within the lower arrangement, the broader domains are considered robust (de Jonge et al., 2018; Kotov et al., 2017) and likely account for the higher than chance comorbidity patterns observed across the lifespan (Kessler, Petukhova, & Zaslavsky, 2011).

Despite evidence that ‘anxious-misery’ and ‘fear’ disorders better predict health outcomes (in contrast to disorder-specific variations) (Eaton et al., 2013), this theoretical framework is rarely used to inform psychiatric screening procedures in health settings. Both the American Heart Association (AHA) and National Heart Foundation (NHF) of Australia recommend routine screening of depression, not anxiety, as an isolated pathway to clinical intervention (Colquhoun et al., 2013; Lichtman et al., 2008), undeterred by the well-known high rates of comorbid anxiety and depression in clinical and community samples (Brown et al., 2001). Further, since the release of that recommendation studies have shown that approximately 50% of coronary heart disease persons have comorbid depression and anxiety (Tully, Cosh,

& Baumeister, 2014). Due to the spotlight now on the high prevalence of anxiety disorders in cardiovascular disease, studies are now attempting to improve its detection rate by reporting on the psychometrics of common anxiety screening tools (Bunevicius et al., 2013). However, given that comorbidity between disorders is the norm rather than the exception (Thibodeau et al., 2015), it is rarely appropriate to limit assessment of mental health to single disorders, and this can have dramatic implications for screening. Indeed, as reflected in the findings by Bunevicius and colleagues, disorder-specific screening omits a substantial number of persons that are potential candidates for intervention (Bunevicius, 2013). It could be argued that at the screening stages, enquires about single disorders are less meaningful when the primary goal is to detect clinically relevant psychological distress and streamline patients into clinical supports. Due to the high likelihood of comorbidity, the aforementioned emotional clusters may aid screening efforts in cardiovascular populations by targeting the common factors (i.e. 'anxious-misery' or 'fear') that contribute to the depression and anxiety disorders.

In addition, to date, interventions in cardiovascular disease have been almost exclusively limited to depression even though disorder-specific interventions pay relatively little attention to comorbidity. Fatigue, loss of energy and sleep disturbances have been shown to persist in coronary heart disease persons even when they no longer meet full diagnostic criteria for depression (Conradi, Ormel, & De Jonge, 2011). Interestingly, fatigability and sleep disturbances are also diagnostic features of GAD and the two disorders (e.g., Major Depression Disorder and GAD) frequently co-occur (Leventhal & Rehm, 2005). The 'anxious-misery' and 'fear' clusters could enable a movement away from individual disorder based treatments to more transdiagnostic methods that allow clinicians to target common symptoms and processes that subsume the broader range of emotional disorders (Barlow et al., 2011). Promisingly, transdiagnostic treatments have been shown to better target comorbid symptoms (Norton et al., 2013), as opposed to single disorder treatments, possibly targeting

the fundamental features of emotional disorders (i.e., negative affectivity). Importantly, the low effect sizes present in randomised control trials (RCT) for depression in coronary heart disease samples underscores the importance of looking beyond depression to improve patient outcomes (Carney & Freedland, 2017). Sufficient evidence now exists to suggest that depression and anxiety in cardiac populations increase the risk of adverse cardiac outcomes independently, as well as some studies suggesting additive risk if two disorders are present (Doering et al., 2010; Phillips et al., 2009; Watkins et al., 2013). Therefore, there is no denying the clinical importance of improving screening and intervention efforts among cardiovascular populations.

Few studies have employed psychiatric theory about the broader emotional clusters to inform screening procedures in a cardiovascular population (Tully & Penninx, 2012). Bearing in mind the limitations of the research above, the objective of the current study is to evaluate the screening utility and diagnostic detection of four common clinical tools for the screening of the emotional disorders in a cardiovascular population. The tools employed were the Patient Health Questionnaire- 9 item (PHQ-9) scale, Generalised Anxiety Disorder- 7 item (GAD-7) scale, Overall Anxiety Severity Impairment Scale (OASIS) and Depression Anxiety Stress Scale (DASS) – Stress subscale. Scores on the PHQ-9, GAD-7, OASIS, and the DASS-stress scale were used to detect the presence or absence of the theoretical groupings of 'anxious-misery' and 'fear' disorders with receiver operating characteristics (ROCs), i.e. the true/false positive detection rates. As it remains unclear as to the optimal placement in this structure for several disorders including OCD (Cox, Clara, Hills, & Sareen, 2010; Prenoveau et al., 2010; Raines, Allan, Oglesby, Short, & Schmidt, 2015), GAD (Mennin, Heimberg, Fresco, & Ritter, 2008), and Panic Disorder (Greene & Eaton, 2016; Wright et al., 2013), different clusters forms will be explored.

The PHQ-9 and the GAD-7 were theorised to reflect the ‘anxious-misery’ cluster given their design was formulated to capture symptoms of depression and generalized anxiety, respectively. Given the OASIS is a measure capturing anxiety and fear, it was theorised to be more associated with the ‘fear’, rather than the ‘anxious-misery’ cluster. The DASS-stress was theorised to reflect both ‘anxious-misery’ and ‘fear’ clusters given it is relatively non-specific (i.e., measures shared trait neuroticism, or, negative affectivity). We hypothesised that the PHQ-9 and the GAD-7 would be superior to the OASIS and the DASS-stress for the ‘anxious-misery’ cluster and that the OASIS will be superior to the PHQ-9, GAD, and DASS-stress for the ‘fear’ cluster. It is hypothesised that the DASS-stress will be associated with both the ‘anxious-misery’ and ‘fear’ clusters.

# Methods

## Design and Procedure

This study presents a secondary analysis of a single-blind randomized control trial to evaluate the feasibility of a unified protocol for the transdiagnostic treatment of emotional disorders intervention in patients recently hospitalised for cardiovascular diseases. The Cardiovascular Health Anxiety Mood Problems Study (CHAMPS) (Tully et al., 2016) study is completed, and the Human Research Ethics Committee (HREC) from the Queen Elizabeth Hospital approved the study design (approval #HREC/15/TQEH47). The screening was a two-step process as recommended by the AHA to confirm elevated symptoms of anxiety and depression after hospitalisation. During the cardiovascular disease admission, each participant was screened with the PHQ-9 and the GAD-7 by an authorised hospital staff member employed as a trial manager in the cardiology department. All patients screening positive (PHQ-9 cut off >9 (Colquhoun et al., 2013), GAD-7 cut off >6 (Kroenke, Spitzer, Williams, & Löwe, 2010)) were screened again approximately 1-2 weeks later with the PHQ-9, GAD-7, OASIS, DASS-stress, and the MINI - International Neuropsychiatric Interview (MINI) to determine eligibility.

