Associations Between Depression and Coronary Heart Disease

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A thesis submitted in fulfillment of the requirements of the degree of Doctor of Philosophy

December 2014

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Abstract

Mental health, such as depression, and cardiovascular disease, such as coronary heart disease (CHD), are among two of the priority areas for health care and research in Australia and worldwide, and share many commonalities. First, depression and CHD are highly prevalent and frequently co-exist. Individually and together, they impose a significant burden of disease. Lastly, a reciprocal relationship exists, such that depressive symptoms are risk factors for the onset and progression of CHD (and vice versa), contributing to further morbidity, decreased quality of life (QoL) and mortality. The autonomic nervous system (ANS) has been implicated in the relationship between depression and CHD; and specifically, reduced heart variability (HRV; a marker of ANS activity) has been associated with both CHD and depression. Accordingly, psychological treatments with potential to enhance HRV (such as mindfulness-based cognitive therapy [MBCT]) may offer significant benefits to patients with either or both diagnoses.

This thesis utilised quantitative statistical analyses to investigate the mental health of Australians, focusing on some actual and potential relationships between CHD, HRV and depression. Three independent but related studies were undertaken. The three published manuscripts, and some additional unpublished results, are presented as chapters in the thesis.

Chapter One provides a context to this research, providing a comprehensive introduction to the literature on depression and its treatment MBCT, cardiac function and CHD, the relationships between depression and CHD, the ANS and HRV. Chapter Two outlines specific gaps identified in the literature leading to the thesis objectives. Chapter Three describes study measurement and types of psychometric questionnaires utilised. The three published manuscripts are then presented in Chapters Four to Six.

Pre-existing datasets were used to investigate the demographic, psychological and cardiac factors associated with depression (Study 1) and subsequent mortality (Study 2) in cardiac patient samples. A clinical pilot study (Study 3) was then designed and conducted to investigate changes in physiology among mental health outpatients undergoing MBCT.

A number of methods were employed to evaluate patient outcomes in the three studies. The major end points of this research focused upon patient-reported health and psychological measures (i.e., depression and QoL) and cardiac measures (i.e., HRV). Cross-sectional and longitudinal analyses were conducted using appropriate statistical analyses. Cross-sectional data were analysed using binary regression or Cox's proportional hazards model (Studies 1 and 2) whereas longitudinal data were analysed as panel data, utilising random effects model and logistic regression (Study 3).

A summary of findings, strengths and weaknesses of the three studies and their implications for future research and clinical practice form the discussion (Chapter Seven). Findings from the three studies have contributed to the epidemiological literature by providing empirical support for the relationships between depression and CHD, and between depression and mortality; and to evidence-based practice by reporting pilot data and methodological considerations concerning evaluation of the potential impact of MBCT on HRV. It is believed that results of this research will contribute to understanding the course and outcomes of depression in CHD and have implications for managing this comorbid condition.

Declaration

I certify that this work contains no material which has been accepted for the award of any other degree or diploma in my name, in any university or other tertiary institution and, to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference has been made in the text. In addition, I certify that no part of this work will, in the future, be used in a submission in my name, for any other degree or diploma in any university or other tertiary institution without the prior approval of the University of Adelaide and where applicable, any partner institution responsible for the joint-award of this degree.

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List of Publications

Publications are listed in order of appearance in this thesis.

Wheeler, A., Schrader, G., Tucker, G., Adams, R., Tavella, R., & Beltrame, J. F. (2013). Prevalence of depression in patients with chest pain and non-obstructive coronary artery disease. *American Journal of Cardiology*, *112*(5), 656-659. doi: 10.1016/j.amjcard.2013.04.042

Wheeler, A., Beltrame, J., Tucker, G., Air, T., Ling, L-H., & Schrader, G. (2012). Depression and 5-year mortality in patients with acute myocardial infarction: Analysis of the IDACC database. *Australian and New Zealand Journal of Psychiatry*, *46*(7), 669-675. doi: 10.1177/0004867412449875

Wheeler, A., Denson, L., Neil, C., Tucker, G., Kenny, M., Beltrame, J. F., Schrader, G., & Proeve, M. (2014). Investigating the effect of mindfulness training on heart rate variability in mental health outpatients: A pilot study. *Behaviour Change*, *31*(3), 175-188. doi: 10.1017/bec.2014.14

Acknowledgements

Having reached the end of this journey, I would like to acknowledge the generous help of those who provided valuable assistance with this thesis.

Sincere thanks to my supervisors Linley Denson and Michael Proeve from the School of Psychology. Without your constant guidance, advice and support in the final stages of completion, this thesis would not have been possible. I cannot thank you both enough for your motivation and encouragement to pursue my goal and reach the end.

Many thanks to the School of Psychology who welcomed my transfer back to their School after Dr Schrader's retirement, thus enabling the completion of my thesis.

To Geoffrey Schrader and John Beltrame for their assistance, advice and supervision. Your dedication and knowledge for this research was inspiring.

Sincere gratitude extends to Graeme Tucker, who provided extensive statistical advice throughout the course of my PhD. Your generosity and assistance with my many statistical enquiries will always be appreciated. To Tracy Air, for sharing her statistical expertise. I appreciate the assistance of Chris Neil, for providing valuable cardiological expert advice, and Maura Kenny from CTAD who facilitated access to patients.

To the ECG technicians at The Queen Elizabeth Hospital, it has been an absolute pleasure working with you. I thoroughly enjoyed our tea breaks and many laughs together. I could not have asked for a kinder group of colleagues to work with. Special thanks to Dianne, for her countless hours and help with my clinical study.

To the many patients, who kindly volunteered their time to participate in this research, thank you.

Finally, warmest thanks to my family, especially my parents, who have always provided me with encouragement, support and love throughout the years. Your belief in me was inspiring and helped me through the challenges and final years of this journey.

List of Abbreviations

ABS	Australian Bureau of Statistics
ACh	acetylcholine
ACS	acute coronary syndrome
ACTH	adrenocorticotrophic hormone
AIC	Akaike's Information Criterion
AIHW	Australian Institute of Health and Welfare
AMI	acute myocardial infarction
ANS	autonomic nervous system
APA	American Psychiatric Association
AV	atrioventricular
BDI	Beck Depression Inventory
BMI	body mass index
Ca^{++}	calcium ion
CAD	coronary artery disease
CBT	cognitive behaviour therapy
CES-D	Center for Epidemiologic Studies Depression Scale
CHD	coronary heart disease
CHF	chronic heart failure
CI	confidence interval
COPD	chronic obstructive pulmonary disease
CRH	corticotrophin-releasing hormone
CSA	chronic stable angina
CTAD	Centre for Treatment of Anxiety and Depression
CVC	cardiac vagal control
CVD	cardiovascular disease
DALYs	disability adjusted life-years
DHA	docosahexaenoic acid
DSM	Diagnostic and Statistical Manual
ECG	electrocardiogram/electrocardiograph
ECT	electroconvulsive therapy
EPA	eicosapentaenoic acid
HADS	Hospital Anxiety and Depression Scale

HF	high frequency
HPA	hypothalamic-pituitary-adrenal
HR[1]	heart rate
HRQoL	health-related quality of life
HRV	heart rate variability
ICD	International Classification of Diseases
IDACC	Identifying Depression as a Comorbid Condition
IL	interleukin
IRSD	Index of Relative Socioeconomic Disadvantage
K^+	potassium ion
LAD	left anterior descending
LCA	left coronary artery
LDL	low-density lipoprotein
LF	low frequency
LF/HF	low frequency to high frequency
LOT	Life Orientation Test
LOT-R	Life Orientation Test-Revised
LVH	left ventricular hypertrophy
MAOI	monoamine oxidase inhibitor
MBCT	mindfulness-based cognitive therapy
MBSR	mindfulness-based stress reduction
MDD	major depressive disorder
MI	myocardial infarction
MSPSS	Multidimensional Scale of Perceived Social Support
MVD	microvascular disease/microvascular dysfunction
Na^+	sodium ion
NE	norepinephrine
NHFA	National Heart Foundation of Australia
NIMH	National Institute of Mental Health
NN	normal to normal
NoCAD	non-obstructive coronary artery disease

[1] In the published manuscript reporting Study 2 (see Chapter Five), hazard ratio was originally abbreviated to HR. However throughout this thesis, to prevent confusion, the abbreviation HR is used only for heart rate, and hazard ratio has not been abbreviated.

NSTEMI	non-ST elevation myocardial infarction
nu	normalised units
NWAHS	North West Adelaide Health Service
OR	odds ratio
PhD	Doctor of Philosophy
PNS	parasympathetic nervous system
PSD	power spectral density
PSSS	Perceived Social Support Scale
PUFAs	polyunsaturated fatty acids
QoL	quality of life
QTc	QT corrected
RCA	right coronary artery
RMSSD	root mean square of successive differences
ROC	receiver operator characteristic
RSA	respiratory sinus arrhythmia
SA	sinoatrial
SAQ	Seattle Angina Questionnaire
SCWT	Stroop Color and Word Test
SDNN	standard deviation of NN
SF-36	Short Form-36
SNRI	serotonin and norepinephrine reuptake inhibitor
SNS	sympathetic nervous system
SPSS	Statistical Package for the Social Sciences
SSRI	selective serotonin reuptake inhibitor
STEMI	ST-elevation myocardial infarction
TAU	treatment as usual
TCA	tricyclic antidepressant
TM	transcendental meditation
TNF	tumour necrosis factor
TQEH	The Queen Elizabeth Hospital
UA	unstable angina
ULF	ultra low frequency
VLF	very low frequency
WHO	World Health Organization

CHAPTER ONE: BACKGROUND

CHAPTER ONE
BACKGROUND

PREAMBLE

In 2006, the following quote appeared in the Harvard University Gazette: "Depression is bad for my heart, and my heart is bad for my depression. How depressing is that!" (Bellas & Harvard News Office, 2006). This statement highlights the reciprocal relationship between depression, a mental disorder, and coronary heart disease (CHD), a cardiovascular disease (CVD), which forms the key focus of this thesis.

Research has shown that mental health disorders and CVD each impose a significant burden of disease, not only in Australia but also on a worldwide scale. On the most recent national list of leading contributors to the total global burden of disease in Australia in 2003, mental disorders and CVD were positioned in the top three (Figure 1), as measured by the Disability Adjusted Life-Years (DALYs, which includes the lost years of life, the prevalence of the disease and a weight factor for the seriousness of the disease) (Australian Institute of Health and Welfare [AIHW], 2012). The projected burden of disease in 2010, based on the 2003 data, also showed a similar pattern of disease burden, with CVD and mental disorders ranking fourth and second (Figure 1). In addition, CHD was ranked first and depression and anxiety second as estimated and projected specific causes of disease burden in both 2003 and 2010 (Table 1) (AIHW, 2008, 2010).

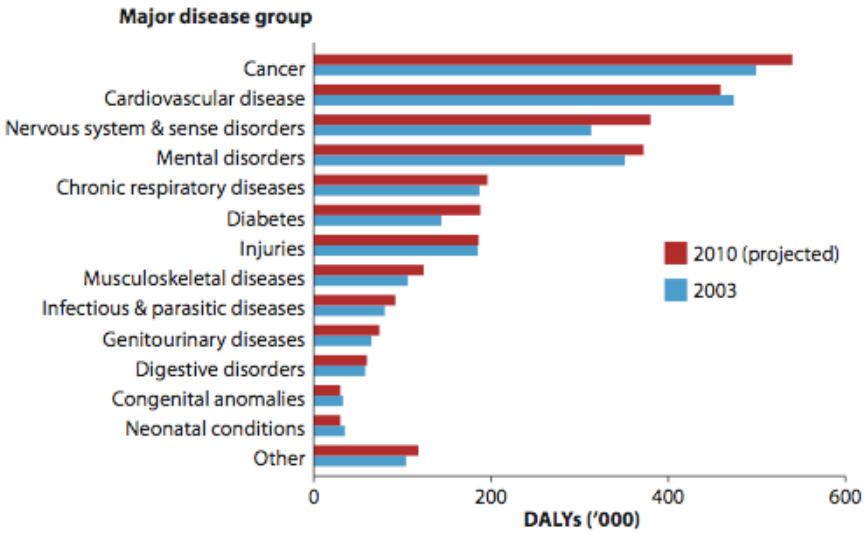

Figure 1. Estimated and projected total burden (DALYs) of major disease groups in 2003 and 2010. Reprinted from *Australia's Health 2012* (Cat. no. AUS 156, p.118), by AIHW, 2012, Canberra, Australia: Author. Reprinted with permission.

Table 1

Estimated and Projected Leading Specific Cause of Disease Burden in 2003 and 2010

Rank	Condition 2003	Condition 2010
1	Coronary heart disease	Coronary heart disease
2	Depression and anxiety	Depression and anxiety
3	Type 2 diabetes	Type 2 diabetes
4	Stroke	Dementia
5	Dementia	Stroke

Note. Adapted from *Australia's Health 2008* (Cat. no. AUS 99, p. 57), by AIHW, 2008, Canberra, Australia: Author, and *Australia's Health 2010* (Australia's health series no. 12. Cat. no. AUS 122), by AIHW, 2010, Canberra, Australia: Author. Adapted with permission.

The figure and table above illustrate that depression and CHD are leading causes of disability and mortality, causing a significant reduction in quality of life (QoL). Occurring singly and together, depression and CHD have a major impact on public health, not only in Australia, but also worldwide. In terms of global burden of disease, depression has been ranked third and CHD ranked fourth (Mathers, Fat, Boerma, & World Health Organization [WHO], 2008). In middle and high income countries

depression and CHD are ranked first and second (Mathers et al., 2008). In the more recent report however, mental disorders and CVD ranked in the top three non-communicable causes of global disease burden, with depression and CHD making the largest contribution to these conditions (Murray et al., 2012). It is further projected that by 2020 and 2030, according to the WHO, depression and ischaemic heart disease will rank among the top three leading causes of disease burden (Mathers et al., 2008; Mathers & Loncar, 2006; Murray & Lopez, 1996).

In addition, it is well established that there is a reciprocal relationship between depression and CHD. They frequently co-exist and are highly prevalent together (Carney & Freedland, 2009), with point prevalence of depression ranging from 14-47% in CHD patients (Ahto et al., 1997; Gonzalez et al., 1996; Lesperance, Frasure-Smith, Juneau, & Theroux, 2000; Lett et al., 2004; Valkamo et al., 2001). As a result, an extensive body of research has focused on the pathways involved in this relationship, although the exact mechanism is unknown. The autonomic nervous system (ANS) has been implicated in the relationship between depression and CHD (Carney, Freedland, Miller, & Jaffe, 2002; Musselman, Evans, & Nemeroff, 1998; Stapelberg, Neumann, Shum, McConnell, & Hamilton-Craig, 2011), as dysfunction of heart rate variability (HRV; a marker of ANS activity) can lead to CHD and has also been associated with depression. In the present thesis, risk factors relating to depression and mortality were explored, and an intervention (mindfulness-based cognitive therapy [MBCT]) with potential ANS impact was trialled.

