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Examining Depressive Symptoms Over Time in Women with Coronary Heart Disease

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EXAMINING DEPRESSIVE SYMPTOMS OVER TIME IN WOMEN WITH CORONARY HEART DISEASE

by

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DEDICATION

I would like to dedicate this body of work to my family: to my parents, Bob and Bonnie, who picked up stakes after 30 years to move with me so I could go to school *again*; to Grace, Trinity, and Blake, who survived mom having as much homework as they did; and to my husband Tom, who graciously supported all of us with love and steady paychecks during this time.

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ABSTRACT

EXAMINING DEPRESSIVE SYMPTOMS OVER TIME IN WOMEN WITH CORONARY HEART DISEASE

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Coronary heart disease (CHD) is the number one killer of women in the US. Women also experience roughly twice as much depression as men, and depression in CHD is associated with increased morbidity and mortality. Despite these facts, women continue to be under-represented in CHD research, and results by gender are not routinely reported. Screening for depression in this population is problematic due to inconsistent inclusion of somatic symptoms on screening instruments and disagreement about appropriate cutoff scores.

This body of work clarifies the concept of depression in women with CHD, presents a systematic review of the longitudinal literature on depressive symptoms in women with CHD examined by instrument, and presents results of a 3-month feasibility study examining women's depressive symptoms. The purpose of the study was to evaluate participant enrollment, data collection, preliminary quantitative trends, and qualitative surveys for qualitative data collection.

Participant recruitment by individuals other than the P.I. was generally poor and attrition was problematic (16.7 – 28%). Prevalence of mean depression screening scores ≥ cutoff values averaged 30% at baseline, 26% at month 2, and 25% at month 3. Trends in symptom severity over the course of the study reflected trends in somatic symptoms and distress but not cognitive symptoms. Current depression was strongly correlated with fatigue and sleep as well as younger age, comorbid diabetes, a history of anxiety, and acute coronary syndrome symptoms. It was

less strongly correlated with a history of depression and cardiac rehabilitation attendance. No correlation was found between current depression and employment status. Qualitative survey uptake was poor and the original survey was too restrictive, requiring modification.

This dissertation clarifies our understanding of the concept of depression in women with CHD and summarizes the longitudinal descriptive literature on depression in women with CHD. The dissertation study enhances our understanding of depressive symptoms experienced in this population, gives some important preliminary data on use of the PROMIS Depression 8b instrument in this population, highlights the importance of screening for depressive symptoms in this population, and emphasizes the ongoing need for CHD studies which examine and report data by gender.

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Chapter I. Introduction

Numerous scientific articles have been published on the connection between mental health and coronary heart disease (CHD), particularly depression. It is now well-established that the development of depression following a cardiac event increases the risk of both morbidity and mortality (Barth, Schumacher, & Herrmann-Lingen, 2004; Carney et al., 2009). In 2014, the American Heart Association recommended that depression be elevated to the status of risk factor for poor prognosis following acute coronary syndrome (Lichtman, 2014). Depression is also now recognized as being a risk factor for the *development* of CHD (O'Neil et al., 2016), with ongoing work exploring this connection from multiple perspectives, including possible genetic linkages.

It is widely recognized that women are affected by depression at a rate of roughly 2:1 compared to men, starting at menarche and continuing until post-menopause. This 2:1 ratio is true in both the general population as well as the CHD population. But as with other previous heart disease research, examination of depression data by gender has not been routinely undertaken and women continue to be under-represented in cardiac research. Studies which have examined women separately have found that women and men do not always have the same CHD experience. This includes symptoms of acute coronary syndrome, acute myocardial infarction, and more recently there is evidence that women experience more microvascular disease and stress-induced ischemia than men (Bairey Merz et al., 2006; Vaccarino et al., 2016). The continued lack of women in CHD research, coupled with lack of data analysis by gender in much of the published literature, has meant that even though women experience twice as much depression as men, their depressive symptom experiences remain largely invisible.

The Concept of Depression in Women with CHD

Research has demonstrated that women with CHD tend to experience more depressive symptoms than men, both initially and over time (Buckland, Pozehl, & Yates, 2019), and women tend to experience more "somatic" (physical) symptoms than men (Frazier et al., 2012; Grace, Yee, Reid, & Stewart, 2014; Roest, Wardenaar, & de Jonge, 2016). However, the instruments used to screen for depressive symptoms vary widely. While DSM-5, the Diagnostic and Statistical Manual of Mental Disorders, fifth edition, defines the criteria for diagnosing depression and all its subtypes, these screening instruments do not necessarily follow DSM criteria. Some, in fact, do not include somatic symptoms at all. This, in effect, creates different *operational* definitions of depression. This poses a significant challenge when using these instruments to screen for depression in women in research studies as well as clinical settings.

Because of the lack of representation of women in heart disease research, and to highlight the problems posed by the widely-varying depression screening instruments, the concept of depression in women with CHD needs to be clarified. Chapter 2 of this dissertation looks at depression in women with CHD as a concept, following the steps of concept analysis as presented by Walker and Avant (Walker & Avant, 2011). Chapter 2, "Clarifying the concept of depression in women with coronary heart disease," was published ahead of print on March 7, 2019 in *Advances in Nursing Science*. The manuscript was co-authored by Dr. Bunny Pozehl, current dissertation committee chair, and Dr. Bernice Yates, previous committee chair.

Depression in Women with CHD: State of the Science

Because depressive symptoms can and do last beyond the acute cardiac event and are associated with worse outcomes, an understanding of what happens with depressive symptoms in this population over time is important. Therefore, an examination of the longitudinal CHD literature which included women, assessed depressive symptoms at more than one timepoint, and reported and/or analyzed data by sex was performed. Chapter 3 of this dissertation reports

the results of this systematic literature review, which also compared findings by depressive screening instrument and, when possible, used prevalence data to compare findings since the results of different screening instruments are not easily compared. Chapter 3, "Depressive symptoms in women with coronary heart disease: a systematic review of the longitudinal literature," was submitted as a manuscript to the *Journal of Cardiovascular Nursing.* It was accepted for prior-to-print publication as an open access article and appears in the January/February 2019 issue. The manuscript was co-authored by Dr. Bunny Pozehl, current dissertation committee chair, and Dr Bernice Yates, previous committee chair.

Results of a Mixed Methods Longitudinal Feasibility Study Examining Depressive Symptoms in Women with Coronary Heart Disease

Given the problematic nature of using various different depressive screening instruments in the CHD population, the lack of longitudinal data which examines women specifically, as well as the difficulty in ascertaining the true nature of somatic symptoms which overlap both CHD and depression, this author chose to explore the feasibility of conducting a study to examine each of these components in women who had recently experienced a cardiac event (acute coronary syndrome, myocardial infarction, percutaneous coronary intervention, or coronary artery bypass graft). The research was guided by Lenz' middle-range Theory of Unpleasant Symptoms and was adapted to a conceptual framework of depressive symptoms in women with coronary heart disease.

Specific Aims

The specific aims of this descriptive longitudinal mixed methods feasibility study were comprised of both qualitative and quantitative aims, and are as follows:

Quantitative

1. Evaluate participant enrollment, including recruitment strategies and efficiency, attrition at each study timepoint, and enrollment and retention problems and solutions.
2. Evaluate data collection at each of the data collection time points of baseline, month 2, and month 3, examining the use of REDCap vs paper, instrument reliability, the time required to complete instruments, and the amount of missing data.
3. Evaluate data for preliminary trends in the following:
    a. the prevalence of women who meet the cut-point criteria for elevated depressive symptoms following a cardiac event at baseline, 2 months and 3 months post study enrollment as measured by 3 commonly-used tools to measure depressive symptoms and compare them to prevalence rates of elevated depressive symptoms found in previous literature.
    b. changes over time (baseline through month 3) in women's depressive symptom dimensions (severity, quality, symptom distress).
    c. the influence of CHD and depression on sleep, fatigue, and gastrointestinal symptoms (loss of appetite, taste, and nausea) post cardiac event at baseline, 2, and 3 months after study enrollment to estimate this effect size.
    d. the influence of age, diabetes, employment status, attendance at cardiac rehabilitation, a history of depression and/or anxiety, and concurrent acute coronary syndrome (ACS) symptoms on depressive symptoms at baseline, 2 months, and 3 months after study enrollment in women post cardiac event.

Qualitative

4. Explore the acceptance and uptake of a qualitative survey as a qualitative data collection method with a sub-sample of 10-15 women who agree to participate at baseline, 2, and 3 months post enrollment.

a. Do the qualitative survey entries provide the type of data sought using the semi-structured survey provided?
b. How many women indicated they would complete qualitative surveys vs how many women actually completed these surveys at all 3 timepoints?
c. Describe how the qualitative data concurred with or differed from the quantitative depression screening instrument scores?

A more detailed discussion of the study and its aims, as well as the study's results and conclusions will be presented in Chapter 4.

Significance and Impact

Heart disease is the leading cause of death among American women – 22.3% of all female deaths in 2015 (https://www.cdc.gov/women/lcod/2015/race-ethnicity/index.htm). Depression is one of the leading causes of disability in the US, affecting roughly 12 million women in the US each year (Mental Health America, 2018), with women ages 40-59 being most affected (CDC, 2018). The cost of heart disease and depression combined is enormous - an estimated $410 billion per year in the US (https://www.cdc.gov/dhdsp/data_statistics/fact_sheets/fs_heart_disease.htm; Workplace Mental Health, 2018). Women with CHD are more frequently affected by depression than men but remain under-represented and understudied.

The cost of underdiagnosed women with CHD who also experience depression – in terms of cost, lost productivity, and morbidity and mortality - is not trivial. We cannot afford to miss women with CHD's symptoms of depression. The concept analysis presented in this dissertation identifies the defining attributes of depression in women with CHD so that those assessing this population may choose instruments that assess these attributes. This is a critical first step in

ensuring that women with CHD and depressive symptoms are correctly identified since we know that those who have CHD and comorbid depression have poorer outcomes.

We also need a better understanding of what happens to women's symptoms over time so that we are able to identify those who are at risk of developing significant depressive symptoms after their initial cardiac event or are at risk of having non-remitting symptoms. This investigation provides a preliminary understanding of the relationship between symptom dimensions as defined by Lenz - timing (here, changes over time), severity, quality (somatic vs cognitive) and distress – as well as the relationship between depressive symptoms, specific influencing factors, and somatic symptoms that overlap with CHD in order to help us to identify these women.

With the new knowledge from these three manuscripts, more thorough assessment and appropriate interventions for women may be developed, leading to less depression burden, better outcomes, and ultimately less cost to the individual, community, and health care system.

Summary

In summary, the purpose of this dissertation is to explore depressive symptoms and their dimensions in women with CHD over time, looking carefully at the instruments used to assess depressive symptoms, the changes in prevalence of depression and its dimensions (as define by Lenz) over time, and the somatic symptoms common to both CHD and depression.

This dissertation has been prepared following the 3-manuscript format as approved by the advisory committee. As noted previously, Chapter 2 has been published in the *Journal of Cardiovascular Nursing*, and Chapter 3 has been published ahead of print in *Advances in Nursing Science*. Chapter 4 contains the manuscript of the dissertation research study results. Finally, Chapter 5 contains an in-depth discussion of the conclusions of the study as well as implications and suggestion for future research and practice.

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Chapter II. Manuscript 1

Clarifying the concept of depression in women with coronary heart disease

*This is a non-final version of an article published in final form in *Advances in Nursing Science*: https://journals.lww.com/advancesinnursingscience/pages/default.aspx

Background

Coronary heart disease (CHD) is the leading killer of women in the US, causing about 1 in every 4 female deaths. And though heart disease mortality has declined significantly since its peak in the 1950s, it has declined less in women. In the mid-1990s, the scientific community began to explore the effects of depression on those with coronary heart disease. Approximately 12 million women in the US are diagnosed with depression every year, and 1 in every 8 women will experience clinical depression in her lifetime. Research suggests that women experience depression at a rate of 2:1 compared to men among those with CHD as well as in the general population (Frazier et al., 2012).

Depression has significant health ramifications in the CHD population. In 2014, the American Heart Association published a scientific statement elevating depression to the status of risk factor for poor prognosis among patients with acute coronary syndrome (Lichtman et al., 2014). There is strong evidence for increased negative outcomes among those who develop depressive symptoms following a cardiac event, including increased morbidity and mortality (Lichtman et al., 2014).

Evidence from work on acute coronary syndrome and acute myocardial infarction has demonstrated that women and men do not necessarily have the same CHD experiences. In fact, recent work has demonstrated that women experience more microvascular disease and stress-induced ischemia than men (Bairey Merz et al., 2006; Vaccarino et al., 2016). However, women are under-represented in CHD research. The continued lack of women in CHD research, coupled

with lack of data analysis by gender in much of the published literature, has meant that even though women experience twice as much depression as men, their depressive symptom experiences remain largely invisible.

While women's depressive symptoms in this population have been explored, our review of the literature suggests that limited research has been done to understand and clarify the conceptual meaning of depression in women with CHD. From this review it appears that the conceptualization of depression in women with CHD is widely variable, and that this variability arises from the way the concept of depression is operationalized – i.e. the instruments used to measure the concept. The literature search conducted for this paper yielded 16 different instruments used to operationalize depression – from a 2-question screening instrument to the gold standard Composite International Diagnostic Interview (see Table 1). Because different instruments ask different questions and not all instruments include questions about certain symptoms of depression (such has somatic symptoms), the *actual* concept of depression in women with CHD may not be captured by the instrument being used to measure the concept. Therefore, research on women with CHD and comorbid depression would benefit by a concept analysis of depression in women with CHD.

Concept analysis, according to Walker and Avant (2011), is a "process of examining the basic elements of a concept… result[ing] in a precise operational definition that by its very nature increases the validity of the construct" (p. 158). Concept analysis can be used for various purposes, including refining ambiguity of a concept in a theory, clarification of an overused or vague concept, construction of a research instrument, or evaluation of existing research instruments.

Aims

The aim of this concept analysis of depression associated with a diagnosis of coronary heart disease in women is concept clarification. Concept analysis for the purpose of concept clarification is appropriate when a concept has a large body of literature defining and describing it, including quantitative instruments for measuring the concept, but the concept is measured using different variables and is applied inconsistently in the research (Morse, Hupcey, Mitcham, & Lenz, 1996). Clarifying the concept of depression in women with coronary heart disease is necessary for a better understanding of women's experiences so that accurate diagnoses can lead to more timely and appropriate interventions.

Design and Methods

This paper is organized according to Walker and Avant's (2011) eight-step approach to concept analysis: 1) selecting a concept; 2) determining the aim or purpose of the analysis; 3) identifying all uses of the concept; 4) determining the concept's defining attributes; 5) identifying a model case; 6) identifying additional cases (borderline and contrary cases); 7) identifying antecedents and consequences, and; 8) defining empirical referents.

To begin this concept analysis, the basic concept of depression was identified, aims determined, and its use in both medical and non-medical settings explored. A literature search from 1990 to August 15, 2018 of English language articles was then performed to explore the concept of depression specifically in women with CHD. A PUBMED search utilizing the terms *coronary heart disease, depression, and sex factors* or *sex differences*, with the filters *female, human*, and *English language* yielded 100 articles. Because this concept analysis focuses specifically on coronary heart disease (rather than the larger concept of cardiovascular disease), articles related to heart failure, stroke, and peripheral vascular disease were removed. Articles describing depression as a risk factor for the *development* of CHD were also excluded. After

these exclusions, 40 articles remained. These articles were used to define the concept's critical attributes, antecedents, and consequences; cases were constructed using the concept; and empirical referents identified. Finally, the use of this concept in future research and clinical practice is discussed.

Uses of the Concept

The word "depression" has several different meanings and uses. Apart from its use in common parlance, usually to indicate a low mood, it is also used in mathematics, astronomy, meteorology, economics, and healthcare. Merriam-Webster's online dictionary lists several definitions: the angular distance of a celestial object below the horizon; the size of an angle of depression; a pressing down, such as a depression of the tab key on a keyboard; a state of feeling sad; a place or part that is lower than the surrounding area; a low, as in a tropical depression, or; a long period of low general economic activity marked especially by rising levels of unemployment.

The National Institutes of Mental Health (NIMH) gives this definition of depression: "Depression (major depressive disorder or clinical depression) is 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. To be diagnosed with depression, the symptoms must be present for at least two weeks"(Nation Institute of Mental Health, 2018).

Hare and Davis (1996), who created the Cardiac Depression Scale to assess for depression in the cardiac population, used the DSM-4 (American Psychiatric Association, 1994) criteria for "adjustment disorder with depressive symptoms" as their definition of depression. According to DSM-4, "adjustment disorder with depressive symptoms" is defined as: "the development of emotional or behavioral symptoms in response to an identifiable stressor(s) occurring within 3 months of the onset of the stressor(s)", creating distress in excess of what

would typically be expected or significant impairment in social or work functioning. These symptoms do not exceed 6 months in duration once the stressor is over.

The Diagnostic and Statistical Manual of Mental Disorders (DSM), published by the American Psychiatric Association (APA), provides the medical diagnostic criteria for depression as a mental health disorder. DSM-5, the most recent edition of the manual, lists eight different diagnoses that fall under the category of depressive disorders: disruptive mood dysregulation disorder, major depressive disorder, persistent depressive disorder (dysthymia), premenstrual dysphoric disorder, substance/medication-induced depressive disorder, depressive disorder due to another medical condition, other specified depressive disorder, and unspecified depressive disorder. Though there are significantly different components to each of these eight diagnoses, they all share common core features: sadness, emptiness, or irritable mood, accompanied by somatic and cognitive changes that significantly impact an individual's ability to function. Per DSM-5 criteria, a diagnosis of major depressive disorder (MDD - the diagnosis most researchers refer to when talking about depression in the CHD population) requires either depressed mood or loss of interest or pleasure (anhedonia) plus 3-4 of the other 7 core symptoms (for a total of at least 5 core symptoms) during a consecutive 2-week period. So-called "minor depression" (or "depressive episode with insufficient symptoms", defined under "other specified depressive disorders" in DSM-5) requires only a depressed affect and 1 of the 8 other core symptoms of MDD, with the same duration and distress or functional impairment as MDD to meet criteria.

More recently, Ormel and de Jonge (2011) developed an integrative model of depression in the setting of CHD. Their model proposes two subtypes of depression: 1) cognitive-affective (also called "typical"), characterized by depressed mood, anhedonia, negative feelings such as self-dislike & sense of failure, guilt, interpersonal sensitivity, and future pessimism; and 2) somatic/affective (also called "somatic"), characterized by fatigue,

psychomotor agitation/retardation, sleep problems, aches and pains, appetite disturbance, weight disturbance, and work difficulty.

These authors are interested specifically in depression in women following a diagnosis of CHD (as opposed to depression as a precursor to its development). In the majority of studies looking at depression in individuals with CHD, the authors do not provide a *conceptual* definition of depression. Rather, depression is given an *operational* definition via the instrument used to assess it. Confusingly, this leads to numerous different *operational* definitions.

Operational definitions.

The gold standard for evaluating patients for depression is the structured clinical interview (American Psychiatric Association, 2018). However, such interviews are usually rather lengthy (45 – 120 minutes) for research participants. Of the 40 articles reviewed for this paper, only 2 used an interview to assess for depression. Therefore, most researchers rely on instruments that screen for depression rather than completing a diagnostic interview, and cutoff scores become a proxy for clinically significant depressive symptom burden. This makes these screening instruments of paramount importance - the symptoms included on the screening instrument become the *operational* definition of depression.

The instruments used to assess depressive symptoms in the CHD population can be grouped into three categories based on the symptoms included/excluded and the origins of their development: 1) instruments based on DSM criteria for depression that include somatic symptoms, 2) instruments that do not include somatic symptoms, and 3) instruments based on other criteria. Because of the multiple instruments used, three commonly used instruments will be discussed as exemplars of the three categories. Table 1 lists all depression assessment instruments found in the literature search, based on the above categories.

Table II-1: Depression screening instruments found in the literature search

DSM* + somatic symptoms	No somatic symptoms	Non-Major Depressive Disorder/Non-DSM* criteria
Beck Depression Inventory	Hospital Anxiety & Depression Scale	Zung Self-Rating Depression Scale
Beck Depression Inventory-II	Patient Health Questionnaire 2-item	Geriatric depression scale
Patient Health Questionnaire 9-item	Global Health Questionnaire 30-item	Hamilton Depression scale***
Center for Epidemiologic Studies Depression scale	PROMIS Depression**	Gotland scale
Center for Epidemiologic Studies Depression scale 8-item		Global Health Questionnaire 60-item
		EuroQuol-5D
		Symptom CheckList 90

*Diagnostic & Statistical Manual
**Instrument not found in the literature search, but increasingly important in research
***Administered by a clinician, but not a diagnostic interview

Instruments based on DSM criteria that include somatic symptoms.

The first category of depression scales is those that were created based on the accepted criteria for major depressive disorder (MDD) at the time of their creation and include both cognitive and somatic symptoms. The best example of this is the Beck Depression Inventory (BDI), originally published in 1961. Beck and his colleagues created a depression measurement instrument by observing attitudes and symptoms displayed by depressed psychiatric inpatients and outpatients at two hospitals in Philadelphia, consulting the newly-published Diagnostic and Statistical Manual of Mental Disorders-I (DSM-I), and finally consolidating these observations into a 21-item questionnaire (A. T. Beck, Ward, Mendelson, Mock, & Erbaugh, 1961). The BDI-II, an update to the original scale, was published in 1996 in response to the publications of DSM-3-R and DSM-4 to make it more consistent with the current diagnostic criteria. Other scales found in this review that are based on DSM criteria and include both cognitive and somatic symptoms include the Center for Epidemiologic Studies Depression scale (CES-D) and its shorter version, the CESD-8, and the Patient Health Questionnaire 9-item (PHQ-9).

Instruments that do not include somatic symptoms.

The second category of scales measuring depression do not include somatic symptoms. These were often developed to avoid measuring somatic symptoms that may have reflected physical rather than mental illness. The hallmark example of this category of scales is the Hospital Anxiety and Depression Scale (HADS). The HADS, developed by Zigmond and Snaith from research conducted in general medical outpatient clinics and originally published in 1983, focused on anhedonia as the central concept of depression. Zigmond and Snaith felt there was no easy way to distinguish between physical symptoms rooted in a physical ailment and physical symptoms reflective of a mental illness. They wanted an easy way to detect *mental* illness in order to avoid a lengthy *physical* work-up. So Zigmond and Snaith created an instrument where "…symptoms which might equally arise from somatic [physical] as from mental disease" were excluded (Zigmond & Snaith, 1983). This concern about inclusion of somatic symptoms (such as fatigue, changes in appetite, or sleep disturbance) measuring a physical rather than mental illness, and subsequent overestimation of depression (Zigmond & Snaith, 1983) is echoed in the more recently developed NIH-sponsored PROMIS depression instruments, which also do not include any somatic depressive symptoms. Other assessment instruments, such as the PHQ-2 and the General Health Questionnaire 30-item, are shortened version of longer instruments which have removed the somatic items.

Instruments based on other criteria.

The last category of depression scales is based on some criteria other than DSM MDD criteria. The exemplar for this category is the Zung Self-Rating Depression Scale. Though DSM-I had been published in 1952 it was not widely used until DSM-3 was published in 1980, representing "a veritable paradigm shift in psychiatry" (Kawa & Giordano, 2012). The Zung scale was created based on combining the results of three "factor analyses" (Zung, 1965). Three

broad domains were identified - pervasive affect, physiological equivalents, and psychological equivalents - and the most commonly-found characteristics in the factor analyses were fitted into these domains and comprised the symptoms assessed by the scale. Subsequently, records of interviews with patients were reviewed and statements which seemed most representative of a particular symptom were chosen to create the scale. The final scale was a 20-item questionnaire. Other examples of instruments in this category include the Geriatric Depression Scale (based on the Research Diagnostic Criteria developed by the National Institutes of Mental Health Psychobiology of Depression Collaborative Study, published in 1978), Gotland scale of male depression (developed in 2002 with alcohol-dependent men, with questions about irritability, aggression, and alcohol use) and the General Health Questionnaire 60-item (developed in the 1970s for identifying minor psychiatric disorders in the general population), among others.

The importance of "minor" depressive symptoms.

Strik and colleagues (2001) argue that the use of self-report depression scales to screen for depression in clinical patients, such as those described above, are only justified if they demonstrate high concurrent validity with DSM criteria for major *and minor* depression (italics added). In a study examining the sensitivity and specificity of three frequently-used questionnaires for depression in myocardial infarction (MI) patients, Strik et al. (2001) noted that optimum cutoff scores (the score which combines maximal sensitivity with optimal specificity on a receiver operating characteristics [ROC] curve) *for MI patients* are *below* the generally accepted cutoff scores (which were determined using the population in which the instrument was originally designed and tested). The generally accepted cutoff scores would capture MDD but miss those with minor depression. Doering et al.'s (2006) study demonstrates this perfectly. Of the 75 women in their study, seven (9.3%) met MDD criteria, while 20 (26.3%)

met criteria for minor depression. Additionally, if women experience a preponderance of somatic symptoms which are not captured on the depression scale being used, they will be under-diagnosed or missed altogether. Ketterer and colleagues argued that there is a problem with the DSM-4 threshold in patients with CHD in that it is too high and likely to overlook patients with depression. That is, "…MDD criteria appear to exclude patients who are at risk for adverse outcomes from CHD. . . . Furthermore, many other investigators have found 'minor' depression to be predictive of CHD morbidity and mortality"(Ketterer et al., 2006, p. 53).