## Participants

The participants in the trial were consenting patients with a primary hospital administration for cardiovascular disease to the Cardiology Department of the Queen Elizabeth Hospital. Inclusion criteria were: 18 years of age, proficiency in the English language, and had a primary hospital admission for a cardiovascular disease (specified by relevant International Classification of Disease codes for CAD, myocardial infarction, heart failure, atrial fibrillation, other ventricular or atrial arrhythmia, coronary revascularization intervention, symptomatic coronary heart disease including unstable angina pectoris, or heart valve

disease). Ineligible participants had a known or observed cognitive impairment or dementia, a medical condition likely to be fatal within one year, or a neurodegenerative condition such as Parkinson's or Multiple Sclerosis. The trial further excluded *n* = 3 persons with substance or alcohol dependence/abuse and these participants were included in the current analyses on psychiatric screening in cardiovascular patients.

## Measures

### Psychiatric Diagnosis

All participants were reviewed psychiatrically using a structured diagnostic interview (MINI) (Sheehan et al., 1998). The MINI served as the 'gold standard' and was performed blinded by study assessors to determine the presence of a primary psychiatric diagnosis (yes/no). The MINI has high sensitivity and specificity to detect the emotional disorders, with Kappa coefficients ($\kappa = .86$ - $.96$) suggesting a favourable agreement with the Diagnostic and Statistical Manual of Mental Disorders-IV (DSM-IV). Participants were included in the 'anxious-misery' cluster [a] if they met criteria for major depression disorder, dysthymia, GAD, post-traumatic stress disorder, and bi-polar disorder (Kotov et al., 2017; Watson, 2009). Participants were included in the fear cluster [a] if they met criteria for panic disorder, agoraphobia, social anxiety disorder, and OCD (Kotov et al., 2017; Watson, 2009). Given the debate about the optimal structure of the lower order emotional disorders (Kotov et al., 2017), the placement of disorders within clusters was investigated to assess their potential to inform screening procedures. The exploratory clusters were as follows: 'anxious-misery' cluster [b] - major depression, dysthymia, GAD, depression melancholic, post-traumatic stress, bi-polar, and OCD; 'anxious-misery' cluster [c]; major depression, dysthymia, generalized anxiety disorder, and depression melancholic; fear cluster [b] panic disorder, agoraphobia, social anxiety disorder, and post-traumatic stress disorder; fear cluster [c]; panic disorder,

agoraphobia, and social anxiety disorder. Notably, emotional disorder comorbidity prohibited participants from being exclusively related to only one of the clusters above.

**Self-reported Distress Scales**

The participants were administered the PHQ-9 item scale (Kroenke, Spitzer, & Williams, 2001), a standardised instrument that incorporates Diagnostic Statistical Manual -V depression criteria into a self-report tool to be used in primary care. Further, the PHQ-9 has been recommended by the AHA for screening in heart disease patients (Lichtman et al., 2008). It is a reliable and well-validated scale where each item is scored from 0 to 3, totalling a maximum score of 27 (Kroenke et al., 2001). The participants were also administered the GAD-7 item scale (Spitzer, Kroenke, Williams, & Löwe, 2006). Participants scored on a scale of 0 to 3 (not at all, several days, more days than half the days, and nearly every day) how often in the last two weeks they were bothered by each symptom item. It does not contain any questions relating to somatic complaints and can distinguish between anxiety and depression making its use in cardiac populations appropriate. The GAD-7 is considered to be a psychometrically sound measure to use in primary care settings (Spitzer et al., 2006).

In addition to the GAD-7 and PHQ-9, the OASIS and the DASS-stress were both administered. The OASIS (Norman, Hami Cissell, Means-Christensen, & Stein, 2006) was developed as a self-report measure of anxiety that assesses multiple domains of clinical severity, including functional impairment, and captures the severity of any anxiety disorder (Campbell-sills et al., 2009). It is a short five-item scale that can be used as a continuous measure of anxiety-related severity and impairment. Participants respond to the items that best describe their experience on a five-point scale (0, little or none; 1, mild; 2, moderate; 3, severe; 4, extreme). The OASIS psychometric properties have been evaluated in primary care settings and are a valid instrument for measuring anxiety severity and impairment in clinical samples (Campbell-Sills et al., 2009). Stress was measured using the stress subscale of the

DASS (Brown, Chorpita, Korotitsch, & Barlow, 1997) a clinical measure used commonly, validated in adults aged to 90 years and in previous studies in cardiovascular populations (Tully, Baker, Knight, Turnbull, & Winefield, 2009; Tully, Baker, Turnbull, Winefield, & Knight, 2009). Overall, there is limited knowledge of the PHQ-9, GAD-7, OASIS, and DASS-stress ROCs in cardiovascular populations.

**Statistical Analysis**

Statistical analysis was performed using MedCalc Statistical Software version, 18.5. The MINI affective diagnosis (yes/no) constituted the criterion standard for the presence or absence of cluster disorders. Scores on the screening measures (PHQ-9, GAD-7, OASIS, and DASS-stress), were used to detect clusters (arranged as 'anxious-misery' and 'fear' [a], [b], and [c]) from normal cases with ROCs, i.e., the true positive rate (sensitivity) plotted against the false positive rate (1-specificity) for all possible cut off points. The area under the curve (AUC), is the percentage of randomly drawn pairs for which the screening measures correctly classifies affected and non-affected cases and represents the diagnostic power of the test. An AUC of 1.0 indicates the measure has perfect diagnostic properties, that is, all cases with the presence of a cluster disorder were detected by the measure, while those in the absence of a cluster disorder are correctly classified. An AUC of 0.5 indicates that the screening measure is no better than chance at detecting affective disorders or clusters. Interpretation of the AUC values were as follows: 0.5 - <0.7 mildly accurate, 0.7 – 0.9 moderately accurate, and 0.9 - <1 highly accurate. The screening measures cut off points were reported for AUC $p$ <.05 and were determined by the maximal Youden Index (sensitivity + specificity – 100). The positive (PPV) (i.e. the likelihood that there is a cluster present given a positive test result) and the negative predictive value (NPV) (i.e. the likelihood that a cluster isn't present given a negative test result) were also calculated. High sensitivity (i.e. a high false positive rate) at the expense of low specificity (i.e. a high false negative rate) also results in an inordinate

number of diagnostic interviews and therefore, a specificity of >75% is desirable for clinical purposes. The AUCs between measures were compared statistically using the methods of DeLong, DeLong, and Clarke-Pearson (1988). A *p*-value < 0.05 was considered as statistically significant, and no adjustment was made for multiple comparisons based on the recommendations of Rothman (1990). The rationale was that the study hypotheses are well defined, and secondly, that the study is exploratory in nature where the risk of Type II error is greater than the risk of Type I error.