The key constructs underpinning this thesis are defined and described in the literature review which follows, including depression, MBCT, cardiac function, CHD and coronary artery disease (CAD), and the ANS and HRV. The mechanisms relating the two conditions of depression and CHD are complex; therefore a detailed review is produced followed by the three published articles and the discussion.

1. DEPRESSION

1.1. Key Concepts

Health and Mental Health

In 1948, the WHO defined health as "a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity" (WHO, 2006, p. 1). More recently the WHO has defined mental health as a state of well-being whereby individuals and groups have the capacity to interact with one another and the environment in ways that promote subjective well-being, optimal development and use of cognitive, affective and relational abilities (WHO, 2005). Mental health comprises an individual's ability to recognise his or her own potential and abilities, and to cope with daily stressors of life without experiencing extensive emotional and behavioural incapacity (WHO, 2005). Improving and maintaining mental health remains a priority for the Australian government, with the aim of lowering the personal costs of ill-health and creating healthy living conditions and environments (Commonwealth Department of Health and Aged Care & AIHW, 1999; WHO, 2005). An individual who is able to manage daily obstacles, function effectively among his or her peers and society, and engage in health-promoting behaviour is said to have a heightened level of mental health (Australian Bureau of Statistics [ABS], 1998).

Mental Disorder

People who suffer from a mental disorder typically have diminished mental health. A mental disorder implies the existence of a clinically significant behavioural or psychological set of symptoms that are commonly associated with distress, pain, disability or a loss of freedom, and interferes with interpersonal relationships and the ability to function effectively (American Psychiatric Association [APA], 1994). Numerous mental disorders have been identified, and can be cognitive, emotional, psychological or behavioural in nature, and may require treatment to alleviate the symptoms (APA, 1994). In Australia, mental disorders remain the largest non-fatal burden of disease, with 45% of Australians reporting a lifetime mental disorder and 20% reporting a mental disorder in the previous 12 months (ABS, 2008a).

Depression

Depression is a type of mental disorder. It is defined in different ways, from a

non-clinical definition which describes transient states of low mood experienced by most people at some stage in their life, through to severe clinical psychiatric disorders (Commonwealth Department of Health and Aged Care & AIHW, 1999). Depression is characterised by feelings of sadness and hopelessness, loss of confidence, self-esteem and interest or pleasure in activities, diminished concentration end energy, suicidal thoughts, and sleep and appetite disturbances (APA, 1994). As depressive feelings are common in life, especially after experiencing setbacks in life, depressive disorder is only diagnosed when the symptoms reach a threshold and last at least two weeks (APA, 1994). Depression varies in severity, ranging from mild to severe and can be episodic, recurrent or chronic (APA, 1994).

The clinical diagnosis of depression is based on numerous signs and symptoms (APA, 1994). During the data collection phase of this thesis, the Diagnostic and Statistical Manual (DSM) of Mental Disorders, fourth edition (DSM-IV; APA, 1994) (which underpins much clinical practice in Australia) and the International Classification of Diseases (ICD), tenth edition (ICD-10) (WHO, 1992) were the most widely used classification system for depressive disorders. The ICD-10 is based on international comparisons and divides depression along a severity continuum: mild, moderate and severe, with or without psychotic symptoms (WHO, 1992).

The mood disorders category of the DSM-IV contains a subcategory 'major depressive disorder' (MDD). The presence of depressive symptoms may predict major depression (Judd, Akiskal, & Paulus, 1997), however in order to receive a diagnosis of MDD, the individual's symptoms must meet the specific criteria. MDD is characterised by one or more episodes of more persistent and pervasive disturbances in mood and symptoms. It is diagnosed by the presence of at least five out of the nine symptoms listed in Table 2 (APA, 1994)**,** including depressed mood or loss of interest for most of the time over the past two weeks.

Table 2

DSM-IV Major Depressive Disorder Symptoms

Symptoms
1. Depressed mood or irritable most of the day, nearly every day.
2. Decreased interest or pleasure in all or most activities, most of the day, nearly every day.
3. Significant increases or decreases in appetite (unintentional weight loss or gain)
4. Insomnia or hypersomnia
5. Psychomotor agitation or retardation
6. Fatigue or loss of energy
7. Feelings of worthlessness, or excessive or inappropriate guilt
8. Diminished ability to concentrate or indecisiveness
9. Recurrent thoughts of death or suicide

Note. Adapted from *Diagnostic and Statistical Manual of Mental Disorders* (4th ed., p. 327), by APA, 1994, Washington, DC: Author. Adapted with permission.

Once a diagnosis of MDD has been made, more detailed information about the diagnosis can be provided in the form of "specifiers" (APA, 1994). The use of specifiers provides more information about a person's condition, helps with choosing which treatment may be most effective, and aids the prediction of the course and prognosis of the illness. Possible specifiers to describe the episode include (APA, 1994):

- Mild, moderate, severe without psychotic features, severe with psychotic features, in partial remission, in full remission
- Chronic
- With catatonic, melancholic, atypical features
- With postpartum onset

It should be noted that the newer edition of the DSM (DSM-5) was released in 2013, with changes to the diagnostic criteria from DSM-IV to DSM-5 (refer to the reference APA, 2013 for a list of changes). However, no major changes were made to the diagnostic criteria for MDD. The core symptoms, as well as the requirement for the symptoms to have lasted for at least two weeks, remain the same (APA, 2013).

For the purpose of this thesis, the term “depression” will mean either a clinical diagnosis based on the DSM-IV (such as MDD) or ICD-10, or feelings and symptoms of depression (as listed above) lasting for at least two weeks. Thus, when depression is

referred to throughout this thesis, it excludes transient states of low mood experienced by most people throughout their life.

1.2. Diagnosis

Clinical Assessment

Before diagnosing a mental health disorder such as depression, a medical practitioner will perform a medical examination to rule out other conditions that may causes symptoms similar to depression (Dale, Sorour, & Milner, 2008; National Institute of Mental Health [NIMH], 2011). The evaluation may include such tests as blood tests to rule out viruses, infection or chronic diseases. Thyroxine (to exclude hypothyroidism), basic electrolytes and serum calcium (to exclude metabolic disturbances) may also be measured in a blood test (Dale et al., 2008; NIMH, 2011).

After medical causes are ruled out, the criterion standard for diagnosing depression in clinical practice and research settings is a structured diagnostic interview, conducted by a suitably trained general practitioner, psychologist or psychiatrist (NIMH, 2011). The assessor will record the person's current circumstances, biological and family history and current symptoms, aiming to formulate the possible biological, psychological or social factors impacting on the individual's mood (NIMH, 2011). The assessment also includes a mental state examination to detect the person's current mood and thought content, in particular thoughts of hopelessness, self-harm or suicide, or an absence of positive thoughts or plans. The patient's current methods of mood regulation, such as use of alcohol or drugs, will also be recorded (NIHM, 2011).

DSM-IV and ICD-10 Criteria

As previously mentioned in Section 1.1, the DSM-IV and ICD-10 have been the most widely used systems for the diagnosis of depression. After the medical, biological, psychological and social factors that may be impacting mood have been assessed, the structured diagnostic interview will form the basis for making a diagnosis of depression according to DSM-IV or ICD-10.

Questionnaires

The diagnostic interview is often too long to be used practically as a tool in research settings (McDowell & Newell, 1996). Therefore, questionnaires have been

developed to screen for depression, such as the Beck Depression Inventory (BDI; Beck, Ward, Medelson, Mock, & Erbaugh, 1961) and the Center for Epidemiologic Studies Depression Scale (CES-D; Radloff, 1977). Several questionnaires were utilised during the course of this research, and the measurement properties of the CES-D (and other questionnaires utilised) are discussed further in Chapters Four, Five and Six. Once diagnosed, the patient can be treated in several ways. The most common treatments are medication and psychotherapy (discussed in Section 1.6).

1.3. Prevalence

Prevalence is a measure of how commonly a condition or illness occurs within a population (ABS, 2008a). Since the 1970's, community surveys have reported the prevalence of depression in adult populations (Wilhelm, Mitchell, Slade, Brownhill, & Andrews, 2003). Estimation of the prevalence of depression in the general community has continued to be of increasing interest over the last two decades (Wilhelm et al., 2003).

Depression is one of the most prevalent psychiatric conditions, and a major cause of morbidity and mortality worldwide (Mathers et al., 2008). One in five people will suffer a lifetime major depressive episode (Judd et al., 2000) and those who experience a single episode often develop chronic depression with up to 80% suffering multiple episodes during their lifetime (Kingston, Dooley, Bates, Lawlor, & Malone, 2007). Each new episode may increase in severity, increase the risk of experiencing another episode, and may indicate decreased survival time between episodes (Hart, Craighead, & Craighead, 2001).

Estimates of the prevalence of major depression range from 2-5% (Myers et al., 1984) to 4-7% in the general population (Ayuso-Mateos et al., 2001; Steffens et al., 2000). Rates are higher in primary care settings at 5-10% (Kessler et al., 1994) and even higher among medical/surgical inpatients at 6-14% (Feldman, Mayou, Hawton, Arden, & Smith, 1987; Katon & Schulberg, 1992; Magni, Schifano, & de Leo, 1986).

Epidemiological studies indicate that the prevalence of depression increases with age into mid-life (but not beyond). A prevalence of 1-2% is reported in school age children (Costello, Mustillo, Erkanii, Keeler, & Angold, 2003), 3-8% in adolescence

(Fergusson, Horwood, Ridder, & Beautrais, 2005) and lifetime prevalence into adulthood is 20% (Kessler et al., 1994).

In Australia, depression is the most commonly diagnosed mental disorder (AIHW, 2008; AIHW, 2010). The 2007 Health and Well-Being Survey conducted by the ABS (ABS, 2008a) sampled adults in urban and rural areas of Australia, and found that depression was the most prevalent affective disorder (i.e., mood disturbance or change in affect), with a 12-month prevalence rate of 4.1% (males 3.1%, females 5.1%). The common finding that women exhibit higher levels of depression compared to males has been widely documented across multiple studies and in a variety of settings (Blazer, Kessler, McGonagle, & Swartz, 1994; Van de Velde, Bracke, & Levecque, 2010; Wilhelm et al., 2003). Numerous explanations have been proposed for the gender differences in depression, including genetic, hormonal, biological, psychological and social factors (Goldberg, 2006; Leach, Christense, Mackinnon, Windsor, & Butterworth, 2008; Piccinelli & Wilkinson, 2000).

Comorbidity refers to the occurrence of two or more disorders at the same time and is commonly found among people with mental disorders (AIHW, 2012). High levels of comorbidity occur between depression, medical illnesses such as CHD (Carney & Freedland, 2009), and other mental disorders such as anxiety (Kaufman & Charney, 2000; Kessler, Chiu, Demler, Merikangas, & Walters, 2005; Merikangas et al., 2003). The point prevalence range of depression has been estimated as 14-47% in CHD patients (Ahto et al., 1997; Gonzalez et al., 1996; Lesperance et al., 2000; Lett et al., 2004; Valkamo et al., 2001). About 50-60% of persons with depression or anxiety have a second diagnosis of anxiety or depression (Kaufman & Charney, 2000; Kessler et al., 2005). The prognosis for people with comorbid depression and anxiety is poorer than for people who have a depression or anxiety disorder alone. They often experience more severe symptoms, increased risk of suicide, a more chronic course and more somatic complaints. In addition, depression and anxiety comorbidity is more difficult to treat as it takes more time to remission and higher doses of medication are often needed (Belzer & Schneier, 2004). In addition, comorbid anxiety is common among depressed CHD patients, with rates ranging between 18-62% (Tully & Cosh, 2013).

1.4. Health Outcomes, Health Status and Quality of Life

Health Outcomes

As well as depression prevalence, researchers often analyse health outcomes, defined as an outcome or result of a health condition or health intervention that affects a person's life (Ware, 1987). A health outcome may be a hospital admission or a death statistic. Meta-analyses suggest an increased risk of mortality in depression (relative risks of 1.81 and 1.58) compared to non-depressed individuals (Cuijpers & Smit, 2002; Cuijpers et al., 2013). This increased risk not only exists in major depression, but also in sub-threshold depression (Cuijpers et al., 2013) and in sub-clinical forms of depression (Cuijpers & Smit, 2002). However, a higher relative risk was not confirmed in all meta-analyses (Van den Akker, Schuurman, Ensinck, & Buntinx, 2003).

Health Status and Quality of Life

Health outcomes and health status represent overlapping concepts and are often used interchangeably. However, while health outcomes refer to an outcome of a health condition or intervention, health status refers to the way a health condition or intervention affects an individual. It is the level of health of an individual or population as subjectivity assessed by the individual (Jaeschke, Singer, & Guyett, 1989). More specifically, health status may be defined as the range of manifestation of disease in a patient, including symptoms, functional limitation, and QoL (Rumsfeld, 2002). Over the years, attention has been given to the effect of depression and its treatments on the health status of the patient, specifically QoL and health-related QOL (HRQoL) (IsHak et al., 2011). Numerous definitions of QoL are reported in the literature and are used interchangeably with functioning, functional impairment, or psychosocial functioning (Greer, Kurian, & Trivedi, 2010). However, according to WHO, QoL refers to "individuals' perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standard and concerns" (WHO, 1997, p. 1). QoL is a broad ranging concept affected in a complex way by the person's: (1) subjective evaluation, (2) physical and psychological status, (3) cultural, social and environmental context, and (4) assessment of specific life domains such as health, work, family and social relations, and leisure activities (WHO, 1997), and includes but should not be confused with the mores specific concept of HRQoL.

The definition of HRQoL is also rarely agreed upon in literature (McDowell & Newell, 1996) but most definitions refer to HRQoL as a multi-dimensional construct that encompasses several dimensions: social, physical, psychological, overall life satisfaction/well-being and perceptions of health status (Patrick & Erickson, 1993). HRQoL differs from QoL in that the focus is on health (Thompson & Roebuck, 2001). The term HRQoL is a distinct construct which refers to the impact that health conditions and their symptoms have on an individual's QoL, and covers aspects of life that are not generally related to health, such as quality of medical treatment (Guyatt, Feeny, & Patrick, 1993). This allows the measurement of the impact of different experiences and treatments for the same condition, or the impact of different treatment across different conditions (Thompson & Roebuck, 2001). Thus, HRQoL assesses the effect of treatment, functional outcome and QoL of disease states. HRQoL is commonly measured using self-report psychometric questionnaires, such as the Short Form-36 (SF-36; Ware & Sherbourne, 1992), which was used in Studies 2 and 3.