Defining Attributes

Walker and Avant (2011) describe the defining attributes of a concept as "a cluster of attributes that are most frequently associated with the concept . . . [and] functions very much like the criteria for making differential diagnoses in medicine" (p. 162). Several authors have argued that individuals with heart disease, and women with CHD in particular, experience more "somatic" symptoms than "cognitive" symptoms (de Miranda Azevedo, Roest, Hoen, & de Jonge, 2014; Grace, Yee, Reid, & Stewart, 2014; Linke et al., 2009; Sanner, Frazier, & Udtha, 2013). Furthermore, low levels of depressive symptoms (i.e., fewer symptoms than required to meet criteria for MDD) are not unusual in those with CHD and have also been associated with worse outcomes such as increased all-cause and cardiac mortality (Lichtman et al., 2014).

Examining specific symptoms as attributes of this concept, several studies have supported a group of symptoms as being the most common in women with CHD. These symptoms include dysphoria/sadness; self-dislike; tiredness/fatigue; loss of energy; sleep disturbances; appetite disturbances; concentration difficulties; indecisiveness; crying; and loss of interest in sex (Doering et al., 2006; Frazier et al., 2012; Grace et al., 2014; Sanner et al., 2013). Some of these symptoms are considered dimensions of the cognitive aspect of depression (dysphoria/sadness, indecisiveness, crying, and self-dislike) and some of these symptoms are

considered dimensions of the somatic aspect of depression (tiredness/fatigue, appetite disturbance, loss of energy, sleep disturbance, and loss of interest in sex) (see Table 2). Frazier et al. (2012) found that women had significantly higher scores than men on the following items from Beck's depression inventory: sadness, self-dislike, crying, indecisiveness, sleep disturbance, appetite disturbance, and loss of interest in sex. Similarly, Grace and colleagues (2014), in comparing men's and women's scores on the BDI-II and the Gotland Scale of Male Depression (GSMD), found that women scored significantly higher than men on indecisiveness (BDI-II), crying (BDI-II), tiredness (BDI-II), loss of energy (BDI-II), inexplicable tiredness (GMSD), sleep problems (GSMD), changes in sleep patterns (BDI-II), loss of interest in sex (BDI-II), concentration difficulty (BDI-II), and changes in appetite (BDI-II).

In addition to women scoring higher on depressive symptoms overall compared to men in both studies, significantly more women in Frazier et al.'s (2012) study reported experiencing somatic symptoms (sleep disturbance, appetite disturbance, and/or fatigue) than men, and in Grace et al.'s (2014) study women scored significantly higher on the "psychomotor fatigue" factor ("i.e. somatic features") than men (p. 948).

The defining attributes delineated here must be present in any operationalized definition of depression in women with CHD. In other words, the screening instruments used in women with CHD must contain these attributes if we hope to adequately and accurately assess this population.

Table II-2: Defining Attributes of depression in women with CHD

Cognitive symptoms	Somatic symptoms
Crying	Tiredness/Fatigue
Dysphoria/sadness	Sleep disturbances
Indecisiveness	Appetite disturbances
Self-dislike/poor self-esteem	Loss of interest in sex
Concentration difficulties	
Hopelessness	

Model case

According to Walker and Avant(2011), a model case is one "that demonstrates all the defining attributes of the concept" (p. 163); an exemplar. They may be found in the literature or created for the purposes of the concept analysis. The following is a model case for depression in women with CHD.

> Marilyn is a 53-year-old divorced female with a personal history of poorly-controlled type-II diabetes, hypertension, anxiety, and obesity who suffered an ST-elevation MI 2 weeks ago. She was treated with an emergent heart catheterization, and two drug-eluting stents were placed at that time. Her father died of an MI at age 46, and her mother had a stroke at age 65. She is now a caregiver for her mother, who resides with her.
>
> Marilyn has returned home from the hospital, but instead of feeling better she finds she is now always tired and has little to no energy. Though she knows she should be attending cardiac rehabilitation, she cannot bring herself to go. She is sleeping poorly and is unable to concentrate on the things she needs to get done. She has no appetite and forgets to eat. She has missed two weeks of work due to her heart attack, and though she typically enjoyed her job, is now ambivalent about returning to work. She often finds herself laying on her bed crying, wondering how she is supposed to "take better care of herself", care for her mother, and go back to work when she cannot even get out of bed in the morning. She hates herself for not having managed her diabetes better, getting so fat and out of shape, and now having heart disease on top of everything else, and cannot imagine how she is ever going to manage.

This model case is a clear example of depression in a woman following a CHD diagnosis.

Additional Cases

Borderline case.

A borderline case will have some but not all of the defining attributes of the concept.

> Marilyn is a 53-year-old divorced female with a personal history of poorly-controlled type-II diabetes, hypertension, anxiety, and obesity who suffered an ST-elevation MI 2 weeks ago. She was treated with an emergent heart catheterization, and two drug-eluting stents were placed at that time. Her father died of an MI at age 46, and her mother had a stroke at age 65. She is now a caregiver for her mother, who resides with her.
>
> Marilyn has returned home from the hospital and remains fatigued with little energy. She knows attending cardiac rehabilitation is important and though she is tired she forces herself to attend anyway. She is less afraid of exercising than she was at first and is sleeping better. Her appetite seems to be improving.

She has missed two weeks of work due to her heart attack, and though she typically enjoyed her job she is now ambivalent about returning. She is working hard at trying to do what she is supposed to be doing (like eating better, checking her blood sugars every morning, and remembering to take her medication every day) and take care of her mother as well.

Contrary Case.

A contrary case would not display the defining attributes of the concept.

Marilyn is a 53-year-old divorced female with a personal history of poorly-controlled type-II diabetes, hypertension, anxiety, and obesity who suffered an ST-elevation MI 2 weeks ago. She was treated with an emergent heart catheterization, and two drug-eluting stents were placed at that time. Her father died of an MI at age 46, and her mother had a stroke at age 65. She is now a caregiver for her mother, who resides with her.

Marilyn has returned home from the hospital and has started attending cardiac rehab. Though she still gets tired, she is feeling much better about how things are going now. She is sleeping well and her appetite is back. She has missed two weeks of work due to her heart attack and was initially apprehensive about returning, but now is feeling more confident and is looking forward to returning once her doctor says it's OK. She has found that in focusing on taking better care of herself she has actually gotten her mother to engage in some healthier choices and increased activity as well, making these lifestyle changes easier to implement.

Antecedents

According to Walker and Avant (2011), antecedents of a concept "must occur or be in place prior to the occurrence of the concept" (p. 167). Two antecedents to the concept of depression in women with CHD are clear: (1) female gender and (2) a diagnosis of coronary heart disease. It has long been recognized that women are at increased risk for depression compared to men. Women experience depression at a rate of roughly 2:1, beginning at menarche and continuing until menopause. The role of fluctuating levels of estrogen has been hypothesized as explaining this difference, since women's rates of depression begin to increase just as hormonal fluctuation begins and decline once these fluctuations cease (Albert, 2015). Women are also more vulnerable to depressive symptoms prior to menstruation, following pregnancy, and during the perimenopausal period (Albert, 2015).

Depression in the CHD population is even more common than in the general population. Those who have had an MI experience depression at a rate of 17%-27% (vs 10%-29% in the general population), and this rate is about twice as high in women with MI versus men (Lichtman et al., 2014). The literature around depression in CHD also suggests that the magnitude of the precipitating cardiac event or severity of the disease does not equate to the emotional response (Doyle, McGee, Conroy, & Delaney, 2011). In other words, a minor heart attack or only minor intervention does not mean a less dramatic emotional response. Likewise, a major heart attack requiring a sizeable surgical intervention does not mean a more significant, deeper depressive response.

Several other possible antecedents for this concept of depression have also been described in the literature. These can be divided into two groups: physiological vulnerabilities, including genetics, younger age, presence of angina, and comorbid diabetes; and psychosocial vulnerabilities, including poor social support following a cardiac event, inability to return to work following the cardiac event, and comorbid anxiety (see Table 3).

Physiological vulnerabilities.

Several authors have explored genetic vulnerability to depression in those with CHD (Kendler, Gardner, Fiske, & Gatz, 2009; Liu et al., 2014; McCaffery et al., 2006). Though an emerging area of scientific inquiry, these studies are beginning to elucidate a genetic link between depression and CHD. McCaffery and colleagues (2006) cite several studies which suggest a possible common genetic “substrate” between CHD and depression and propose several candidate genes involving the inflammation and serotonin-mediated platelet aggregation pathway. Liu and colleagues (2014), in examining seven possible single nucleotide polymorphisms (SNPs) on the brain-derived neurotrophic factor (BDNF) gene, were able to identify a single SNP which demonstrated a significant association with CHD-induced depression.

A twin study performed from the Swedish twin registry done by Kendler and colleagues (2009) found a moderately strong genetic correlation between major depression and CHD, which is slightly higher in women than men (+0.67 vs +0.62, respectively).

Several studies have indicated that younger women with CHD appear more vulnerable to developing depression than older women (Doering et al., 2006; Grace et al., 2005; Naqvi et al., 2007). This may be due to younger women underestimating their risk for a cardiac event (Doering et al., 2006), or greater difficulty in adjusting to the uncertainties of a future that now includes a chronic illness in conjunction to the usual stressors of work and family roles (Grace et al., 2005). Pre- and peri-menopausal women will also still be vulnerable to fluctuating levels of hormones, as mentioned previously.

The presence of angina appears to be significantly associated with depression in those with CHD (Jespersen, Abildstrom, Hvelplund, & Prescott, 2013; Portillo, White, Baisden, & Dawson, 1995). Women, particularly American women, experience more angina than men (Hemingway et al., 2008). Those who experience angina consistently scored higher on depression assessment instruments than those who did not (Jespersen et al., 2013). Portillo et al.'s study (1995) in Mexican-American women showed that more women with angina experienced depression than women who did not have angina, and that this group also had significantly more problems with functional impairment (which may in turn exacerbate depressive symptoms). In Jespersen et al.'s (2013) study, angina was also significantly associated with anxiety.

Comorbidity with diabetes has also been strongly connected to depression in women with CHD in several studies (Annunziato et al., 2015; Kronish et al., 2006; Murphy et al., 2008). Kronish et al. (2006), in their study of ACS patients, noted that women with CHD and comorbid diabetes were more likely to report still being depressed 3 months after their cardiac incident

than women without diabetes. Murphy et al.'s (2008) 12-month study of women after an acute cardiac supports Kronish's earlier finding of a link between higher incidence of depression in women with comorbid diabetes. Annunzio et al.'s (2015) study found significantly elevated risk of depression as well as suicidality in individuals with CHD and comorbid diabetes. Annunzio et al. conclude that "it appears that having diabetes and CVD may be more concerning from a [mental health] perspective than an MI" (p. 1282).

Psychosocial vulnerabilities.

Several psychosocial vulnerabilities have been identified in the literature regarding women with CHD and depression. Poor social support as a risk factor for depression in women following a cardiac event has been explored in several studies (Barefoot et al., 2000; Compare et al., 2013b; ENRICHD, 2001). Barefoot et al.'s (2000) work examining the link between depression and social support found that those with CHD and poor social support exhibited higher levels of depression compared to those with good social support. Interestingly, social support seemed to be a bigger factor in depression among younger patients with CHD than older patients. The ENRICHD study, a groundbreaking study in the research of CHD and depression, found that over 1/3 (34%) of patients in the study experienced both depression and low perceived social support, and these were predominantly women (ENRICHD, 2001). Compare et al.'s (2013a) ten-year literature review examining the relationship between social support and depression in CHD patients (including marital relationships and social relationships) concluded that low levels of social support is important risk factor for both development and worsening of depression.

Contrary to early hypotheses regarding work stress in women with CHD, research has shown that women who are unable to return to gainful employment experience more depression than those who are able to return to work (Blom et al., 2007; Boudrez & De Backer, 2000). Blom and colleagues (2007) examined 105 women of working age with CHD to determine

the association between work and depressive symptoms. They concluded that women who were working demonstrated lower levels of depressive symptoms than those who were not, regardless of age, educational status, or risk factors for CHD (including diabetes). Work also increased the degree of social support experienced by these women. Boudrez and DeBacker (2000) examined return to work in acute myocardial infarction or coronary artery bypass graft patients. They found that, after one year, those who had returned to work demonstrated more positive affect, less negative affect, and fewer somatic complaints.

Anxiety has been shown to have significant co-occurrence with depression in both the general population as well as the CHD population and is a significant risk factor for developing depression. Murphy and colleagues (2008) noted in their study which followed women for 12 months after a cardiac event that those who had anxiety were more likely to also have depression than those who did not have anxiety. Doering and colleagues (2011), in their study spanning three continents, found that women with CHD who experienced depression were 50% more likely than men to report also having anxiety. Such is the degree of overlap that one of the 12 Research Planning Conferences prior to the publication of DSM-5 was dedicated entirely to the "comorbidity of depression and generalized anxiety disorder" (Watson, 2009, p. 222).

Table II-3: Antecedents of depression

Female gender	Coronary heart disease diagnosis
Other possible antecedents to depression in women	
Physiological vulnerability: • Genetic mechanisms • Younger age • Angina • Comorbid diabetes	Psychosocial vulnerability: • Poor social support • Inability to return to work • Comorbid anxiety

Consequences

The consequences of both heart disease and depression in women are substantial. It has been clearly demonstrated that individuals with CHD and comorbid depression have both

increased morbidity and increased mortality compared to those without depression. “Among women with MI or other forms of ischemic heart disease, depression is associated with an approximate 3-fold increased risk for death or subsequent cardiac events independent of severity of depression” (Mehta et al., 2016). Shah and colleagues (2014) found that depressed women, ≤55 years of age, had substantially higher CHD comorbidity and worse prognosis. These findings stress the need for more research on CHD and psychosocial factors, particularly depression, in young women, who are often under-represented in clinical studies of cardiovascular disease.

Women also experience significant alterations in role function, self-image, and self-management, including secondary risk factor reduction (Kronish et al., 2006; Norris & King, 2009). Perhaps most important of these secondary risk reduction practices is exercise. Evidence supports depressive symptom improvement with attendance at cardiac rehabilitation (CR), regardless of the participant’s gender (Caulin-Glaser, Maciejewski, Snow, LaLonde, & Mazure, 2007). However, those with depression are less likely to attend CR, and less likely to complete CR if they do attend initially.

Empirical Referents

Walker and Avant define empirical referents as “classes or categories of actual phenomena that by their existence or presence demonstrate the occurrence of the concept itself” (2011, p. 168). They are “a means by which you can recognize or *measure* [emphasis added] the defining characteristics or attributes…” (Walker & Avant, 2011, pp. 168, italics added). As has been discussed, the screening instruments to measure the presence or absence of “depression” are not consistent in regard to which attributes are being measured, and prior work calls into question how much of these attributes are required to be clinically significant in this population. Therefore, these commonly-used instruments in conjunction with their

standard cutoff criteria appear inadequate when it comes to measuring depression in women with CHD.

Conclusions and Relevance to Clinical Practice

As previously stated, the purpose for this concept analysis was to clarify the concept of depression in women following a diagnosis of CHD. A better understanding of women's experiences of depressive symptoms in this population will allow more accurate diagnoses to be made and timely and appropriate interventions to be initiated. Based on this concept analysis, it appears that depression in women with CHD has been operationalized as a somatic and cognitive experience; only a cognitive experience; and as a pervasive affective, physical, and psychological experience, among many others. This concept analysis has illustrated the need to revisit these myriad operational definitions of depression as they pertain to this population in order to be more congruent with the conceptual definition as defined by DSM-5. Based on the literature reviewed for this analysis, women appear to experience both cognitive and somatic depressive symptoms but be more burdened by somatic symptoms than men, and to experience depressive symptoms at higher rates than men. Additionally, a specific group of symptoms (e.g., tiredness/fatigue, appetite disturbance, concentration difficulties, etc. - see Table 2) has been identified as being the most common depressive symptoms in women with CHD. Further qualitative studies which lend support to this group of symptoms as being the most commonly-experienced and germane symptoms in this population is recommended.

Women with CHD who present with antecedent conditions, including a significant family history of depression, younger age, angina, comorbid diabetes, poor social support, the inability to return to work, or comorbid anxiety should be carefully monitored for the development of depression as these conditions have clearly been identified with an increased risk of depression. Women with CHD who present with somatic complaints need to be evaluated for possible

depression, as these symptoms appear to be particularly salient to women's depressive experience and may also be perceived as "safer" to report given the stigma still associated with mental illness by some (Grace, Yee, Reid, & Stewart, 2014). Screening for depression in women with CHD is problematic due to the multiple instruments currently used to measure the concept. Careful consideration should be given to the assessment instrument being used. If an instrument with no somatic symptoms is chosen (such as HADS or PROMIS), some other means of capturing these symptoms needs to be utilized and justification needs to be offered if the instrument is being used for research purposes. When assessing this population, using MDD criteria alone and excluding "minor" depression criteria to define who may need further evaluation may not be appropriate since this criterion is likely to miss a significant percentage of women who do in fact have depressive symptoms that may lead to worse outcomes. Consideration should be given to using different cutoff scores on depressive symptom assessment instruments, such as those proposed by Strik et al. (2001), Moullec et al. (2015), and Haddad et al. (2013) when assessing this population.

Several instruments which were originally developed in non-cardiac populations have been analyzed for use in the CHD population, including the Beck Depression Inventory I and II, the PHQ-9, and HADS. Usually such analyses are performed to determine appropriateness for use in the population and/or optimal cutoff scores for detecting clinically significant depressive symptoms. However, these authors are unaware of any study which has compared the most used and/or recommended depressive symptom screening instruments to a diagnostic interview specifically in women with CHD to determine which instrument has the best Area Under the Curve (indicating the best sensitivity/specificity for detecting depression in the population). This is a significant gap in our ability to accurately assess women with CHD.

However, thinking in the psychiatric community seem to be shifting away from the previously-embraced “prescriptive” approach to diagnosis. The shortcomings of drawing hard boundaries between mental health diagnoses and the significant overlap between such conditions as anxiety and depression have forced what feels like another paradigm shift in mental health. There is no clear consensus on the definition of depression. In a 2017 editorial, Stringaris (2017) noted that “psychiatrists love to argue about [the definition of depression]. . . . even two experienced practitioners would have a hard time agreeing on what depression is” (p. 1287). He notes the questionable coefficient K (a statistic of agreement between raters) for adults in the DSM reliability field trials, situation-bound changes, the question of depressive subtypes, and the concern of over-pathologizing normal low mood responses.

Still, it is undisputable that poor outcomes in women with CHD are associated with the group of symptoms we currently call “depression”. The cost in terms of time and money, and availability of resources for long diagnostic interviews will no doubt continue to prevent them from being routinely used in research or primary care settings. Until such time as technology (such as computer adaptive testing or artificial intelligence) makes screening instruments obsolete and/or the very definition of depression is re-written, depression screening instruments will continue to be used in both research and clinical settings. This analysis clarifies the concept of depression in women with CHD and outlines its defining attributes along with its antecedents and consequences. A model case, along with borderline and contrary cases, are provided to make identification of this concept clear. In conclusion, as CHD research moves forward researchers and clinicians need to be cognizant of utilizing instruments which operationalize the concept of depression in women with CHD as presented in this concept analysis.

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Chapter III. Manuscript 2

Depressive Symptoms in Women with Coronary Heart Disease: A systematic review of the longitudinal literature.

The role of sex/gender in coronary heart disease (CHD) has been extensively studied since its importance was recognized in the 1980s (Lerner & Kannel, 1986; Wenger, 1985, 1990). Similarly, the role of depression in CHD has been studied since the 1990s (de Miranda Azevedo, Roest, Hoen, & de Jonge, 2014; Leung et al., 2012; Nicholson, Kuper, & Hemingway, 2006). Depression is now recognized as a risk factor for poor outcomes in CHD (Barth, Schumacher, & Herrmann-Lingen, 2004; Leung et al., 2012; Lichtman et al., 2014). Both CHD and depression place a tremendous burden on women: CHD is the leading cause of death among women; women have poorer outcomes following a cardiac event compared to men (Doering & Eastwood, 2011; McSweeney et al., 2016); and women are affected by depression at a 2:1 rate compared to men (Mazure, Keita, & Blehar, 2002; Shanmugasegaram, Russell, Kovacs, Stewart, & Grace, 2012). Despite the frequent occurrence of both CHD and depression in women, interpreting studies about women with heart disease and depressive symptoms is challenging for several reasons. Women continue to be under-represented in research despite legislation requiring their inclusion, making interpretation of studies with small numbers of women problematic. Often data are not presented separately by sex/gender, so examination and interpretation of women's data apart from men's is not possible. Many studies do not look at depressive symptoms over time, leaving our understanding of what happens to women over time incomplete. Finally, the use of multiple depressive symptom assessment instruments makes comparisons between studies problematic.

This state of the science review examined depressive symptom data from longitudinal studies of CHD which included women, collected depressive symptom data at more than one

time-point, and reported and/or analyzed data by sex. When possible, studies were examined by comparing the *prevalence* of elevated depressive symptoms (percentage of individuals meeting cutoff criteria on assessment instruments) as different instruments' results cannot be easily compared. Studies were also examined based on which instrument was used. For the purposes of this review, "sex" and "gender" were used interchangeably given the psychosocial influences that "gender" – a social construct rather than a biological state – may confer in the context of illness development and symptom experience.

Methods

Search Strategy

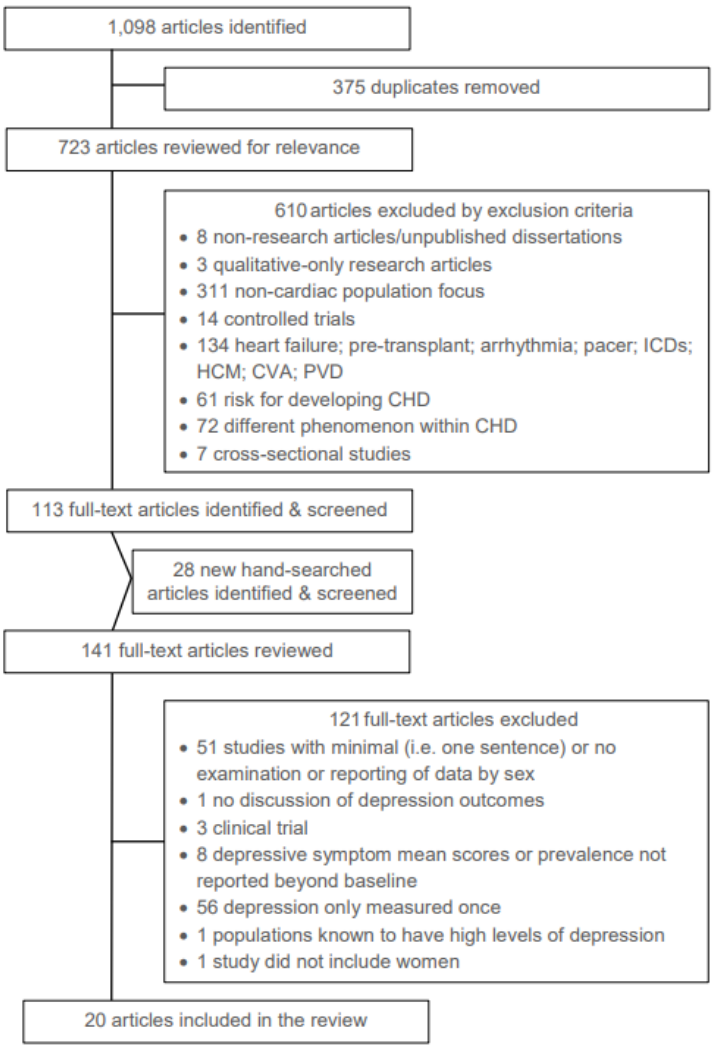

Figure III-1: PRISMA Schema

This literature review process follows the PRISMA 2009 checklist (see Figure 1)(Moher, Liberati, Tetzlaff, Altman, & Prisma Group, 2009). A search of databases including Medline via PubMed, CINAHL, Embase, and PsycInfo was performed on February 1, 2016 and updated April 26, 2018 for any recent additions. Terms searched included *coronary artery disease, coronary arteriosclerosis, depression, depressions, depression+,*

depression/exp, major depression, anaclitic depression, dysthymic disorder, endogenous depression, postpartum depression, reactive depression, recurrent depression, treatment resistant depression, and *depressi**. Search limiters or filters included *female, not male, English, humans, adult: 19+ years, longitudinal, longitudinal study, peer reviewed,* and *1990-2017*.

Study selection

Because the exploration of the role of depression in CHD began in the 1990s, the year 1990 is used as a starting point for article inclusion. Journal articles were included if they met the following criteria: the study examined ischemic CHD and had a descriptive, longitudinal design; the study included women; depressive symptoms were assessed at more than one timepoint; results were reported and/or analyzed by sex; and the article was published in a peer-reviewed journal. This search retrieved 1,098 articles. Removal of duplicates left 723 articles. Articles were then excluded for the following reasons: non-research articles (such as reviews); qualitative articles; non-cardiac populations (such as diabetes); controlled trials (where an intervention may have affected depressive symptoms); studies of other cardiac conditions (transplants, heart failure, arrhythmia/pacer/ICDs, etc.); studies focused on *risk for* CHD; different phenomenon within CHD (such as medications, biomarkers, or *ST* depression); populations known to have high depression levels (abused women); or studies where minimal (i.e. one sentence) examination or reporting of data by sex was performed. One-hundred thirteen full-text articles were screened, and 28 hand-searched articles were identified and screened at that time. No grey literature was searched. Twenty articles met inclusion criteria and were reviewed and included in Appendix A.

Prevalence and cutoff criteria

When possible, studies were examined by comparing the prevalence of elevated depressive symptoms. Prevalence is the proportion of a population affected by a certain condition. In the

reviewed articles, prevalence was expressed as the percentage of participants meeting cutoff criteria on the depressive symptom measurement instrument used by the author. Cutoff scores are determined by receiver operating characteristic analysis (ROC), with the area under the curve representing the score with the greatest sensitivity and specificity for correctly identifying the presence of a condition. These scores are not diagnostic, but rather serve as a proxy for a clinically significant level of impaired functioning in the individual.