## Results

A total of *n* = 85 patients were included and of those 59 (69.4%) were male (see *Figure 1* (Appendix A) for eligibility flowchart). In regards to CVD characteristics, 34.1% had angina pectoris, 25.9% had other ventricular or atrial arrhythmia, 25.9% had atrial fibrillation, 22.4% had coronary heart disease, 21.2% had a previous myocardial infarction (heart attack), 12.9% had acute myocardial infarction (heart attack), 10.6% had other symptomatic coronary heart disease, 9.4 % had heart valve disease, 8.2% had an implanted cardiac defibrillator, 5.9% had a biventricular pacemaker, and 3.5% had coronary artery disease. Hypertension and Hypercholesterolemia were highly prevalent in 56 (65.9%), and 48 (56.5%) of the patients, respectively. In regards to psychiatric intervention, 4 (4.7%) were receiving antidepressant medical treatment, 2 (2.4%) had received counselling from a general practitioner, 1 (1.2%) was using anxiolytic medication, 1 (1.2%) was being treated by a psychiatrist, and no persons had been seen by a psychologist.

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INSERT FIGURE ONE ABOUT HERE (SEE APPENDIX A)

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The number of patients diagnosed with affective disorders on the MINI were as follows: major depression (*n* = 20, 23.5%), depression with melancholy (*n* = 11), GAD (*n* = 7, 8.2%), agoraphobia (*n* = 9, 10.6%), panic disorder (*n* = 6, 7.1%), bipolar (*n* = 4, 4.7%), social phobia (*n* = 2, 2.4%), post-traumatic stress disorder (*n* = 2, 2.4%), OCD (*n* = 1, 1.2%), and dysthymia (*n* = 0). Further, there were patients meeting criteria for alcohol dependence (*n* = 3, 3.5%), and alcohol abuse (*n* = 1, 1.2%). In regards to comorbidity, the number of patients with comorbid affective disorders were as follows: no disorder (57, 67.1%), one disorder

(12, 14.1%), two disorders (4, 4.7%), three disorders (7, 8.2%), four disorders (3, 3.5%), six disorders (1, 1.2%), and seven disorders (1, 1.2%).

**Area under the Curve (AUC)**

***'Anxious-misery' cluster [a]***. There were *n* = 21 (24.7%) persons meeting at least one diagnosis from the 'anxious-misery' cluster [a] (Note. Due to comorbidity between disorders the total number of depression, dysthymia, GAD, depression melancholic, post-traumatic stress disorder and bipolar surpasses 21). The ROCs are presented in *Table 1*. The AUC was greatest for the PHQ-9, followed by the GAD-7, the DASS-stress, and the OASIS. Using a cut-point of 6, the PHQ-9 showed favourable sensitivity (85.71%) and specificity (82.94%), while employing a cut point of 4 the GAD-7 yielded comparable sensitivity (85.71%) and specificity (82.81%). Employing a cut point of 2 the DASS-stress scale had a sensitivity of 80.95%. However, a specificity of 58.81% and therefore, indicating suboptimal screening. The sensitivity of the OASIS was below 70%, also suggesting poor screening properties in detection of the 'anxious-misery' cluster [a]. Employing DeLong et al. (1988) methodology to compare the AUCs, the PHQ-9 ($p = 0.049$) and the GAD-7 ($p = 0.048$) had significantly higher AUCs than the OASIS. All other screening measures had comparable accuracy in detecting the 'anxious-misery' cluster [a]. Despite the DASS-stress scale indicating it is diagnostically comparable to the GAD-7 and the PHQ-9, its specificity values indicated otherwise (specificity, 57.81%).

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INSERT TABLE ONE ABOUT HERE (SEE APPENDIX B)

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***'Anxious-misery' cluster [b]*** *n* = 21 (24.70%). The AUC was greatest for the PHQ-9. Employing a cut off of 7, the PHQ-9, again, showed desirable sensitivity (80.95%) and

specificity (94.12%), while the GAD-7 required a cut point of 4 for a sensitivity of 85.71% and specificity of 84.31%. The DASS-stress scale and the OASIS, again, demonstrated suboptimal screening properties in the detection of the 'anxious-misery' cluster [b]. Post hoc tests revealed that the GAD-7 ($p = 0.031$) and PHQ-9 ($p = 0.031$) AUCs were both statistically different from the OASIS highlighting the GAD-7 and PHQ-9 as more desirable for screening purposes. There were no other statistically discernible differences, and thus, again, the DASS stress-scale was considered to have a comparable diagnostic accuracy to the GAD-7 and PHQ-9. However, unlike the GAD-7 and PHQ-9, its specificity (62.75%) values yielded it diagnostically unfavourable.

***'Anxious-misery' cluster*** [c] $n = 21$ (24.70%). The AUC values in descending order were as follows: the PHQ-9, GAD-7, DASS-stress, and OASIS. Again, the PHQ-9 showed favourable sensitivity (85.71%) and specificity (82.94%), while employing a cut point of 4 the GAD-7 also yielded a highly favourable sensitivity of 80.95% and a specificity of 94.12%. When using a cut-point of 2, the DASS-stress scale had a sensitivity of 80.95%. However, its specificity (57.81%) was unfavourable. The OASIS also continued to show poor screening ability. The GAD-7 ($p = 0.048$) and PHQ-9 ($p = 0.049$) AUCs were statistically significant when compared to the AUC of the OASIS. Again, the DASS- stress scale was considered to have a comparable diagnostic accuracy to the GAD-7 and PHQ-9, despite unfavourable specificity values yielded by the DASS-stress (62.75%).