HRQoL is increasingly being viewed as a marker of health care quality and for disease management programs. Thus, it is often analysed as an endpoint in clinical trials in order to further understand patient outcomes (Dougherty, Dewhurst, Nichol, & Spertus, 1998). With regard to depression, research has consistently demonstrated that depressed peoples' HRQoL is significantly impaired compared to healthy non-depressed individuals (IsHak et al., 2011; Lenox-Smith et al., 2013; ten Doesschate, Koeter, Bockting, & Schene, 2010) and also lower than that of people with chronic medical illnesses, including CHD, hypertension, diabetes, cancer and chronic pain (Bonicatto, Dew, Zaratiegui, Lorenzo, & Pecina, 2001; Wells & Sherbourne, 1999; Wells et al., 1989). In addition, depressed people were found to have longer-lasting decrements (over the 2 year follow-up) in HRQoL domains than those with chronic medical illnesses (Hays, Wells, Sherbourne, Rogers, & Spritzer, 1995). When depression is comorbid with other medical and psychiatric illnesses such as anxiety, panic disorder or CHD, the deterioration in HRQoL is compounded (Mittal, Fortney, Pyne, Edlund, & Wetherell, 2006; Ruo et al., 2003; Swenson et al., 2003).

1.5. Aetiology: Risk and Protective Factors

Given the high prevalence of depression and the associated adverse consequences, such as impaired general functioning, decreased QoL and increased

mortality, understanding the aetiology of this disorder is important. This may assist in understanding risk factors and thus in the detection and treatment of depression, and in reducing symptoms, improving QoL and preventing an unfavourable prognosis. The aetiology of depression is complex and is affected by a wide variety of factors, from those at the biological level to social factors. The experience of certain factors may increase the individual's vulnerability to depression, whereas other factors may act as a protective barrier against depressive symptomology.

In addition, many contributors to depression aetiology are also shared with CHD aetiology. Depression aetiology will therefore only be discussed here in brief, as the mechanisms linking depression and CHD are discussed thoroughly in Section 6.2. As many factors are associated with depression, only some of the main risk factors are examined. Dobson and Dozois (2008) provide a more extensive review of the risk factors for depression.

Genetic Factors

Evidence that depression runs in families continues to grow. Genetic factors are one mechanism of familial transmission. Findings from a meta-analysis support the familial aggregation of depression (P. F. Sullivan, Neale, & Kendler, 2000). First-degree relatives of people with depression are at a two-fold increased risk of experiencing depression themselves (Shortt & Spence, 2006). In addition, research support higher concordance rates for depression in monozygotic twin pairs (genetically identical twins) than dizygotic twins (fraternal twins who share half their genes on average), suggesting the involvement of a genetic component in depression susceptibility (P. F. Sullivan et al., 2000). P. F. Sullivan and colleagues (2000) further concluded from their meta-analysis of five twin studies that familial aggregation was due to additive genetic effects (37%) and individual-specific environmental effects (63%), with a minimal contribution of shared environmental effects.

Genome linkage scans of recurrent depression disorder have provided evidence for the linkage of several chromosomal regions. Chromosome variants linked to depression, for example 12q, 13q and 15q, have been previously implicated in panic, unipolar and bipolar disorders (Forty, Zammit, & Craddock, 2008). A variant of 12q also contains a gene, DAO, which has been associated with both bipolar disorder and

schizophrenia (Forty et al., 2008). Other genes have also been implicated in depression. The polymorphism of the 5-HTT serotonin transporter gene (which codes for the serotonin transporter protein and facilitates the reuptake of serotonin from the synaptic cleft in serotonergic neurons) is linked to the pathogenesis of depression (Furlong et al., 1998; Ogilvie et al., 1996; Owens & Nemeroff, 1994). People with one or two short alleles of the gene become depressed more often after stressful events than people who have two long alleles of this gene (Caspi et al., 2003). While several other genetic polymorphisms of monoamine systems – MAO-A or COMT have been implicated in depression, particular attention has been devoted to the contribution of the serotonin gene. Genetic factors are discussed in more detail in Section 6.2.

Biological Factors

The 5-HTT serotonin transporter gene can be used to predict selective serotonin reuptake inhibitor (SSRI) response in the context of life stress (Caspi et al., 2003). Thus, depression also involves the interaction of life stress with genetic factors to produce physiological and psychological dysfunction. Prolonged exposure to stress can produce characteristic alterations in brain transmitter function often described as a "chemical imbalance". This refers to alterations in the major chemical messenger systems responsible for neuronal transmission: serotonin (5HT), norepinephrine (NE; also known as noradrenaline) and dopamine (Saveanu & Nemeroff, 2012). Depression has been associated with reductions in neurotransmission in these systems, and the alterations produce the psychological and somatic symptoms characteristic of depression (Saveanu & Nemeroff, 2012).

Depression has further been associated with dysfunction in circadian rhythms, such as sleep disturbances, including insomnia or hypersomnia, nightmares and nocturnal panic attacks, and fragmented sleep, including an increased latency to sleep, increased number and duration of nocturnal awakenings and difficulty falling or staying asleep (Germain & Thase, 2008). In addition, alterations in the timing, duration and intensity of rapid and non-rapid eye movement sleep have been reported (Germain & Thase, 2008). It has been suggested that sleep disturbances, such as those listed above, are not only correlates of the disorder and risk factors for recurrence, but are correlates of vulnerability to and onset of the disorder (Germain & Thase, 2008). Insomnia, for example, has been reported to precede the onset of a first depressive episode in 40% of

depressed people, and preceded the recurrence of depression in 56% of cases (Ohayon & Roth, 2003). Several models have been proposed to explain how sleep disturbances contribute to the pathogenesis of depression (Dobson & Dozois, 2008; Chapter Five).

Autonomic Factors

Research suggests that autonomic factors are important in contributing to the onset of depression. People who are depressed often show signs of dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis. Since the relationship between the ANS and depression and CHD is a main topic of this thesis, autonomic processes (including the HPA) are extensively analysed in Section 7.4. Therefore, it is discussed in brief here. The HPA is a stress regulation system (Tortora & Derrickson, 2012). Psychological events can trigger this dysregulation, which has been associated with psychological disorders such as depression (Musselman et al., 1998; Stapelberg et al., 2011). This, in turn, has been linked to decreased cardiac vagal control (CVC; discussed in Section 7.2) and HRV (Thayer & Sternberg, 2006).

Inflammatory Factors

The immune system can be activated by the build-up of atherosclerotic lesions, resulting in increased cytokine production (Tousoulis, Davies, Stefandis, Toutouzas, & Ambrose, 2003). It has been suggested that atherosclerosis is a risk factor for depression (Frasure-Smith & Lesperance, 2005), as increased levels of cytokines cause depressive-related symptoms such as loss of appetite, fatigue and social withdrawal (Frasure-Smith & Lesperance, 2005). In addition, it is believed that atherosclerosis compromises cerebral blood supply, causing neuronal loss in brain regions involved in mood and cognition, resulting in depression (Alexopoulos et al., 1997; Frasure-Smith & Lesperance, 2005). This theory is known as the 'vascular depression hypothesis' (Alexopoulos et al., 1997).

Behavioural Factors

Poor health behaviours such as high use of tobacco, alcohol and cannabis are associated with depression, and these behaviours are more common in men than women (Leach et al., 2008). In addition, not only is a lack of physical activity associated with depression (Leach et al., 2008), but decreased activity level and poor diet can lead to obesity, and obesity is a known risk factor for depression. A meta-analysis of 15 studies

found that obesity increased the risk of depression (Luppino et al., 2010). Furthermore, metabolic syndrome (a combination of metabolic conditions such as obesity and diabetes) has been associated with an increased prevalence of depression in men and women (Skilton, Moulin, Terra, & Bonnet, 2007).

Cognitive Factors

Cognitive theorists have suggested that emotions and behaviour are determined not just by events per se, but by interpretation, thoughts, expectancies and beliefs about the events (Shortt & Spence, 2006). Many cognitive models of psychopathology utilise diathesis-stress formulations, proposing that certain styles of thinking represent a diathesis that in the presence of negative life stress increases vulnerability to depression (Shortt & Spence, 2006). These cognitive theories and models include the cognitive thread theory and schemas, learned helplessness model and the attributional style theory. However, alternatives to the cognitive vulnerability theories include the differential activation hypothesis, response-style theory (about rumination, problem-solving and distraction), and theories of optimism and pessimism.

Social Factors

Life events are strongly related to depression and a reciprocal relationship exists between the two. Individuals in their first episode of depression are more likely to have experienced preceding stressful life events than those with a recurrence. In turn, stressful life events strongly predict the onset of depression, rather than recurrence (Harkness, 2008). A review showed that significantly more depressed patients had at least one major negative event, and also had significantly more events prior to onset, than controls in a comparable time period (Mazure, 1998). Depressed patients were 2.5 times more likely to experience a major life event prior to onset than controls (Mazure, 1998). Similarly, severe events, such as a partner's affair, physical abuse or a low-income single mother losing a job, are also associated with depression, with women being 3 times more likely to have suffered a severe life event prior to onset (Harkness, 2008). Although it is known that life events and depression are correlated, it has been also suggested that the correlation may be further mediated by the underlying shared genetic vulnerability. That is, the same genetic traits may underlie an individuals' risk of exposure to stressful situations (Harkness, 2008).

Furthermore, a number of interpersonal factors have been implicated as increasing the risk for depression. Relationship instability and interpersonal problems, particularly involving family, were associated with depression in women, whereas employment problems were common amongst men (Leach et al., 2008). Many studies have shown poor interpersonal skills, small social networks, low social support, social withdrawal and isolation are predictors of depression (Joutsenniemi, Martelin, Martikainen, Pirkola, & Koskinen, 2006; Lakey & Cronin, 2008; Leach et al., 2008). Similarly, studies have consistently demonstrated that depressed people perceive they have less support than non-depressed people (Lakey & Cronin, 2008).

Protective Factors

The greater the number of risk factors experienced, the higher the likelihood of developing problems. However, not all people exposed to one or more risk factors develop depression (Shortt & Spence, 2006). Protective factors decrease the likelihood of undesirable outcomes or increase the likelihood of positive outcomes. Many protective factors represent the opposite end of a risk factor.

Many protective factors exist and not all can be discussed in this thesis. However, some protective factors include high self-esteem, the ability to self-reflect and a belief in a higher power beyond oneself (Shortt & Spence, 2006). Cognitive protective factors include optimism, attributional style, functional attitudes and problem-solving ability. The latter three can either have a direct risk or protective effect on depression, or buffer against depression in the presence of negative life stressors (Shortt & Spence, 2006). Active coping, for example, is associated with decreased emotional and behavioural problems, whereas avoidant coping is associated with increased mental health problems and decreased coping strategies (Dumont & Provost, 1999). Furthermore, optimists' coping strategies are more adaptive than pessimists, often using problem-solving strategies (Peterson, 2000). Optimism is also related to positive goal pursuit and action, and increased control beliefs such as self-esteem, which may prevent catastrophic thinking (Peterson, 2000) and depressive symptoms. Social factors also act as a positive mediator. Although the research surrounding social support is controversial (Lakey & Cronin, 2008), many studies have found that social support and good interpersonal skills were protective against depression (Leach et al., 2008; Shortt & Spence, 2006). A common behavioural protective factor is physical activity, which in

turn helps to fight obesity. Exercise, for example, is known to increase well-being and thus also protects against depressive symptomology (Leach et al., 2008; Shortt & Spence, 2006). Healthy eating and regular exercise may, in turn, help maintain healthy blood pressure, cholesterol and blood sugar levels, all of which can are risk factors for the development and progression of atherosclerosis (Tortora & Derrickson, 2012). As stated earlier, atherosclerosis may be a risk factor for depression (Frasure-Smith & Lesperance, 2005).

Although a majority of these risk and protective factors associated with depression have been studied comprehensively, other mechanisms, such as relations with the ANS, require further investigation. Understanding relationships of depression with the ANS may be beneficial in further understanding the course and outcome of depression, and may assist in the development on treatment strategies.

1.6. Treatment and Prognosis

Given the high prevalence of depression and its significant effect on mental and physical health, treatment programs have been designed to decrease depressive symptomology and increase QoL. Maintaining the state of wellness has become a primary challenge for mental health professionals (Mueller et al., 1999). The three most common treatments for depression are medication, electroconvulsive therapy (ECT) and psychotherapy.

Antidepressant Medication

Antidepressants are classified by their mechanism of action, including tricyclic antidepressants (TCAs), monoamine oxidase inhibitors (MAOIs), selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs) and "atypical" antidepressants. To find the most effective antidepressant for an individual that minimises side-effects, the dosage can be adjusted, or different classes of antidepressants can be utilised (NIMH, 2011). A substantial amount of evidence investigating the efficacy of antidepressant medication exists. Response rates to the first antidepressant medication administered range from 50-75%, and it can take six to eight weeks from the start of medication to remission for the patient to feel "normal" again (Karasu, Gelenberg, Merriam, Wang, & APA, 2000). Treatment is usually continued for 16-20 weeks after remission (Karasu et al., 2000), and sometimes up to a year is

recommended (Thase, 2006) to minimise the chance of recurrence. Individuals with chronic depression may need to take medication indefinitely to avoid relapse (NIMH, 2011). However, approximately 5-10% of patients maintained on antidepressants relapse yearly (Thase, 2006).

TCAs and MAOIs are among the oldest classes of antidepressants, and are thought to work by inhibiting the brain's reuptake of serotonin and/or NE (Holtzheimer & Nemeroff, 2006). For many years TCAs were the first choice of medication for depressed patients (Holtzheimer & Nemeroff, 2006). The efficacy of TCAs has been demonstrated (Arroll et al., 2005; Potter, Manji, & Rudorfer, 1998). However, because TCAs have such a broad mechanisms of action, they tend to have a high level of anticholinergic and antihistamine side effects, including dry mouth and eyes, constipation, blurred vision, difficulty urinating, mild cognitive disturbance, tachycardia, sedation and weight gain; moreover, overdose can be fatal (Holtzheimer & Nemeroff, 2006). MAOIs are also highly efficacious in the treatment of depression (Krishnan, 1998). However, they are limited in the requirement for patients to adhere to a low tyramine diet to prevent hypertension, and they carry greater drug-interaction risks than do other medications (Holtzheimer & Nemeroff, 2006). As a result of the negative side effects of TCAs and MAOIs, SNRIs and SSRIs were designed to provide the pharmacological benefit but with lower side effects. Current data indicate that SNRIs are effective antidepressants, even in "sensitive" groups such as the elderly (Detke et al., 2004; Nelson et al., 2005).