Results

Prevalence of Depressive Symptoms

Prevalence in women at baseline.

Of the 20 studies that met inclusion criteria, only 8 provided *prevalence* data on women participants separately from men (Caulin-Glaser, Maciejewski, Snow, LaLonde, & Mazure, 2007; Doering, Magsarili, Howitt, & Cowan, 2006; Hunt-Shanks, Blanchard, & Reid, 2009; Josephson, Casey, Waechter, Rosneck, & Hughes, 2006; Lavie, Milani, Cassidy, & Gilliland, 1999; Norris, Hegadoren, & Pilote, 2007; Sanderson & Bittner, 2005; Shin, Hagerty, & Williams, 2010). The prevalence of elevated depressive symptoms in women during hospitalization for an index cardiac event ranged from 27.9% (Hunt-Shanks et al., 2009) to 40.3% (Norris et al., 2007), with a calculated average of 35.75% across the 8 studies (see Figure 2). The studies which utilized the Beck Depression Inventory-II (BDI-II) showed the highest prevalence: 38.8% and 40.3% in patients with acute coronary syndrome (ACS) and myocardial infarction (MI), respectively (Norris et al., 2007; Shin et al., 2010). The single study which used the Depression Interview and Structured Hamilton (DISH) found a prevalence of 36% prior to hospital discharge (Doering et al., 2006). A much lower prevalence of elevated depressive symptoms (27.9%) was found in the study which utilized the Hospital Anxiety and Depression Scale (HADS) tool (Hunt-Shanks et al., 2009). Two studies (Josephson et al., 2006; Sanderson & Bittner, 2005) used the measurement

of depressive symptoms prior to beginning cardiac rehabilitation (typically 2-3 weeks after hospital discharge) as the baseline time-point, though one additional study measured symptoms at this time as a *second* measurement time-point - "post-discharge" (Doering et al., 2006). Among these studies, the Beck instruments (BDI and BDI-II) demonstrated the highest prevalence: 36% (Josephson et al., 2006) and 31%(Sanderson & Bittner, 2005) respectively. The "post-discharge" study, which utilized the DISH, had a much lower prevalence of only 16.4% (Doering et al., 2006).

Longitudinal prevalence among women.

Of the 20 studies which met inclusion criteria, only 5 provided *prevalence* data for more than one time-point (Doering et al., 2006; Hunt-Shanks et al., 2009; Lavie et al., 1999; Norris et al., 2007; Shin et al., 2010). The average prevalence of elevated depressive symptoms among women across studies decreased from 35.75% during hospitalization to 27.8% 2-3 weeks post-discharge, to a calculated average of 22.71% over the next 24 months (see Figure 2). The trend overall was for improvement in depressive symptoms through the first 6 months, with levelling off between 6 to 24 months. However, one study demonstrated a small, statistically non-significant *increase* in prevalence from hospitalization (40.3%) to 12 months (40.4%) using the BDI-II (Norris et al., 2007).

An examination of the available longitudinal data shows conflicting findings from hospitalization to one month. Prevalence of elevated depressive symptoms dropped significantly, from 36% to 16.4%, in a study (Doering et al., 2006) of post-CABG patients using DISH, but only slightly (and statistically non-significantly) from 38.8% to 26.3% in a study of ACS patients that used the BDI-II (Shin et al., 2010). A drop from 23% at 1 month to 12% at 4 months post-hospitalization in women referred to CR was noted using the Kellner questionnaire (Lavie et al., 1999). Doering at al.'s (Doering et al., 2006) study showed a nearly 3-fold drop in

prevalence from 36% at hospitalization to 12.7% at 6 months using the DISH. Hunt-Shanks et al.'s (Hunt-Shanks et al., 2009) study showed a smaller decline between hospitalization and 6 months: from 27.9% to 20.6% using the BDI. However, Hunt Shanks et al. (Hunt-Shanks et al., 2009) reported a non-significant drop from 6 months (20.6%), to 19.2% at both 12 and 24 months. Norris et al.'s (Norris et al., 2007) study noted a small *increase* in prevalence from 40.3% during hospitalization to 40.4% at 12 months using BDI-II. No differences were noted based on the year the study was conducted, despite significant changes to diagnostic and treatment approaches over the intervening years (1999 – 2010).

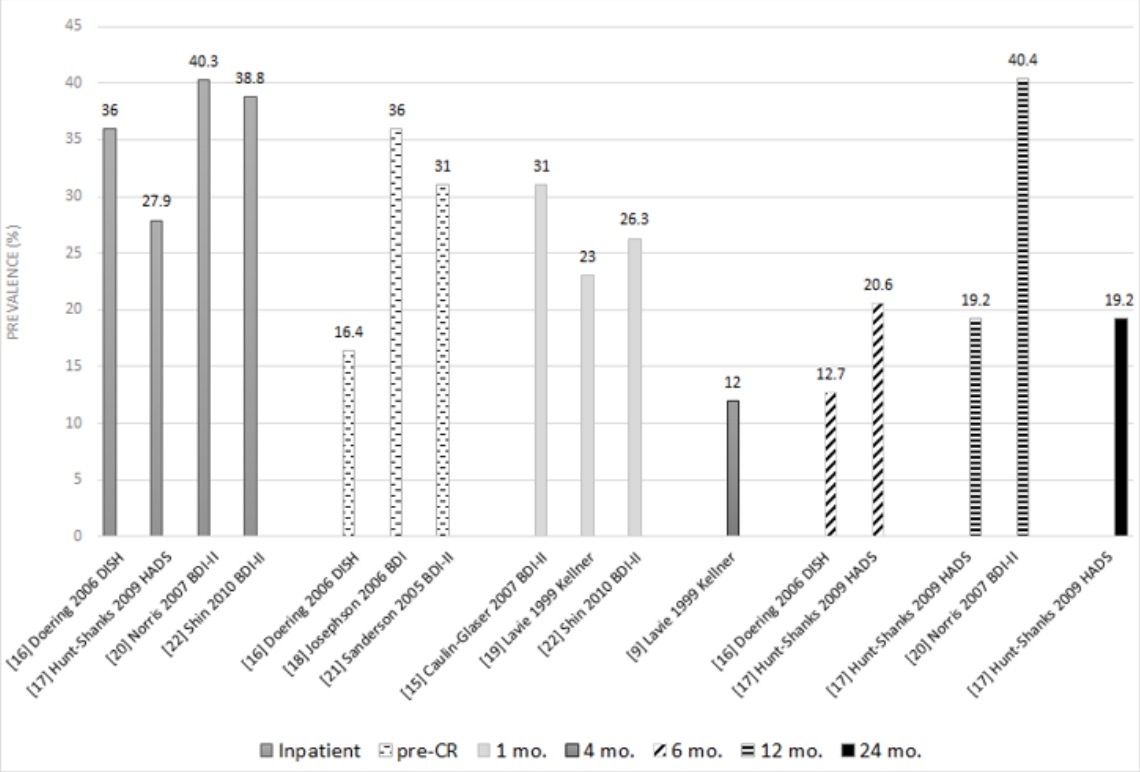

Figure III-2: Prevalence of elevated depressive symptoms in women over time

Sex Differences

Prevalence in men vs women.

Five of the twenty studies reviewed provided prevalence data for both men and women (Caulin-Glaser et al., 2007; Hunt-Shanks et al., 2009; Josephson et al., 2006; Norris et al., 2007;

Shin et al., 2010). All five studies, regardless of assessment tool used, showed a higher baseline prevalence of elevated depressive symptoms in women than in men, and all but one study (Shin et al., 2010) also demonstrated a statistically significant difference between sexes (see Figure 3). The average calculated baseline prevalence in men across these six studies was 23.46%, versus 34.8% in women. Of the depressive symptom assessment instruments used, the HADS showed the lowest baseline prevalence in both men (18.7%) and women (27.9%)(Hunt-Shanks et al., 2009). The highest prevalence for both sexes was found using the BDI-II: 32.7% in men and 40.3% in women (Norris et al., 2007). Three of the five studies provided prevalence data for both sexes beyond baseline, (Hunt-Shanks et al., 2009; Norris et al., 2007; Shin et al., 2010) with length of follow-up time ranging from 4 weeks (Shin et al., 2010) to 2 years (Hunt-Shanks et al., 2009). All three studies showed a higher prevalence of elevated depressive symptoms among women than men regardless of assessment tool used, though not all were statistically significant. For both sexes, the HADS yielded the lowest prevalence, while BDI-II yielded the highest prevalence.

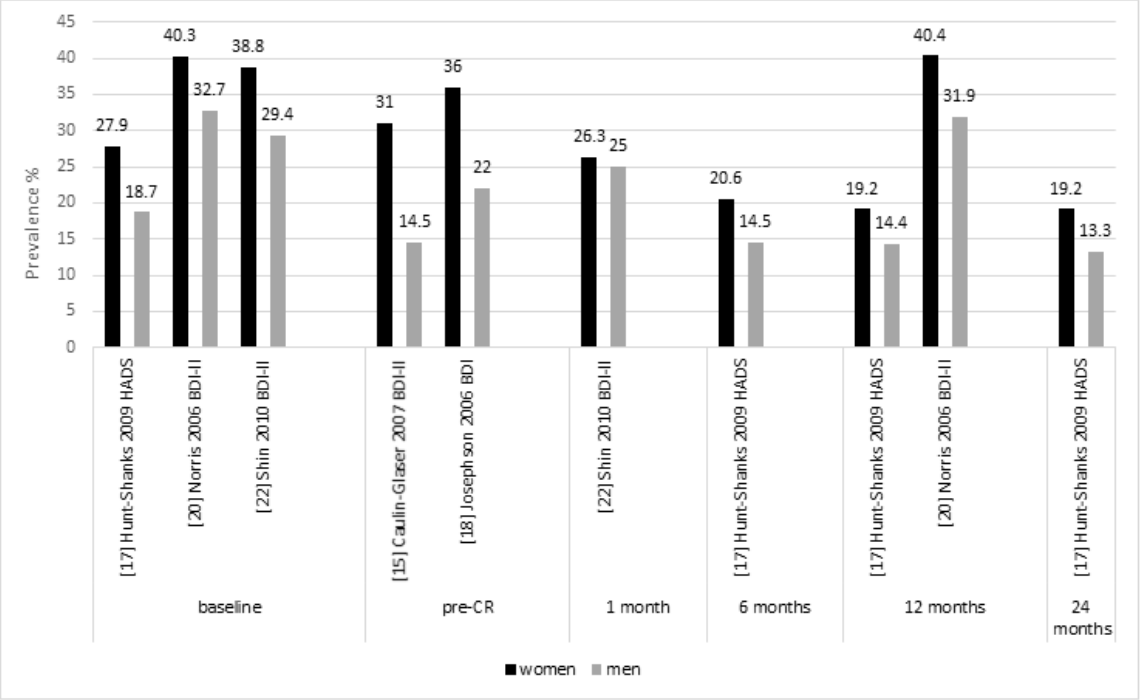

Figure III-3: Prevalence of elevated depressive symptoms – women vs. men

Non-prevalence findings in men and women at baseline.

Twelve of the 20 studies provided mean depressive symptom scores rather than prevalence data (Barth et al., 2009; Bogg, Thornton, & Bundred, 2000; Brink, Grankvist, Karlson, & Hallberg, 2005; Duits et al., 1998; Grace et al., 2005; Grace, Grewal, Arthur, Abramson, & Stewart, 2008; Gravely, 2007; Gupta, Sanderson, & Bittner, 2007; Lavie & Milani, 1995; McGrady, McGinnis, Badenhop, Bentle, & Rajput, 2009; Phillips Bute et al., 2003; Zaninotto, Sacker, Breeze, McMunn, & Steptoe, 2016). Of these studies, 1 measured baseline 2 weeks prior to CABG (Duits et al., 1998), 7 measured baseline during hospitalization (Bogg et al., 2000; Brink et al., 2005; Grace et al., 2005; Grace et al., 2008; Gupta et al., 2007; Phillips Bute et al., 2003; Zaninotto et al., 2016), 3 measured baseline prior to CR (Barth et al., 2009; Lavie & Milani, 1995; McGrady et al., 2009), and 1 measured baseline 45 days post-cardiac event (Gravely, 2007). Six studies (2 post-CABG studies and 4 post-CHD hospitalization studies) found women to have significantly higher mean scores than men at baseline, regardless of instrument used (Duits et al., 1998;

Grace et al., 2005; Gravely, 2007; McGrady et al., 2009; Phillips Bute et al., 2003; Zaninotto et al., 2016). One study (Gupta et al., 2007) reported only a slightly lower mean score for men compared to women on the BDI-II pre-CR. Three studies found no significant difference between men and women at baseline post-MI (Brink et al., 2005; McGrady et al., 2009) or pre-CR (Barth et al., 2009) using the HADS (Barth et al., 2009; Brink et al., 2005) and Kellner (McGrady et al., 2009) questionnaires. Grace and colleagues (Grace et al., 2008) found no significant difference between CR participants and non-participants at baseline in their all-female study using the HADS. Brink et al. (2005) found women to have slightly (though statistically insignificantly) *lower* levels of depressive symptoms than men at baseline using the HADS.

Non-prevalence findings in men and women after baseline.

Post-baseline timepoints ranged from 1 week (Duits et al., 1998) to 2 years (Zaninotto et al., 2016). Over half of the studies found improvement in symptoms for both genders within 3-6 months following hospitalization, regardless of instrument used (Bogg et al., 2000; Duits et al., 1998; Gravely, 2007; McGrady et al., 2009; Phillips Bute et al., 2003; Zaninotto et al., 2016). Two studies had contrary findings: Brink and colleagues (Brink et al., 2005) found significantly increased depressive symptom scores for both sexes between baseline and 5 months on the HADS after a first-time MI; and Lavie and Milani (Lavie & Milani, 1995) found a significant decrease in depressive symptom scores *in men only* following CR using the Kellner questionnaire. For the remaining three studies, the measurement timeframe was much broader. Philips Bute et al.'s (Phillips Bute et al., 2003) 12-month study using the Center for Epidemiological Studies - Depression scale (CES-D) found statistically significantly higher levels of depressive symptom both pre-CABG and 1 year post-op among women compared to men, though both sexes also experienced significant improvements in depressive symptoms over the 1-year interval. Grace et al.'s (Grace et al., 2008) study found an improvement on the BDI at 18

months compared to baseline in women who had *not* participated in CR compared to women who had. Zaninotto and colleagues (2016) found that among those who had experienced angina or an MI in the past 2 years, women demonstrated a 13% higher probability of meeting cutoff criteria compared to men both at baseline and at 2-year follow-up; this decreased to 5% at 4-year follow-up using the CESD-8 (an abbreviated version of the CES-D containing only 8 items).

Discussion

This review of 20 longitudinal studies examining elevated depressive symptoms in women with CHD yielded several important findings. It demonstrated that the prevalence of elevated depressive symptoms among women at the time of CHD diagnosis was high, with a calculated average of 35.75% – higher than men (23%), and higher than the commonly perceived prevalence in the CHD population (20%), and this is true both at baseline and over time. Prevalence varied by measurement instrument rather than participant inclusion criteria (ACS, MI, PCI, general CHD), with the exception of CABG; this also held true over time. This review also supported the perception that most women's symptoms do improve, and that this improvement largely occurs within the first 6 months after the index cardiac event.

However, the 20 articles summarized in this review varied widely in terms of timespan covered (1 month - 2 years), and participant inclusion criteria. Prior research suggests that those who have undergone CABG tend to experience fewer depressive symptoms than those who have not, particularly compared to those who are medically managed after MI without intervention (Pajak et al., 2013) or those with unstable angina (Geovanini et al., 2014; Lotufo et al., 2013). Only two studies in this review focused exclusively on post-CABG patients. Of these, only one provided prevalence data, and this was an all-woman study. Exclusion of this study made little difference to the calculated average prevalence among women at hospitalization

(35.75% with the study, 35.66% without), but it did correlate to the lowest prevalence among the studies at each of its follow-up timepoints (2-3 weeks, and 6 months).

Study follow-up timeframes may have also affected results. Due to the small number of studies that examined symptoms beyond 6 months, the apparent improvement associated with this timeframe may be a reflection of the paucity of longer studies rather than actual increased improvement in this early stage of recovery. Stapelberg and colleagues (Stapelberg, Neumann, Shum, McConnell, & Hamilton-Craig, 2013) indicated that one of the main gaps in understanding the link between depression and CHD is failing to examine the follow-up timeframe. The authors are not aware of any large studies where quantitative changes in severity of major depressive disorder are followed at regular intervals over time. It is recommended that frequent measures of patient mental state be correlated over time with measures of cardiac health to provide more accurate longitudinal estimates of patient progress (Stapelberg et al., 2013).

The examination of prevalence data in this review demonstrated a difference in findings based on instrument, with the BDI and BDI-II demonstrating much higher prevalence than the HADS or Kellner questionnaire. A critical difference between instruments is the inclusion or exclusion of somatic depressive symptoms (such as fatigue, alterations in sleep, or changes in appetite). Instruments which included somatic symptoms yielded higher scores. Ormel and de Jonge (Ormel & de Jonge, 2011) made a case for two different types of depression in CHD patients: “typical depression” (characterized by vulnerability and stressful life events) and “somatic depression” (triggered by “the presence of vascular disease, systemic inflammation and atherosclerosis”). A study testing their integrative model supported their conclusion: those with somatic depression were at risk for increased mortality (Roest, Wardenaar, & de Jonge, 2016). They noted that those with persistent somatic depressive symptoms were more likely to be older women. The exception in this review regarding higher prevalence on instruments with

somatic symptoms was the results for the DISH instrument. It detected a much lower prevalence than the Beck instruments at baseline and pre-CR, and HADS at 6 months despite including somatic symptoms. This may, however, reflect the CABG population it was used with rather than its inclusion of somatic symptoms.

While it appears that there is a relationship between somatic symptoms and an increased risk of mortality in CHD patients, it remains unclear if these somatic symptoms are depressive in nature or are related to the underlying heart disease itself. Both depression and heart disease in women can manifest as fatigue, sleep disturbances, and/or gastrointestinal symptoms such as appetite changes (DeVon, Pettey, Vuckovic, Koenig, & McSweeney, 2016; Doering et al., 2006; Kohlmann, Gierk, Hummelgen, Blankenberg, & Lowe, 2013; Sanner, Frazier, & Udtha, 2013). The HADS tool deliberately does not contain questions about somatic symptoms since the authors were concerned about confounding symptoms of physical illness with symptoms of depression (Snaith & Zigmond, 1986). DeVon, who evaluated ACS patients using the HADS, stated that these overlapping symptoms "confound [the] clinical picture" (DeVon et al., 2016). DeVon used the HADS specifically because it does not measure physical symptoms which could be heart disease rather than depression (DeVon, personal communication, October 14, 2016). Thus, while it appears that these symptoms are significant and should be assessed, it remains unclear whether they indicate depressive symptoms or rather reflect a physical disease process. Since management will differ depending on the symptom's source, further investigation of the source of these somatic symptoms is warranted.

The reviewed studies also demonstrated the difficulty in trying to compare findings between studies that use different measures of depressive symptoms. Use of item response theory and the development of common metrics for assessing depressive symptoms as a means to generate easily compare-able findings across studies has begun. PROMIS, a set of 90+ assessment

instruments, was developed using item response theory and proposed as a common metric, but the depressive symptom assessment instrument does not contain somatic symptoms. Stapelberg and colleagues (Stapelberg et al., 2013) recommend a combination of interview and DSM criteria-based self-report instruments to assess depression. This would facilitate a more accurate diagnosis of major depressive disorder, increase accuracy in assessing symptom severity, and potentially allow for a comparison between the two methods. Until an agreed-upon common metric for measuring depressive symptoms is available, reporting *prevalence* data either with or without an accompanying diagnostic interview will allow simple, direct comparison between studies.

This review demonstrated that women continue to be under-represented in mixed-sex studies of CHD, with women comprising an average of only 28.9% of study participants in this review. The lack of data regarding women has been reflected in other reviews (McSweeney et al., 2016). By not separating data by sex, the differences between men's and women's symptoms continue to be obscured due to this underrepresentation. In order to understand women's unique experiences (and to create interventions which meet women's needs), data must be separately analyzed and reported by sex, a practice now expected by the National Institutes of Health (2015). Ouyang and colleagues (Ouyang et al., 2016) also suggest encouraging, if not requiring, data reporting by gender by both research sponsors and journal editors.

While much has been learned over the past 30 years about women with heart disease and comorbid depressive symptoms, this review highlights just how much remains unknown. Further longitudinal studies and secondary analyses of existing longitudinal data which focus on sex differences are needed to further elucidate women's experiences and symptom trajectories. The reporting of data by sex needs to become standard practice, particularly in light of the

difficulty in recruiting equal numbers of women into clinical trials alongside NIH's recognition of sex as an important biological variable. While use of item response theory and the development of common metrics for assessing depressive symptoms are underway, a simple solution currently for reporting this data in a manner easily comparable is to report such data as prevalence. These steps will provide a fuller picture of women with CHD and depressive symptoms and allow development of more efficacious interventions for women.

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Chapter IV. Manuscript 3

Results of a Mixed Methods Longitudinal Feasibility Study Examining Depressive Symptoms in Women with Coronary Heart Disease

Introduction

Understanding the role of mood in the development of and in response to the diagnosis of coronary heart disease (CHD) has been a significant advancement in our understanding of the disease. It is now believed that mood, particularly depressed mood, plays a significant role in outcomes following a cardiac event. Individuals who develop depression following a cardiac event are at increased risk for morbidity and mortality (Lichtman et al., 2014). Evidence now suggests that those who have depression are at increased risk of developing CHD as well (Kollia et al., 2017; O'Neil et al., 2016). Women are known to have higher rates of depression compared to men – approximately 2:1 - both in the general and the CHD populations (Moller-Leimkuhler, 2008).

There is a wealth of literature examining the relationship between depressive symptoms at the time of a cardiac event and both cardiac as well as all-cause outcomes. However, there is far less literature examining the trajectory of depressive symptoms in patients over time following a cardiac event. Even fewer studies examine data by gender and identify those who have met cut-off criteria on the depressive screening instruments used in the study. Those studies that examine gender have used a variety of depressive symptom screening tools making it difficult to synthesize and draw conclusions from this literature.

Some studies suggest that somatic depressive symptoms are particularly prevalent among women with CHD (Peter de Jonge et al., 2006; Roest, Wardenaar, & de Jonge, 2016). However, the assessment of somatic depressive symptoms in the CHD population is problematic since several of the most common symptoms overlap between the two diagnoses. Specifically,

fatigue and sleep disturbances appear in both CHD and depressed patients, making their origin difficult to ascertain. Several factors have also been noted to influence the development of depressive symptoms in women with CHD. These include 1) age, 2) employment status, 3) comorbidity with diabetes, 4) attendance at cardiac rehabilitation (CR), 5) a history of depression, 6) a history of anxiety, and 7) acute coronary syndrome (ACS) symptoms (May Blom et al., 2007; Caulin-Glaser, Maciejewski, Snow, LaLonde, & Mazure, 2007; Kohlmann, Gierk, Hummelgen, Blankenberg, & Lowe, 2013; Kronish et al., 2006; Lesperance, Frasure-Smith, & Talajic, 1996; Shah et al., 2014; Smolderen et al., 2015).

We know that some women who experience a cardiac event will experience significant depressive symptoms at the time of the event, others will experience such symptoms later in the recovery period, while others will not experience significant depressive symptoms at all. It is not clear what accounts for the variability in prevalence of significant depressive symptom rates at the time of the initial incident, the subsequent variability in recovery patterns, and the differences in type of symptoms experienced. Two possibilities need to be considered: 1) the way in which depressive symptoms are being measured, and 2) other factors influencing depressive symptoms.

Materials and Methods

The purpose of this study was to examine the feasibility of conducting a study to examine depressive symptoms in women ages 19 and over with CHD from the time of an index cardiac event (defined as myocardial infarction ([MI], acute coronary syndrome [ACS], percutaneous coronary intervention [PCI], or coronary artery bypass graft [CABG]) through the first three months of recovery, exploring depressive symptom dimensions; incidence of depressive symptoms; the influence of CHD and depression on sleep and fatigue; and the influence of certain factors on depressive symptoms in this population.

Theoretical Framework

This study was guided by Lenz's middle-range Theory of Unpleasant Symptoms (Lenz, Pugh, Milligan, Gift, & Suppe, 1997; Lenz, Suppe, Gift, Pugh, & Milligan, 1995). Lenz's theory proposes that three factors – physiological, situational, and psychological - influence symptoms. Symptoms have four dimensions which are common across symptoms as well as clinical populations. These four dimensions are intensity (or severity), timing, level of perceived distress, and quality. Symptoms, in turn, influence performance (functional and cognitive activities). The theory also posits reciprocal relationships between the theory's components.