***Fear cluster*** [a]**.** $n = 17$ (21.52%). The AUC was greatest for the GAD-7 employing a cut off of 4 and favourable sensitivity (81.25%) and specificity (76.81%). A cut-off point of 7 on the PHQ-9 showed a sensitivity of 68.75% and a specificity of 82.61% and therefore, considered unfavourable for screening purposes. Further, the OASIS and the DASS-stress yield matching sensitivity scores (75%) but, unfavourable specificity values (57.97% and 53.62%, respectively). Employing DeLong, DeLong, and Clarke-Pearson methodology, the

GAD-7 was statistically significantly different from the DASS-stress scale ($p$ = 0.046). The GAD-7 was the only measure to demonstrate suitable sensitivity and specificity values in this cluster. Further, there were no other statistically discernible differences between the AUCs indicating the other screening measures had comparable diagnostic accuracy.

***Fear cluster*** [b] $n$ = 16 (18.82%). The AUC values in descending order were as follows: GAD-7, PHQ-9, OASIS, and DASS-stress. The GAD-7 was not statistically discernible from PHQ-9 or the OASIS, suggesting comparable diagnostic accuracy for detecting fear cluster [b] disorders. However, the GAD-7 was statistically different from the DASS-stress scale ($p$ = 0.027). Irrespective, the GAD-7 was not considered to be diagnostically more appropriate (sensitivity, 68.75%) There were no other statistically relevant differences, nor, did any of the sensitivity or specificity values indicate superior diagnostic qualities.

***Fear cluster*** [c] $n$ = 15 (17.6%). Employing a cut-off of 7, the GAD-7 and the PHQ-9 yielded unfavourable sensitivity scores (sensitivity, 66.67%), while the OASIS and the DASS-stress scale had specificity values considered to be suboptimal (specificity, <70). The GAD-7 was considered to be diagnostically more accurate than the DASS-stress scale in fear cluster [c] disorders ($p$ = 0.024). Despite this finding, no measures in this cluster had suitable screening properties when evaluating the sensitivity and specificity values. Further, there were no other statistically discernible differences across measures.

**Sensitivity Analysis**

The main ROC analyses were repeated in sensitivity analyses using the primary formulation of 'anxious-misery' cluster [a] ($n$ = 17, 21.52%), and 'fear' cluster [a] ($n$ = 14, 17.72%) excluding persons receiving current treatment. The ROCs are presented in *Table 2*. Similar findings were observed for detecting the 'anxious-misery' cluster. Employing a cut point of 7, with the PHQ-9 and GAD-7 revealed favourable sensitivity (82.35% and 70.59%,

respectively) and specificity (90.32% and 95.16%, respectively). The OASIS and the DASS-stress scale yielded unfavourable values. The AUC for the PHQ-9 ($p$ = 0.043) was significantly different from the DASS-stress scale indicating further screening benefits of the PHQ-9. There were no further statistically discernible differences between the AUCs in the 'anxious-misery' cluster [a], indicating comparable diagnostic accuracy. Employing a cut point of 4, the GAD-7 was the only screening measure from the 'fear' cluster [a] with favourable diagnostic qualities (sensitivity, 78.57%; specificity, 78.46%). Comparison of ROC curves did not yield any statistically significant differences between the screening measures suggesting similar screening accuracy across outcomes.

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INSERT TABLE TWO ABOUT HERE (SEE APPENDIX C)

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## Discussion

This study was particularly unique in its investigation of the emotional disorder clusters and their ability to inform screening procedures in cardiovascular disease populations. The ROC analysis supported the GAD-7 and the PHQ-9 for the screening of the 'anxious-misery' cluster, irrespective of cluster variations. While post hoc tests did not reveal any differences in the DASS-stress scales ability compared to the GAD-7 and the PHQ-9 to screen 'anxious-misery' clusters indicating similar screening abilities, the specificity of the DASS-stress scale was unfavourable (specificity, <63%) when compared to the GAD-7 and the PHQ-9 (specificities >85%). The OASIS also yielded unfavourable screening properties and therefore, as hypothesised, the PHQ-9 and GAD-7 were superior to the OASIS in all the 'anxious-misery' clusters. Further, these results did not change for 'anxious-misery' cluster [a] in sensitivity analysis. The PHQ-9 and the GAD-7 also had high sensitivity and NPVs as compared to the other screening tools, with sensitivities above 80% and NPVs approximately 95% or higher for the 'anxious-misery' clusters. Given that for screening purposes it is advantageous to attain high sensitivity and NPVs than high specificity and PPVs, the findings demonstrate that in the prediction of 'anxious-misery' disorders, the GAD-7 and PHQ-9 are effective for screening purposes in cardiovascular disease irrespective of the cluster variations.

However, the PPV of the PHQ-9 was also high for 'anxious-misery' [b] cluster (77.5%) indicating that approximately three-quarters of the sample who had a positive result on the screening met the diagnostic criteria for one or more of the 'anxious-misery' cluster [b] disorders. These results are promising given the aim is to distinguish patients with clinically relevant disorders from those with more acute short-term distress. Bunevicius et al. (2013) showed that the Hospital and Depression Scale-Anxiety (HADS-A), the Spielberger State-Trait Anxiety Inventory (STAI), and the Spielberger State Anxiety Inventory (SSAI) for

anxiety disorder screening, yielded high false positive rates, indicating that their routine use would put excessive demands on healthcare resources. The high specificities and PPVs, and high sensitivities and NPVs of the PHQ-9 for the 'anxious-misery' cluster [b], indicate that clinicians can be confident in excluding the presence of 'anxious-misery' cluster [b] disorders in respondents below recommended cut-points, and that patients who screen positive are likely to be clinically distressed and require clinical supports, despite lack of confirmation of a specific diagnosis.

As the overall performance of the PHQ-9 and GAD-7 were remarkably similar in the 'anxious-misery' clusters, the current findings suggest as single constructs identifying a 'anxious-misery' cluster, either measure might be considered. One explanation for the similarities in screening properties is that the questions of the PHQ-9 and GAD-7 also cover some of the core symptoms of other 'anxious-misery' disorders. For example, the PHQ-9 questions pertaining to restlessness, fatigue, difficulty concentrating, and sleep disturbances are similar symptoms experienced by other 'anxious-misery' disorders, while other common 'anxious-misery' symptoms such as concentration difficulties, easily annoyed, irritable and agitation or restlessness are also covered by the GAD-7. Indeed, in a factor analytic study there were high correlations between PHQ-9 and GAD-7, and cross loading of GAD-7 items (e.g., trouble relaxing, restlessness and irritability) with the depression items. As a result, the researchers concluded that it is hard to differentiate between 'anxious' and 'depressive' distress (Böhnke, Lutz, & Delgadillo, 2014). The promising screening abilities of the PHQ-9 and the GAD-7 to capture the 'anxious-misery' cluster may reflect a large extent the measures' abilities to capture a single factor dimension, such as negative affectivity (Böhnke et al., 2014).