SSRIs have replaced TCAs and MAOIs as the first-line medication in the treatment of depression, owing to their relatively benign side effects and limited drug-drug interactions (Tollefson & Rosenbaum, 1998). SSRIs act on the brain neurotransmitter serotonin. They have been shown to have little to no anticholinergic or antihistamine side effects. They may cause insomnia, nervousness, agitation, sexual dysfunction, and gastrointestinal problems, such as nausea, diarrhoea and constipation, (Holtzheimer & Nemeroff, 2006), but these side effects are often tolerated by patients. Numerous trials have demonstrated the efficacy of SSRIs (Rush et al., 2004; Tollefson & Rosenbaum, 1998) and found little difference in efficacy between different types of SSRI (Kroenke, West et al., 2001; Stahl, 2000). Though effective, SSRIs, on average, have a small effect when used alone and some patients may improve insufficiently and

remain depressed (Bridge et al., 2007; Weisz, McCarthy, & Valeri, 2006). Combined psychotherapy and pharmacological treatment has been found to be more effective than medication alone (Pampallona, Bollini, Tibaldi, Kupelnick, & Munissa, 2004; Thase et al., 1997).

"Atypical" antidepressants (e.g., nefazodone and trazodone), so named because they don't fit into other classes of antidepressant, although each one works in a different way, are also widely used. The side effects vary according to the specific drug, and include seizures, sleepiness, weight gain and nervousness (Owens, Ieni, Knight, Winders, & Nemeroff, 1995; Owens, Morgan, Plott, & Nemeroff, 1997; Thase et al., 2005). Atypical medication is well tolerated by patients and has shown substantial evidence of effectiveness in the treatment of depression (Fawcett & Barkin, 1998; Keller et al., 2000; Thase et al., 2005).

Electroconvulsive Therapy

In ECT, pulses of electricity are sent through the brain via electrodes attached to the scalp, to induce a seizure while the patient is under general anaesthesia (Holtzheimer & Nemeroff, 2006). ECT is often seen as the 'last resort' for patients with severe major depression who have not responded to antidepressant medication, or less often, psychotherapy (NIMH, 2011). ECT has been found to be an effective treatment for depression, with response rates as high as 50-90%, even in patients who are resistant to other forms of treatment (Avery & Lubrano, 1979; Avery & Winokur, 1977; Avery & Winokur, 1978; Husain et al., 2004; Prudic et al., 1996, Sackeim et al., 2009). Furthermore, suicide attempt rates and mortality rates in depressed patients over 3 years of follow-up are lower with ECT (Avery & Lubrano, 1979; Avery & Winokur, 1977; Avery & Winokur, 1978; Prudic et al, 1996). Despite these benefits, ECT can have risks and side effects including memory disturbance, confusion, disorientation and cardiopulmonary complications (Fink, 2001; Zielinski, Roose, Devanand, Woodring, & Sackeim, 1993). However, these cognitive effects are often short-lived, with no evidence of persistent effects on memory (NIMH, 2011). A major limitation of ECT is its short-term effect and the high relapse rate. Without continuation pharmacotherapy, the risk of relapse is more than 80% within a year, making continued treatment necessary (Sackeim et al., 2001). Effective pharmacotherapy can lower the relapse rate to approximately 40% (Sackeim et al., 2001) while a combination of pharmacotherapy

and continued ECT can reduce rates even further (Ottosson & Odeberg, 2012). Although the ECT procedure has essentially remained unchanged since its introduction, advances in anaesthesiology have greatly improved its safety and tolerability (Holtzheimer & Nemeroff, 2006). Despite this, ECT remains a controversial treatment, and debate on its efficacy and safety continues (Ingram, Saling, & Schweitzer, 2008; Reisner, 2003).

Psychotherapy

Psychotherapy can be delivered to individuals or groups as a treatment for depression, and is recommended as one of two first-line treatment options (antidepressant medication being the other) for people with persistent depressive symptoms or mild to moderate severity depression (NIMH, 2011). However, for severe depression or for certain people psychotherapy may not be enough, and as discussed previously, ECT may be an option (NIMH 2011). Psychotherapy is often used in conjunction with medication (Thase, 1999). Various types of therapy have been shown to be effective, including interpersonal psychotherapy (Cuijpers et al., 2011; van Hees, Rotter, Ellermann, & Evers, 2013), problem-solving therapy (Arean, Hegel, Vannoy, Fan, & Unuzter, 2008; Bell & D'Zurilla, 2009) and mindfulness-based cognitive therapy (MBCT), of which the most popular and well researched is cognitive behaviour therapy (CBT).

The underlying concept of CBT is that thoughts and feelings influence behaviour. CBT aims to teach patients to recognise, restructure and replace maladaptive cognitions, emotions and behaviour with adaptive ones, by challenging the individuals thought process and reactions (Dobson & Dozois, 2001). A substantial body of evidence supports the short and long-term efficacy of CBT for depression in adults (DeRubeis, Gelfand, Tang, & Simons, 1999; Gloaguen, Cottrauxa, Cucherat, & Blackburn, 1998; Mann, 2005) and youth (Klein, Jacobs, & Reinecke, 2007; Weersing & Gonzalez, 2009). CBT has also shown to be efficacious for depression in cardiac patients (Carney, Freedland, Stein et al., 2000; Freedland et al., 2009) suffering acute myocardial infarction (AMI; discussed in Section 4.4.1) (Freedland et al., 2012) and chronic heart failure (CHF) (Tully, Selkow, Bengel, & Rafanelli, 2014). Although the volume of research is small, a recent meta-analysis concluded that individuals also benefited from group CBT (Huntley, Araya, & Salisbury, 2012). The benefits were maintained in the

short, medium, and long-term (Huntley et al., 2012). CBT has been said to have a "preventative" effect long-term (Gloaguen et al., 1998). In addition, combined treatment of medication and CBT has been found to be even more effective than CBT alone (Keller et al., 2000), and may improve the treatment response and reduce the risk of a relapse (Pampallona et al., 2004).

Although medication, ECT and psychotherapy have shown themselves effective in treating depression, the negative consequences of this disorder are not always averted, because a significant number of patients do not fully respond. Despite adequate treatment, up to 20% may show minimal or no response to aggressive interventions (Fink, 2001; Sackeim, 2001) and almost half of depressed patients continue to have some residual depressive symptoms or may relapse in the future (Fava, 2003). Others may not be able to tolerate the available treatment (Holtzheimer & Nemeroff, 2006). MBCT, a relatively new psychotherapy designed initially for the treatment of recurrent depression, has shown potential for symptom and health gains. MBCT is described in greater detail in the next section.

2. MINDFULNESS-BASED COGNITIVE THERAPY

Although psychotherapy (such as CBT) has been efficacious in treating depression by reducing depressive symptoms and relapse rates, the waiting lists for individual therapy are long, making treatment difficult to access (Hollon et al., 2005). In Australia up to two-thirds of people with anxiety and depression do not access effective treatment (Andrews & the Tolkien II Team, 2006). Pressure on health care resources and high relapse rates have increased the demand for continuation-phase treatments and/or prophylactic treatments (Vittengl, Clark, Dunn, & Jarrett, 2007). MBCT is one such treatment, as it is a group-based intervention and focuses on relapse prevention.

2.1. History of Mindfulness-Based Cognitive Therapy

Prior to MBCT, mindfulness-based stress reduction (MBSR), developed by Kabat-Zinn in the 1970's (Kabat-Zinn, 1982), was the first mindfulness group program to be developed and scientifically evaluated. The 8-week MBSR program was designed to help patients with chronic pain/diseases and health problems learn ways to manage and reduce stress and negative moods. By practising simple yoga postures, body scanning and various meditation techniques, including techniques focused on breathing and body awareness, MBSR focuses upon the progression of mindful awareness, or mindfulness (Grossman, Niemann, Schmidt, & Walach, 2004), by purposefully attending to the present moment with friendly interest and in a non-judgmental manner (Kabat-Zinn, 1990; Baer, 2003)

In the 1990s, three psychologists (Segal, Williams and Teasdale) proposed that depressed individuals could be taught to relate differently to their thoughts, emotional states and physical sensations that preceded a depressive episode. In doing so, the re-occurrence of and relapse into depression could be prevented (Segal, Williams, & Teasdale, 2002). Well-versed in CBT, they believed it was possible to develop a maintenance version of CBT, which could be applied to patients in recovery from depression (Segal et al., 2002; Teasdale, Segal, & Williams, 1995). Also aware of the work by Kabat-Zinn, they became intrigued that MBSR took an alternative perspective by teaching people to pay attention to their thoughts and emotional states as they occurred, but without judgement or trying to change them into something else (Segal et al., 2002).

As a result, Segal, Williams and Teasdale developed MBCT. MBCT was derived from a model of cognitive vulnerability to depressive relapse (Segal, Williams, Teasdale, & Gemar, 1996; Teasdale, 1988; Teasdale et al., 1995). According to the model, the pattern of negative thinking (that becomes activated in mildly depressed mood) differs for those who have previously experienced a depressive episode compared to those who have not. Downward mood shifts are more likely to produce recurrence, because they activate patterns of self-denigrating depressogenic thinking similar to those that prevailed in preceding episodes (Segal et al., 2002).

MBCT integrates aspects of CBT with MBSR but MBCT differs in terms of its focus on ruminative thinking in depression, and its delivery within a cognitive therapy paradigm. It is an 8-week group based intervention, whereby participants are trained in techniques derived from both mindfulness meditation and cognitive therapy (Kingston et al., 2007). MBCT is designed to teach participants to disengage from habitual and repetitive patterns of negative thinking (e.g., rumination and worry) that are thought to increase vulnerability to depression, and to improve awareness and non-reactive acceptance of negative thoughts and feelings (Segal et al., 2002) by purposefully attending to the present moment with friendly interest and in a non-judgmental manner (Baer, 2003; Kabat-Zinn, 1990). It is hypothesised that this reduces rumination and assists in responding more adaptively to depressive and anxious symptoms (Williams, 2008). MBCT also includes basic education about depression and a number of exercises derived from cognitive therapy that demonstrate the links between thinking and feeling and how participants can care for themselves, especially when they notice a downturn in their mood (Williams & Kuyken, 2012). Unlike CBT, MBCT does not try to change the content of negative thinking; rather it encourages participants to relate differently to their thoughts, feelings and body sensations (Williams & Kuyken, 2012). In doing so, participants learn to recognise when mood is decreasing, and to relate to thoughts and feelings as passing events in their mind, rather than to identify or treat them as accurate representations of reality. This breaks the old association between negative mood and negative thinking that would lead to rumination and is seen as a way to reduce future risk of relapse and recurrence of depression (Williams & Kuyken, 2012). Participants learn that distressing emotions, thoughts and sensations come and go, and to stay in touch with the present moment instead of ruminating about the past or worrying about the future (Williams & Kuyken, 2012).

Although initially designed for the prevention and treatment of relapse in depression, MBCT has also been applied to the treatment of active depression and anxiety (Evans et al., 2008; Kenny & Williams, 2007; Teasdale et al., 2000, van Aalderen et al., 2012).

2.2. Mindfulness-Based Cognitive Therapy and Depression Literature

Since its introduction, interest in MBCT has increased significantly, with the growth in evidence for its effectiveness in preventing relapse of depression and reduction in depressive symptoms. Reduced relapse rates of recurrent depression were found by Teasdale and colleagues (2000); 40% of patients with a history of three or more major depressive episodes who participated in MBCT experienced relapse, as compared with 66% in the treatment as usual (TAU) group. Similarly, a replication study by Ma and Teasdale (2004) found relapse rates of 36% for the MBCT participants and 78% for TAU group, thus, obtaining an even larger effect size. Consequently, research continues to show a relapse-preventing effect (Godfrin & van Herringen, 2010; Kuyken et al., 2008; Williams et al., 2008). Some of these trials suggest relapse rates can be reduced to about 50% in the first 12-months after treatment completion. Recently, research has also investigated use of MBCT as a treatment for people who are currently actively and recurrently depressed. Barnhofer and colleagues (2009) showed that MBCT not only prevented relapse, but also successfully reduced symptoms (with large reductions, from the severe to the mild range, on the BDI) in patients with recurrent depression who were currently symptomatic. Further studies report the effectiveness of MBCT in reducing depressive symptoms post-treatment (Finucane & Mercer, 2006; Kingston et al., 2007; van Aalderen et al., 2012). Furthermore, studies have found MBCT to improve QoL in depressed clinical (Godfrin & van Herringen, 2010; Kuyken et al., 2008), non-clinical (Kaviani, Hatami, & Shafiabadi, 2009; Kaviani, Javaheri, & Hatami, 2011), and sub-clinical populations (Kaviani, Hatami, & Javaheri, 2012) and in patients with medical and mental health problems (Roth & Robbins, 2004).

Similarly, uncontrolled trials have yielded symptom improvements in the medium to large effect size range for outpatient samples including treatment-resistant depression (Eisendrath et al., 2008; Finucane & Mercer, 2006; Kenny & Williams, 2007), generalised anxiety disorder (Evans et al., 2008; Craigie, Rees, Marsh, &

Nathan, 2008), and mixed anxiety and mood disorders (Ree & Craigie, 2007). These trials provide supportive evidence that MBCT is clinically applicable to clients with a range of severe and chronic mental health problems. Consistent with previous findings, a recent and robust meta-analysis showed that mindfulness-based therapy (mainly MBCT and MBSR) was associated with large improvements in anxious and depressive symptom in adults with a primary problem of anxiety and depression; and medium improvements in patients with health-related problems (Hofmann, Sawyer, Witt, & Oh, 2010). The analysis showed that improvements occurred across a wide range of disorders at varying levels of severity, with improvements generally maintained at follow-up. Hofmann and colleagues (2010) concluded that the benefits of mindfulness-based therapies are transdiagnostic in nature, that is, they have a broad range of applicability, as they appear to address emotional and cognitive processes underlying the maintenance of a range of disorders.

2.3. Mindfulness-Based Cognitive Therapy and Physiology

While numerous studies on the association between MBCT and psychological and neurological changes exist, physiological studies are limited. Altered HRV, a marker of ANS dysfunction, is common in both depressed and CHD patients. Whether MBCT is a suitable treatment for patients with medical illnesses, such as comorbid depression and CHD, remains unanswered. Future analysis of the effect of MBCT on HRV in medical and mental health patients is indicated. This is further discussed in Section 8.6.