The examination of depressive symptoms in the CHD literature has largely been limited to the dimension of severity, though a smaller body of literature has also explored quality (somatic vs cognitive symptoms). For this study, a conceptual framework of depressive symptoms in women with CHD was proposed, applying Lenz's model to this population (see Figure IV-1). Depressive symptoms were defined as "the presence of a sad, empty, or irritable mood" (American Psychiatric Association, 1994) after the cardiac event. Given that symptoms change over time as individuals adjust to their new health status, timing was

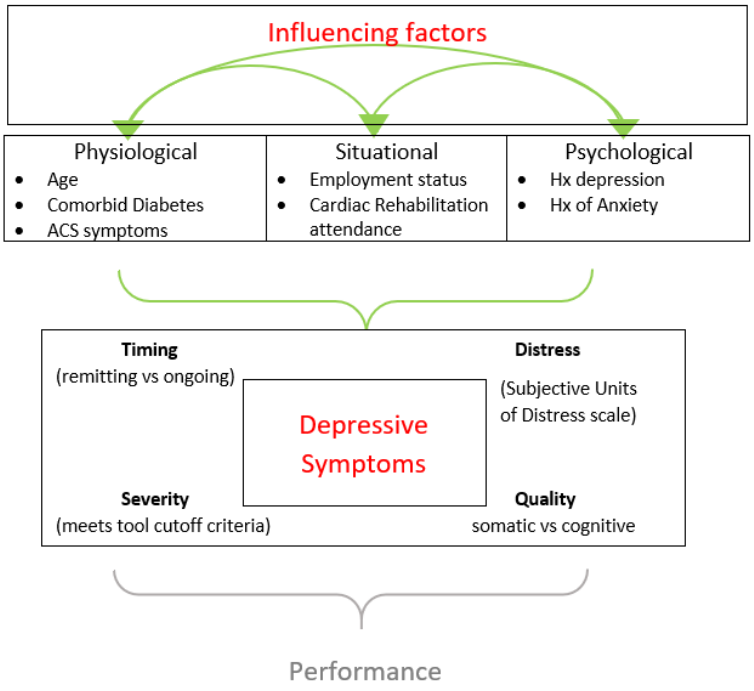

Figure IV-1: Conceptual framework of depressive symptoms in women with coronary heart disease

operationalized in months, beginning at the time of the cardiac event. Severity of symptoms was determined by individual scores in relation to the tools' cut-point score (which indicates significant functional impairment). Quality was operationalized as either somatic (physical) or cognitive symptoms. Symptom distress was determined utilizing the "Subjective Units of Distress" scale. In this study, the relationship between all four individual depressive symptom dimensions in women with CHD was explored, taking significant influencing factors (see Aim 4) into consideration.

Specific Aims

The specific aims of the study were as follows:

Feasibility: Evaluate participant recruitment and retention, data collection (computer vs paper, instrument reliability, time burden, missing data), and uptake and data quality of qualitative surveys.

Quantitative: Evaluate data for preliminary trends in the following:

(1) the prevalence of women who meet the cut-point criteria for elevated depressive symptoms following a cardiac event at baseline, 2 months and 3 months post study enrolment as measured by 3 commonly-used tools to measure depressive symptoms, comparing them to prevalence rates of elevated depressive symptoms found in previous literature

(2) changes over time (baseline through month 3) in women's depressive symptom dimensions (timing, severity, quality, symptom distress).

(3) the influence of CHD and depression on sleep and fatigue post cardiac event at baseline, 2, and 3 months.

(4) the influence of age, diabetes, employment status, CR attendance, a history of depression and/or anxiety, and ACS symptoms on depressive symptoms at baseline, 2 months, and 3 months.

Qualitative: Explore the acceptance, uptake, and quality of a qualitative survey as a data collection method with a sub-sample of women who agree to participate at baseline, 2, and 3 months post enrolment.

Mixed methods: Describe how the qualitative data concurred with or differed from the quantitative depression screening instrument scores.

Design

This study was a longitudinal, observational feasibility study using an embedded mixed methods design. Both quantitative and qualitative data were collected simultaneously at each point in the study, analysed separately, and combined at the end of the study. An embedded mixed methods approach was chosen to provide a forum for women to discuss symptoms and their dimensions that may not have been present on quantitative data collection instruments. Institutional Review Board approval for conducting the study was obtained from the University of Nebraska Medical Center (UNMC) (#567-17-EP) and Nebraska Methodist Hospital (#1372). One regional hospital in a non-urban setting also served as a recruitment site under the UNMC IRB. Inclusion and exclusion criteria were as follows:

Inclusion:

- Female sex
- age 19 + (the age of majority in Nebraska)
- experienced a cardiac event (MI, ACS, PCI, or CABG) during the current hospitalization
- cognitively intact, indicated by being able to describe what participation in the study will involve

Exclusion:

- Diagnosis of chronic congestive heart failure (due to increased depressive symptoms in this population) (Rutledge, Reis, Linke, Greenberg, & Mills, 2006)
- Any orthopedic or neurological condition which limits day-to-day physical activity (since these are known to limit women's participation in cardiac rehabilitation, and non-participation is associated with greater depression) (Supervía et al., 2017)
- CABG within the last 6 months
- Pregnancy or planning to become pregnant in the next 6 months (due to both altered physical and emotional responses during pregnancy) (Dolatian et al., 2016; Vogt et al., 2014).

Sampling

Participants were recruited within one month of hospital admission via convenience sampling from two urban and one regional Midwestern U.S. hospital. Women who met criteria were identified by hospital staff and approached about study participation while in the hospital. The study was explained and informed consent was obtained by the principal investigator (PI) Buckland either face-to-face or via computer (in the case of the regional hospital). Baseline quantitative surveys were either e-mailed or sent out via USPS once informed consent was obtained. Data were collected again 2 months and 3 months after consent. Participants elected to complete surveys on-line via REDCap (Research Electronic Data Capture) or on paper. Qualitative surveys were used to collect qualitative data, and participation in this portion of the study was optional. If participants elected to participate, they were asked to write for 15 minutes on 3 out of 7 days of the same week that they completed the quantitative surveys. Semi-structured questions were provided. Surveys were returned to the PI along with the quantitative surveys if submitted on paper, or via encrypted e-mail if done on the computer.

Measures

Demographics:

Demographic information was obtained from each participant following consent. This included age, race, level of education, employment, income, and marital status. Health history questions, including what type of cardiac event the woman was hospitalized for, and any history of diabetes, depression, or anxiety were also asked. Two demographics questions were asked at the 2 and 3-month time points: employment (whether or not the woman had held a steady job in the past month) and attendance at cardiac rehabilitation.

Depressive symptom measurement instruments:

Three depressive symptom measurement instruments were used in order to compare prevalence findings: the Beck Depression Inventory II (BDI-II), the Patient Health Questionnaire 9-item (PHQ-9), and the Patient-Reported Outcomes Measurement Information System Depression 8b (PROMIS Depression 8b). The BDI-II is a frequently-used instrument for assessing depressive symptoms in the cardiac population and contains 21 cognitive and somatic items. It has previously demonstrated an average Cronbach's alpha coefficient of 0.9, test-retest reliability of 0.73-0.96, concurrent validity with the Revised Hamilton Rating Scale for Depression of 0.66-0.75, and discriminant validity with the Beck Anxiety Inventory of 0.56-0.69 (Wang & Gorenstein, 2013). BDI-II $\geq$ 20 is considered the typical cut-off value for this scale (Beck, Steer, Ball, & Ranieri, 1996). Cut-off scores indicate the likely threshold for symptoms creating interference in a person's function.

The PHQ-9 was endorsed by the American Heart Association for use in assessing depressive symptoms in cardiac patients (Lichtman et al., 2008), and also contains both cognitive and somatic symptoms. It has demonstrated internal consistency with a Cronbach alpha of 0.89, test-retest reliability of 0.84, and area under the curve of 0.95 in a receiver

operating characteristics curve analysis for diagnosing major depressive disorder. PHQ-9 ≥ 10 is considered the typical cut-off value for this scale (Kroenke, Spitzer, & Williams, 2001).

The PROMIS set of assessment instruments was developed with prior funding from the National Institutes of Health in order to be able to compare results of instruments across multiple conditions (https://commonfund.nih.gov/promis/index). The PROMIS does not contain somatic symptoms and has had minimal use in the cardiac population. It has previously demonstrated reliability with a Cronbach alpha of 0.92, convergent validity with PHQ-9 of 0.72 – 0.81 (Pilkonis et al., 2014). Previous work suggests that instruments which do not include somatic symptoms yield lower prevalence rates (Buckland, Pozehl, & Yates, 2019). Since cut-off scores have not been established for the PROMIS tool, cut-offs based on Wahl et al.'s (2014) calculations for a common metric among for 11 self-report depression assessment instruments were used.

Distress instrument

Because distress is not measured as a component of any of the depression screening instruments, the Subjective Units of Distress measure was chosen to measure this symptom dimension. The Subjective Units of Distress scale is a 10-point scale where lower scores indicate less symptom distress and higher scores indicate more symptom distress. The scales has demonstrated correlations with the State/Trait Anxiety Inventory (r=0.72, $p<.05$) and with the Multiple Affect Adjective Check List (MAACL) (r=0.59, $p<.05$) (Kaplan, Smith, & Coons, 1995)

Overlapping somatic symptom assessment instruments

Several symptoms of CHD and depression overlap, including fatigue and sleep disturbance. Fatigue was assessed with the Fatigue Symptom Inventory (FSI), a 13-item questionnaire which examines degree of fatigue as well as how much fatigue has interfered with function. The FSI has demonstrated good reliability (0.93 in women, 0.95 in men) and

convergent validity with the Profile Of Mood States (F=0.66-0.75) (Hann, Denniston, & Baker, 2000). Sleep was assessed with the PROMIS short form v.1 Sleep Disturbance 8b (PROMIS Sleep 8b), an 8-item scale assessing sleep disturbance. The PROMIS Sleep Disturbance 8b has demonstrated reliability of 0.90 and convergent validity of .083 with Pittsburgh Sleep Index (Yu et al., 2011). In order to ascertain whether the participant was experiencing ongoing acute coronary symptoms as well, the Acute Coronary Syndrome (ACS) symptoms checklist was also used. The ACS symptom checklist has demonstrated sensitivity of 14-72% and specificity of 33-78% (DeVon, Rosenfeld, Steffen, & Daya, 2014).

Analysis

Quantitative: A fully powered study based on a priori power analysis using G*Power 3.1.9.2 and assuming a 10% attrition rate would have required 75 participants. A feasibility study, according to the National Institute for Health Research, should be of a size "adequate to estimate the critical parameters (e.g. recruitment rate) to the necessary degree of precision" (Arain, Campbell, Cooper, & Lancaster, 2010, p. 4). Assuming that recruitment of between ¼ and ⅓ of the total number for a fully-powered study would allow for adequate estimation of critical parameters (recruitment rate, uptake of qualitative surveys, preliminary data trends), 20 to 25 participants were deemed adequate for a feasibility study.

Quantitative data were analysed using IBM SPSS Statistics version 25. Descriptive statistics were used for demographic data and mean scores. Paired T-tests were used to examine differences in mean depressive symptoms scores between timepoints. Independent T-tests were used to examine differences in age based on whether or not the participant met cut-point criteria on the depressive symptom screening instrument. The quality of depressive symptoms – somatic vs cognitive – was determined by averaging scores of symptoms which have been designated as somatic or cognitive by previous authors. Since the PROMIS instrument

does not contain somatic items, it was not included. The BDI-II categories were based on Thombs et al.'s (2010) article, which designates BDI-II items 1-14 as cognitive and 15-21 as somatic. The PHQ-9 categories were based on de Jonge, Manago, & Whooley's (2007) article which identified questions 1, 2, 6, 7, and 9 as cognitive and questions 3, 4, 5, and 8 as somatic. For all correlations, non-parametrics using Spearman's rho were performed due to non-normal distribution of the study data secondary to small sample size.

Qualitative: Women were asked to think about and write answers to the qualitative survey questions on 3 of the 7 days of the same week in which they completed the quantitative surveys. Qualitative data was sought in order to more fully explore women's emotional experiences following their cardiac event, particularly the four symptoms dimensions posited in the theoretical framework (symptom severity, timing, quality, and level of perceived distress). Terry and Braun (2017) recommend using thematic analysis for analyzing qualitative survey data. The goal was to explore the views of participants as expressed in their own words as a means of following the humanistic aim of empowerment (Jansen, 2010). Therefore, the approach to the data analysis was inductive ("bottom-up") rather than theoretical ("top-down"), and the entire data set was analyzed rather than focusing solely on those pieces which explicitly addressed questions regarding the four dimensions of the theoretical framework. The six phases of thematic analysis as described by Braun and Clarke (2006) were followed. These are: a) familiarizing yourself with your data, b) generating initial codes, c) searching for themes, d) reviewing themes, e) defining and naming themes, and f) producing the report (Braun & Clarke, 2006).

Qualitative data was analysed using Atlas.ti 8 software. All journal entries were read in their entirety, and then re-read. Quotations of interest were identified and assigned open codes from the original text. Codes were then examined and grouped as initial themes were identified.

These themes were reviewed once all coded text had been grouped, and final themes subsequently named.

Mixed Methods: Women who participated in the qualitative portion of the study were identified as having scored above or below the cut-point on any of the depression screening instruments. The originally-identified quotations for each individual theme were then examined based on the participant's depression screening scores, looking for patterns in responses based on these scores. The themes themselves were then divided based on differences noted between women who had met cut-point criteria and women who had not, and quotations supporting the differences were provided.

Results

Feasibility

Recruitment: Recruitment was problematic, due in part to issues of ethical access to the population. Numerous staff members were approached about and agreed to recruit for the study. However, only three of the nine individuals who agreed to recruit actually

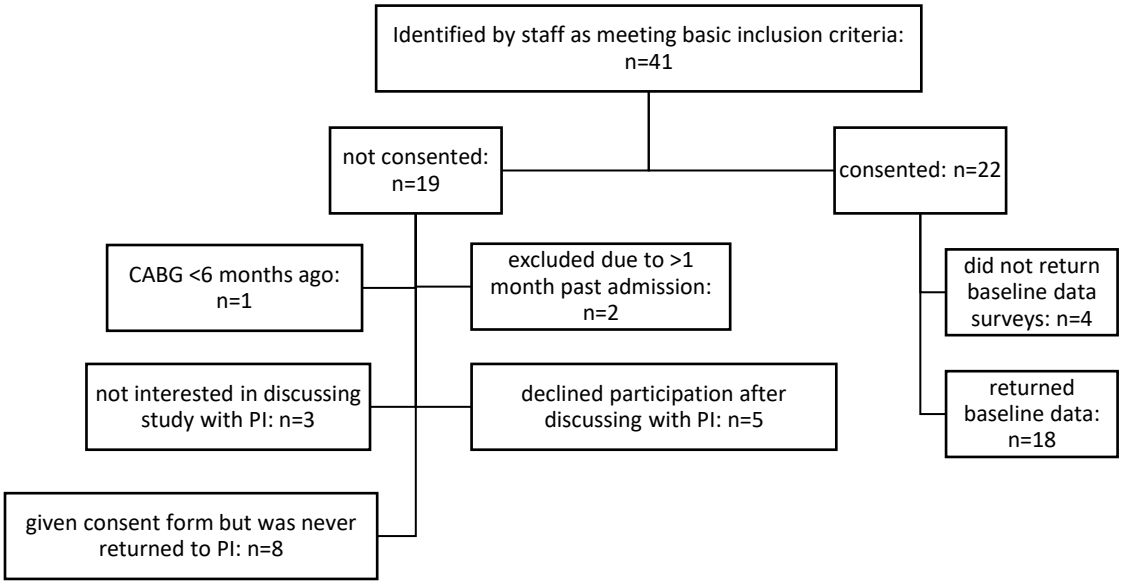

Figure IV-2: Participant recruitment

recruited participants using the original strategy. Inclusion criteria as well as post-admission timeframes were expanded in an effort to recruit more participants while still utilizing the original recruitment strategy. A revised strategy for recruitment which required less of the hospital staff's time but required the PI to be at the bedside daily for participant recruitment was finally implemented with significant improvement in recruitment rates. Details of participant recruitment are provided in Figure IV-2.

Retention: Of the 22 women who signed a consent to participate, 18 returned the baseline survey. At month 2, only 13 participants returned surveys. At both time points, the PI called those who had not returned surveys up to two times and left messages along with the PI's contact information. At month 3, participants who had not returned their surveys within 1 week of them being sent out were mailed a written reminder to return the surveys. This increased the number who returned surveys to 15. This represents a 16.7% attrition from the original 18 participants who returned baseline surveys; or 31.82% from the initial 22 who signed consents.

Quantitative data collection: Participants were given a choice at the time of enrolment to complete the study via REDCap, a secure HIPAA-compliant cloud-based application designed to support data capture for research studies, or via paper. Of the 22 women who signed consents, 50% chose to do the study on-line and 50% on paper. Of those who did not complete the baseline data, again 50% chose on-line and 50% paper. Average data collection time (based on on-line responses, which were time-stamped) showed that baseline data took an average of 17 minutes to complete, and months 2 and 3 took an average of 11 and 12 minutes respectively to complete. There was very little missing data. Two individual data points from two different participants were missing from PHQ-9. These values were substituted with the average scores of the non-missing items (National Health Service, 2019). One participant did not complete the PROMIS Depression 8b survey at baseline (though did complete the instrument at the other two

data collection points). Because the on-line surveys required complete responses to move on to the next survey, there was no incomplete data from REDCap.

Participant characteristics	N (%)
Age:	
Mean	64.22
Median	66
Range	40-88
Race:	
White	16 (88.9)
Black/African-American	1 (5.6)
Other	1 (5.6)
Education:	
Less than high school	2 (11.1)
High school graduate	8 (44.4)
Some college	3 (16.7)
Associates degree	1 (2.2)
Technical degree	0
Bachelor's degree	2 (11.1)
Master's degree	2 (11.1)
Doctorate	0
Income:	
$0 - $25,000	8 (17.4)
$25,000 - $50,000	7 (15.2)
$50,000 - $75,000	1 (2.2)
$75,000 - $100,000	1 (2.2)
No answer	1 (2.2)
Marital Status:	
Single, never married	2 (4.3)
Married	11 (23.9)
Domestic partner	0
Divorced	1 (2.2)
Widowed	4 (8.7)
Employment:	
Baseline (n=18)	
Yes	6 (13)
No/retired	12 (26.1)
Month 2 (n=13)	
Yes	5
No/retired	8
Month 3 (n=15)	
Yes	6
No/retired	9
Health history positive for:	
Diabetes	5 (10.9)
Depression	5 (10.9)
Anxiety	6 (13.1)
Admitting cardiac event:	
Heart attack	5 (27)
Unstable angina	3 (17)
PCI	8 (44)
CABG	2 (11)
Attendance at cardiac rehab:	
At month 2 (n=13)	
Not at all	4
<50% of sessions	2
>50% of sessions	2
100% of sessions	5
At month 3 (n=15)	
Not at all	4
<50% of sessions	3
>50% of sessions	3
100% of sessions	5

Table IV-1: Participant characteristics

Uptake and quality of qualitative surveys:

Participation in the qualitative portion of the study was optional. Twelve women indicated that they would participate, but only six returned baseline qualitative surveys. This number dropped to three at month 2, and remained at three for month 3. Only two women provided qualitative survey data at all three timepoints, with two more providing data at two timepoints. The amount of data generated per participant varied widely. Not all participants wrote for the 3 days requested. Some responses were very short - 119 words – and others much longer – 1,303 words. Because most were hand-written, the survey reposes were dictated into Word documents for improved readability and ease of analysis.

Participant Characteristics

Women who participated in the study ranged in age from 40 to 88 years old, with a median age of 6. Participants were predominantly white (89%), married (61.1%), with a high school education (44.4%). 47.1% of participants reported an annual household income of

under $25,000/year, and 41.2% reported between $25,000 and $50,000 per year. 33% of the sample had “held a steady job in the past 6 months” at baseline. Of the admitting cardiac events, 27% of participants had been admitted for MI, 17% for unstable angina, 44% for PCI, and 11% for CABG. In terms of health history, 28% of participants reported a history of diabetes; 28% reported a history of depression; and 33% reported a history of anxiety. Of the four women who signed consents but did not return baseline data, 2 had undergone PCI and 2 had undergone CABG (see Table IV-1).

Quantitative Data Trends

Prevalence of Elevated Depressive Symptoms. The prevalence of women who met the cut-point criteria for elevated depressive symptoms on the three depressive symptom screening instruments (BDI-II, PHQ-9, and PROMIS Depression 8b) was evaluated. Mean scores at all timepoints fell below the cut-off scores for each of the scales used. Over 20% of women scored over the scales’ cut-offs at each timepoint (see Table IV-2). When comparing prevalence among individual screening instruments, the PHQ-9 prevalence was an average of 9% lower than the BDI-II, and 6.7% lower than the PROMIS despite its inclusion of somatic symptoms.

Changes over time in women's depressive symptom dimensions.

Severity: There were no statistically significant differences between severity of depressive symptoms (as determined by mean scores at each timepoint) on any of the three screening instruments at any timepoint. However, trends in changes were noted. Severity of depressive symptoms appeared to decrease between baseline and month 2, and then increase somewhat at month 3 on two of the three screening instruments (PHQ-9 & PROMIS) but decrease at month 3 on one instrument (BDI-II) (see Table IV-2).

Depression screening instrument	Baseline mean score	# women ≥ established cutoff score	Month 2 mean score	# women ≥ established cutoff score	Month 3 mean score	# women ≥ established cutoff score
BDI-II (Cutoff ≥20)	17.17	6 (33%)	14.15	4 (31%)	14.07	4 (27%)
PHQ-9 (Cutoff ≥10)	8.35	4 (22%)	5.54	3 (23%)	6.21	3 (20%)
PROMIS sum & T-scores (Cutoff ≥19)	17.82* 53.48*	4 (22%)*	14.15 48.14	3 (23%)	15.53 50.37	4 (27%)

*n=17

Table IV-2: Depression mean scores and prevalence

Distress: There were no statistically significant differences between scores at any timepoint, but again trends in changes were noted. The average value at baseline was 3 (±2.80), which decreased to 2.92 (±2.56) at month 2, but then increased at month 3 to 3.2 (±2.24).

Quality: There were no statistically significant differences between mean scores for somatic and cognitive items on either the BDI-II or PHQ-9 at any timepoint. Trends in scores demonstrated that the mean scores for somatic items were higher than those of cognitive items. As with overall scale scores, mean somatic symptom scores decreased between baseline and month 2, but then increased from month 2 to month 3. However, mean cognitive scores decreased at each timepoint without an increase noted at month 3 (see Table 3).

	Baseline		Month 2		Month 3	
	Cognitive	Somatic	Cognitive	Somatic	Cognitive	Somatic
BDI-II	8.56	8.61	6.69	7.46	6.40	7.67
PHQ-9	3.76	4.56	2.77	2.77	2.73	3.47

Table IV-3: Mean cognitive and somatic depressive symptom scores

The influence of CHD and depression on sleep and fatigue. Given the small sample size of the study, neither ANOVA nor effect sizes could be reliably calculated. Nonparametric correlations using Spearman's rho between CHD, depression (as measured by the three depression screening instruments), and the identified somatic symptoms were performed and

then compared. Because all women in the study had CHD, the ACS symptom scale was used as a proxy for CHD. (See Tables IV-4 & IV-5 for correlation coefficients).

Fatigue	BDI-II Baseline Month 2 Month 3	PHQ-9 Baseline Month 2 Month 3	PROMIS Depr. 8b Baseline Month 2 Month 3	ACS symptoms Baseline Month 2 Month 3
Baseline				
• Severity	.671**	.782**	.808**	.855**
• Interference	.778**	.884**	.780**	.831**
Month 2				
• Severity	.821**	.821**	.889**	.716*
• Interference	.774**	.818**	.786**	.705*
Month 3				
• Severity	.881*	.858**	.871**	.575*
• Interference	.770**	.744**	.722**	.697**

*p<.05
**p<.005

Table IV-4: Correlation (R) between fatigue severity & interference, depression scores, and CHD

PROMIS Sleep 8b	BDI-II Baseline Month 2 Month 3	PHQ-9 Baseline Month 2 Month 3	PROMIS Depr. 8b Baseline Month 2 Month 3	ACS scale Baseline Month 2 Month 3
Baseline	.735**	.796**	.628**	.637**
Month 2	.754**	.662*	.791*	.668*
Month 3	.760**	.719**	.823**	.560*

*p<.05
**p<.005

Table IV-5: Correlation (R) between sleep, depression scores, and CHD

Depression screening scores demonstrated significant positive correlations with fatigue (both severity and interference with function) and sleep. All fatigue severity and interference scores at a given timepoint and the depression scores at the corresponding timepoint had positive correlations significant at p<.005. Sleep scores at a given timepoint and the depression scores at the corresponding timepoint had positive correlations significant at p<.005 for baseline and month 3, and significant at p<.05 at month 2.

ACS scores also demonstrated significant though slightly less robust positive correlations with fatigue and sleep. All fatigue severity and interference scores at a given timepoint and the ACS scores at the corresponding timepoint had positive correlations significant at $p \leq .05$. All sleep scores at a given timepoint and the ACS scores at the corresponding timepoint were significantly positively correlated at $p < .05$.

The influence of demographic factors on depressive symptoms. Given the small sample size of the study, ANOVA could not be reliably calculated. Therefore, simple correlations between factors found to be significant in previous literature (age, diabetes, a history of depression and/or anxiety, employment status, attendance at CR, and ACS symptoms) and depression (as measured by the three depression screening instruments) were performed and then compared (see Table IV-6 for correlation coefficients).

Age and Diabetes: There was a negative correlation significant at $p < .05$ noted between age and depression scores at baseline and month 3, though not at month 2. A more granular examination of the correlation between age and depression score found that the average ages of those who met cut-off criteria on the three depression screening instruments at baseline were 54.5 years (SD 14.1) for BDI-II; 46.3 years (SD 7.5) for PHQ-9; and 51.7 years (SD 12.2) for PROMIS. The average age of those not depressed at baseline were 69.1 years (SD 13.3) for BDI-II; 69.4 years (SD 12.8) for PHQ-9; and 70.9 years (SD 12.7) for PROMIS. Diabetes was found to have significant ($p < .05$) positive correlation to depression at all timepoint on all screening instruments except BDI-II at month 2.

History of depression or anxiety: Having a history of depression was found to be significantly ($p < .05$) positively correlated with current depression screening scores baseline and month 3 for all instruments except BDI-II at baseline. None demonstrated significant correlations at month 2. A history of anxiety demonstrated stronger correlations to current

depression screening scores, with significant (p<.05) positive correlations at all timepoints on all instruments except BDI-II at month 2.