The only diagnostically accurate tool for the 'fear' clusters was the GAD-7 yielding promising sensitivity (81.25%), and specificity (76.81%), but only in regards to 'fear' cluster

[a] (i.e. panic, agoraphobia, social anxiety, and OCD). Further, this did not change during sensitivity analysis. Recently, it was suggested that 'worry' may be best modelled at the broadest structural level, rather than an indicator of just 'fear' or 'anxious-misery' clusters (Naragon-Gainey, Prenoveau, Brown, & Zinbarg, 2016). This finding provides a worthy explanation for the ability of the GAD-7 to screen both 'fear' and 'anxious-misery' clusters (Naragon-Gainey et al., 2016). However, interestingly, the removal of OCD (*n*= 1) yielded screening inadequate for 'fear' cluster [c]. The increase in the sensitivity of 'fear' cluster [a] as a result of including OCD may simply be due to some overlap in the symptoms of OCD and those captured by the GAD-7 (e.g., feeling anxious or on edge, trouble relaxing, and feeling afraid something awful might happen). In addition, 'worries' can also be present in individuals with OCD (Abramowitz & Foa, 1998), and given their similarities 'obsessions' might be described by patients as 'worries' yielding the GAD-7 highly sensitive for individuals with OCD. A recent systematic review and meta-analysis indicated that further studies are still needed in primary care to determine if the GAD-7, a tool primarily formulated for GAD, is proficient in detecting other 'fear' disorders, including OCD (Plummer, Manea, Trepel, & McMillan, 2016).

The finding that the OASIS screening properties were unfavourable for the 'anxious-misery' clusters was not surprising, given that the OASIS AUC is only considered 'fair', but not 'excellent' at detecting the anxiety disorders it was designed for (Ito et al., 2015). Notably, none of those disorders was considered in the 'anxious-misery' cluster. Further, given that now the group of researchers have designed a scale to measure mood symptoms more specifically (i.e. Overall Depression Impairment Scale (ODIS); Bentley, Gallagher, Carl, & Barlow, 2014), this provides further evidence for the limitations of the OASIS in regards to the 'anxious-misery' cluster. An explanation for the low sensitivity (<55%) produced by the OASIS in the current study is that the measure was designed to tap the behavioural (i.e.

avoidance) and functional aspects (i.e. impairment in work, or, interpersonal relationships) of disorder severity, whereas the GAD-7 and PHQ-9 are likely affected by the frequency of cognitive-affective and/or somatic aspects of anxiety or depression (Ito et al., 2015). The symptoms experienced by heart disease patients might be different in that somatic/cognitive symptoms for the 'anxious-misery' cluster (e.g., feeling down, worry, irritability, poor concentration, and sleep problems) are a better predictor of clinical dysfunction, than avoidance or functional impairment.

While avoidance is generally considered a hallmark of the 'fear' cluster (Mineka & Zinbarg, 2006) and therefore, may explain the lack of sensitivity in predicting the 'anxious-misery' cluster, interestingly, the OASIS did not yield appropriate screening properties (specificity <60) for the 'fear' cluster, either. Consequently, the hypothesis that the OASIS would provide superior diagnostic qualities to the other measures in the 'fear' cluster was not supported. This was surprising given that the sample pertaining to the 'fear' cluster constituted agoraphobia, panic disorder, social anxiety disorder, and depending on the cluster variation, OCD, disorders whose hallmark is avoidance and associated functional impairment (Mineka & Zinbarg, 2006). In the current sample, the AUC was considered 'mildly accurate', and this is in line with previous research (Ito et al., 2015) reporting on the OASIS' ability to detect 'fear' disorders (i.e. panic disorder, social anxiety disorder, and OCD)

The hypotheses that the DASS-stress measure would be associated with both the 'anxious-misery' and 'fear' clusters was partially supported. The AUC was considered to be 'mildly' accurate at detecting the 'fear' clusters and 'moderately' accurate at detecting the 'anxious-misery' clusters. There is some debate over whether the DASS-stress measures a construct that is 'similar' to depression and anxiety (but not the same), since it nestles itself under the umbrella of the higher order negative affectivity factor, or, whether there are no discernible differences (Norton, 2007). Interestingly in the current study, the DASS-stress appeared to be

more sensitive to the ‘anxious-misery’ cluster, than the ‘fear’ cluster (sensitivity, 80.95% vs. 73.33-75%, respectively) indicating some differences in the way the DASS-stress performs in regards to the distinct clusters. An explanation for this could be that ‘stress’ and ‘worry’ might be intimately linked. For example, there is some evidence to suggest that individuals with non-clinical levels of ‘worry’ have been found to frequently and uncontrollably experience a high level of stress as measured by the DASS-stress (Szabó, 2011). Further, there is evidence that the DASS-stress scale can differentiate between patients with GAD and mood disorders from the other diagnostic groups (Brown et al., 1997).

As mentioned earlier, recent research indicated that ‘worry’ more strongly loaded onto the general factor (i.e. negative affectivity) as opposed to the ‘fear’ or ‘anxious-misery’ clusters, and therefore, might be better modelled at the broadest structural level as a basic ‘emotional disorder’ (Brown, Chorpita, & Barlow, 1998; Naragon-Gainey et al., 2016). As mentioned above, if ‘worry’ and ‘stress’ are interlinked, then we might expect the DASS-stress to perform equally across clusters, however, this was not the case. An explanation for this is that GAD was included only in the ‘anxious-misery’ cluster and therefore, it was not considered as a ‘fear’ disorder. Given the close relationship speculated between GAD and the general factor (i.e. negative affectivity) (Naragon-Gainey et al., 2016), we might expect the DASS-stress scale to perform differently depending on the position of GAD within the cluster variations.