Research into the ANS and HRV remains an important means of providing targets for future therapies, which depressed patients may benefit from. Given that dysregulation and dysfunction of the ANS has been associated with CHD as well as with depression, patients with CHD may also benefit from these therapies.

3. THE HEART

This section of the thesis introduces the anatomy and physiology of the heart, relevant to the three studies. It begins by describing the structure and function of the heart and conduction system followed by the coronary blood circulation and factors that influence coronary artery blood flow and pressure. In subsequent sections, the pathophysiology of CHD and each specific cardiac condition studied in the manuscripts are explained in detail, with a key focus on obstructive coronary artery disease (CAD). Methods of diagnosis of CHD are also examined. Lastly, key concepts of non-obstructive CAD (NoCAD) are discussed.

3.1. Structure and Function of the Heart and Arteries

3.1.1. Components of the Heart

Layers of the Heart Wall

The heart is the centre of the cardiovascular system. The pericardium is the membrane that surrounds and protects the heart. The wall of the heart consists of three layers: the epicardium (external layer), the myocardium (middle layer), and the endocardium (inner layer) (Tortora & Derrickson, 2012). The epicardium is composed of two tissue layers and contains lymphatic and blood vessels, such as coronary arteries, that supply the myocardium. The innermost endocardium is a thin layer of endothelium overlying a thin layer of connective tissue. It provides a smooth lining for the chambers of the heart and is continuous with the endothelial lining of the large blood vessels attached to the heart, minimising surface friction as blood passes through the heart (Tortora & Derrickson, 2012). The middle layer, myocardium, comprises cardiac muscle tissue and makes up the bulk of the heart wall, approximately 95% (Tortora & Derrickson, 2012). The myocardium is the heart muscle responsible for the pumping action of the heart. This pump maintains the coronary circulation that supplies the heart with oxygen and nutrients to maintain cardiac function in order to supply the remainder of the body with blood (Canty, 2012).

Chambers of the Heart

The interior of the heart is divided into four chambers, which receive the circulating blood (Figure 2). The two upper chambers are called the right and left atria

(which pump blood into the ventricles) and the two lower chambers are the right ventricle (which pumps blood into the pulmonary circulation to/for the lungs) and left ventricle (which pumps blood into the systematic circulation through the aorta for the rest of the body), and are separated by an interventricular septum (a dividing wall or partition) (Tortora & Derrickson, 2012).

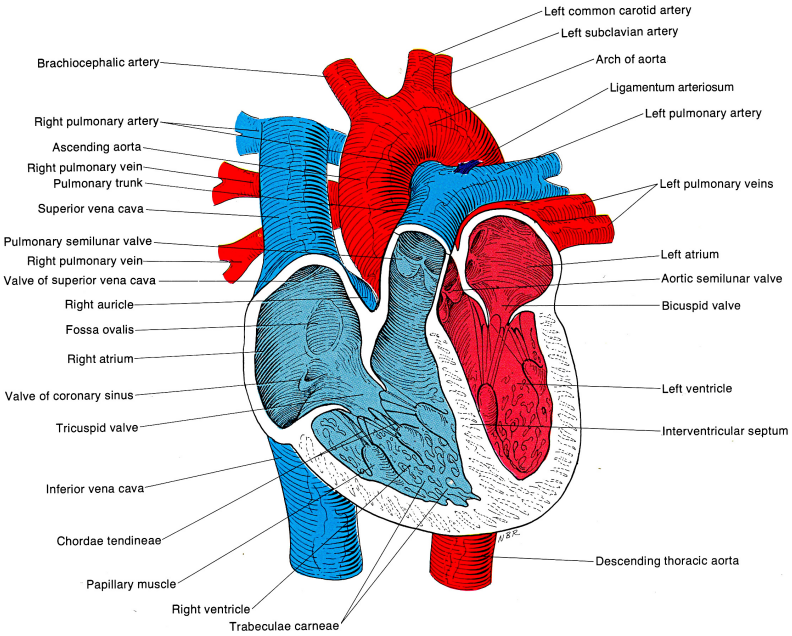

Figure 2. Structure of the heart. Reprinted from *Principles of Anatomy and Physiology* (3rd ed., p. 464), by G. J. Tortora and N. P. Anagnostakos, 1981, New York, NY: Harper and Row, Publishers, Inc. Reprinted with permission.

The flow of blood through the heart is depicted in Figure 3. The right atrium receives blood from all parts of the body (except the lungs) and pumps it into the right ventricle where it is pumped into the lungs. In the lungs, the blood releases carbon dioxide and takes up oxygen (Tortora & Derrickson, 2012). The oxygenated blood returns to the heart via the left atrium and is then pumped into the left ventricle, which then pumps the blood into the ascending aorta. From here, aortic blood is passed into a number of blood vessels to transport the blood to all parts of the body, excluding the lungs but including the coronary arteries, which supply the myocardium (Tortora & Derrickson, 2012).

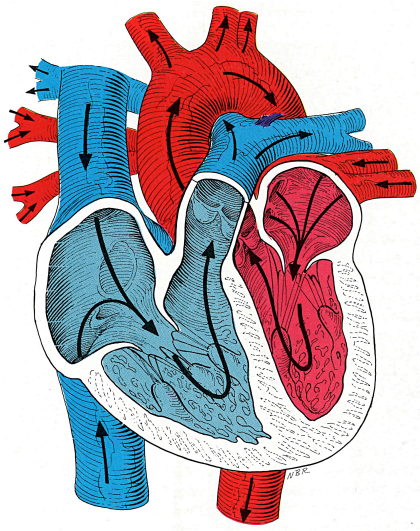

Figure 3. Path of blood flow through the heart. Reprinted from *Principles of Anatomy and Physiology* (3rd ed., p. 465), by G. J. Tortora and N. P. Anagnostakos, 1981, New York, NY: Harper and Row, Publishers, Inc. Reprinted with permission.

3.1.2. Electrical Conduction in the Heart

Conduction System of the Heart

The electrical conduction system enables the chamber walls of the heart to contract and relax in a coordinated manner so that the heart is an effective pump. This system consists of specialised cardiac muscle fibres that generate and distribute action potentials/electrical impulses that trigger heart contractions. Action potentials propagate through the conduction system from one muscle tissue to the next in a specific sequence. These specialised muscle tissues include the sinoatrial (SA) node (also known as the pacemaker), the atrioventricular (AV) node, the AV bundle (bundle of His), the bundle branches, and the Purkinje fibres (Tortora & Derrickson, 2012). Figure 4 shows a diagram of the conduction pathway. Each cardiac cycle is initiated by the SA node (located in the right atrium), which stimulates other areas before they are able to generate an action potential of their own, and thereby sets the basic rhythm of electrical excitation and pace for heart rate (HR) – hence its common name, pacemaker. However, the rate set (i.e., the timing and strength of each heartbeat) by the SA node (but not the cardiac rhythm) can be altered by nervous impulses from the ANS or by blood-borne chemicals such as thyroid hormone and epinephrine (also known as adrenaline) (Tortora & Derrickson, 2012). The impulses from the SA node spread to the right and left atria causing them to contract, and to the AV node. Thereafter, conduction continues down the AV bundle and then divides in the septum between the ventricles into right and left

bundle branches (Tortora & Derrickson, 2012). Finally, the Purkinje fibres that emerge from the bundle branches and pass into the cells of the myocardium stimulate contraction of the ventricles (Tortora & Derrickson, 2012). The contraction pushes blood upward toward the aorta (which supplies blood to the body and coronary arteries) and the pulmonary trunk (which carries blood to the lungs) (Tortora & Derrickson, 2012).

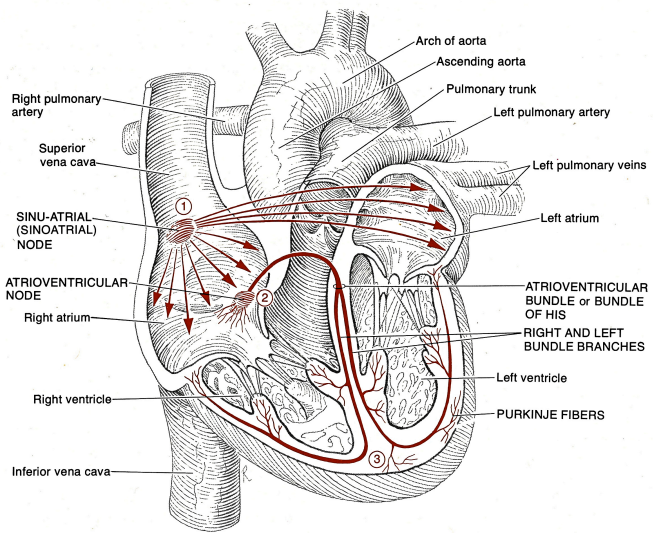

Figure 4. Conduction system of the heart. The conduction sequence of the heart marked by the numbers 1 to 3 generates the electrocardiographic pattern shown in Figure 5. Reprinted from *Principles of Anatomy and Physiology* (3rd ed., p. 469), by G. J. Tortora and N. P. Anagnostakos, 1981, New York, NY: Harper and Row, Publishers, Inc. Reprinted with permission.

Cardiac Cycle and the Electrocardiogram

In a normal heartbeat, the two atria contract simultaneously while the two ventricles relax, and vice versa. The term systole refers to the phase of contraction; diastole is the phase of relaxation (Tortora & Derrickson, 2012). A cardiac cycle, or complete heartbeat, consists of the systole and diastole of both atria and both ventricles (Tortora & Derrickson, 2012). The contraction and relaxation of the heart generates electrical changes throughout the conduction system. These changes can be detected by electrodes attached to the chest. The machine that records the patient's electrocardiogram (ECG) is called an electrocardiograph (also ECG). Each portion of the cardiac cycle produces a different electrical impulse. On an ECG these impulses appear as a series of up and down waves called deflection waves (Tortora & Derrickson,

2012). In a typical ECG record, three waves accompany each cardiac cycle (Figure 5). The P wave is a small upward wave that indicates atrial depolarisation; the spread of an impulse from the SA node through the left and right atrium, quickly followed by contraction of the atria (Tortora & Derrickson, 2012). This is the start of atrial systole. The QRS wave then begins as a small downward deflection, continues as a large, upright, triangular wave and ends as a small downward wave at its base. This wave represents ventricular depolarisation, that is, the spread of the electrical impulse through the ventricles (Tortora & Derrickson, 2012). This is ventricular systole. Atrial repolarisation is not visible on an ECG tracing because it occurs during ventricular depolarisation and is masked by the larger QRS wave. The dome-shaped T wave indicates ventricular repolarisation and occurs as the ventricles begin to relax (Tortora & Derrickson, 2012). Repolarisation occurs at a slower rate than depolarisation, which explains why the T wave is smaller and wider than the QRS wave. During the period of steady depolarisation, the ECG tracing is flat (Tortora & Derrickson, 2012). Heartbeat is made up of each of these three waves, and is derived from the interval between RR waves in the ECG.

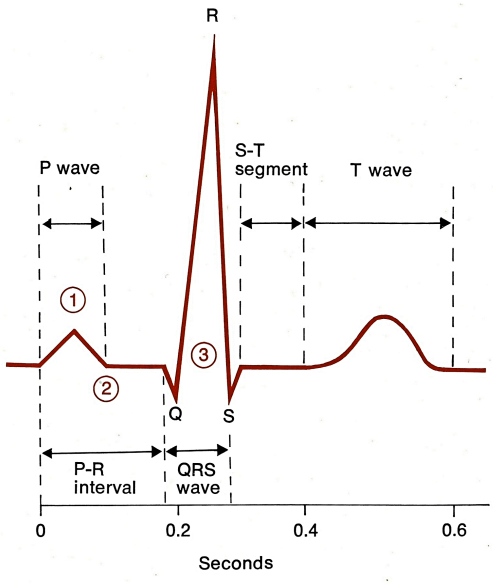

Figure 5. Normal electrocardiogram. The electrocardiographic pattern marked by numbers 1 to 3 reflects the conduction sequence of the heart shown in Figure 4. Reprinted from *Principles of Anatomy and Physiology* (3rd ed., p. 469), by G. J. Tortora and N. P. Anagnostakos, 1981, New York, NY: Harper and Row, Publishers, Inc. Reprinted with permission.

In reading an ECG, it is important to note the size of the waves and the time intervals because this can assist in diagnosis of heart conditions. An enlarged Q wave, for example, may indicate myocardial infarction (MI; i.e., heart attack) (Tortora & Derrickson, 2012). The ST segment (which begins at the end of the S wave and ends at the beginning of the T wave) represents the time between the end of the spread of the impulse through the ventricles and start of repolarisation of the ventricles (Tortora & Derrickson, 2012). The ST segment can be elevated or not in acute MI (AMI) and depressed in Cardiac Syndrome X (Section 5.3.1). Patients with ST-elevation MI (STEMI) will exhibit an elevated ST segment whereas those with non-ST elevation MI (NSTEMI) will not (Antman, 2012) (Section 4.4.1). When the heart muscle receives insufficient oxygen, as in the case of arteriosclerotic heart disease, the ST segment is depressed or the T wave is flat.

3.1.3. Coronary Arteries

Coronary Circulation

The nutrients from the blood in the heart chambers are unable to diffuse quickly enough to reach all layers of cells of the heart wall. For this reason, like any other tissue, the walls of the heart have their own blood vessels. The flow of blood through the blood vessels of the myocardium is called the coronary circulation (Tortora & Derrickson, 2012). Coronary arteries deliver oxygen-rich blood to the myocardium and cardiac veins remove the deoxygenated blood from the heart muscle. As a key focus of this thesis is obstructive CAD (which involves coronary arteries), coronary veins will not be explored and only the main coronary arteries are discussed.

The heart has two primary coronary arteries: the right coronary artery (RCA) and the left coronary artery (LCA), which divides into the anterior interventricular branch or left anterior descending (LAD) artery and the circumflex artery (Tortora & Derrickson, 2012) (Figure 6). Thus, the RCA, LAD and circumflex are considered the three main coronary arteries. Blood flows to the myocardium first through these large coronary arteries, then through branches of thousands of microvessels called arterioles (i.e., small arteries) (Tortora & Derrickson, 2012).