Influencing factors	BDI-II Baseline Month 2 Month 3	PHQ-9 Baseline Month 2 Month 3	PROMIS Depr. 8b Baseline Month 2 Month 3
Age	-.507* -.471 -.582*	-.660** -.499 -.607*	-.574* -.558* -.633*
Diabetes	.589* .514 .620*	.542* .575* .628*	.585* .590* .629*
History of Depression	.409 .244 .526*	.651* .394 .541*	.492* .404 .516*
History of Anxiety	.560* .446 .658*	.760** .584* .708*	.647* .599* .684*
Employment Baseline	-.171 .106 .197	.038 .341 .256	-.063 .350 .317
Employment Month 2	.106 .106 .255	.255 .341 .333	.222 .350 .391
Employment Month 3	-.032 .103 .095	.269 .270 .111	.144 .341 .144
Card. Rehab Month 2	-.589* -.556* -.651*	-.629* -.570* -.645*	-.775** -.571* -.684*
Card. Rehab Month 3	-.636* -.495 -.555*	-.672* -.449 -.580*	-.835** -.510 -.628*
ACS symptoms Baseline	.625* .444 .774**	.737** .528 .806**	.672** .569* .812**
ACS symptoms Month 2	.573* .680* .845**	.666* .665* .820**	.589* .694* .814**
ACS symptoms Month 3	.624* .638* .788**	.752* .566* .745**	.651* .683* .763**

*p<.05
**p<.005

Table IV-6: Correlations (R) between influencing factors, depression, and CHD

Cardiac Rehabilitation attendance, employment status, and acute coronary syndrome symptoms: Depression scores at all timepoints on all screening instruments demonstrated a significant (p<.05) negative correlation to cardiac rehabilitation (CR) attendance at month 2, and scores at baseline and month 3 (but not month 2) on all depression screening instruments had a significant (p<.05) negative correlation to cardiac rehabilitation (CR) attendance at month 3. Those whose depression screening scores were higher (meaning more depressive symptom burden) were less likely to attend CR. ACS symptoms demonstrated a significant (p<.05) positive correlation with depression screening scores on all instruments at all timepoints, though the 3-

month depression screening scores demonstrated the strongest correlation to ACS symptoms at any timepoint, reaching a significance of p<.005 on all three instruments. Employment status did not show any significant correlation to depression screening scores at any timepoint, contrary to previous literature.

Qualitative Data Findings

Three main themes were identified from the qualitative survey data: 1) health care system interactions, 2) social engagement, and 3) individual response to the health event. Women described experiences that negatively impacted their mood. First women felt angry or upset because of poor interactions with their physicians.

> 06: *"Dr. [X] hollers at me."*
> 06: *"… the cold wind makes my chest hurt and has for several years. Doctor [X] says to just live with it…"*

> 14: *"I think the very worst part of my heart problems is that doctors look at me like I'm a menopausal woman who doesn't know what I'm talking about. They make me feel fat and lazy because there are so many things I used to love to do that I can't do anymore. The very worst thing is being lumped in and called a drug seeker! I have better stuff at home - why the hell would I care about their drugs?"*

The health care system was also a source of distress for women related to insurance and lack of adequate coverage. Though she never states her frustration directly, one participant describes more than one instance where poor insurance coverage prevented her from getting the care she would otherwise have sought, such as secondary prevention.

> 06: *"Heart Dr. wants me to do heart rehab exercise but I can't. My insurance won't pay."*

In another instance she experiences a frightening health-related episode and concludes,

> 06: *"No I didn't go to the doctor - it was Saturday and ER would have run a million dollars + tests and I have [name of insurance] that doesn't pay it all."*

Good relationships with care providers were also described that supported women's emotional well-being.

> 09: *"Felt very relieved that the heart cath. went well because of my allergy to IV contrast dye. Can thank Dr. [X] for his protocol that prevented a severe reaction."*
> 09: *"I was so grateful for the excellent care I received in the hospital. I felt confident and comfortable with Dr. [X] and Dr. [Y] doing the heart cath. and the angioplasty."*

22: *"It is an encouragement to me to have the coronary artery disease diagnosed and a treatment plan begun. It was worrisome not to know for sure what was causing my extreme fatigue."*

The second theme, identified was social engagement. Every woman in the study wrote about how the level of social interaction affected her feelings. Several women noted that it was in the moments when they were alone that they felt most down. Women valued contact with family, but the a lack of family members close-by to created loneliness and isolation. Widowed women found the absence of their spouse to exacerbate feelings of loneliness and isolation.

06: *"I lost my husband in April, don't have any 'real' friends to do things with so when I come home from work its Blah."*

07: *"Emotions –evenings are hard, my [late] husband and I always watched TV together in the evenings. … [My sons] know evenings are my worst time, (alone) they call, and lift my spirits."*

14: *"I really miss my family and my best friend lives in [far away state] and the one sister I'm closest to lives in [far away state] so we don't see each other all I can do is text everybody."*

Social interaction with friends and family were described by women as "perking them up" and lifted their mood.

06: *"Got up in a good mood. 2 of my out of town friends called last night."*

11: *"I did notice that my feeling + mood did change. I feel tired if I start worrying why my children haven't called. …So, I took time off, called a friend and asked her if she can send her son to my house. He is nine years old. I have him help me put videos away or organize them. He tells me about school, we go to the store, take a walk at the park. And by the time I notice, [my worry] all goes away."*

09: *"Over the course of the last several days, I have heard from lots of my friends… It was great to hear from each and every one. Several, [names of friends], also came to visit. Friends are real blessing."*

22: *"Interacting with people usually perks me up and I forget the tiredness or get a boost of energy."*

The last theme was individual response to the health event. These emotional responses stemmed from women's perceptions of their own health and whether it had significantly changed. Changes were often described in terms of emotional responses to somatic and cognitive symptoms. Disappointment was expressed over experiencing unexpected fatigue following their cardiac event.

22: *"I think I expected a significant improvement in my energy level after the stent was put in place. While the shortness of breath has improved, I still feel the fatigue and this*

makes me consider the likelihood that I may not experience a return to full energy and motivation."

06: *"Everyone says 'Oh should feel better now.' I didn't feel bad before but now I seem to have fatigue more – a lot more."*

Another participant lamented her loss of physical function.

14: *"...there are so many things I used to love to do that I can't do anymore."*

14: *"I can't walk very far or very fast because of my heart and my hips"*

More than one participant expressed anhedonia and problems with concentration or focus that then led to depressed mood.

07: *"I'm feeling more depressed than usual. I don't enjoy things like I used to."*

22: *"I don't care about anything" is the best way I can describe the mood and I would say it has been significant."*

22: *"I feel like my brain is wandering and I am having trouble with focus. Also, I feel very fatigued and simply don't want to do anything focused."*

Feeling "down", self-dislike, and crying were also described.

14: *"I don't look in the mirror anymore. I don't care for my body as much now."*

14: *"I'm so used to feeling down I guess I don't notice things as much."*

06: *"I cry a lot – lonesome (?), Sad (?) don't know –teary as I write now"*

These experiences were not universal, however. Some participants felt that their cardiac event did not have a significant impact on their emotions and denied any somatic or cognitive symptoms.

09: *"My general feelings remain positive with no depression at all."*

11: *"I haven't lost interest in doing activities, going places, and seeing people. I don't blame my mood or feelings on my heart disease. I blame them on situations or things that occur."*

Mixed Methods Results

The purpose of conducting a mixed-methods analysis was to compare the qualitative and quantitative data, looking for similarities and differences. Of particular interest was whether women who met cut-off scores on depression screening tools provided substantively different responses to women who did not. At baseline, four of the six women who provided qualitative survey data met cut-off scores on at least one of the depression screening instruments. At month 2, two of the three women met cut-off scores, and at month 3, one of the three women met cut-off scores.

Findings of the mixed methods analysis are summarized in Table IV-7. The theme health care system interactions demonstrated a clear pattern based on depression screening scores. Participants who scored below cut-off on depression screening instruments had positive interactions with the health care system, and those whose depression screening scores were above cut-offs had negative experiences with the health care system.

These results did not hold regarding social engagement. Women universally agreed that social engagement lifted their mood, and that the times they were alone were more difficult emotionally. The difference between women who did or did not meet cut-off criteria in this category appeared to be two-fold: 1) the woman's perceived availability of social contact, and 2) the woman's internal motivation to seek contact. Those who perceived less availability of social contact had higher depression screening sores. Those who had more internal motivation for seeking social contact had lower depression screening scores. One participant whose depression screening scores were above cut-off values wrote frequently about social engagements, but also frequently lamented about how alone she was. She did not write about seeking out contact. Other participants who did not meet cut-off criteria on depression screening instruments wrote about making themselves engage. One wrote, "I just have to get up and do something". Another stated, "I tend to push through it…".

Finally, the theme individual response to the health event demonstrated mixed results. Women who denied changes in their feelings due to the change in their health status all scored below cut-off on depression screening. However, those who did report changes in feelings after their cardiac event had depression screening scores both above and below cut-off values and expressed experiencing both somatic and cognitive symptoms in their qualitative surveys.

	Theme	Depression score ≥ or < cutoff	Supporting qualitative data
1	health care	< cutoff	• "Felt very relieved that the heart cath went well because of

	system-level interaction		my allergy to IV contrast dye. Can think Dr. [X] for his protocol that prevented a severe reaction." • "It is an encouragement to me to have the coronary artery disease diagnosed and a treatment plan begun. It was worrisome not to know for sure what was causing my extreme fatigue." • "I was so grateful for the excellent care are received in the hospital. I felt confident and comfortable with Dr. [X] and Dr. [Y] doing the heart cath and the angioplasty."
		≥ cutoff	• "I think the very worst part of my heart problems is that doctors look at me like I'm a menopausal woman who doesn't know what I'm talking about. They make me feel fat and lazy because there are so many things I used to love to do that I can't do anymore. The very worst thing is being lumped in and called a drug seeker! I have better stuff at home - why the hell would I care about their drugs?" • "Dr. [X] hollers at me." • "No I didn't go to the doctor - it was Saturday and ER would have run a million dollars + tests and I have Humana that doesn't pay it all."
2	social-level engagement	< cutoff	• "Interacting with people usually perks me up and I forget the tiredness or get a boost of energy" • "Over the course of the last several days, I have heard from lots of my friends… It was great to hear from each and every one. Several, [names of friends], also came to visit. Friends are real blessing." • "I did notice that my feeling + mood did change. I feel tired if I start worrying why my children haven't called. …So, I took time off, called a friend and asked her if she can send her son to my house. He is nine years old. I have him help me put videos away or organize them. He tells me about school, we go to the store, take a walk at the park. And by the time I notice, [my worry] all goes away."
		≥ cutoff	• "I'm alone except for work. Sometimes the neighbor brings food but not often. I go to church but nobody there checks on me. Guess that's why I work - get out and see people." • "Wally & I drove to Paxton to eat turkey dinner. He said I needed to get outta town and it was nice." • "I really miss my family and my best friend lives in New York and the one sister I'm closest to lives in Ohio so we don't see each other all I can do is text everybody." • "I've been feeling very down lately...I feel like [my husband] doesn't really care about my heart anymore. I do what I can but he just doesn't get it. … He thinks this is just a game I'm playing for attention. He's also refused to take me for counseling or cardiac rehab."

3	individual-level response to the health event	< cutoff Unchanged	• "My general feelings remain positive with no depression at all." • "I haven't lost interest in doing activities, going places, and seeing people. I don't blame my mood or feelings on my heart disease. I blame them on situations or things that occur."
		< cutoff Changed somatic	• "I think I expected a significant improvement in my energy level after the stent was put in place. While the shortness of breath has improved, I still feel the fatigue and this makes me consider the likelihood that I may not experience a return to full energy and motivation."
		cognitive	• "I'm feeling more depressed than usual. I don't enjoy things like I used to." • "I don't care about anything" is the best way I can describe the mood…" • "I feel like my brain is wandering and I am having trouble with focus. Also, I feel very fatigued and simply don't want to do anything focused."
		≥ cutoff somatic	• "Everyone says 'Oh should feel better now.' I didn't feel bad before but now I seem to have fatigue more – a lot more." • "I can't walk very far because of my heart and my hips"
		cognitive	• "I've been eating way too much to try and fill the hole I feel inside." • "I cry a lot – lonesome (?), Sad (?) don't know –teary as I write now." • "I worry a lot about the future" • "I'm so used to feeling down I guess I don't notice things as much." • "I don't look in the mirror anymore. I don't care for my body as much now."

Table IV-7: Mixed Methods results

Discussion

This study provided important information about the feasibility of the utilized recruitment strategies, retention strategies, and the use of qualitative surveys for qualitative data collection, and adds important detail to our understanding of depressive symptoms in women with CHD. When a future study is undertaken, a dedicated study recruiter will need to

be identified and available on-site for participant recruitment. Anticipation of a 20-30% attrition rate would be a more reasonable assumption given these initial results. Attrition after baseline did not seem to improve with phone calls, but did with written reminders to return surveys. Therefore, a plan to send written reminders to those who have not returned data may be a good strategy to minimize attrition. The use of REDCap as a means of data collection was not a significant improvement over paper in this population, though no missing data occurred with use of REDCap. Continued use of both methods depending on participant preference appears to be a reasonable strategy. Length of time to complete surveys was actually quite short, demonstrating minimal participant burden.

These authors would make several changes to the approach used with qualitative surveys as a method of qualitative data. First, more open-ended survey questions would be beneficial so that women would feel more at liberty to write what came to mind about their emotional experiences. Next, iterative revisions to the survey at each timepoint would help to ensure that the desired information was being generated. Finally, the importance of following through with qualitative surveys if the participant indicated they would participate should be emphasized during the consenting process, perhaps attached to a larger incentive for the participant given the poor return rate for qualitative surveys despite stated interest. The costs and benefits of doing serial interviews with select participants should be weighed against this less time-consuming but also less controllable (and, at least in this feasibility study, less reliable) method of data collection.

The depressive screening instrument data from this study demonstrated prevalence rates similar to previous studies. The average prevalence of depressive symptoms at baseline in this study (30%) was slightly lower than the 36% found during hospitalization but slightly higher than the 28% found at 2-3 weeks post-discharge in Buckland, Pozehl, & Yates's (2019)

systematic review of longitudinal literature on depressive symptoms in women with CHD. The review found an average prevalence of 27% at 1 month, similar to the prevalence found in this study at 2 months (26%). The 3-month prevalence in this study (25%) is far higher than the 12% prevalence found at 4 months in the review (though this timepoint was represented by only 1 study).

A more granular examination of individual instruments yielded unexpected findings: the BDI-II and PROMIS Depression 8b yielded more similar results than the BDI-II and PHQ-9, despite the PROMIS not including somatic symptoms. This is in contrast to the finding of lower prevalence among instrument which did not contain somatic symptoms in Buckland, Pozehl, & Yates' (2019) review.

Some authors have argued that including somatic symptoms on depression screening instruments confuses the clinical picture and makes correct diagnosis more difficult (DeVon, personal communication, 2014; (Snaith & Zigmond, 1986). Others point to these symptoms as indicators of potential worse outcomes in CHD patients (de Miranda Azevedo, Roest, Hoen, & de Jonge, 2014) or as a means of deciphering the underlying CHD from depression (McGuire, Eastwood, Hays, Macabasco-O'Connell, & Doering, 2014). Given the performance of the PROMIS Depression 8b in this study, this instrument may provide measures similar to somatic item-containing instruments. However, because of such small numbers of study participants this may be more a reflection of a small sample than actual meaningful differences. A repeated evaluation of these same measures in a larger sample size is needed.

The differences in depressive symptoms scores over time did not reach statistical significance in this study, again likely due to the small sample size. However, severity of overall depressive symptoms in this sample yielded an interesting trend. There was a trend toward symptom improvement between baseline and month 2, with a worsening in symptoms at

month 3 on two of the three instruments (PHQ-9 and PROMIS). This same trend was reflected in the measure of distress as well. Even if the 3-month data from those who did not respond at month 2 are removed, the mean scores on PHQ-9 and PROMIS remained higher at month 3 than month 2. Interestingly, this trend seemed to reflect the changes in somatic depressive symptoms but not cognitive symptoms, which continued to decrease across all time points. Somatic symptom scores were higher than cognitive scores in this study, supporting the idea that somatic symptoms in women are of particular importance. These differences and depressive symptom trends should be interpreted with caution and would need to be validated in a larger sample.

The significant overlap between the somatic symptoms of sleep disturbance and fatigue was examined in this feasibility study. This preliminary examination of these symptoms demonstrated that there was a significant correlation between the depressive screening scores and both fatigue and sleep. This is consistent with previous findings (Doering & Eastwood, 2011; Frazier et al., 2012; Sanner, Frazier, & Udtha, 2013). Though not a specific study aim, individual scale analysis showed that the items with the highest mean scores on the BDI-II and PHQ-9 in this study were *somatic* symptoms: sleep changes, fatigue & loss of energy, appetite changes, and loss of interest in sex. The only cognitive symptom with a similarly high mean score was anhedonia. Changes in thinking regarding depression have led some to recommend more focus be placed on individual symptoms versus sum scores: individual symptoms may be more reflective of underlying biology and may also affect the degree of impairment of the individual (Fried & Nesse, 2015). A recent study by Carney et al. (2018) examining residual depressive symptoms in the CHD population after treatment with 6-12 sessions of individual cognitive behavior therapy (CBT) found that loss of energy (69.1% of participants) and fatigue (55.6% of participants) were the most commonly cited residual symptoms. The third most common, and

only other symptom to affect >50% of participants post-treatment, was anhedonia (51.6% of participants). Thus, the feasibility study findings appear to be consistent with other study findings, but they are also concerning since these women appear to be experiencing the symptoms that are most resistant to treatment (Carney et al., 2018).

A significant though less robust correlation between ACS and sleep disturbance and fatigue was also found. These correlations support those found in previous literature on physical symptoms in CHD (Kohlmann et al, 2013). However, fatigue is a component of the ACS symptom checklist, so its measurement with this instrument may be redundant (DeVon et al, 2014). For this reason, a different measure for CHD such as the Duke Coronary Artery Disease Index (Mark, Nelson, Califf et al., 1994) or a biomarker risk score (Ghasemzedah et al., 2017) may be a better choice. If this component of the study were to be repeated in the future study, a different measure for CHD would likely need to be identified.

Several factors have been found in prior research to influence the development of depressive symptoms in CHD patients. The preliminary results from this study demonstrated very robust negative correlations between depression scores and participant age. Consistent with prior research, depression appears to be worse in women who develop CHD at a younger age (Mallik et al., 2006; Sanner et al., 2013). In this study, the average age of women who met cut-off criteria for depression on the screening instruments was nearly 20 years younger than those who did not. At age 46 (the mean age of the younger women in this study), women are more likely to still be working, may still have children at home, may be caring for grandchildren and/or be caring for aging parents. A significant change in health status may be quite disruptive to these women's' roles and responsibilities, decreasing their ability to provide both tangible and emotional support to their families. A recent study looking at perceived stress post MI in young and middle-aged women compared to men found that women had higher stress levels

initially and over the next 12 months compared to men (Xu et al., 2017). Shah et al.'s (2014) study examining the association of depression with CHD and adverse cardiac events found a correlation between depression and CHD and risk of death in women age ≤ 55. These findings suggest that not only are younger women with CHD struggling, but their lives may be at risk if they develop clinically significant depression.

The results from this study also demonstrated very robust positive correlation between depression scores and diabetes. This is also consistent with previous research (Murphy et al., 2008; Pajak et al., 2013). The correlation between diabetes and depression, even without the presence of CHD, has been found to be significant (Kanapathy & Bogle, 2019). CHD co-morbidity with diabetes may be more depressogenic due to the difficulty of managing diabetes and the mental burden of having two significant chronic medical conditions. The combination of diabetes, depression, and CHD also puts women at even greater risk of poor outcomes than diabetes and depression alone (Pan et al., 2011). Research exploring a possible common root cause for both CHD and diabetes has been a topic of interest, leading to studies of genetic overlap (Amare, Schubert, Klingler-Hoffmann, Cohen-Woods, & Baune, 2017) as well as development of systems biological models (Stapelberg, Neumann, Shum, McConnell, & Hamilton-Craig, 2015). Women experiencing comorbidity with diabetes and CHD will need significant amounts of education, close follow-up, and both tangible and emotional support. The importance of exercise in improving diabetes, depression, and CHD needs to be clearly conveyed.

A history of anxiety also demonstrated a significant correlation to depression scores on all screening instruments at all timepoints except BDI-II at month 2. Prior research has found comorbidity of depression and anxiety to be common, particularly in women, and this appears to be true in the CHD population as well (Sundel, Stain-Mahngren, Andersson, Aberg-Wistedt, &

Schenck-Gustafsson, 2007; van Montfort, Denollet, Vermunt, Widdershoven, & Kupper, 2017). Prior studies have also shown a history of anxiety to be a significant predictor of subsequent depression in CHD patients (Murphy et al., 2014; Schrader, Cheok, Hordacre, & Marker, 2006). Interestingly, this feasibility study demonstrated a stronger association between a history of anxiety and current depression than a history of depression and current depression (though both demonstrated significance at more than one timepoint). This may be a reflection of small participant numbers, and more participants with a history of anxiety than depression in this study. A recent scoping review of risk factors for depression in individuals with CHD found a history of depression to be a stronger predictor of subsequent depression than a history of anxiety (Greenman et al., 2018). Given the small sample size in this study, results should be treated as preliminary and interpreted with caution.

This study found a strong correlation between depressive symptom scores and attendance at cardiac rehabilitation, with women who had higher depression scores attending cardiac rehabilitation less than those who had lower scores. This is consistent with prior literature showing that women with greater depressive symptom burden are less likely to complete cardiac rehabilitation (Sanderson & Bittner, 2005). In a systematic review of studies examining the effects of exercise on depression in CHD patients, exercise has demonstrated improvement in depression both in the short and long term in those with increased levels of depression (Verschueren et al., 2018). Even in women with microvascular disease, a relatively recently discovered and still poorly understood condition more often affecting women than men, exercise appears to improve quality of life (Szot, Zając, Kostkiewicz, Owoc, & Bojar, 2015). This underscores the importance of screening for depressive symptoms prior to discharge so that women who demonstrate elevated symptoms receive targeted emphasis on the benefits of attendance for both overall health and improved mood.

No significant correlation was noted between depression and employment status in this study. This was an unexpected finding. A recent meta-analysis of observational studies examining risk factors for post-ACS depression found that “housewife status” was a risk factor for developing depression whereas being employed was protective (Mei-zhen et al., 2019). This lack of correlation may be related to the way this question was posed in the survey. Women were asked if they had held a steady job in the past 6 months – “yes” or “no/retired”. Because those who are not working by choice (retired) may feel quite different from those who are involuntarily unemployed, this answer choice may have masked the negative feelings of those who were unemployed but desired to work. A future study will need to change wording to ensure that responses separate those who are unemployed by choice from those who are not.

Depressive symptom scores also correlated with ACS symptoms in this study. Angina in particular has been associated with higher depressive symptom burden in prior studies (Jespersen, Abildstrom, Hvelplund, & Prescott, 2013; Sundel et al., 2007). A meta-analysis of studies across 31 countries demonstrated that women were more likely to experience angina than men (Hemingway et al., 2008). Angina appears to be a more significant problem in those who do not have “classic” coronary artery disease which is amenable to intervention such as stenting or bypass (Jespersen, Abildstrom, Hvelplund, & Prescott, 2013). Because non-obstructive disease is more common in women (Pasupathy, Tavella, & Beltrame, 2016), women appear to be at higher risk of developing associated depression. Evidence-based therapies for people who experience cardiac ischemia without obstruction (INOCA) are just evolving, and the Cardiovascular Disease in Women Committee of the American College of Cardiology have developed an agenda to advance this area (Bairey Merz, Pepine, Walsh, & Fleg, 2017). Follow-up visits need to include assessment of ongoing ACS symptoms to identify women who may be at greater risk of developing depressive symptoms.

Interactions with the health care system are unavoidable for those who have a chronic illness. Relationships with care providers may either encourage or discourage women from successfully managing their health. Likewise, financial concerns and insurance coverage issues may prevent women from following through with important secondary risk reduction such as cardiac rehabilitation. Social isolation, particularly for women who have lost their spouses or who do not have family close by, may have a significant negative impact on women's mental health. Isolation may be exacerbated if they have experienced a decline in physical health as a result of their cardiac event. Conversely, interactions with friends and family appear to have a very positive affect on mental health. Assessing women's social support following a cardiac event may be important for determining risk for poor mental health. Finally, women had varied responses to their health event. Some appeared to feel as if their health was largely unchanged after their cardiac event. Other women who experienced somatic and/or cognitive symptoms following their cardiac event seemed to feel that their cardiac event signalled a significant change in their health. Cultivating a positive relationship with these women will help elicit these responses and significantly aid in individualizing care.

There does appear to be a relationship between increased depressive symptom burden and a negative relationship with the health care system, poor perceived social support, and a perception of changed health status following the cardiac event in this population. While it is unclear if the depressive symptoms caused these issues or were the result of these issues, previous research is clear in regards to increased depressive symptom burden leading to worse health outcomes. Unfortunately, prior research attempting to modify perceived social support and depression has not yielded significant improvements in morbidity and mortality. The landmark ENRICHD study, which examined the effects of treatment for low perceived social support (LPSS) and depression in 2,481 individuals with an acute MI randomized to usual care or

treatment with cognitive behavioural therapy found improvements in psychosocial outcomes but no significant difference in “event-free survival” after an average follow-up period of 29 months (Berkman et al., 2003). Since that time, other studies have explored peer support interventions (Colella & King-Shier, 2018), stress management via group sessions (M. Blom et al., 2009), and online community building to increase risk-modifying behaviour (Richardson et al., 2010), with minimal success. Other researchers have looked at the possible effects of depressive symptom clusters on adherence outcomes (Versteeg, van Montfort, Denollet, & Kupper, 2016) and the relationships between social strain, social support, quantity of social ties and multi-system risk (via allostatic load) (Seeman, Gruenewald, Cohen, Williams, & Matthews, 2014). The research community has yet to discover scalable interventions which improve depressive symptoms, perceived social support, *and* cardiovascular outcomes.