Generally, the performance of the PHQ-9 and GAD-7 measures as compared to the MINI was as good as reported in prior studies utilising other depression and anxiety scales for screening purposes in coronary heart disease patients. For example, the Hospital Anxiety and Depression Scale (HADS), measured against any diagnosis of depression and anxiety from the Clinical Interview Schedule-Revised (CIS-R), sensitivities and specificities were 85.78%, and 82.55%, respectively, while the NPV was 97.63% (Palacios, Khondoker, Achilla, Tylee,

& Hotopf, 2016), findings comparable to ours. More recently, the HADS was tested in acute coronary syndrome and CAD where screening properties were again comparable (sensitivity, 83.8% and 83.1%, respectively and specificity, 80.3% and 86.3%, respectively) (Tesio et al., 2017). Some researchers (Kroenke et al., 2016) have attempted to amalgamate the GAD-7 and the PHQ-9 (i.e., Patient Health Questionnaire-Anxiety Depression Scale (PHQ-ADS)) as a measure of overall psychological distress when the former is complicated by varying levels of depressive and anxiety symptoms (Chilcot et al., 2018). The findings here suggest that the clustering of highly comorbid disorders may eliminate the need for the bundling of already proficient screeners to create larger psychological batteries that are more time consuming for clinicians.

While the AHA recommends routine screening of depression in cardiac populations (Lichtman et al., 2008), this guideline is challenged due to the paucity of evidence that systematic screening for depression is helpful to improve the outcome of coronary heart disease patients (Lichtman et al., 2014; Thombs et al., 2012). An explanation for this could be the treatment of single diagnoses failing to represent the comorbidity and clinical complexity of patients in real-world settings (Barlow et al., 2017). This study increases the breadth of screening to include anxiety disorders, which commonly co-occur with depression (Kessler et al., 2012), and which are important to recognise due to the substantial influence they can have on mental and physical health in this at-risk cohort (Celano, Suarez, Mastromauro, Januzzi, & Huffman, 2013). Cluster screening has the power to increase identification of comorbid emotional disorders that when undetected may reduce the efficacy of treatment on the other (Celano et al., 2012). Comorbidity of anxiety and depression is now the rule rather than the exception (Spinhoven, van Balkom, & Nolen, 2011) highlighting the problems with single disorder treatment protocols. Cluster screening accommodates highly comorbid emotional disorders and may improve patient treatment outcomes with the employment of

transdiagnostic interventions. In comparison to disorder-specific treatments, there is some evidence that transdiagnostic treatments are as effective for reducing anxiety, and may be superior for reducing depression (Newby, McKinnon, Kuyken, Gilbody, & Dalgleish, 2015). A large-scale Cochrane review also demonstrated the efficacy of interdisciplinary interventions. Specifically, they found that decreases in anxiety and depression were found with patients receiving collaborative care for up to two years compared to routine care (Archer et al., 2012). These findings indicate sufficient evidence to suggest that patients might benefit from emotional disorder screening in the context of an interdisciplinary treatment approach (McGuire, Emanuela, & Doering, 2015).

**Limitations and Future Directions**

The results of this study should be interpreted recognising several limitations including that the hierarchical structure of mental disorders is still debated in the literature (Beesdo-baum et al., 2009) and not always supported (Conway & Brown, 2018). This debate and uncertainty are partly reflected in the number of structural models tested here, and therefore, interpretation of the ROCs utility for screening is tied to the validity of such disorder structures. Further, the current study did not include the externalizing disorder cluster (e.g., substance abuse and antisocial behaviour; (Kotov et al., 2017)) (Forbes et al., 2017). Since clinical trials in cardiovascular populations typically exclude patients with externalizing disorders, the significance of this group, including prevalence and prognosis of such disorders are lesser known. Concerning the sample, the MINI utilises hierarchical exclusion rules which may lower comorbidity rates and thus, resulted in no dysthymia cases in this sample. Given that there was also a small number of OCD, PTSD and bipolar disorder diagnoses in the current study, further investigation in diverse and larger samples of cardiovascular patients is justified to reproduce the current findings. Further, though this sample was derived from a cardiac in-patient ward, it is possible that some persons were without true

cardiovascular disease, given the known association between panic disorder and cardiovascular symptoms which frequently results in a misdiagnosis. Concerning the measures, older populations, low socio-economic, diverse ethnicities, and indigenous populations are also over-represented in cardiovascular settings, therefore, such psychological batteries may not be appropriate for all presenting patients (e.g., may have had trouble understanding the content of self-report questionnaires). The timing of the assessment (e.g., during or near an index cardiovascular admission) also may spuriously inflate symptoms, particularly somatic symptoms that are commonly experienced during hospitalisation and partially overlap with some mental disorders. Future research using factor analysis might be valuable in cardiovascular patients who experience a high number of somatic symptoms. Lastly, this was a single-centre design from a public hospital and therefore, our results may not generalise to other private hospitals or geographic regions. In light of these limitations,to the best of our knowledge this was one of the first studies to connect psychiatric theory to cardiovascular research and therefore, there is strength in its novelty and individuality.

**Conclusions**

In summary, the GAD-7 and PHQ-9 self-report scales provide sufficient screening measures to identify the ‘anxious-misery’ cluster. The GAD-7 also provided acceptable screening properties for the ‘fear’ cluster. Given the high likelihood of comorbidity, health-care settings should be aware of the potential advantages of shifting from traditional psychiatric taxonomies to an emphasis on the commonality and unity of psychiatric disorders, particularly as it may evidently provide an opportunity to benefit screening procedures in high-risk cohorts. Cluster-based screening in a CVD groups may also be a fruitful approach to increase the efficacy of current mental health interventions with the use of transdiagnostic intervening methods. Given that this is one of the first studies to evaluate the potential

screening benefits of employing hierarchical theory in a cardiovascular population, future research should continue to validate the diagnostic utility of the clusters in this high-risk cohort.