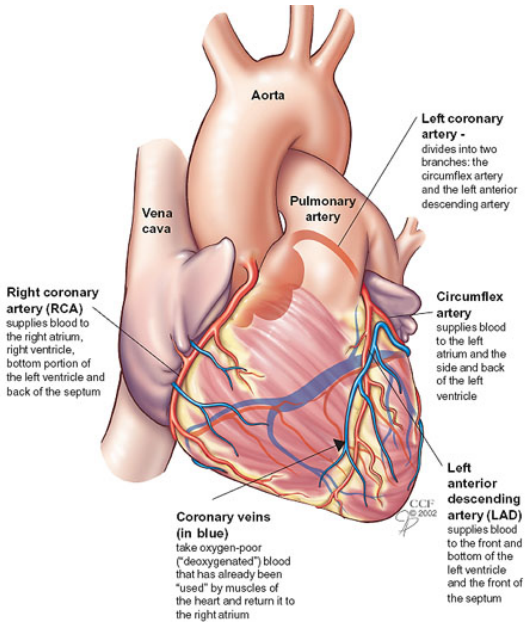

Figure 6. Coronary arteries. Reprinted from *The Coronary Arteries*, by Cleveland Clinic, 2009, Retrieved from http://my.clevelandclinic.org/heart/heartworks/coronary artery.aspx. Reprinted with permission.

The LCA and RCA originate from the left side of the heart as a branch of the ascending aorta and are often called epicardial coronary arteries because they run on the surface of the heart (Tortora & Derrickson, 2012). The RCA runs under the right atrium and divides into branches, which supply blood to the right atrium, right ventricle, lower portion of the left atrium and back of the septum (Cleveland Clinic, 2009; Tortora & Derrickson, 2012). The LCA (which supplies blood to two thirds of the heart) runs under the left atrium and divides into two arteries: the circumflex artery and the LAD. The circumflex artery supplies blood to the left atrium and the side and back of the left ventricle, and the LAD artery supplies blood to the front and bottom of the left ventricle and the front of the septum (Cleveland Clinic, 2009; Tortora & Derrickson, 2012).

Coronary arteries exhibit some degree of autoregulation, that is, an intrinsic ability to automatically regulate coronary blood flow to match metabolic demands and maintain a blood supply appropriate to the needs of the heart muscle (Tortora & Derrickson, 2012). However, coronary arteries are commonly affected by atherosclerosis (the build-up of plaque) and can become blocked, causing myocardial ischaemia (the restriction of blood flow), angina pectoris (chest pain) or MI. The coronary arteries are the only source of blood supply to the myocardium, and therefore

there is very little redundant blood supply, which is why blockage of these vessels can be critical. In obstructive CAD, blockages typically occur in one or more of the three main arteries (RCA, LAD and circumflex artery). In contrast, in NoCAD, the microvessels that branch off from the main arteries are damaged (Bugiardini & Bairey Merz, 2005).

Vasomotor Tone

Vasomotor tone (also called vascular tone) refers to the contractile activity (i.e., vasoconstriction and vasodilation) of vascular smooth muscle cells in the walls of atrial blood vessels (Jackson, 2000). The microvasculature (i.e., the arterioles) is the primary resistance site to the coronary blood flow. Vasomotor tone therefore plays an important role in the regulation of blood pressure and the distribution of blood flow between and within the tissues and organs of the body (Jackson, 2000).

The contractile activity of vascular smooth muscle cells is regulated by a number of mechanisms acting on the blood vessel: intrinsic factors originating from the blood vessel itself or the immediate surrounding tissue; and extrinsic factors originating from outside of the tissue or organ where the blood vessel is located (Klabunde, 2007). The dynamic balance between these mechanisms determines the contractive activity of the muscle cell and hence the diameter and resistance of a blood vessel (Jackson, 2000). Intrinsic factors regulate local blood flow and include: (1) myogenic mechanisms which originate from the smooth muscle in arteriole walls and play a role in autoregulation (Tortora & Derrickson, 2012); (2) vascular smooth muscle ion channels, such as K^+ (potassium ion) or voltage-gated Ca^{++} (calcium ion) channels (Jackson, 2000); and (3) endothelium-dependent vasoactive factors; chemicals released by the inner lining of the artery. Prostacyclin and nitric oxide, for example, cause dilation whereas endothelin acts as a vasoconstrictor (Luscher, Noll, Spieker, Roberto, & Pepine, 2005). The primary function of extrinsic factors is to regulate arterial blood pressure by altering systemic vascular resistance (Klabunde, 2007). These include: (1) ANS innervation of the heart and vasculature (Tortora & Derrickson, 2012) (described in Sections 7.1 and 7.2); and (2) circulating factors, such as catecholamines and angiotensin, which causes vasoconstriction (Tortora & Derrickson, 2012). The numerous factors and processes influencing vasomotor tone are complicated. For further information refer to Jackson (2000), Luscher and colleagues (2005) or Tortora and Derrickson (2012).

Changes to vasomotor tone can have an affect on blood flow and cause complications in various heart disorders such as obstructive CAD and NoCAD. Injury to the endothelium, for example, can cause decreased production of the endothelial derived vasodilating factor nitric oxide and an increase in constrictor tone (Luscher et al., 2005). As a result, vasomotor tone becomes inadequate and maintenance of the appropriate diameter of blood vessels becomes a problem. Furthermore, decreased production of endothelial factors can lead to increased platelet adhesion and aggregation, and therefore enhanced thromobogenesis (Luscher et al., 2005). A loss of tone is often seen in patients with atherosclerosis (commonly in obstructive CAD) or NoCAD (i.e., coronary microvascular disease/dysfunction [MVD]; Section 5.3.1).

4. CORONARY HEART DISEASE

Over the past few centuries, economic and social transformations have resulted in dramatic shifts in diseases responsible for illness and death (Gaziano & Gaziano, 2012). Cardiovascular disease (CVD), defined as any disease that affects the heart or blood vessels (arteries, capillaries and veins), and including CHD, heart failure, peripheral vascular disease and cerebrovascular disease (stroke), has become the greatest disease epidemic worldwide (Gaziano & Gaziano, 2012). Its increased prevalence and impact has largely resulted from global changes in economic, social structures and lifestyles, and parallel increases in life expectancy throughout the 20th century (Gaziano & Gaziano, 2012). Consequently, improving cardiovascular health has been a major focus worldwide. There has been significant progress in reducing some risk factors and overall death rates, along with major advances in treatment (Gaziano & Gaziano, 2012). However, CVD continues to impose a heavy burden on Australians in terms of illness, disability and premature death (Gaziano & Gaziano, 2012).

CHD is by far the most dominant form of CVD; up to five times as common as stroke (Gaziano & Gaziano, 2012). An umbrella term, CHD includes all diseases of the coronary network, including coronary conditions such as CAD, MI and coronary vasospasm.

Figure 7, diagram (a) depicts a normal coronary artery, unaffected by CHD. CHD is defined as the narrowing or blockage or coronary arteries, commonly caused by the build-up of cholesterol and fatty deposits (atheroma plaques) in the inner artery walls, in a process known as atherosclerosis (Figure 7, diagram b). The plaques can thicken and calcify and cause ischaemia, that is, the restriction of blood flow to the heart muscle (myocardium) (Canty, 2012). If a blood clot forms at the site of the plaque, in a process known as coronary thrombosis or coronary occlusion, blood flow can be further reduced (Antman, 2012). As a result, the myocardium is deprived of oxygen and can be damaged causing the following conditions, alone or in combination: chest pain (angina pectoris), death of heart muscle (MI/AMI or heart attack) and gradual failure of the pumping function of the heart (heart failure) (Canty, 2012; Sabatine & Cannon, 2012).

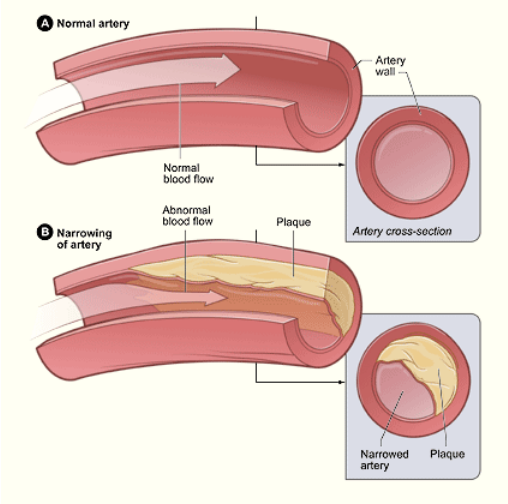

Figure 7. Plaque build-up in an artery. Reprinted from *What is Angina?* by the National Heart, Lung, and Blood Institute, 2011a, Retrieved from http://www.nhlbi.nih.gov/health/health-topics/topics/angina/. Reprinted with permission.

4.1. Prevalence

Many forms of heart disease exist, including cardiomyopathy (disease of the heart muscle), heart failure and congenital heart disease. However, CHD is the most common form in Australia. Data from the most recent 2011-12 Australian Health Survey (ABS, 2013) reported that 5% of Australians (of approximately 1.1 million people) had heart, stroke and vascular disease. Similar prevalence rates were reported from the National Health Survey 2007-08 (5.4%). However, within that category of diseases, CHD was by far the most prevalent, with an estimated 685,000 people with CHD in 2007-08 (ABS, 2009). Although the prevalence of CHD has been declining, it still affected 582,400 people in 2011-12 (ABS, 2013). In addition, it is a common finding that the prevalence of CHD increases with age, with higher rates in males (ABS, 2009, 2013).

In Australia, CHD accounts for more deaths than any other disease. In fact, CHD has been the leading cause of death in Australia since 2000, with 20,046 (13.6% of all deaths) registered in 2012 (ABS, 2014). Not only is CHD associated with a high level of mortality but is also a major contributor to morbidity, with 153,700 hospitalisations (an age-standardised rate of 615 per 100,000) attributed to this disorder in 2011-12 (AIHW, 2014). Furthermore, CHD makes the largest contribution to CVD in terms of leading cause of global burden of disease (Murray et al., 2012). It is predicted

that by 2020 and 2030 CHD will rank among the top three leading cause of global disease burden (Mathers et al., 2008; Mathers & Loncar, 2006; Murray & Lopez, 1996) and by 2030 will be the top leading cause of disability-adjusted life years lost (Mathers et al., 2008; Mathers & Loncar, 2006). These statistics highlight the ongoing need for further understanding into the pathophysiology and progression of CHD, which may provide insights into developing future prevention and treatment programs.

4.2. Common Symptoms

Chest Pain

Chest pain symptoms are common and often benign. Chest pain is not synonymous with angina pectoris, but is one symptom of angina. Although chest pain is one of the cardinal manifestations of CHD, such pain may originate not only in the heart but also in a variety of non-cardiac structures (Fang & O'Gara, 2012). One in four people in the population experiences an episode of chest pain annually (Eslick, Coulshed, & Talley, 2005). Of those who present to hospital, nearly two-thirds have non-cardiac chest pain (Eslick et al., 2005). For this reason, identification of the cause of chest pain is essential. However, diagnosis can be difficult.

Pain, experienced during chest pain, is an "unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage" (International Association for the Study of Pain, 1979, p. 250). Thus pain is both a sensation (conscious awareness of a noxious stimulus) and an emotional experience (intense feelings of displeasure resulting in a pattern of reactive behaviour) (Ripamonti, 2012) and is always subjective; it is what the patient says it is (International Association for the Study of Pain, 1979). An individual's subjective sensation of pain may be affected by emotional, social, and spiritual components (Ripamonti, 2012). In addition, because many structures in the chest may cause pain, diagnosis can be extremely difficult. Chest pain is therefore considered a heterogeneous condition, in that the pain may be non-cardiac or cardiac in origin.

The duration of pain is important in determining its origin, and thus determining a diagnosis (Fang & O'Gara, 2012). Chest pain of brief duration (less than 15 seconds) may be of non-cardiac origin (e.g., musculoskeletal). Pain from 5 to 30 minutes could represent a cardiac condition, such as angina. Long lasting pain (for hours) may be seen

with non-cardiac conditions (e.g., AMI, herpes zoster, anxiety, cocaine abuse), but is commonly associated with cardiac conditions (e.g., pericarditis, anxiety, aortic dissection) (Fang & O'Gara, 2012). Chest pain aetiology is discussed further in Section 5.3.

Angina Pectoris

Angina pectoris is not a disease but rather a syndrome of symptoms (including chest pain) reflecting an underlying heart condition. It is the most common manifestation of CHD (Sabatine & Cannon, 2012), with an estimated global prevalence of 54 million people (Mathers et al., 2008).

The term 'angina pectoris' is derived from the Greek word 'ankhone' meaning "a strangling sensation", and 'pectoris' referring to the chest. Thus, angina is characterised as discomfort in the chest (Sabatine & Cannon, 2012). This symptom is often caused by impaired myocardial perfusion (blood flow to the myocardium) or the presence of myocardial ischaemia (insufficient blood supply to the myocardium).

Heberden (1772) initially described the term 'angina' as a sense of "strangling and anxiety" that may radiate to adjacent areas including the neck, jaw, shoulders and arms. Heaviness, pressing or squeezing on the chest, difficulty breathing and feelings of choking, are other symptoms of angina often reported by patients (Sabatine & Cannon, 2012).

Angina is normally described in the context of its occurrence. Characteristically, it occurs on exertion, particularly when walking up an incline but can also occur with excitement, emotional stress or fright (e.g., a nightmare), such as in chronic stable angina (CSA) (Cannon & Braunwald, 2012). However, not all forms of angina occur this way. Some forms of angina occur at rest with minimal or no exertion, as in unstable angina (UA) whereas others occur during both exertion and rest, as in Prinzmetal angina (Cannon & Braunwald, 2012). The intensity of angina may vary from day to day and throughout the day in the same patient, with pain usually lasting between 2 to 10 minutes (Fang & O'Gara, 2012) although it can last for 20 minutes or more (Cannon & Braunwald, 2012). Considering that chest pain is the most common symptom of angina,

distinguishing between the two clinically may be difficult. Therefore, a thorough evaluation of history and symptoms is crucial for differentiation.

4.3. Pathophysiology

Theories of the pathophysiology of CHD have significantly changed over the years. Research into the development and progression of the disease now suggests an inter-relationship between atheroma, thrombosis, inflammation and vascular reactivity (Libby & Theroux, 2005).