Strengths and Limitations

One of the strengths of this study is recruitment of women from three different types of institutions - a large urban public hospital, a large urban private hospital, and a smaller regional hospital – providing a wide representation of women despite its small size. This study adds needed granular details regarding depressive experiences of women with CHD over time to the existing literature. It also provides a preliminary assessment of one of the PROMIS Depression short form tools in the CHD population. The mixed methods design produced qualitative data showing that women with higher depressive symptom scores report different experiences post cardiac event than women who experience fewer depressive symptoms.

There were several limitations to this study. The small sample size limited the statistical analyses that were possible to perform, particularly estimating an effect size for influence of CHD and depression on two common overlapping somatic symptoms. Poor uptake of the qualitative survey limited the available qualitative data available for analysis. The study did not

assess who was and was not on antidepressant medications and/or undergoing counselling for depression at the start and during the study. This may have influenced outcomes. The grouping of retired and unemployed women together may be responsible for the lack of correlation between depression scores and employment, as those who are unemployed by choice may feel very differently about their status than those who are not working because they are not able.

Conclusions and Future Recommendations

These study findings suggest that the PROMIS Depression 8b may be an excellent choice of instrument for those who have significant concerns about measuring somatic symptoms and wish to choose an instrument that does not contain somatic items since it demonstrated prevalence similar to BDI-II. Performance of the PROMIS Depression 8b in the female CHD patient population would benefit from further examination in a larger sample. A dedicated study examining ROC curves for sensitivity and specificity of the PROMIS Depression 8b versus other measures containing somatic symptoms compared to diagnostic interview findings in this population would also be beneficial.

The finding that overall mean depression scores as well as distress scores trended in the same direction as the somatic symptom scores supports the centrality of somatic symptoms in women's experience of depressive symptoms but also suggest that women in particular may be at increased risk of having residual depressive symptoms, even if they receive appropriate treatment (Carney et al., 2018). A multi-modality approach may be required to alleviate these somatic symptoms given the difficulty in treating them to remission with CBT alone (Carney, 2018). The study findings also suggest that ongoing assessment of depressive symptoms in women in this population is important since depressive symptoms are associated with worse outcomes (Lichtman et al., 2014). The role of somatic depressive symptoms in this population needs to continue to be explored. Analysis of individual depressive symptoms to elucidate

further which specific symptoms are most often reported, by whom, and which remain unresolved following treatment will aid in development of approaches which can target these symptoms, preventing persistent depression and potential worse outcomes.

This and other prior research have demonstrated that younger women with CHD experience much more depression than older women. Studies which elucidate younger women's depression risk factors are needed to determine which are amenable to intervention. Women with comorbid diabetes are another group who clearly demonstrated more depression in this study than women who do not have diabetes. The co-occurrence of depression in multi-morbid individuals is not a unique finding to this study. Because diabetes, depression, and CHD all respond positively to physical activity, studies comparing different strategies already shown to promote physical activity in this population should be undertaken.

The strong correlation between baseline depressive symptom scores and attendance at cardiac rehabilitation has implications for post-discharge care of these cardiac patients. This relationship suggests that women who are depressed early on after their cardiac event may not be as attuned to care needs later on in the recovery period. The importance of attending cardiac rehabilitation needs to be emphasized to women who screen positive for elevated depressive symptoms either during their hospital stay or at their initial follow-up appointment since these women appear to be at significant risk of non-attendance.

Intervention studies which address depressive symptoms and low perceived social support in women with CHD that also improve cardiovascular outcomes and are scalable continue to be needed. Finally, dedicated efforts to include women and men in equal numbers in CHD studies and data analysis by gender in all manuscripts from studies which include both men and women participants need to be priorities in CHD research moving forward if we are to improve outcomes in women.

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Chapter V. Conclusion

Discussion

Concept Analysis

The literature on depressive symptoms in women with CHD, though significantly more substantive since the mid-1990s, continued to demonstrate some important gaps. The concept of depression in women with CHD itself was problematic, and information regarding what happens to depressive symptoms in women over time was also lacking. Chapter two of this dissertation provided a concept analysis of depression in women with CHD, following the steps laid out by Walker and Avant (Walker & Avant, 2011). The mismatch between the actual concept and the operational definition of the concept as represented by the depression screening instruments was discussed. Key attributes of depression in women with CHD were identified, along with actual and potential antecedents. Finally, the importance of applying these findings to research and practice was discussed.

Literature Review

Chapter three of the dissertation provided a systematic review of the longitudinal literature on depressive symptoms in women with CHD. Following PRISMA guidelines, twenty articles met inclusion criteria for this systematic review. The key findings from this review were that 35.75% of women experience depression at the time of CHD diagnosis but most appear to improve over the first 3-6 months. However, this may be a reflection of few studies extending beyond 6 months. Women also experience more depression than men both at the time of diagnosis and across time. The instrument used to measure depressive symptoms had a significant impact on findings, with instruments measuring somatic symptoms yielding significantly higher prevalence than those that did not (with the exception of results in the coronary artery bypass graft [CABG] population). The review reinforced that women continue to

be under-represented in CHD studies and lack of data analysis by gender also continues to be a gap.

Dissertation Study

Chapter four of the dissertation reported results of the feasibility study examining depressive symptoms in women with CHD over time. The aims of this study included a) evaluating the feasibly of enrollment and data collection strategies used in this study, b) evaluating the quantitative data for preliminary trends, and c) evaluating the qualitative data collection method and the data generated via this method.

Feasibility Aims

The feasibility aims of this study included evaluating enrollment (recruitment strategies and efficiency, attrition, problems and solutions) and data collection (use of REDCap vs paper, instruments reliability, time required, missing data). Recruitment was problematic, due in part to issues of ethical access to the population. A successful strategy was finally discovered which minimized time demands for those identifying potential participants, but also required the PI to be available at the bedside. Prior research has demonstrated that recruitment for research is a significant problem. A recent review of phases 2 and 3 intervention clinical trials that ended in 2011 and were registered with the National Library of Medicine clinical trial registry found that 19% - nearly 1 in 5 - “either terminated for failed accrual or completed with less than 85% expected enrolment [sic]” (Carlisle, Kimmelman, Ramsay, & MacKinnon, 2014, p. 77). Very little data is available on nursing research specifically. An article by Badger and Werrett (2005) out of the UK examining nursing research published in 2002 in one of three journals (Journal of Advanced Nursing, Journal of Clinical Nursing, or International Journal of Nursing Studies) found mean “response rates” of 75%, 74% and 62% for quantitative, qualitative, and mixed methods

articles respectively. This author's experience and the statistics regarding recruitment support and highlight the importance of feasibility work prior to beginning a fully-powered study.

Attrition was also a problem which was exacerbated by the small number of participants. Month two, the timepoint with the fewest participants (13), represented a 28% attrition rate from the 18 who returned baseline surveys (or 41% from the 22 who signed consent forms) despite the time burden for survey completion being minimal (ave. <20 minutes). According to the literature, the average rate of attrition across all types of clinical trials is 30% (Lopienski, 2015). Longitudinal studies report attrition rates between 30-70%, with longer studies generally experiencing greater attrition (Gustavson, von Soest, Karevold, & Røysamb, 2012). From this perspective a 28% attrition rate is not unusual, though with a small number of study participants results are much more likely to be impacted. The qualitative portion of the study demonstrated higher attrition, with only 50% of the original journaling participants at baseline still submitting journal entries at month three. SmithBattle and colleagues recently performed a methodological review of 77 qualitative longitudinal nursing research studies which found that of the 44 studies that reported sample sizes at both the start and end of the study, 20% experienced >50% attrition (SmithBattle, Lorenz, Reangsing, Palmer, & Pitroff, 2018). Numerous authors have explored methods to improve recruitment and minimize attrition, including some which were employed in this study (such as phone calls to participants, mailing reminders, minimizing study burden, incentive payments), with noted varying degrees of success (Aitken, Gallagher, & Madronio, 2003; Treweek et al., 2013). However, it does appear that this author's challenges with recruitment from these particular institutions is not unique, as demonstrated by a study by Dr. Weierback, a PhD Neifdelt Research Fellow at the University of Nebraska Medical Center (2010), where "during 12 months

of recruitment, 28 individuals consented to participate in the study, and 20 were interviewed…"(p. 46).

Quantitative Data

Evaluation of the quantitative data for preliminary trends focused on four specific areas of exploration: prevalence data from three different measurement instruments; changes over time in depressive symptom dimensions; the influence of CHD and depression on three overlapping somatic symptoms; and the influence of pre-identified factors on depressive symptom burden. Findings regarding prevalence were similar to prior research findings at baseline with a decrease at month two, but remained higher at month three than prevalence rates in prior studies (Buckland, Pozehl, & Yates, 2019). The role of screening for depression in the CHD population has been debated ever since the American Heart Association recommended performing screenings in 2008 (Lichtman et al., 2008), with several authors arguing that it does not improve outcomes (Thombs et al., 2013; Ziegelstein, Thombs, Coyne, & de Jonge, 2009) and others arguing that it is financially feasible and does improve depression, which has other positive ripple effects (Ski et al., 2012; Sowden, Mastromauro, Januzzi, Fricchione, & Huffman, 2010). The results of this study suggest that perhaps screening in certain CHD sub-populations may be beneficial.

The comparison of instruments in this feasibility study yielded valuable new information. The PROMIS Depression 8b, a relatively new instrument that has not yet been used extensively in the cardiac population and does not contain somatic symptoms, was compared to the BDI-II and PHQ-9 which both contain somatic symptoms. It was expected that the PROMIS would yield significantly lower prevalence of depression based on previous findings in other instruments that do not contain somatic symptoms (Buckland et al., 2019). However, the prevalence for this instrument was comparable to BDI-II and PHQ-9 – an unexpected finding.

Some authors have argued that including somatic symptoms on depression screening instruments confuses the clinical picture and makes correct diagnosis more difficult (DeVon, personal communication, 2014; (Snaith & Zigmond, 1986). Others point to these symptoms as indicators of potential worse outcomes in CHD patients (de Miranda Azevedo, Roest, Hoen, & de Jonge, 2014) or as a means of deciphering the underlying CHD from depression (McGuire, Eastwood, Hays, Macabasco-O'Connell, & Doering, 2014). Given the performance of the PROMIS Depression 8b in this study, this instrument may provide measures similar to somatic item-containing instruments.

Changes over time in depressive symptom dimensions as defined by Lenz et al. in their Theory of Unpleasant Symptoms (timing, severity, symptom distress, and quality – here, somatic vs cognitive) showed an interesting trend. Mean scores on the depressive symptom instruments (severity) and scores on the Subjective Units of Distress scale (distress) demonstrated a decrease between baseline and month 2 but then showed an increase between months 2 and three, though the increase in scores were not statistically significant. This pattern was also noted in changes in somatic depressive symptom scores but not in cognitive symptom scores. Prior studies have found varying patterns of change in women's symptom severity over time, though most appear to improve (Buckland et al., 2019). The fact that overall mean depression scores as well as symptom distress scores followed the same pattern as somatic symptom scores supports the centrality of somatic symptoms in women's experience of depressive symptoms in this population.

This study proposed to examine the influence of CHD and depression on three overlapping somatic symptoms: sleep, fatigue, and GI symptoms. There was a very strong correlation between both depression scores and ACS scores (used as a proxy for CHD in this study), and sleep and fatigue. Though not a specific study aim, individual scale analysis showed

that the items with the highest mean scores on the BDI-II and PHQ-9 in this study were *somatic* symptoms: sleep changes, fatigue & loss of energy, appetite changes, and loss of interest in sex. The only cognitive symptom with a similarly high mean score was anhedonia. Changes in thinking regarding depression have led some to recommend more focus be placed on individual symptoms versus sum scores: individual symptoms may be more reflective of underlying biology and may also affect the degree of impairment of the individual (Fried & Nesse, 2015). A recent study by Carney et al. (2018) examining residual depressive symptoms in the CHD population after treatment with 6-12 sessions of individual cognitive behavior therapy (CBT) found that loss of energy (69.1% of participants) and fatigue (55.6% of participants) were the most commonly cited residual symptoms. The third most common, and only other symptom to affect >50% of participants post-treatment, was anhedonia (51.6% of participants). Thus, the feasibility study findings appear to be consistent with other study findings, but they are also concerning since these women appear to be experiencing the symptoms that are most resistant to treatment. Weaker correlations were found between depression scores and GI symptom scores over time, though there was a robust correlation between GI symptom presence at baseline and depression screening scores across time. More consistent correlations were noted between GI symptom scores and the corresponding ACS scores across time. The generally weaker correlations between GI symptoms and depression screening scores may be a result of the poor reliability of the instrument in this study. It may also be a reflection of symptoms on the scale not associated with depression, such as lack of taste and nausea. While the ACS symptom checklist found statistically significant correlations with the three overlapping somatic symptoms (fatigue, sleep changes, and GI symptoms), this may in fact be a reflection of measurement redundancy since the ACS symptom checklist contains items related to both fatigue and GI symptoms.

The influence of pre-identified factors on depressive symptom burden was also examined in this study: specifically, the influence of age, diabetes, a history of depression and/or anxiety, attendance at cardiac rehabilitation, ACS symptoms, and employment status. There was a strong correlation between age and depressive symptom burden in this study.

Women whose scores on the depression screening instruments met cutoff criteria had a mean age of 46.25, versus a mean age of 69.38 for those who did not. At age 46, women are more likely to still be working, may still have children at home, may be caring for grandchildren and/or be caring for aging parents. A significant change in health status may be quite disruptive to these women's' roles and responsibilities, decreasing their ability to provide both tangible and emotional support to their families. A recent study looking at perceived stress post MI in young and middle-aged women compared to men found that women had higher stress levels initially and over the next 12 months compared to men (Xu et al., 2017). Shah et al.'s (2014) study examining the association of depression with CHD and adverse cardiac events found a correlation between depression and CHD and risk of death in women age ≤ 55. These findings suggest that not only are younger women with CHD struggling, but their lives may be at risk if they develop clinically significant depression.

This feasibility study also found a very strong correlation between depression and a history of diabetes. The correlation between diabetes and depression, even without the presence of CHD, has been found to be significant (Kanapathy & Bogle, 2019). The combination of diabetes, depression, and CHD puts women at even greater risk of poor outcomes than diabetes and depression alone (Pan et al., 2011). Research exploring a possible common root cause for both CHD and diabetes has been a topic of interest, leading to studies of genetic overlap (Amare, Schubert, Klingler-Hoffmann, Cohen-Woods, & Baune, 2017) as well as development of systems biological models (Stapelberg, Neumann, Shum, McConnell, & Hamilton-Craig, 2015). Women

experiencing comorbidity with diabetes and CHD will need significant amounts of education, close follow-up, and both tangible and emotional support. The importance of exercise in improving diabetes, depression, and CHD needs to be clearly conveyed. Cardiac rehabilitation, which has been shown to be effective in improving depressive symptoms as well as lowering cardiac risk (Rutledge, Redwine, Linke, & Mills, 2013) will be particularly important in this group of patients. Approaches such as behavioral activation, which has been delivered as a manualized intervention (Ekers, Richards, McMillan, Bland, & Gilbody, 2011; Pasterfield et al., 2014) as well as on-line (Spates, Kalata, Ozeki, Stanton, & Peters, 2013) may be a viable option to keep patients motivated following cardiac rehabilitation.

Current depressive symptoms were strongly associated with a history of anxiety in this study. Prior research has found comorbidity of depression and anxiety to be common, particularly in women, and this appears to be true in the CHD population as well (Sundel, Stain-Mahngren, Andersson, Aberg-Wistedt, & Schenck-Gustafsson, 2007; van Montfort, Denollet, Vermunt, Widdershoven, & Kupper, 2017). Prior studies have also shown a history of anxiety to be a significant predictor of subsequent depression in CHD patients (Murphy et al., 2014; Schrader, Cheok, Hordacre, & Marker, 2006). Interestingly, this feasibility study demonstrated a stronger association between a history of anxiety and current depression than a history of depression and current depression (though both demonstrated significance at more than one timepoint). This may be a reflection of small participant numbers, and more participants with a history of anxiety than depression in this study. A recent scoping review of risk factors for depression in individuals with CHD found a history of depression to be a stronger predictor of subsequent depression than a history of anxiety (Greenman et al., 2018).

This study found a strong correlation between depressive symptom scores and attendance at cardiac rehabilitation, with women who had higher depression scores attending

cardiac rehabilitation less than those who had lower scores. This is consistent with prior literature showing that women with greater depressive symptom burden are less likely to complete cardiac rehabilitation (Sanderson & Bittner, 2005). In a systematic review of studies examining the effects of exercise on depression in CHD patients, exercise has demonstrated improvement in depression both in the short and long term in those with increased levels of depression (Verschueren et al., 2018). Even in women with microvascular disease, a relatively recently discovered and still poorly understood condition more often affecting women than men, exercise appears to improve quality of life (Szot, Zając, Kostkiewicz, Owoc, & Bojar, 2015).

There was a strong correlation between depressive symptom scores and ACS scores in this study. ACS symptoms, particularly angina, have been associated with increased depressive symptom burden in CHD patients in general and women in particular (Jespersen, Abildstrom, Hvelplund, & Prescott, 2013; Sundel et al., 2007; Trivedi et al., 2015). A meta-analysis of studies across 31 countries demonstrated that women were more likely to experience angina than men (Hemingway et al., 2008). Angina appears to be a more significant problem in those who do not have “classic” coronary artery disease which is amenable to intervention such as stenting or bypass (Jespersen et al., 2013). Because non-obstructive disease is more common in women (Pasupathy, Tavella, & Beltrame, 2016), women appear to be at higher risk of developing associated depression. Evidence-based therapies for people who experience cardiac ischemia without obstruction (INOCA) are just evolving, and the Cardiovascular Disease in Women Committee of the American College of Cardiology have developed an agenda to advance this area (Bairey Merz, Pepine, Walsh, & Fleg, 2017)

No significant correlation was noted between depression and employment status in this study. This was an unexpected finding. A recent meta-analysis of observational studies examining risk factors for post-ACS depression found that “housewife status” was a risk factor

for developing depression whereas being employed was protective (Mei-zhen et al., 2019). This lack of correlation may be related to the way this question was posed in the survey. Women were asked if they had held a steady job in the past 6 months – "yes" or "no/retired". Because those who are not working by choice (retired) may feel quite different from those who are involuntarily unemployed, this answer choice may have masked the negative feelings of those who were unemployed but desired to work. A future study will need to change wording to ensure that responses separate those who are unemployed by choice from those who are not.

Qualitative Data

Unlike focus groups, individual interviews, or qualitative questions at the end of quantitative surveys, the use of "purely qualitative" survey as a means of collecting qualitative data has not been widely used in health care research (Terry & Braun, 2017, p. 17). Little guidance from the literature exists for qualitative survey as a means of data collection. In his paper on qualitative survey research, Jansen (2010) describes qualitative survey as "the study of diversity (not distribution) in a population" (section 2.0, para. 6). According to Jansen (2010) qualitative surveys may use either open-ended or pre-structured questions, and that "the qualitative-versus-quantitative nature of data is established in the analysis. It is not inherent ontology but analysis which determines whether a study is qualitative or quantitative" (section 2.1, para. 3). Terry and Braun (2017) view qualitative surveys as being suitable to answer questions about people's experiences, practices, views and perspectives.

Due to concerns about influencing participants because of the longitudinal nature of the study as well as the fact that objective data was also being collected at the same time, a method which would generate rich data while minimizing contact with study participants was sought. Qualitative survey was felt to be a good choice. However, given the longitudinal nature of this study and the three distinctive writing periods (as opposed to one single period of writing), the

study would have benefitted from iteratively revising the survey based on the previous survey content. Participation in the qualitative surveys in this study was poor. This may be due in part to the fact that the qualitative survey was optional in this study and the PI did not stress the importance of carrying through with the surveys if participants stated they were interested. More practical issues also arose, such as participants not being sure what to physically write "on" (a personal diary, ruled notebook paper, etc). Despite offering to have participants answer the survey in a word processing program and submit responses electronically, only one participant chose to use this method. While interesting and useful data was generated in this study, the use of qualitative survey as a means of qualitative data collection would need to be significantly improved if it were to be used in a future study and would certainly require a small pilot study of its own to ensure adequacy of adjustments.

Strengths and Limitations

One of the strengths of this study is recruitment of women from three different types of institutions - a large urban public hospital, a large urban private hospital, and a smaller regional hospital – providing a wide representation of women despite its small size. This study adds needed granular details regarding depressive experiences of women with CHD over time to the existing literature. It also provides a preliminary assessment of one of the PROMIS Depression short form tools in the CHD population. The mixed methods design produced qualitative data showing that women with higher depressive symptom scores report different experiences post cardiac event than women who experience fewer depressive symptoms.

There were several limitations to this study. The small sample size limited the statistical analyses that were possible to perform, particularly estimating an effect size for influence of CHD and depression on three common overlapping somatic symptoms. Poor uptake of the qualitative survey limited the available quantitative data available for analysis. The study did

not assess who was and was not on antidepressant medications and/or undergoing counseling for depression at the start and during the study. This may have influenced outcomes. The grouping of retired and unemployed women together may be responsible for the lack of correlation between depression scores and employment, as those who are unemployed by choice may feel very differently about their status than those who are not working because they are not able. Finally, the poor reliability of the GI symptom instrument is likely responsible for the lack of correlation between GI somatic symptom and depression scores. Alternative measures should be considered in future studies.

Conclusions and Future Recommendations

These study findings suggest that the PROMIS may be an excellent choice of instrument for those who have significant concerns about measuring somatic symptoms and wish to choose an instrument that does not contain somatic items since it demonstrated prevalence similar to BDI-II. Performance of the PROMIS Depression 8b in the female CHD patient population would benefit from further examination in a larger sample. A dedicated study examining ROC curves for sensitivity and specificity of the PROMIS Depression 8b versus other measures containing somatic symptoms compared to diagnostic interview findings in this population would also be beneficial.

The finding that overall mean depression scores as well as distress scores trended in the same direction as the somatic symptom scores supports the centrality of somatic symptoms in women's experience of depressive symptoms but also suggest that women in particular may be at increased risk of having residual depressive symptoms, even if they receive appropriate treatment (Carney et al., 2018). A multi-modality approach may be required to alleviate these somatic symptoms given the difficulty in treating them to remission with CBT alone (Carney, 2018). The study findings also suggest that ongoing assessment of depressive symptoms in

women in this population is important since depressive symptoms are associated with worse outcomes (Lichtman et al., 2014). The role of somatic depressive symptoms in this population needs to continue to be explored. Analysis of individual depressive symptoms to elucidate further which specific symptoms are most often reported, by whom, and which remain unresolved following treatment will aid in development of approaches which can target these symptoms, preventing persistent depression and potential worse outcomes.

This and other prior research have demonstrated that younger women experience much more depression than older women. Why this particular group of women is at elevated risk remains a question. Risk factors need to be elucidated to determine which are amenable to intervention. Women with comorbid diabetes are another group who clearly demonstrated more depression in this study than women who do not have diabetes. The co-occurrence of depression in multi-morbid individuals is not a unique finding to this study. Because diabetes, depression, and CHD all respond positively to physical activity, studies comparing different strategies already shown to promote physical activity in this population should be undertaken.

The strong correlation between baseline depressive symptom scores and attendance at cardiac rehabilitation has implications for post-discharge care of these cardiac patients. This relationship suggests that women who are depressed early on after their cardiac event may not be as attuned to care needs later on in the recovery period. The importance of attending cardiac rehabilitation needs to be emphasized to women who screen positive for elevated depressive symptoms either during their hospital stay or at their initial follow-up appointment since these women appear to be at significant risk of non-attendance.

Finally, dedicated efforts to include women and men in equal numbers in CHD studies and data analysis by gender in all manuscripts from studies which include both men and women

participants need to be priorities in CHD research moving forward if we are to improve outcomes in women.