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**APPENDIX A**

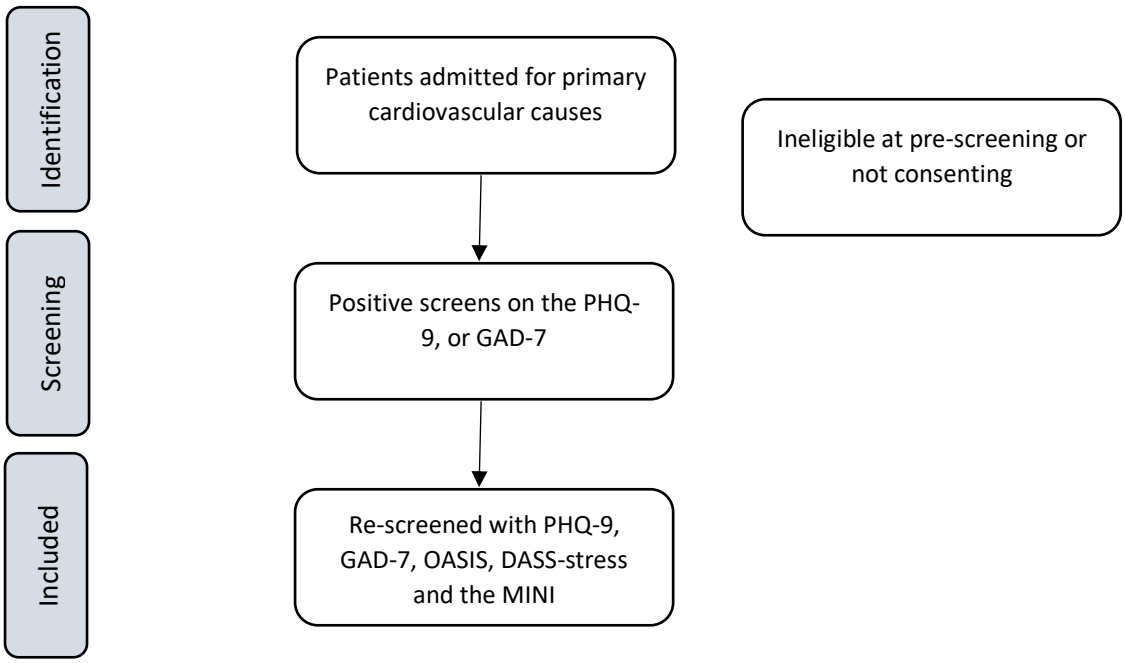


*Figure 1*. Flowchart of the screening process to determine eligibility. PHQ-9, Patient Health Questionnaire 9 item scale; GAD-7, Generalized anxiety disorder 7 item scale; OASIS, Overall Anxiety Severity Impairment Scale; DASS-stress, Depression Anxiety Stress Scale – stress subscale.

**APPENDIX B**

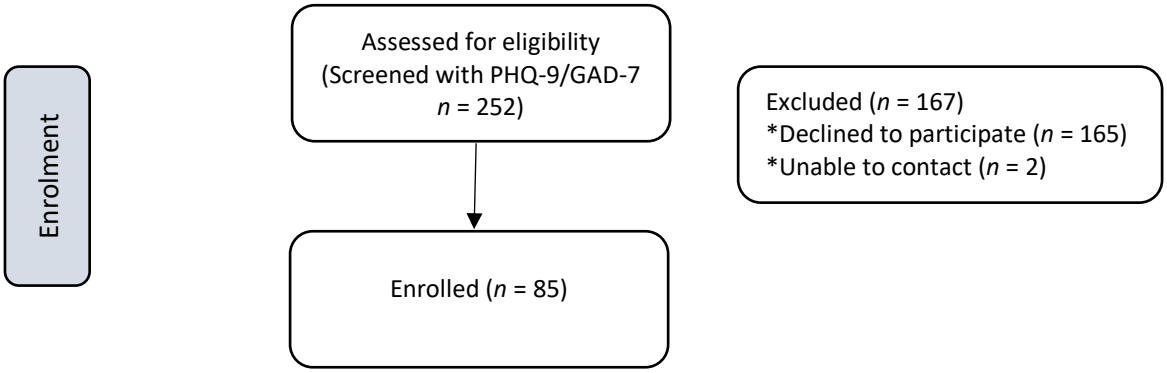


*Figure 2*. Flowchart of participant eligibility.

## APPENDIX C

Table 1

*Receiver Operating Characteristics of Clusters and Depression and Anxiety screening measures*

| Clusters | AUC (SE) | 95% CI | Cut-off | Sens. True + | Spec. True - | Youden Index | PPV | NPV |
|---|---|---|---|---|---|---|---|---|
| **Anxious-misery [a] (*n* = 21)** | | | | | | | | |
| GAD-7[d] | .856 (.060) | .763-.923 | 4 | 85.71 | 82.81 | 68.53 | 55.5 | 95.9 |
| PHQ-9[e] | .873 (.058) | .783-.935 | 6 | 85.71 | 85.94 | 71.65 | 66.7 | 94.8 |
| OASIS | .692 (0.72) | .582-.787 | 2 | 52.38 | 84.37 | 36.75 | 52.4 | 84.4 |
| DASS | .732 (0.60) | .625-.822 | 2 | 80.95 | 57.81 | 38.76 | 38.6 | 90.2 |
| **Anxious-misery [b] (*n* = 21)** | | | | | | | | |
| GAD-7[d] | .860 (.060) | .758-.930 | 4 | 85.71 | 84.31 | 70.03 | 57.5 | 95.8 |
| PHQ-9[e] | .879 (.057) | .780-.944 | 7 | 80.95 | 94.12 | 75.07 | 77.5 | 95.2 |
| OASIS | .680 (.074) | .560-.785 | 3 | 47.62 | 88.24 | 35.85 | 50.3 | 87.1 |
| DASS | .747 (.061) | .631-.842 | 2 | 80.95 | 62.75 | 43.70 | 35.2 | 92.9 |
| **Anxious-misery [c] (*n* = 21)** | | | | | | | | |
| GAD-7[d] | .856 (.060) | .763-.923 | 4 | 85.71 | 82.81 | 68.53 | 55.5 | 95.9 |
| PHQ-9[e] | .873 (.058) | .783-.935 | 6 | 85.71 | 85.94 | 71.65 | 60.4 | 96.0 |
| OASIS | .692 (.072) | .582-.787 | 2 | 52.38 | 84.37 | 36.76 | 45.6 | 87.6 |
| DASS | .732 (.060) | .625-.822 | 2 | 80.95 | 57.81 | 38.76 | 32.4 | 92.4 |
| **Fear [a] (*n*=17)** | | | | | | | | |
| GAD-7[f] | .776 (.076) | .673-.860 | 4 | 81.25 | 76.81 | 58.06 | 38.2 | 95.9 |
| PHQ-9 | .719 (.082) | .611-.811 | 7 | 68.75 | 82.61 | 51.36 | 41.1 | 93.7 |
| OASIS | .673 (.073) | .563-.771 | 0 | 75.00 | 57.97 | 32.97 | 29.3 | 90.9 |
| DASS | .626 (.077) | .474-.777 | 2 | 75.00 | 53.62 | 28.62 | 22.2 | 92.4 |
| **Fear [b] (*n* = 16)** | | | | | | | | |
| GAD-7 | .787 (.077) | .684-.868 | 7 | 68.75 | 91.30 | 60.05 | 58.3 | 94.3 |
| PHQ-9 | .732 (.084) | .625-.823 | 7 | 68.75 | 82.61 | 51.36 | 41.1 | 93.7 |
| OASIS | .669 (.072) | .559-.768 | 0 | 75.00 | 57.97 | 32.97 | 23.9 | 92.9 |
| DASS | .621 (.074) | .510-.724 | 2 | 75.00 | 53.62 | 28.62 | 22.2 | 92.4 |
| **Fear [c] (*n* = 15)** | | | | | | | | |
| GAD-7[g] | .768 (.080) | .663-.852 | 7 | 66.67 | 90.00 | 56.67 | 54.1 | 93.9 |
| PHQ-9 | .710 (.087) | .601-.803 | 7 | 66.67 | 81.43 | 48.10 | 38.8 | 93.3 |
| OASIS | .642 (.074) | .531-.743 | 0 | 73.33 | 57.14 | 30.48 | 23.2 | 92.4 |
| DASS | .592 (.075) | .480-.698 | 2 | 73.33 | 52.86 | 26.19 | 21.5 | 91.8 |