In medical literature, the terms CHD and CAD are often used interchangeably. However, CAD is a common manifestation of CHD, and refers specifically to the development of atheroma that manifests as atherosclerotic plaques inside the epicardial coronary artery walls, which impedes blood flow to the myocardium (Tortora & Derrickson, 2012). Previously, CAD was considered a cholesterol storage disease, whereby the formation of atherosclerotic plaques typically begins when excess low-density lipoprotein (LDL; 'bad cholesterol') from the blood accumulate in the inner layer of the artery wall (Tortora & Derrickson, 2012). However, the development of atherosclerotic plaques is now known to be critically dependent upon inflammation - a defensive response of the body to tissue damage - and is associated with endothelial dysfunction (Vane, Anggard, & Botting, 1990). Endothelial dysfunction is a condition whereby the endothelium of blood vessels does not function normally. Tissue damage (e.g., caused by trauma or infection/disease) disrupts endothelial function, causing blood vessels to dilate and increase in permeability. As a result macrophages ('fighting' cells that protect the body by ingesting pathogens) increase in numbers (Tortora & Derrickson, 2012). A plaque forms when the blood flow contains excess LDL, which accumulates in the artery wall; the lipids and proteins in the LDLs undergo oxidation (removal of electrons); and the proteins bind to sugars (Tortora & Derrickson, 2012). In response, endothelial and smooth muscle cells of the artery secrete substances that attract macrophages, which ingest and become filled with oxidised LDL particles. Microscopically these cells have a foamy appearance, hence their name 'foam cells'. T cells ('fighting' white blood cells) then enter the artery where they release chemicals that intensify the inflammatory responses. Together, the foam cells, macrophages and T cells form a fatty streak, the beginning of an atherosclerotic plaque (Tortora & Derrickson, 2012). Macrophages also secrete chemicals that cause smooth muscle cells

of the middle layer of the artery to migrate to the top of the atherosclerotic plaque, forming a cap over it and thus walling it off from the blood (Tortora & Derrickson, 2012).

At the same time, damage to the endothelium increases smooth muscle cell proliferation, platelet aggregation and thrombosis, and thus affects vasoregulation and vasomotor tone (Vane et al., 1990). These features are key events in the development of atherosclerosis manifesting as CAD (Fuster, Badimon, Badimon, & Chesebro, 1992; Tortora & Derrickson, 2012). Furthermore, studies have shown an association between atherosclerotic plaques and impaired vascular reactivity, whereby the endothelium-mediated regulation of vascular tone is impaired (Ludmer et al., 1986; Zeiher, Drexler, Wollschlager, & Just, 1991).

Vascular reactivity plays an important role in vascular function of both large coronary arteries (macrovascular arterial system) and small coronary arteries (microvascular arterial system). The majority of research has focused on vasomotor dysfunction at the macrovascular level; however these large arteries contribute to less than 10% of the coronary vascular resistance and only become of haemodynamic significance with a stenosis (i.e., narrowing of the artery) of at least 70% (Gould, Lipscomb, & Hamilton, 1974). The microvasculature is the primary resistance site to the coronary blood flow and therefore plays an essential role in regulating myocardial perfusion (Jackson, 2000).

CHD is traditionally viewed as narrowing of the large coronary arteries resulting in myocardial ischaemia. However, coronary blood flow may also be restricted by pathophysiological mechanisms other than obstructive atherosclerotic plaques, such as disorders specific to NoCAD patients; namely MVD (Section 5.3.1). Regardless of aetiology (CAD or NoCAD), ischaemic episodes are often aggravated or triggered causing an increase myocardial oxygen demand or decrease oxygen supply (Section 4.3.1), which in turn results in a series of biochemical events called an ischaemic cascade (Detry, 1996; Nesto & Kowalchuk, 1987).

The ischaemic cascade is a sequence of haemodynamic and ECG events that culminate in angina (Detry, 1996). These events represent a continuum whereby one

event triggers the next. The cascade begins with the onset of haemodynamic changes including abnormal myocardial perfusion, diastolic dysfunction (characterised by impaired ventricular relaxation) and systolic dysfunction (characterised by abnormal left ventricular motion and decreased left ventricular ejection fraction - the volumetric fraction of blood pumped out of the ventricle) (Detry, 1996, Nesto & Kowalchuk, 1987). If the ischaemia persists, ECG abnormalities follow, including ST-segment and T wave changes. Lastly, symptoms manifest as angina, indicating severe ischaemia in a given area of the myocardium (Detry, 1996; Nesto & Kowalchuk, 1987). When the coronary blood flow is restored after a brief interruption, all these abnormalities disappear progressively. However, if the blood is not restored, myocardial necrosis will begin (Detry, 1996).

4.3.1. Myocardial Ischaemia

When blood flow to the myocardium is impaired, as a result of a partial or complete blockage of a coronary artery by a build up of plaque, myocardial ischaemia occurs. Angina pectoris is the clinical manifestation of myocardial ischaemia. If ischaemia is prolonged, then myocardial cell necrosis (i.e., MI) may ensue. Myocardial ischaemia is characterised by an imbalance between myocardial oxygen supply and demand (Canty, 2012). The major determinants of myocardial oxygen supply include coronary blood flow and coronary arterial oxygen content, whereas myocardial oxygen demand is influenced by increased HR, myocardial contractibility and myocardial wall tension/stress (Ardehali & Ports, 1990; Canty, 2012). In order for the heart to respond to metabolic demands, an adequate coronary blood flow is essential. Abnormalities in the coronary artery may impair coronary perfusion (Bradley & Alpert, 1991).

Myocardial Oxygen Demand and Supply

The concept of the myocardial oxygen demand and supply relationship is that for any given oxygen need, the heart will be supplied with a sufficient quantity to prevent underperfusion leading to ischemia or infarction (Canty, 2012). As such, the heart regulates the amount of vasodilation or vasoconstriction of the coronary arteries based upon the required amount of oxygen. Obstructive CAD caused by atherosclerotic lesions of greater than or equal to 70% obstruction in the epicardial arteries, is the most common cause of myocardial ischaemia. Stenosis of this severity can greatly impact myocardial oxygen balance, because it limits the ability of coronary circulation to

increase blood flow such that it cannot deliver adequate oxygen when demand is increased (Canty, 2012). This acute imbalance between the metabolic needs of the myocardium (demand) and coronary blood flow (supply) is the cause of myocardial ischaemia. Myocardial ischaemia occurs when myocardial oxygen demand exceeds myocardial oxygen supply (Canty, 2012). Coronary artery stenosis sets a fixed limit to the potential increase in myocardial blood flow so that angina occurs whenever oxygen supply is short, as during exertional angina. Typically, a lesion must cause at least 70% obstruction to impede coronary flow during exertion and cause angina (Gould et al., 1974). However, because the LCA supplies blood to two thirds of the heart, a lesion of more than 50% can impede blood flow. Severe lesions of at least 90% not only reduce the coronary flow reserve but also the resting coronary blood flow, thereby causing rest angina **(**Baltzan, 1955**)**. Angina and myocardial ischaemia can also occur from other causes of impaired blood flow in the absence of stenotic lesions, such as vasospasm or MVD (Section 5.3.1). To improve the myocardial supply/demand ratio, patients are commonly treated with beta-blockers (to decrease myocardial demand) or nitrates (to increase myocardial supply).

4.4. Coronary Angina Syndromes

The clinical syndrome of CHD that manifests as angina has many individual variations. Angina syndromes can be classified according to the clinical presentation as either acute or chronic in nature.

Chronic coronary syndromes are characterised by predictable chest pain that occurs on exertion or under mental or emotional strain, including CSA and Cardiac Syndrome X (patients exhibit ST induced changes on exercise stress testing and normal coronary arteries on angiography) (Cannon & Braunwald, 2012). In contrast, acute coronary syndromes (ACS) are identified by the presence of unpredictable chest pain that occurs at rest or on minimal exertion (Cannon & Braunwald, 2012). Acute syndromes refer to a group of disorders attributed to occlusion of the coronary arteries and, therefore, often reflect a degree of damage to the coronaries by atherosclerosis (Antman, 2012). The three disorders in the ACS group include UA, acute STEMI and acute NSTEMI (mentioned previously in Section 3.1.2).

4.4.1. Acute Coronary Syndromes

Over time, patches of coronary atheroma (called plaques) can progress in size and thickness (Antman, 2012). When plaque disruption occurs (e.g., due to plaque rupture or erosion), thrombogenic substances that become exposed promote platelet activation and aggregation, thrombin generation, and ultimately thrombus (clot) formation (Antman, 2012). The resultant thrombus (made of platelets, fibrin and red blood cells) that is formed interrupts blood flow causing either complete or partial acute coronary occlusion (Antman, 2012). As a result, acute coronary angina syndromes occur.

Acute Myocardial Infarction

AMI (also known as a heart attack) occurs as a result of plaque disruption resulting in sudden thrombotic occlusion of a coronary artery, causing haemodynamic disturbance and myocardial cell necrosis (Antman, 2012). The following features are present in AMI: ischaemic symptoms, ischaemic ECG changes, and elevated cardiac markers such as troponin (an indicator of myocardial cell death). Previously, the less specific and sensitive cardiac marker creatine kinase was used, which sometimes failed to detect small myocardial infarcts or classified them as UA. The redefinition of AMI (Alpert, Thygesen, Antman, & Bassand, 2000; The Joint European Society of Cardiology/American College of Cardiology Committee, 2000), based on raised troponin levels, has increased the number of myocardial infarcts identified. Therefore, testing for troponin levels is essential in the accurate diagnosis of ACS, either in the clinical or research setting.

MI can be classified according to the appearance of the ECG as either NSTEMI or STEMI. The difference between the two types of MI presentation was initially noticed when STEMI patients benefited from thrombolytic therapy whereas it was harmful to NSTEMI patients (The TIMI IIIB Investigators, 1994). STEMI is characterised by ST-segment elevation, with/without associated T wave changes and the subsequent development of Q waves (Antman, 2012). This type of MI occurs when the epicardial coronary artery is completely occluded by a thrombus (Antman, 2012). Conversely, NSTEMI does not present with ST-segment elevation, but may include ST depression and/or T wave changes (Cannon & Braunwald, 2012). This type of MI is the result of a non-occlusive thrombus and therefore some blood flow is maintained

(Cannon & Braunwald, 2012). Despite the difference in presentation, STEMI and NSTEMI are comparable in terms of inpatient health outcomes and at one-year follow-up (Montalescot et al., 2007). The MI patients analysed in the studies presented in Chapters Four (Study 1) and Five (Study 2) did not receive an ECG, and were therefore not differentiated as either STEMI or NSTEMI. However, as previous studies have reported that health status is similar for both MI types, whether patients were STEMI or NSTEMI would not have affected study results.

Unstable Angina

The pathophysiological process contributing to the development of UA is similar to NSTEMI. When an atherosclerotic plaque associated with a thrombus ruptures or erodes, the coronary artery may become partially blocked, and UA typically develops (Cannon & Braunwald, 2012). UA is characterised by unpredictable (the attacks may vary in how often they occur, what triggers them and how severe the pain is), prolonged, frequent chest pain at rest or on minimal exertion (usually lasting more than 20 minutes without the use of nitroglycerin), and may be accompanied by reversible ST-segment changes on the ECG (Cannon & Braunwald, 2012). It is differentiated from AMI by the absence of myocardial cell necrosis and raised troponin levels. However, this syndrome is considered high-risk as it can progress into MI, identifiable by increases in cardiac markers such as troponin (Cannon & Braunwald, 2012).

4.4.2. Chronic Coronary Syndromes

Chronic Stable Angina

CSA, or stable angina, is the most prevalent manifestation of CHD, occurring in almost half of patients with CHD (Murabito, Evans, Larson, & Levy, 1993). It is distinguishable from ACS, in that unlike ACS, CSA develops during exertion, emotional stress or excitement and relieved within 5 to 15 minutes by rest or nitroglycerin (Cannon & Braunwald, 2012). As such, CSA is considered less serious than UA because it is predictable and tends to have a regular pattern (i.e., one can determine how of often the angina occurs or what factors trigger it). Symptoms are consistent with Heberden's initial description (Section 4.2) and are stable for at least one month. The most common underlying cause of CSA is obstructive CAD, however it may also occur as a result of MVD (Section 5.3.1). Although CSA can be painful or

uncomfortable and impair functioning, the long-term prognosis is generally good. Clinical trials have found the risk of cardiac events to be lower for CSA patients compared to ACS patients, with rates of cardiac death ranging from 0.9-1.2%, and rates of non-fatal AMI between 1-2.6% (Daly et al., 2006). Considering that UA is a more serious condition than CSA, it seems reasonable to assume that health status, such as depression symptomology, may differ for these two groups. Therefore, in order to analyse the predictors of depression in Study 1 (Chapter Four), US and CSA patients were delineated based on their angina presentation.

4.5. Diagnosis

Given the high prevalence of morbidity and mortality associated with CHD, accurate evaluation and diagnosis is essential in the treatment of this disorder. Assessment of patients with suspected CHD typically involves an evaluation of: (a) the clinical history, for features consistent with angina; (b) a physical examination to exclude non-coronary causes of chest pain; and (c) cardiac investigation for the presence of CAD (Fang & O'Gara, 2012).

Numerous cardiac procedures are available in the investigation of chest pain and suspected CHD. The specific procedure depends on the signs and symptoms of the individual and includes coronary computer tomography angiogram, echocardiography, myocardial perfusion imaging, coronary angiography and ECG. Only the methods of investigations relevant to this research project (ECG and coronary angiography) are discussed in detail.

Electrocardiography

In the 20th century, the ECG became the first and most common bioelectrical signal to be computer-processed and it is now a commonly used and standard cardiac diagnostic test for heart abnormalities. The ECG has vital significance in the diagnosis of acute and chronic coronary syndromes, including heart failure, the presence and severity of acute myocardial ischaemia and the distinction between STEMI and NSTEMI (Mirvis & Goldberger, 2012). The ECG has further been used in the analysis of beat-to-beat changes in HR (Mirvis & Goldberger, 2012), termed HRV (discussed in Section 8). HRV was measured in in Study 3 (Chapter Six).

The ECG is a procedure that measures the electrical activity generated by the heart as it contracts. Typically, ten electrodes are attached to the chest (6 electrodes) and limbs (4 electrodes) to form a 12-lead ECG. The electrodes usually consist of a conducting gel, embedded in the middle of a self-adhesive pad onto which leads clip (Mirvis & Goldberger, 2012). However, sometimes seven electrodes (7-lead ECG) are used, as was the case in Study 3 (Chapter Six). The electrical activity of the heart muscle (i.e., action potentials produced by all the heart muscle fibres during each heartbeat) is recorded (Tortora & Derrickson, 2012). Each chest and limb electrode records slightly different electrical activity because of the difference in its position relative to the heart. The data are displayed as a set of traces on a screen or on paper, which is then interpreted by a medical practitioner (Tortora & Derrickson, 2012). An ECG from a normal patient will have a characteristic shape (Section 3.1.2). Any irregularity in the heart rhythm or damage to the heart muscle can change the electrical activity of the heart so that the shape of the ECG is changed (Tortora & Derrickson, 2012).