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APPENDIX A: Longitudinal studies of depressive symptoms in women with CHD

Author & date	Study purpose	Study design	Sample	Depression scale/other	Results (% or average score ± SD)
1. Barth et al., 2009	Examine whether women & men benefit equally from outpatient CR[1] in reduction in psychological symptoms, & whether women show more impaired psychological health at baseline than men.	• Quasi-experimental, longitudinal Time-points: • Baseline: 2-4 weeks post acute event • Time 2: post-CR	441 patients: Women: 89 (20.2%) Men: 352 (79.8%) Inclusion: post acute coronary event, cardiac decomp., PCI[2], or heart surgery	• Anxiety & Depression: German version of HADS[3]	Baseline prevalence of HADS-D>7: 15% (no separation by gender) • Baseline depression (difference: p=0.29) ○ Women: 3.6 ± 3.0 ○ Men: 3.9 ± 3.5 • Depressive symptoms post CR (p=0.626) ○ Women: 3.1 ±3.2 ○ Men: 3.1 ± 3.1 ○ No age difference between men & women in this study (unusual)
Bogg et al., 2000	Assess the influence of gender on outcomes after a cardiac episode.	• Prospective longitudinal cohort study Time-points: • Baseline: 3-4 days post MI • Time 2: 1 month post MI • Time 3: 3 months post MI • Time 4: 6 months post MI	220 patients: Women: 51 (23%) Men: 169 (77%) Inclusion: MI within 4 days	• Depression: HADS	Baseline depression (nonsignificant) • Women: 4.7 ± 3.4 • Men: 4.0 ± 3.2 1 month post MI (p≥0.01; T=2.68) • Women: 5.6 ± 3.1 • Men: 4.4 ± 3.9 3 months: (p≥0.01; T=2.62)

[1] Cardiac rehabilitation
[2] Percutaneous coronary intervention
[3] Hospital Anxiety & Depression Scale

				of admit, age<75.		• Women: 5.9 ± 3.4 • Men: 3.9 ± 3.1 6 months (nonsignificant) • Women: 4.7 ± 3.0 • Men: 3.9 ± 3.5 Depression was a major predictor of physical quality of life.
2.	Brink et al., 2005	Detect changes in HRQOL over time, and predict HRQOL at 1 year based on measures at 1 week & 5 months post 1st-time MI.	• Longitudinal descriptive study Time-points: • Baseline: 1 week post MI • Time 2: 5 months • Time 3: 1 year	98 patients: Women: 33 (34%) Men: 65 (66%)	• Depression: HADS	Baseline depression (estimated, based on graphic) • Women: 2.4 • Men: 2.7 5 months • Women: 4.1 ± 3.2 • Men: 3.8 ± 3.8 12 months • Women: 2.8 ± 2.8 • Men: 3.4 ± 3.5 Statistically significant decrease in women between 5 months and 1 year ($p<0.01$) 13% of all respondents scored possible or likely depression 1 year after MI. No gender differences at 1 year post MI.
3.	Caulin-Glaser et al., 2007	Determine the effects of depressive symptoms & sex on completion rates in CR and, in CR completers, examine clinical	• Retrospective cohort analysis Time-points: • Baseline: 4-6 weeks post hospital discharge • Time 2: post-CR.	348 patients: Women: 100 (28.7%) Men: 248 (71.3%) Inclusion: Enrollment in	• Depressive symptoms: BDI-II[4] (Completion of CR: >7 weeks'	Baseline BDI-ll ≥14: • Women: 31% • Men: 14.5% 53 people/29 women (54.7%) did not complete CR. • 29 (54.7%) CR non-completers had BDI-II ≥14 at baseline. Pts with baseline BDI-ll ≥14 had greater symptom

[4] Beck Depression Inventory - ll

		outcomes.		a 12-wk CR program	participation of 12-week program)	reduction after CR vs. pts with baseline BDI-ll<14 • ≥14: pre-CR=20.6; post-CR=10.4 • <14: pre-CR=5.8; post-CR=3.5 No statistically significant difference between amount of change on BDI-II after CR between men & women
4.	Doering et al., 2006	Describe prevalence of clinical depression at 3 timepoints among women, comparing frequency of somatic & affective symptoms	• Longitudinal descriptive study Time-points: • Baseline measure: inpatient • Time 2: 2-4 weeks post discharge • Time 3: 6 months	75 women • 55 retained at 6 months Inclusion: 1st-time CABG[5]	• Depressive symptoms: DISH[6] • Hx depression	Baseline Depressed: 36% Time 2 Depressed: 16.3% Time 3 Depressed: 12.7% • Depressed women were younger (57 vs 64.2) • More of the depressed women had hx of depression vs those with no hx of depression (40.7% vs 18.8%) • Depressed women consistently had higher rates of fatigue, anhedonia, & dysphoria vs non-depressed women over the 6-month period.
5.	Duits et al., 1998	Examine variations over time in anxiety & depression in pts undergoing CABG	• Longitudinal descriptive study Time-points: • Time 1: 2 weeks pre-op • Time 2: 1 day pre-op • Time 3: 7 days post-op • Time 4: 6 months post-op	217 patients: Women: 41 (19%) Men: 176 (81%) Inclusion: elective CABG	• Depression: HADS	Time 1 • Women: 7.5 ± 4.7 • Men: 4.7 ± 3.7 Time 3 • Women: 5.4 ± 3.4 • Men: 4.9 ± 3.6 Time 4 • Women: 4.9 ± 4.0 • Men: 3.4 ± 3.5 Both significant time effect, & significant time modified by gender effects were noted.
6.	Grace et la., 2005	Examine the prevalence & course	• Longitudinal observational study	913 patients Women: 323	• Depression: BDI	BDI ≥10: Baseline :31.1%.

[5] Coronary artery bypass graft
[6] Diagnostic Interview & Structured Hamilton

		of depressive symptoms x 1 yr after ACS, & the effect of CR on this trajectory	Time-points: • Baseline: inpatient • Time 2: 6 months • Time 3: 1 year	(35%) Men: 590 (65%) Inclusion: MI[7] or UA[8]		6 months: 25.2% 12 months: 21.7% • Those with higher BDI scores at 6 months attended significantly fewer CR sessions than those with lower BDI scores (p=0.02). • Depressive symptoms improved for all, regardless of CR participation. • Younger participants were more depressed
7.	Grace et al., 2008	Prospectively assess changes in psychosocial health, comparing women who participated in CR with those who did not.	• Secondary analysis of prospective, controlled quasi-experimental design study Time-points: • Baseline (inpatient) • 18 months	157 women • 110 retained at 18 months Inclusion: ACS, PCI, or CABG.	• Anxiety & depressive symptoms: HADS	51 women (45.1%) participated in CR Baseline: (nonsignificant difference between groups) • CR: 4.6 ± 3.5 • Non-CR: 5.0 ± 2.8 18 months: • CR: 4.3 ± 3.7 • Non-CR: 4.1 ± 3.3 Women who did ***not*** participate in CR by 18 months had improvement in depressive symptoms**.**
8.	Gravely-Witte et al., 2007	Examine the impact of angina and cardiac hx on depression and HRQOL in CHD pts.	• Prospective longitudinal study Time-points: • Baseline: 45 days post-cardiac event • Time 2: 6 months after baseline	171 patients: Women: 27 (16%) Men: 147 (84%) @6 mo: 121 Women: 17 (14%) Men: 104 (86%)	• Depression: SCL-90	Baseline: • Women no prior CHD: 1.45 ± 0.17 • Men no prior CHD: 1.39 ± 0.14 • Women prior CHD: 1.51 ± 0.11 • Men prior CHD: 1.45 ± 0.13 6 months • Women no prior CHD: 1.39 ± 0.17 • Men no prior CHD: 1.34 ± 0.13 • Women prior CHD: 1.47 ± 0.11 • Men prior CHD: 1.44 ± 0.13 Cardiac hx not predictive of higher depression levels at

[7] Myocardial infarction
[8] Unstable angina

				Inclusion: MI, PCI, CABG; age<70.		baseline, but predictive at 6 months. Women had higher depression levels than men at baseline. Depression scores in pts with CHD hx remained stable, whereas pts with no cardiac hx had improvement.
9.	Gupta et al., 2007	To see if benefits from CR are maintained at 1 yr, & if there are any gender-specific differences.	• Longitudinal descriptive study Time-points: • Baseline: CR entry • Time 2: 6 months • Time 3: 1 year	533 patients. Women: 161 (30.2%) Men: 372 (69.8%) 244 at 1-yr • Women: 68 (28%) • Men: 176 (72.1%)) Inclusion: dx of CAD[9]	• Depression: BDI-II	Baseline • Women: 9.7 • Men: 9.29 CR completion • Women: 6.9 • Men: 5.4 1 year • Women: 7.3 • Men: 5.81 Both men & women showed significant improvement in depressive symptoms… • between baseline & end of CR, and • between baseline & 1 yr but *not* between end of CR & 1 yr.
10.	Hunt-Shanks et al., 2009	Examine 1) Autonomic anxiety, negative affect, & depression over a 2-year period in cardiac pts. 2) Whether gender moderated the exercise/ affective	• Longitudinal descriptive study Time-points: • Baseline: inpatient • Time 2: 6 months • Time 3: 12 months • Time 4: 24 months	801 patients Women: 197 (24.5%) Men: 604 (75.4%) Inclusion: Cardiac patients, but no unstable	• Depression & anxiety: HADS	HADS-D>7 Baseline: • Women: 27.9% • Men: 18.7% 6 months • Women: 20.6% • Men: 14.5% 12 months • Women: 19.2% • Men: 14.4% 24 months

[9] Coronary artery disease

		relationship 3) Whether changes in exercise mediated the gender/affective relationship		cardiac conditions		• Women: 19.2% • Men: 13.3% Women demonstrated more autonomic anxiety & depression than men across entire study Exercise did not mediate any gender/affective relation-ships No moderation by gender
11.	Josephson et al., 2006	Investigate gender differences in depressive symptoms among cardiac pts in CR.	• Retrospective analysis of prospectively collected longitudinal data Time-points: • Baseline: Pre-CR • Time 2: post-CR	402 patients Women: 113 (28%) Men: 289 (72%) Inclusion: Cardiac diagnosis	• Depressive symptoms: BDI	BDI≥10 Baseline: • Women: 36% • Men: 22% Baseline (mean score) • Women: 8.73 ± 7.68 • Men: 6.44 ± 6.2 Post-CR • Women: 5.44 ± 5.76 • Men: 4.21 ± 4.76 Pts had significantly higher BDI scores prior to CR compared to after. Women showed a larger reduction in BDI scores after CR than men. Pts who did not complete CR had higher BDI scores than those who did complete CR.
12.	Lavie & Milani, 1995	Assess 1) gender differences post cardiac event in baseline exercise capacity, obesity, lipids, behavior characteristics, & QOL & 2) improvement in these after CR.	• Retrospective data review Time-points: • Baseline: pre-CR • Time 2: post-CR	458 people Women: 85 (18.5%) Men: 375 (81.8%) 151 post-CR Women: 31 (20.5%) Men: 120	• Anxiety, somati-zation, hostility, & depression: Kellner Symptom Question-naire	Baseline • Women: 3 ± 4 • Men: 3 ± 5 Post-CR • Women: 3 ± 5 • Men: 2 ± 4 Depressive symptoms were significantly reduced in men following CR but ***not*** in women.

				(79.5%) Inclusion: major ischemic CAD event	Depression cutoff: ≥7	
13.	Lavie et al., 1999	Investigate the effects of depression in women with CAD, & assessed the modulatory effects of CR & exercise training programs	• Prospective longitudinal descriptive study Time-points: • Baseline: pre-CR (4-5 wks post cardiac event) • Time 2: 1 week after CR completion.	102 women • Depressed: 23 • Non-depressed: 79 Inclusion: CAD dx	• Anxiety, somati-zation, hostility, & depression: Kellner Symptom Question-naire (Depression cutoff: ≥7)	Baseline depression ≥7: 22.5% Post-CR depression ≥7: 12% • Study supported frequency of depression in women with CAD. • Improvement in depressive symptoms following CR. • Baseline characteristics failed to identify the depressed women who improved following CR
14.	McGrady et al., 2009	Determine the effects of depression & anxiety on patient completion of structured CR.	• Longitudinal, descriptive, retrospective chart review Time-points: • Baseline: start of CR • Time 2: end of CR	380 subjects Women: 139 (37%) Men: 241 (63%) Inclusion: MI, CABG, angina, or CHF (NYHA class I or II) or other (A-fib, diastolic dysfunction, aortic repair,	• Depression: BDI-II	Baseline (mean) • Women: 10.9 ± 8.4 • Men: 8.3 ± 7.3 Baseline (BDI-II >10 or BAI>15) • Women: 17.4 ± 6.6 • Men: 20.0 ± 8.1 Post-CR (BDI-II >10 or BAI>15 at baseline) • Women: 10.5 ± 6.2 • Men: 12.9 ± 9.4 Women had overall higher BDI-II scores than men at baseline. No statistically significant gender differences in outcomes post-program. Significant differences in baseline BDI-II between completers & dropouts (8.6 vs 11.7, p=0.001)

				heart transplant)		Younger, female patients had higher dropout rates.
15.	Norris et al., 2007	Examine gender differences in specific depressive symptoms as they relate to HRQOL post MI.	• Longitudinal, prospective cohort study Time-points: • Baseline: inpatient • Time 2: 1 year	486 patients Women: 102 (21%) Men: 384 (79%) Inclusion: Admission through ED w. dx of AMI	• Depressive symptoms: BDI-II	Baseline BDI-II ≥10: • Women: 40.3% • Men: 32.7% 1-yr BDI-II≥10: • Women: 40.4% • Men: 31.9% No significant differences in depression scores between men & women at baseline. Women had worsening mean BDI-II scores over the 1st year post-AMI. Women more likely to have DM, HTN
16.	Phillips Bute et al., 2003	Examine QOL & cognitive outcomes after CABG in men & women, carefully adjusting for baseline differences & known pre-op risk factors for poor outcomes.	• Prospective longitudinal observational study Time-points: • Baseline: inpatient • Time 2: 1 year	343 pts at baseline 280 at 1 year No number breakdown by gender Inclusion: Elective CABG	• Depression: CES-D	Baseline • Women: 16.95 ± 11.06 • Men: 11.10 ± 9.39 12 months • Women: 13.91 ± 9.58 • Men: 9.02 ± 8.48 Women's scores significantly higher than men's at both time points. Women's recovery not significantly different from men's - differences could be attributed to pre-op differences in depression levels.
17.	Sanderson & Bittner, 2005	Compare baseline characteristics between CR completers & non-completers; ID factors associated w. CR completers; describe outcomes	• Longitudinal descriptive study Time-points: • Baseline: pre-CR • Time 1: post-CR	228 women: • 121 CR completers • 107 CR non-completers Inclusion:	• Depression: BDI-II	Baseline BDI-II≥14: 31% After CR: • 67% of women had improved BDI-II scores • 6% had no change • 27% had higher scores compared to baseline • 50% of CR non-completers had a BDI-II score >14 vs 16% among completers.

		among CR completers.		Dx of ischemic heart disease		• CR non-completers were younger, more obese than completers. Women who had higher scores after CR than at baseline still had mean score <14.
18.	Shin et al., 2010	Explore gender differences in the hx of depression, depressive symptoms, & use of anti-depressants in pts hospitalized for ACS & 1-month post-discharge.	• Prospective longitudinal design Time-points: • Baseline: inpatient • Time 1: 4 weeks after discharge	100 patients Women: 49 Men: 51 1 mo.: 82 Women: 38 Men: 44 Inclusion: Documented ACS	• Depression: BDI-II • Hx depression	BDI-II≥14 Baseline: • Women: 38.8% • men=29.4% 1 month: • women: 26.3% • men=25% Hx depression: • Women: 34.7% • Men: 17.6% Taking antidepressants (baseline) • Women: 38.8% • Men: 15.7% _____ No statistical difference in severity of depressive symptoms by gender at either time-point. No improvement from baseline to 1 month More women than men had hx of depression
19.	Zaninotto et al., 2016	Explore gender-specific changes in well-being in older people with CHD vs those without over a 6-year period.	• retrospective longitudinal case-control study Time-points: • Baseline: within 2 yrs of a CHD event • Time 2: 1 year after baseline • Time 3: 2 years after baseline	895 with CHD: Women: 377 Men: 518 3601 w/o CHD: Women: 1899 Men: 1702	• Depression: CES-D8	Prevalence of depressive “caseness” was higher in CHD vs healthy group • For women with CHD, presence of depressive caseness was constant between baseline and 2-yr f/u, but 8% lower at 4-yr f/u compared to baseline. • At baseline & 2-yr f/u, women had 13% higher probability of depressive caseness vs men. ○ This decreased to 5% at 4-yr f/u. Among CHD pts, depressive caseness was constant over time among men while women reported

improvements.

APPENDIX B: Institutional Review Board Approval Letter UNMC

University of Nebraska Medical Center

NEBRASKA'S HEALTH SCIENCE CENTER

Office of Regulatory Affairs (ORA)
Institutional Review Board (IRB)

October 24, 2017

Sydney Buckland, MSN, APRN
CON-Omaha Division
UNMC - 5330

IRB # 567-17-EP

TITLE OF PROPOSAL: Examining emotional symptoms in women with coronary heart disease over time: a convergent mixed methods study

DATE OF EXPEDITED REVIEW: 09/07/2017

DATE OF FINAL APPROVAL AND RELEASE:10/24/2017 **VALID UNTIL:** 09/07/2018

CLASSIFICATION OF RISK: Minimal

EXPEDITED CATEGORY OF REVIEW: 45 CFR 46.110; 21 CFR 56.110, Category 6, 7

The IRB has completed its review of the above-titled protocol. The IRB has determined you are in compliance with HHS Regulations (45 CFR 46), applicable FDA Regulations (21 CFR 50, 56) and the Organization's HRPP policies. Furthermore, the IRB is satisfied you have provided adequate safeguards for protecting the rights and welfare of the subjects to be involved in this study. This letter constitutes official notification of final approval and release of your project by the IRB. You are authorized to implement this study as of the above date of final approval.

Please be advised that only the IRB approved and stamped consent form(s) can be used to make copies to enroll subjects. Also, at the time of consent all subjects must be given a copy of *The Rights of Research Subjects* and "What Do I Need to Know" forms.

The IRB wishes to remind you that the PI is ultimately responsible for ensuring that this research is conducted in full compliance with the protocol, applicable Federal Regulations, and Organizational policies.

Finally, under the provisions of this institution's Federal Wide Assurance (FWA00002939), the PI is directly responsible for submitting to the IRB any proposed change in the research or the consent form(s)/information sheet(s). In addition, any adverse events, unanticipated problems involving risk to the subject or others, noncompliance, and complaints must be promptly reported to the IRB in accordance with HRPP policies.

This project is subject to periodic review and surveillance by the IRB and, as part of the Board's surveillance, the IRB may request periodic progress reports. For projects which continue beyond one year, it is the responsibility of the PI to initiate a request to the IRB for continuing review and update of the research project.

On behalf of the IRB,

Signed on: 2017-10-24 08:52:00.000

Bryan Ludwig, BA
IRB Administrator II
Office of Regulatory Affairs

cc: Bruce G. Gordon M.D.
IRB Executive Chair

APPENDIX C: Institutional Review Board Approval Letter Methodist

METHODIST HOSPITAL
An Affiliate of Methodist Health System
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Omaha, NE 68114
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January 9, 2018

Sydney Buckland
UNMC College of Nursing
985330 Nebraska Medical Center
4111 Dewey Avenue
Omaha, NE 68198-5330

Dear Ms. Buckland,

The Nebraska Methodist Hospital Institutional Review Board granted approval to the following:

Date of Action: December 4, 2017

Type of review:		
	Initial review	X
	Continuing review	
	Amendment	
	Adverse Event	
	Closure	

Examining emotional symptoms in women with coronary heart disease over time: a convergent mixed methods study
Consent form reviewed/approved (12/04/2017)

**Principal Investigator will report back to the Board in 6 months on accrual and number of subjects referred to the ED and to Primary Care physicians.

This action was taken by the full IRB unless indicated by a check mark for Expedited Review Action as follows:
Expedited Review Action

The Nebraska Methodist Hospital IRB operates in compliance with federal laws and regulations governing institutional review boards, including the federal Common Rule and FDA regulations. The Methodist IRB operates under the following Federal Wide Assurance number: FWA 00003377

You must submit a status report on this study, following the IRB's approved reporting form, one year from the date of IRB action, unless the IRB specified a shorter period. If you do not do so, your study will be suspended.

Implementation/continuation of this study is subject to the requirements and standards set forth in the *Nebraska Methodist Hospital Handbook for IRB Members and Investigators*. You should particularly note the statements of Ethical Principles under Tab II of the *Handbook*, and the Investigator Responsibilities and Standards under Tab VI.

Should you have any questions please do not hesitate to contact the Chairman of the Institutional Review Board or the Medical Staff Office at 354-4038.

Sincerely,

William Lydiatt

William Lydiatt, M.D.
Chairman, Institutional Review Board
(402) 354-4038 – phone
(402) 354-4785 – fax

APPENDIX D: Letter of Support Great Plains Health

August 4, 2017

Sydney Buckland, APRN, PhDc
College of Nursing
University of Nebraska Medical Center
985330 Nebraska Medical Center
Omaha, NE 68198-5330

Dear Ms. Buckland:

We are willing to serve as a recruitment site for your proposed study: "Examining emotional symptoms in women with coronary heart disease over time: a convergent mixed methods study." We understand our role is to share the study information with eligible women from our recruitment site. The women will then have one week from hospital admission to contact you for more information and be enrolled.

We look forward to the opportunity to partner in this study.

Sincerely,

Mel McNea

Mel McNea
Chief Executive Officer

APPENDIX E: Single Subject Protocol Deviation Approval

University of Nebraska Medical Center

NEBRASKA'S HEALTH SCIENCE CENTER

Office of Regulatory Affairs (ORA)
Institutional Review Board (IRB)

May 25, 2018

Sydney Buckland, MSN, APRN
CON-Omaha Division
UNMC - 5330

IRB # 567-17-EP

TITLE OF PROPOSAL: Examining emotional symptoms in women with coronary heart disease over time: a convergent mixed methods study

SUBJECT: Single Subject Protocol Deviation Request, dated *05/25/2018*

Dear Ms. Buckland,

This letter constitutes approval of the Single Subject Protocol Deviation Request for the above-named protocol. Approval for this deviation was granted by Bruce Gordon, M.D. IRB Executive Chair on 05/25/2018.

The IRB has determined that this deviation meets the requirements of HHS regulations at 45 CFR 46.110(b)(2) and FDA regulations at 21 CFR 56.110(b)(2). The documentation has been placed in the file for purposes of the record. No further action is required.

If you have any questions or require further assistance, please do not hesitate to contact me at 402-559-8561.

Sincerely,

Signed on: 2018-05-25 14:24:00.000

Bryan Ludwig, BA
IRB Administrator II
Office of Regulatory Affairs

cc: Bruce G. Gordon M.D.
IRB Executive Chair

APPENDIX F: Institutional Review Board Protocol Change Approvals UNMC
January 12, 2018

University of Nebraska Medical Center

NEBRASKA'S HEALTH SCIENCE CENTER

Office of Regulatory Affairs (ORA)
Institutional Review Board (IRB)

January 12, 2018

Sydney Buckland, MSN, APRN
CON-Omaha Division
UNMC - 5330

IRB # 567-17-EP

TITLE OF PROPOSAL: Examining emotional symptoms in women with coronary heart disease over time: a convergent mixed methods study

DATE OF CHANGE REQUEST ***12/19/2017***

DATE OF IRB EXPEDITED REVIEW: *01/12/2018*

Dear Ms. Buckland,

The UNMC IRB has completed its review of the above mentioned Request for Change involving the addition of Tamara Bernard Cardiology Clinical Research Coordinator to assist with recruitment. It is understood that Ms. Bernard will screen incoming cardiology clinic patients and approach them for possible participation in the research and request permission to share their contact information with the PI.

This letter constitutes official notification of IRB approval of the revised IRB Application Version#2. The IRB has determined that the amended research protocol continues to satisfy all the criteria set forth at 1) 45 CFR 46.111; 2) 21 CFR 56.111 (as applicable); 3) 45 CFR 46 Subparts B, C or D (as applicable); 4) 21 CFR 50 Subpart D (as applicable); and 5) HRPP policies.

You are authorized to implement this change accordingly.

Respectfully Submitted on Behalf of the IRB,

Signed on: 2018-01-12 11:31:00.000

Bryan Ludwig, BA
IRB Administrator II
Office of Regulatory Affairs

cc: Bruce G. Gordon M.D.
IRB Executive Chair

March 7, 2018

University of Nebraska Medical Center

NEBRASKA'S HEALTH SCIENCE CENTER

Office of Regulatory Affairs (ORA)
Institutional Review Board (IRB)

March 7, 2018

Sydney Buckland, MSN, APRN
CON-Omaha Division
UNMC - 5330

IRB # 567-17-EP

TITLE OF PROPOSAL: Examining emotional symptoms in women with coronary heart disease over time: a convergent mixed methods study

DATE OF CHANGE REQUEST *03/04/2018*

DATE OF IRB EXPEDITED REVIEW: *03/07/2018*

Dear Ms. Buckland,

The UNMC IRB has completed its review of the above mentioned Request for Change involving addition of Methodist Health System as a study site with Methodist IRB approval, modifications to the recruitment process, modified recruitment flyers, and clarification to the exclusion criteria.

This letter constitutes official notification of IRB approval of the revised IRB Application Version#3 and the revised Informed Consent Version#2 The IRB has determined that the amended research protocol continues to satisfy all the criteria set forth at 45 CFR 46.111, and HRPP policies.

All copies of the outdated consent form(s)/information sheet(s) must be discarded immediately. The previously approved IRB stamped form was automatically archived by the RSS electronic system and can be found under the heading ARCHIVED CONSENTS.

You are authorized to implement this change accordingly.

Respectfully Submitted on Behalf of the IRB,

Signed on: 2018-03-08 09:34:00.000

Bryan Ludwig, BA
IRB Administrator II
Office of Regulatory Affairs

cc: Bruce G. Gordon M.D.
IRB Executive Chair

May 29, 2018

University of Nebraska Medical Center

NEBRASKA'S HEALTH SCIENCE CENTER

Office of Regulatory Affairs (ORA)
Institutional Review Board (IRB)

May 29, 2018

Sydney Buckland, MSN, APRN
CON-Omaha Division
UNMC - 5330

IRB # 567-17-EP

TITLE OF PROPOSAL: Examining emotional symptoms in women with coronary heart disease over time: a convergent mixed methods study

DATE OF CHANGE REQUEST *05/25/2018*

DATE OF IRB EXPEDITED REVIEW: *05/29/2018*

Dear Ms. Buckland

The UNMC IRB has completed its review of the above mentioned Request for Change involving modifications to recruitment fliers, personnel, eligibility to include subjects with coronary artery bypass graft, methods, and recruitment.