*Note.* AUC = area under the curve; CI = confidence interval; Sens = Sensitivity; Spec = specificity; NPV = negative predictive value; PPV = positive predictive value; SE = standard error, GAD-7 = Generalized Anxiety Disorder- 7 item scale, PHQ-9 = Patient Health Questionnaire 9 item scale, OASIS = Overall Anxiety Severity Impairment Scale, DASS = Depression Anxiety Stress Scale – Stress subscale

Current psychiatric disorders were derived by a structured clinical interview with the MINI

[a] Anxious-misery' group comprises major depression, dysthymia, generalized anxiety disorder, depression melancholic, post-traumatic stress, and bi-polar; Fear disorders group comprises panic disorder, agoraphobia, social anxiety disorder, and obsessive-compulsive disorder

[b] Anxious-misery' group comprises major depression, dysthymia, generalized anxiety disorder, depression melancholic, bi-polar and obsessive-compulsive disorder; Fear disorders group comprises panic disorder, agoraphobia, social anxiety disorder, and post-traumatic stress disorder

[c] 'anxious-misery' group comprises major depression, dysthymia, generalized anxiety disorder, and depression melancholic; 'Fear' disorders group comprises panic disorder, agoraphobia, and social anxiety disorder

[d] – The GAD-7 was significantly different ($p < .05$) from the OASIS

[e] – The PHQ-9 was significantly different ($p < .05$) from the OASIS

[f] – The GAD-7 was significantly different ($p < .05$) from the DASS-stress

[g] – The GAD-7 was significantly different ($p < .05$) from the DASS-stress

## APPENDIX D

Table 2

*Receiver Operating Characteristics of Clusters and Depression and Anxiety screening measures*

| Clusters | AUC (SE) | 95% CI | Cut-off | Sens. True + | Spec. True - | Youden Index | PPV | NPV |
|---|---|---|---|---|---|---|---|---|
| **Anxious-misery[a] (*n* = 17)** | | | | | | | | |
| GAD-7 | .836 (.719) | .736-.910 | 7 | 70.59 | 95.16 | 65.75 | 78.5 | 92.8 |
| PHQ-9[c] | .856 (.070) | .759-.925 | 7 | 82.35 | 90.32 | 72.68 | 68.0 | 95.3 |
| OASIS | .647 (.080) | .531-.751 | 2 | 47.06 | 87.10 | 34.16 | 47.7 | 86.8 |
| DASS | .679 (.068) | .565-.780 | 2 | 76.47 | 56.45 | 32.92 | 28.5 | 91.6 |
| **Fear[a] (*n* = 14)** | | | | | | | | |
| GAD-7 | .762 (.084) | .653-.851 | 4 | 78.57 | 78.46 | 57.03 | 39.2 | 95.4 |
| PHQ-9 | .701 (.090) | .588-.799 | 7 | 64.29 | 83.08 | 47.36 | 40.1 | 92.9 |
| OASIS | .675 (.077) | .561-.776 | 0 | 71.43 | 61.54 | 32.97 | 24.7 | 92.4 |
| DASS | .605 (.081) | .489-.713 | 2 | 71.43 | 53.85 | 25.27 | 21.5 | 91.4 |

*Note.* AUC = area under the curve; CI = confidence interval; Sens = Sensitivity; Spec = specificity; NPV = negative predictive value; PPV = positive predictive value; SE = standard error, GAD-7 = Generalized Anxiety Disorder- 7 item scale, PHQ-9 = Patient Health Questionnaire 9 item scale, OASIS = Overall Anxiety Severity Impairment Scale, DASS = Depression Anxiety Stress Scale – Stress subscale

Current psychiatric disorders were derived by a structured clinical interview with the MINI

[a] Anxious-misery group comprises major depression, dysthymia, GAD, depression melancholic, post-traumatic stress, and bi-polar; [a] Fear disorders group comprises panic disorders, agoraphobia, social anxiety disorder, and obsessive-compulsive disorder

[c] - The PHQ-9 was significantly different ($p < .05$) from the DASS-stress

## APPENDIX E (JOURNAL INSTRUCTIONS)

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Lewis SW, Reveley A, Reveley M, Chitkara B, Murray RM (1987) The familial/sporadic distinction as a strategy in schizophrenia research. *Br J Psychiatry* 151:306-313.
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h) **Figure legends**: Figure legends must be submitted for all figures. They should be brief and specific, and they should be listed in the text file on a single page after the references.

**3. Table Files:** Tables must be labeled individually with a brief but descriptive title and submitted as separate electronic files. Tables should be submitted in their original file format (Word or Excel) and not as graphics files.

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a) Creating Digital Artwork

- Learn about the publication requirements for Digital Artwork: http://links.lww.com/ES/A42
- Create, Scan and Save your artwork and compare your final figure to the Digital Artwork Guideline Checklist (below).
- Upload each figure to Editorial Manager in conjunction with your manuscript text and tables.

b) Digital Artwork Guideline Checklist

Here are the basics to have in place before submitting your digital artwork:

- Artwork should be saved as TIFF, EPS, or MS Office (DOC, PPT, XLS) files.
- Crop out any white or black space surrounding the image.
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- Photographs and radiographs with text must be saved as postscript or at a resolution of at least 600 dpi.
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Remember:

- Cite figures and tables consecutively in your manuscript.
- Number figures in the figure legend in the order in which they are discussed.
- Upload figures consecutively to the Editorial Manager web site and enter figure numbers consecutively in the Description field when uploading the files.
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