This letter constitutes official notification of IRB approval of the revised IRB Application Version#4. The IRB has determined that the amended research protocol continues to satisfy all the criteria set forth at 1) 45 CFR 46.111; 2) 21 CFR 56.111 (as applicable); 3) 45 CFR 46 Subparts B, or D (as applicable); 4) 21 CFR 50 Subpart D (as applicable); and 5) HRPP policies.

All copies of the outdated consent form(s) must be discarded immediately. The previously approved IRB stamped form was automatically archived by the RSS electronic system and can be found under the heading ARCHIVED CONSENTS.

You are authorized to implement this change accordingly.

Respectfully Submitted on Behalf of the IRB,

Signed on: 2018-05-29 10:32:00.000

Bryan Ludwig, BA
IRB Administrator II
Office of Regulatory Affairs

cc: Bruce G. Gordon M.D.
IRB Executive Chair

September 12, 2018

University of Nebraska Medical Center

NEBRASKA'S HEALTH SCIENCE CENTER

Office of Regulatory Affairs (ORA)
Institutional Review Board (IRB)

September 12, 2018

Sydney Buckland, MSN, APRN
CON-Omaha Division
UNMC - 5330

IRB # 567-17-EP

TITLE OF PROPOSAL: Examining emotional symptoms in women with coronary heart disease over time: a convergent mixed methods study

DATE OF CHANGE REQUEST ***09/05/2018***

DATE OF IRB EXPEDITED REVIEW: *09/12/2018*

Dear Ms. Buckland,

The UNMC IRB has completed its review of the above mentioned Request for Change involving changing the study design to a feasibility study, modification to the purpose, accrual, methods, modification of the journaling guide and other administrative changes.

This letter constitutes official notification of IRB approval of the revised IRB Application Version#5. The IRB has determined that the amended research protocol continues to satisfy all the criteria set forth at 1) 45 CFR 46.111; 2) 21 CFR 56.111 (as applicable); 3) 45 CFR 46 Subparts B, C or D (as applicable); 4) 21 CFR 50 Subpart D (as applicable); and 5) HRPP policies.

You are authorized to implement this change accordingly.

Respectfully Submitted on Behalf of the IRB,

Signed on: 2018-09-12 13:50:00.000

Bryan Ludwig, BA
IRB Administrator II
Office of Regulatory Affairs

cc: Bruce G. Gordon M.D.
IRB Executive Chair

Academic and Research Services Building 3000 / 987830 Nebraska Medical Center / Omaha, NE 68198-7830
402-559-6463 / FAX: 402-559-3300 / Email: irbora@unmc.edu / http://www.unmc.edu/irb

APPENDIX G: Institutional Review Board Renewal Approval UNMC

University of Nebraska Medical Center

NEBRASKA'S HEALTH SCIENCE CENTER

Office of Regulatory Affairs (ORA)
Institutional Review Board (IRB)

August 31, 2018

Sydney Buckland, MSN, APRN
CON-Omaha Division
UNMC - 5330

IRB # 567-17-EP

TITLE OF PROPOSAL: Examining emotional symptoms in women with coronary heart disease over time: a convergent mixed methods study

DATE OF EXPEDITED REVIEW: 08/31/2018

VALID UNTIL: 08/31/2019

EXPEDITED CATEGORY OF REVIEW: 45 CFR 46.110; 21 CFR 56.110, Category 6,7

The UNMC IRB has completed its review of the Application for Continuing Review for the above titled research project including the complete protocol file and has expressed it as their opinion that you have provided adequate safeguards for the rights and welfare of the subjects involved in this study and are in compliance with HHS regulations (45 CFR 46) and FDA regulations (21 CFR 50.56) as applicable.

This letter constitutes official notification of the re-approval of your research project (Application V.4 7 Adult CF V.3) by the IRB for the IRB approval period indicated above. You are therefore authorized to continue this study. **All copies of the outdated consent form must be discarded immediately.** The original IRB stamped form may be archived.

We wish to remind you that, under the provisions of the Federal Wide Assurance (FWA 00002939) from the Institution to HHS, the Principal Investigator is directly responsible for keeping the IRB informed of any proposed changes involved in the procedures or methodology in the protocol and for promptly reporting to the Board any unanticipated problems involving risks to the subjects or others.

In accordance with HRPP policies, this project is subject to periodic review and monitoring by the IRB and, as part of their monitoring, the IRB may request periodic reports of progress and results. For projects which continue, it is also the responsibility of the Principal Investigator to initiate a request to the IRB for Continuing Review of the research project in consideration of the IRB approval period.

On Behalf of the IRB,

Signed on: 2018-08-31 11:22:00.000

Bobbi Chapman, MS
IRB Administrator/Continuing Review Coordinator
Office of Regulatory Affairs

Academic and Research Services Building 3000 / 987830 Nebraska Medical Center / Omaha, NE 68198-7830
402-559-6463 / FAX: 402-559-3300 / Email: irbora@unmc.edu / http://www.unmc.edu/irb

APPENDIX H: Institutional Review Board Protocol Change Approvals Methodist

METHODIST HOSPITAL
An Affiliate of Methodist Health System
8303 Dodge Street
Omaha, NE 68114
Office Phone: (402) 354-4000
www.bestcare.org

March 28, 2018

Sydney Buckland
UNMC College of Nursing
985330 Nebraska Medical Center
4111 Dewey Ave
Omaha, NE 68198-5330

Dear Ms. Buckland,

The Nebraska Methodist Hospital Institutional Review Board granted approval to the following:

Date of Action: March 26, 2018

Type of review:		
	Initial review	____
	Continuing review	____
	Amendment	X
	Adverse Event	____
	Closure	____

IRB #1372: Examining emotional symptoms in women with coronary heart disease over time: a convergent mixed methods study

As part of the modification, the Board approved the partial HIPAA waiver (for subject recruitment purposes)

This action was taken by the full IRB unless indicated by a check mark for Expedited Review Action as follows: Expedited Review Action

The Nebraska Methodist Hospital IRB operates in compliance with federal laws and regulations governing institutional review boards, including the federal Common Rule and FDA regulations. The Methodist IRB operates under the following Federal Wide Assurance number: FWA 00003377

Implementation/continuation of this study is subject to the requirements and standards set forth in the *Nebraska Methodist Hospital Handbook for IRB Members and Investigators*. You should particularly note the statements of Ethical Principles under Tab II of the *Handbook*, and the Investigator Responsibilities and Standards under Tab VI.

Should you have any questions please do not hesitate to contact the Chairman of the Institutional Review Board or the Medical Staff Office at 354-4038.

Sincerely,

William Lydiatt, M.D.
Chairman, Institutional Review Board
(402) 354-4038 – phone
(402) 354-4785 – fax

APPENDIX I: Demographics collection tools

Confidential

Demographics

Please complete the survey below.

Thank you!

1) Please enter today's date. _____

2) What is your age? _____

3) What race do you identify as? Mark all that apply.

- ☐ Black/African American
- ☐ White/Caucasian
- ☐ Asian
- ☐ Native American
- ☐ Hawaiian/Pacific Islander
- ☐ Other

4) What is the highest level of education you have completed?

- ○ less than high school graduate
- ○ high school graduate
- ○ some college
- ○ associates degree
- ○ technical degree
- ○ bachelor's degree
- ○ master's degree
- ○ doctorate

5) What was your total annual income last year?

- ○ $0 - $25,000
- ○ $25,000 - $50,000
- ○ $50,000 - $75,000
- ○ $75,000 - $100,000
- ○ $100,000 or more

6) What is your marital status?

- ○ single, never married
- ○ married
- ○ domestic partner
- ○ divorced
- ○ widowed

7) Have you held a steady job in the past month?

○ Yes ○ No, I am unemployed or retired

8) What cardiac event brought you in to the hospital?

○ heart attack ○ unstable chest pain without heart attack ○ balloon angioplasty with or without stents

9) Do you have a history of diabetes?

○ Yes ○ No

10) Do you have a history of depression?

- ○ no
- ○ yes, diagnosed and treated with therapy
- ○ yes, diagnosed and treated with medication
- ○ yes, diagnosed and treated with both therapy and medication

11) Do you have a history of anxiety?

- ○ no
- ○ yes, diagnosed and treated with therapy
- ○ yes, diagnosed and treated with medication
- ○ yes, diagnosed and treated with both therapy and medication.

Updated demographics

Please complete the survey below.

Thank you!

12) Have you held a steady job in the past month?

○ Yes ○ No, I am unemployed or retired

13) Please describe your attendance at cardiac rehabilitation

○ I have not attended cardiac rehabilitation at all
○ I have attended less than 50% of the sessions
○ I have attended more than 50% of the sessions
○ I attended every session of cardiac rehabilitation

APPENDIX J: Patient Health Questionnaire 9-item

Patient Health Questionnaire 9

Please complete the survey below.

Thank you!

Over the last week how often have you been bothered by any of the following problems? (Click the circle to indicate your answer)	
1. Little interest or pleasure in doing things	◯ 0- Not at all ◯ 1- Several days ◯ 2- More than half the days ◯ 3- Nearly every day
2. Feeling down, depressed, or hopeless	◯ 0- Not at all ◯ 1- Several days ◯ 2- More than half the days ◯ 3- Nearly every day
3. Trouble falling or staying asleep, or sleeping too much	◯ 0- Not at all ◯ 1- Several days ◯ 2- More than half the days ◯ 3- Nearly every day
4. Feeling tired or having little energy	◯ 0- Not at all ◯ 1- Several days ◯ 2- More than half the days ◯ 3- Nearly every day
5. Poor appetite or overeating	◯ 0- Not at all ◯ 1- Several days ◯ 2- More than half the days ◯ 3- Nearly every day
6. Feeling bad about yourself -- or that you are a failure or have let yourself or your family down	◯ 0- Not at all ◯ 1- Several days ◯ 2- More than half the days ◯ 3- Nearly every day
7. Trouble concentrating on things, such as reading the newspaper or watching television	◯ 0- Not at all ◯ 1- Several days ◯ 2- More than half the days ◯ 3- Nearly every day
8. Moving or speaking so slowly that other people could have noticed? Or the opposite -- being so fidgety or restless that you have been moving around a lot more than usual	◯ 0- Not at all ◯ 1- Several days ◯ 2- More than half the days ◯ 3- Nearly every day
9. Thoughts that you would be better off dead or of hurting yourself in some way	◯ 0- Not at all ◯ 1- Several days ◯ 2- More than half the days ◯ 3- Nearly every day
If you checked off any problems, how difficult have these problems made it for you to do your work, take care of things at home, or get along with other people?	◯ 1- Not difficult at all ◯ 2- Somewhat difficult ◯ 3- Very difficult ◯ 4- Extremely difficult

APPENDIX K: PROMIS short form v1.0 Depression 8b

PROMIS SF v1.0 - Depression 8b

Please complete the survey below.

Thank you!

In the past 7 days I felt worthless	◯ Never ◯ Rarely ◯ Sometimes ◯ Often ◯ Always
In the past 7 days I felt that I had nothing to look forward to	◯ Never ◯ Rarely ◯ Sometimes ◯ Often ◯ Always
In the past 7 days I felt helpless	◯ Never ◯ Rarely ◯ Sometimes ◯ Often ◯ Always
In the past 7 days I felt sad	◯ Never ◯ Rarely ◯ Sometimes ◯ Often ◯ Always
In the past 7 days I felt like a failure	◯ Never ◯ Rarely ◯ Sometimes ◯ Often ◯ Always
In the past 7 days I felt depressed	◯ Never ◯ Rarely ◯ Sometimes ◯ Often ◯ Always
In the past 7 days I felt unhappy	◯ Never ◯ Rarely ◯ Sometimes ◯ Often ◯ Always
In the past 7 days I felt hopeless	◯ Never ◯ Rarely ◯ Sometimes ◯ Often ◯ Always

APPENDIX L: Revised Subjective Units of Distress scale

Revised SUDS

Please complete the survey below.

Thank you!

Try to get used to rating you distress on a scale of 0-10. Imagine you have a "distress thermometer" to measure you feelings according to the following scale. Notice how your level of distress changes over time and in different situations.

- ◯ 10 - Highest distress that you have ever felt
- ◯ 9 - Extremely distressed
- ◯ 8 - Very distressed, can't concentrate
- ◯ 7 - Quite distressed, interfering with performance
- ◯ 6
- ◯ 5 - Moderate distress, uncomfortable but can continue to perform
- ◯ 4
- ◯ 3 - Mild distress, no interference with performance
- ◯ 2 - Minimal distress
- ◯ 1 - Alert and awake, concentrating well
- ◯ 0 - Totally relaxed

APPENDIX M: Fatigue Symptom Inventory

Fatigue Symptom Inventory

Please complete the survey below.

Thank you!

For each of the following, click on the one number that best indicates how that item applies to you.

Rate your level of fatigue on the day you felt most fatigued during the past week:
(0 - Not at all fatigued, 10 - As fatigued as I could be)

○ 0 ○ 1 ○ 2 ○ 3 ○ 4 ○ 5 ○ 6 ○ 7 ○ 8 ○ 9 ○ 10

Rate your level of fatigue on the day you felt least fatigued during the past week:
(0 - Not at all fatigued, 10 - As fatigued as I could be)

○ 0 ○ 1 ○ 2 ○ 3 ○ 4 ○ 5 ○ 6 ○ 7 ○ 8 ○ 9 ○ 10

Rate your level of fatigue on the average during the past week:
(0 - Not at all fatigued, 10 - As fatigued as I could be)

○ 0 ○ 1 ○ 2 ○ 3 ○ 4 ○ 5 ○ 6 ○ 7 ○ 8 ○ 9 ○ 10

Rate your level of fatigue right now:
(0 - Not at all fatigued, 10 - As fatigued as I could be)

○ 0 ○ 1 ○ 2 ○ 3 ○ 4 ○ 5 ○ 6 ○ 7 ○ 8 ○ 9 ○ 10

Rate how much, in the past week, fatigue interfered with your general level of activity:
(0 - No interference, 10 - Extreme interference)

○ 0 ○ 1 ○ 2 ○ 3 ○ 4 ○ 5 ○ 6 ○ 7 ○ 8 ○ 9 ○ 10

Rate how much, in the past week, fatigue interfered with you ability to bathe and dress yourself:
(0 - No interference, 10 - Extreme interference)

○ 0 ○ 1 ○ 2 ○ 3 ○ 4 ○ 5 ○ 6 ○ 7 ○ 8 ○ 9 ○ 10

Rate how much, in the past week, fatigue interfered with your normal work activity (includes both work outside the home and housework):
(0 - No interference, 10 - Extreme interference)

○ 0 ○ 1 ○ 2 ○ 3 ○ 4 ○ 5 ○ 6 ○ 7 ○ 8 ○ 9 ○ 10

Rate how much, in the past week, fatigue interfered with your ability to concentrate:
(0 - No interference, 10 - Extreme interference)

○ 0 ○ 1 ○ 2 ○ 3 ○ 4 ○ 5 ○ 6 ○ 7 ○ 8 ○ 9 ○ 10

Rate how much, in the past week, fatigue interfered with your relations with other people:
(0 - No interference, 10 - Extreme interference)

○ 0 ○ 1 ○ 2 ○ 3 ○ 4 ○ 5 ○ 6 ○ 7 ○ 8 ○ 9 ○ 10

Rate how much, in the past week, fatigue interfered with your mood:
(0 - No interference, 10 - Extreme interference)

○ 0 ○ 1 ○ 2 ○ 3 ○ 4 ○ 5 ○ 6 ○ 7 ○ 8 ○ 9 ○ 10

Indicate how many days, in the past week, you felt fatigued for any part of the day:
(Days)

○ 0 ○ 1 ○ 2 ○ 3 ○ 4 ○ 5 ○ 6 ○ 7

Rate how much of the day, on average, you felt fatigued in the past week:
(0 - None of the day, 10 - The entire day)

○ 0 ○ 1 ○ 2 ○ 3 ○ 4 ○ 5 ○ 6 ○ 7 ○ 8 ○ 9 ○ 10

Indicate which of the following best describes the daily pattern of your fatigue in the past week:

- ○ Not at all fatigued
- ○ Worse in the morning
- ○ Worse in the afternoon
- ○ Worse in the evening
- ○ No consistent daily pattern of fatigue

APPENDIX N: PROMIS sf v1.0 Sleep Disturbance 8b

PROMIS SF v1.0 - Sleep Disturb 8b

Please complete the survey below.

Thank you!

In the past 7 days My sleep was restless.	◯ Not at all ◯ A little bit ◯ Somewhat ◯ Quite a bit ◯ Very much
In the past 7 days I was satisfied with my sleep.	◯ Not at all ◯ A little bit ◯ Somewhat ◯ Quite a bit ◯ Very much
In the past 7 days My sleep was refreshing.	◯ Not at all ◯ A little bit ◯ Somewhat ◯ Quite a bit ◯ Very much
In the past 7 days I had difficulty falling asleep.	◯ Not at all ◯ A little bit ◯ Somewhat ◯ Quite a bit ◯ Very much
In the past 7 days I had trouble staying asleep.	◯ Never ◯ Rarely ◯ Sometimes ◯ Often ◯ Always
In the past 7 days I had trouble sleeping.	◯ Never ◯ Rarely ◯ Sometimes ◯ Often ◯ Always
In the past 7 days I got enough sleep.	◯ Never ◯ Rarely ◯ Sometimes ◯ Often ◯ Always
In the past 7 days My sleep quality was...	◯ Very poor ◯ Poor ◯ Fair ◯ Good ◯ Very good

APPENDIX O: GI symptom frequency & symptoms distress scale

GI Symptom Frequency & Symptom Distress Scale

Please complete the survey below.

Thank you!

Since being in the hospital, do you have this symptom? If yes, how frequently?

Do you have problems with poor appetite?

◯ Never ◯ Rarely/sometimes ◯ Often/always

Do you have problems with lack of taste?

◯ Never ◯ Rarely/sometimes ◯ Often/always

Do you have problems with nausea?

◯ Never ◯ Rarely/sometimes ◯ Often/always

If you have this symptom, how upsetting is it to you?

How upsetting is loss of appetite to you?

◯ Not at all ◯ A little/moderately ◯ Quite a bit/extremely ◯ I don't have this symptom

How upsetting is lack of taste to you?

◯ Not at all ◯ A little/moderately ◯ Quite a bit/extremely ◯ I don't have this symptom

How upsetting is nausea to you?

◯ Not at all ◯ A little/moderately ◯ Quite a bit/extremely ◯ I don't have this symptom

APPENDIX P: ACS Symptoms Checklist

ACS Symptoms Checklist

Please complete the survey below.

Thank you!

Please indicate all symptoms that you experience in the past week and rate the severity of the symptoms on a scale of 0 (none) to 10 (worst)

Chest Pressure
(0 - none, 10 - worst)

- ◯ 0
- ◯ 1
- ◯ 2
- ◯ 3
- ◯ 4
- ◯ 5
- ◯ 6
- ◯ 7
- ◯ 8
- ◯ 9
- ◯ 10
- ◯ I did not have this symptom in the past week

Shoulder Pain
(0 - none, 10 - worst)

- ◯ 0
- ◯ 1
- ◯ 2
- ◯ 3
- ◯ 4
- ◯ 5
- ◯ 6
- ◯ 7
- ◯ 8
- ◯ 9
- ◯ 10
- ◯ I did not have this symptom in the past week

Sweating
(0 - none, 10 - worst)

- ◯ 0
- ◯ 1
- ◯ 2
- ◯ 3
- ◯ 4
- ◯ 5
- ◯ 6
- ◯ 7
- ◯ 8
- ◯ 9
- ◯ 10
- ◯ I did not have this symptom in the past week

Palpitations
(0 - none, 10 - worst)

- ◯ 0
- ◯ 1
- ◯ 2
- ◯ 3
- ◯ 4
- ◯ 5
- ◯ 6
- ◯ 7
- ◯ 8
- ◯ 9
- ◯ 10
- ◯ I did not have this symptom in the past week

Chest Discomfort
(0 - none, 10 - worst)

- ◯ 0
- ◯ 1
- ◯ 2
- ◯ 3
- ◯ 4
- ◯ 5
- ◯ 6
- ◯ 7
- ◯ 8
- ◯ 9
- ◯ 10
- ◯ I did not have this symptom in the past week

Upper Back Pain
(0 - none, 10 - worst)

- ◯ 0
- ◯ 1
- ◯ 2
- ◯ 3
- ◯ 4
- ◯ 5
- ◯ 6
- ◯ 7
- ◯ 8
- ◯ 9
- ◯ 10
- ◯ I did not have this symptom in the past week

Short of Breath
(0 - none, 10 - worst)

- ◯ 0
- ◯ 1
- ◯ 2
- ◯ 3
- ◯ 4
- ◯ 5
- ◯ 6
- ◯ 7
- ◯ 8
- ◯ 9
- ◯ 10
- ◯ I did not have this symptom in the past week

Arm Pain
(0 - none, 10 - worst)

- ◯ 0
- ◯ 1
- ◯ 2
- ◯ 3
- ◯ 4
- ◯ 5
- ◯ 6
- ◯ 7
- ◯ 8
- ◯ 9
- ◯ 10
- ◯ I did not have this symptom in the past week

Unusual Fatigue
(0 - none, 10 - worst)

- ◯ 0
- ◯ 1
- ◯ 2
- ◯ 3
- ◯ 4
- ◯ 5
- ◯ 6
- ◯ 7
- ◯ 8
- ◯ 9
- ◯ 10
- ◯ I did not have this symptom in the past week

Nausea
(0 - none, 10 - worst)

- ◯ 0
- ◯ 1
- ◯ 2
- ◯ 3
- ◯ 4
- ◯ 5
- ◯ 6
- ◯ 7
- ◯ 8
- ◯ 9
- ◯ 10
- ◯ I did not have this symptom in the past week

Lightheaded
(0 - none, 10 - worst)

- ◯ 0
- ◯ 1
- ◯ 2
- ◯ 3
- ◯ 4
- ◯ 5
- ◯ 6
- ◯ 7
- ◯ 8
- ◯ 9
- ◯ 10
- ◯ I did not have this symptom in the past week

Chest Pain
(0 - none, 10 - worst)

- ◯ 0
- ◯ 1
- ◯ 2
- ◯ 3
- ◯ 4
- ◯ 5
- ◯ 6
- ◯ 7
- ◯ 8
- ◯ 9
- ◯ 10
- ◯ I did not have this symptom in the past week

Indigestion
(0 - none, 10 - worst)

- ◯ 0
- ◯ 1
- ◯ 2
- ◯ 3
- ◯ 4
- ◯ 5
- ◯ 6
- ◯ 7
- ◯ 8
- ◯ 9
- ◯ 10
- ◯ I did not have this symptom in the past week

Other
(0 - none, 10 - worst)

- ◯ 0
- ◯ 1
- ◯ 2
- ◯ 3
- ◯ 4
- ◯ 5
- ◯ 6
- ◯ 7
- ◯ 8
- ◯ 9
- ◯ 10
- ◯ I did not have this symptom in the past week

If you indicated other, please write in your symptom here.

APPENDIX Q: Original Journaling Guide

Journaling Instructions

The purpose of this journal is to give the researcher (me) a more detailed way to understand what you are feeling – particularly feelings of depression. People experience symptoms of depression in many different ways. It may not be clear to you if what you are feeling is depression or anxiety or anger or even symptoms of your heart disease. That's OK. Please include anything that you think will help me understand what you are feeling.

Please spend at least 15 minutes a day, at least 3 out of the next 7 days, writing in this journal. The following list contains examples of the kinds of things I hope you will comment on/write about.

1. The timing of your depressive symptoms
    - Have you noticed that your emotions/mood changes with the time of day, or during certain parts of the week?
    - Do your emotions change (improve or get worse) with certain activities, and if so what are those activities?
    - Have you noticed a "trend" in your mood overall – either improvement or decline?
2. The severity of your depressive symptoms
    - If you have noticed a certain feeling (for example, fatigue or trouble concentrating), has it been mild/minor or has it been rather significant/severe?
    - Have you noticed if anything in particular seems to change the severity of your symptoms (either for better or worse)?
3. The distress caused by your depressive symptoms
    - How bothered or distressed by your mood/feelings have you been?
4. The quality of your depressive symptoms
    - What "cognitive" (emotional) symptoms have you been experiencing (such as feeling down or not being interested in doing anything)?
    - What "somatic" (physical) symptoms have you been experiencing (such as fatigue or poor appetite) that you think are related to your feelings rather than your heart disease?

APPENDIX R: Revised Journaling Guide

Journaling Instructions

The purpose of this journal is to give the researcher (me) a more detailed way to understand what you are feeling, particularly in regards to your mood/emotions. People experience many different feelings after they are diagnosed with a chronic illness such as coronary heart disease. It may not be clear to you if what you are feeling is depression or anxiety or anger or even symptoms of your heart disease (as things like fatigue and poor sleep can be mood-related as well as disease-related). That's OK. Please include anything that you think will help me understand what you are feeling.

Please spend at least 15 minutes a day, at least 3 out of the next 7 days, writing in this journal. The following list contains examples of the kinds of things I hope you will comment on/write about.

5. The timing of your feelings/mood changes
    - Have you noticed that your emotions/mood changes with the time of day, or during certain parts of the week?
    - Does your mood change (improve or get worse) with certain activities, and if so what are those activities?
    - Have you noticed a "trend" in your mood overall – either improvement or decline?
6. The "severity" of your feelings/mood
    - If you have noticed a certain mood, has it been mild/minor or has it been rather significant/severe?
    - Have you noticed if anything in particular seems to change the severity of your feelings (either for better or worse)?
7. The distress caused by your feelings
    - How bothered or distressed by your mood/feelings have you been?
8. The quality of your feelings/mood
    - What "cognitive" (thinking/brain) symptoms have you been experiencing (such as feeling down or not being interested in doing anything)?
    - What "somatic" (physical/body) symptoms have you been experiencing (such as fatigue or poor appetite) that you think are related to your feelings rather than your heart disease?