Invasive Coronary Angiography

An invasive procedure, coronary angiography is currently the gold standard for determining the presence or absence of abnormal arterial narrowing related to atherosclerosis (Popma, 2012). The procedure was first performed by Sones in 1959 (Sones & Shirey, 1962) and since then methods have substantially improved so that complications are less than 2% and mortality is 0.10-0.14% (Samal & White, 2002). It is one of the most widely used invasive procedures in cardiovascular medicine (Bruschke, Sheldon, Shirey, & Proudfit, 2009). Patients undergoing angiography for the evaluation of chest pain formed The Queen Elizabeth Hospital (TQEH) coronary angiogram cohort analysed in Study 1 (Chapter Four).

Coronary angiography is a procedure that uses dye (contrast medium) and x-rays to visualise how the blood flows through the coronary arteries (Popma, 2012). Coronary angiography involves a process called cardiac catheterisation, whereby a thin, flexible, hollow tube called a catheter is inserted into a blood vessel usually in the arm or groin and threaded into the coronary arteries. Once the catheter is in place, a dye (contrast medium) is injected into the catheter and x-ray images are taken while the dye travels through the coronary arteries (Popma, 2012). The major epicardial coronary arteries can

be visualised; however due to their size, the smaller branches are generally not seen (Popma, 2012). The angiographer can visually assess the site and severity of stenosis of the arteries and determine whether the patient has obstructive CAD. A "positive" angiogram means significant areas of blockage were identified in the major coronary arteries). Conversely, a "negative" angiogram means that no significant areas of blockages were found in the major coronary arteries. However, abnormalities in the microvessels (as is the case in NoCAD) are generally not detected by coronary angiography and these arteries are said to be 'normal' or 'near-normal' on angiography.

The presence of obstructive CAD is defined as an arterial stenosis diameter of greater than or equal to 50% in one or more of the three major coronary arteries (Popma, 2012), and the angiogram is said to be positive. However, if the stenosis is minor and less than 50% (and located in the microvessels), the patient is diagnosed as having normal or near-normal coronary arteries, and said to have NoCAD (Bugiardini & Bairey Merz, 2005). The angiogram is therefore said to be negative. Although a stenosis must be 70% to impede blood flow and cause myocardial ischaemia (previously described in Section 4.3.1), the accuracy of reading angiograms is limited so that a 50-70% stenosis may actually be 70%. Accordingly, to ensure that the stenosis is not significant, NoCAD is characterised by <50% obstruction. The next section of this thesis will discuss NoCAD.

5. NON-OBSTRUCTIVE CORONARY HEART DISEASE

With the introduction of coronary angiography, it became clear that a proportion of patients with chest pain showed no visible evidence of obstructive CAD. This syndrome was first described by William Osler in 1910 (Osler, 1910). However, it has only been in the last 40 years that this population has been investigated. This population of patients (who experience chest pain but have normal or near-normal coronary arteries on angiogram) are said to have NoCAD. This diagnosis is relevant to Study 1 (Chapter Four).

NoCAD is often viewed as an alternative mechanism to the traditional obstructive CAD causing chest pain, in that the small coronary arteries are affected. Considering that NoCAD is defined as less than 50% stenosis, the microvessels can still have atheroma, whether or not coronary angiography detects any visible stenosis. As previously stated in Section 4.3.1, a stenosis must be at least 70% to impede blood flow. Therefore, in contrast to obstructive CAD, in NoCAD blood flow through the microvessels is less restricted, yet patients complain of chest pains. In the case of ischaemia, patients with NoCAD typically also present with coronary MVD (defined in Section 5.3.1). Thus, NoCAD remains a difficult problem for the clinician, with symptoms often indistinguishable from those of obstructive CAD (Bugiardini & Bairey Merz, 2005). As a result, patients with chest pain and normal or near-normal coronary arteries following angiography are often offered no specific treatment and usually told that they have no significant heart disease (Panza, 2002).

5.1. Prevalence

The majority of studies investigating non-specific chest pain are hospital-based, revealing that up to 30% of patients undergoing coronary angiography for angina-like chest pain exhibit normal or near-normal epicardial coronary arteries (Bass, Wade, Hand, & Jackson, 1983; Kemp, Vokonas, Cohn, & Gorlin, 1973; Marchandise, Bourassa, Chaitman, & Lesperance, 1978; Pasternak, Thibault, Savoia, DeSanctis, & Hutter, 1980; Wielgosz et al., 1984). Approximately 10% to 25% of women and 6% to 10% of men presenting with ACS exhibit NoCAD (Glaser et al., 2002).

5.2. Prognosis

Some previous longitudinal studies have suggested that the prognosis of patients with chest pain and NoCAD is benign, with the combined risk of MI and death being less than 1% for up to 10 years (Bass et al., 1983; Kemp et al., 1973; Marchandise et al., 1978; Pasternak et al., 1980; Papanicolaou et al., 1986; Wielgosz et al., 1984). Despite the favourable outlook, several other follow-up studies have shown that a significant proportion of patients (approximately 50-75%) remain disabled and continue to experience chest pain, causing work incapacity, functional limitation and psychological distress (Bass et al., 1983; Ockene, Shay, Alpert, Weiner, & Dalen, 1980; Papanicolaou et al., 1986). These symptoms persisted for patients who did not respond to reassurance about their illness (Potts & Bass, 1993). It is now accepted that the prognosis is not as benign as previously reported and as commonly assumed by clinicians (Bugiardini & Bairey Merz, 2005).

The short-term prognosis for NoCAD patients includes a 2% risk of MI or death at 30 day follow-up (Diver et al., 1994). In a more recent study, patients with NoCAD and myocardial ischemia were found to have poorer prognosis than NoCAD without myocardial ischemia (Johnson et al., 2004). More than 40% of these patients were re-admitted for chest pain more than once, and despite demonstration of normal coronary arteries on angiography during a prior hospitalisation, 30% undergo repeat angiography within 5 years (Cannon et al., 1994). In addition, these patients are at an increased risk for cardiovascular events including premature death, MI and stroke (Halcox et al., 2002). Hence, numerous investigations have been carried out in search of the aetiology of this chest pain syndrome.

5.3. Aetiology of Non-Obstructive Coronary Heart Disease

As previously stated in Section 4.2, chest pain is considered a heterogeneous disorder: some patients with NoCAD are found to have chest pain of non-cardiac origin, while others have chest pain of cardiac origin (Table 3).

Table 3

Differential Diagnosis of Chest Pain

Cardiac Aetiologies	
Coronary disease	Angina (stable and unstable)
	Acute myocardial infarction
	Variant angina (Prinzmetal angina)
	Microvascular angina (Cardiac Syndrome X)
Non-coronary disease	Pericarditis, myocarditis
	Cardiomyopathy
	Aortic dissection, aortic stenosis
	Mitral prolapse
Non-Cardiac Aetiologies	
Gastrointestinal system	Gastro-oesophageal reflux
	Oesophagitis, oesophageal spasm
	Gallbladder disease
	Pancreatitis
	Hiatus hernia
	Peptic ulcer
Respiratory/pulmonary	Pneumonia
	Pulmonary embolism, pulmonary infarction, pulmonary hypertension
	Pneumothorax, pneumomediastinum
	Asthma/reactive airways disease
	Cancer
Musculoskeletal	Arthritis
	Chest wall syndromes, costochondritis
	Fibromyalgia
	Muscular/joint strain, rib fracture, thoracic disk problems
	Myofascitis
Psychological	Depression, anxiety, panic disorder
Other causes	Cervical spondylosis
	Thyroid/adrenal problems
	Anemia
	Herpes zoster
	Drug usage (cocaine)

Note. Adapted from "Clinical Presentation and Diagnosis of Coronary Artery Disease: Stable Angina", by S. W. Davies, 2001, *British Medical Bulletin, 59,* p. 18, and "An Approach to the Initial Care of Patients with Chest Pain in an Emergency Department Located in a Non-Cardiac Center", by A. A. Agostini-Miranda and L. A. Crown, 2009, *American Journal of Clinical Medicine, 6,* p. 24. Adapted with permission.

5.3.1. Cardiac Aetiology

Chest pain arising from cardiac causes can be further differentiated into coronary and non-coronary conditions (Table 3). Many non-coronary conditions, such as pericarditis or aortic stenosis, can usually be determined from patient history, clinical examination and cardiac investigations. In relation to coronary conditions, numerous aetiological mechanisms have been proposed to explain chest pain in the presence of normal coronary arteries, the most commonly discussed being microvascular disorders (Achem & DeVault, 2000; Benjamin, 1992; Richter, 1991).

Coronary Microvascular Disorders

Studies of patients with normal coronary arteries have reported abnormalities in the structure and function of the coronary microcirculation, resulting in abnormal constricting and relaxing of the microvessels (Bugiardini & Bairey Merz, 2005). Coronary MVD therefore refers to abnormal vasomotor regulation of the small coronary arteries, known as arterioles (Vaccarino et al., 2009). Figure 8, diagram (b) shows a large coronary artery with plaque build-up, such as in obstructive CAD. Figure 8, diagram (a) shows the small coronary artery network (microvasculature), containing a normal microvessel and a microvessel with coronary MVD. In the case of MVD, tightening of the arteries can cause spasms, myocardial ischaemia and chest pain (Sheps et al., 2001). The pathophysiology underlying an abnormal vasomotor tone may be an attenuated augmentation of coronary blood flow in response to increased myocardial oxygen demand (Camici et al., 1991; Opherk et al., 1981). This may arise from excessive vasoconstriction or impaired compensatory vasodilatory mechanisms.

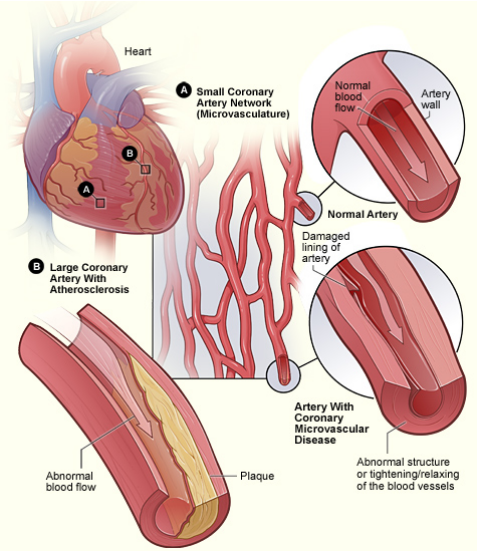

Figure 8. Coronary microvascular disease. Reprinted from *What is Coronary Microvascular Disease?* by the National Heart, Lung, and Blood Institute, 2011b, Retrieved from http://www.nhlbi.nih.gov/health/health-topics/topics/cmd/. Reprinted with permission.

Diagnosing coronary MVD is a challenge, as standard tests used to diagnose CHD do not detect abnormalities in coronary microvessels. Detection is, therefore, time consuming and requires specialised investigations such as a special type of coronary angiogram used to measure coronary artery flow reserve. Thus, there is limited understanding of the clinical and mechanistic aspects of these conditions. Coronary MVD disorders include the Coronary Slow Flow Phenomenon, microvascular angina, variant angina and Cardiac Syndrome X. These specific disorders are not relevant to the research manuscripts, and therefore they are not discussed further.

5.3.2. Non-Cardiac Aetiology

In up to 50% of cases of chest pain, non-cardiac causes are implicated (Mayou, Bryant, Forfar, & Clark, 1994) and the chest pain may be attributed to a variety of disorders including oesophageal (Achem & DeVault, 2000; Karnath, Holden, & Hussain, 2004; Richter, 1991; Richter, Bradley, & Castell, 1989; Watson, 2006), respiratory (Brims, Davies, & Lee, 2010; Karnath et al., 2004), musculoskeletal (Achem & DeVault, 2000; Epstein, Gerber, & Borer, 1979; Karnath et al., 2004; Watson, 2006; Wise, Semble, & Dalton, 1992), and psychiatric (Achem & DeVault, 2000; Katon et al.,

1988; Olden, 2004; Watson, 2006), where symptoms of these disorders mimic chest pain.

Oesophageal, Respiratory and Musculoskeletal Causes

Some studies have reported the oesophagus to be the most common source of non-cardiac chest pain, with gastro-oesophageal reflux disease accounting for up to 60% of cases (Cherian et al., 1995; Hewson, Sinclair, Dalton, & Richter, 1991). Irritation to the oesophageal lining, caused by gastric contents and acid reflux back into the oesophagus, may be perceived as chest pain (Dekel et al., 2003). In addition, oesophageal disorders are common in depressed patients with normal coronary arteries (Colgan et al., 1988). Chest pain of pulmonary origins can exist in conditions such as pulmonary embolism (Hull et al., 1988; Stein & Henry, 1997) and chronic obstructive pulmonary disease (COPD) (Brims et al., 2010). Research has shown that a large proportion of chest pain patients who have normal coronary arteries also have hyperactive airways (Sax, Cannon, Hanson, & Epstein, 1987). Depression is also prevalent in COPD patients (Lacasse, Rousseau, & Maltais, 2001; Prigatano, Wright, & Levin, 1984). Furthermore, musculoskeletal chest pain can arise from fractures, dislocation or inflammation of bones, muscles or joints around the thoracic wall, spine or shoulders (Jensen, 2001), and has been implicated in 13-19% of chest pain cases (Bechgaard, 1981; Wolf & Stern, 1976). A confident diagnosis of musculoskeletal chest pain can be difficult, as patients with chest pain and normal arteries commonly experience chest wall tenderness (Achem & DeVault, 2000). It is not uncommon for some of these disorders to co-exist, which highlights the difficulties of diagnosing a cause in non-cardiac chest pain presenters.

Psychiatric Causes

A relationship between psychiatric disorders and chest pain has long been recognised, with some older studies focusing on depression. The prevalence of depression has been shown to be greater in chest pain patients with normal coronary arteries compared to healthy controls and chest pain patients with a positive angiogram (Ketterer et al., 1996), while older studies examining depression in patients with NoCAD reported that patients with a negative angiogram exhibited higher levels of depression than those with a positive angiogram (Carney, Freedland, Ludbrook, Saunders, & Jaffe, 1990; Channer, James, Papouchado, & Rees, 1985, Katon et al.,

1988; Lantinga et al., 1988). However, the physiologic mechanisms are unclear. Although clinicians may be aware of the relationship between depression and CAD, NoCAD patients are not always followed up in a similar way. Given the potential health consequences of untreated depression, routine screening of angiographic patients for psychological disorders and accurate identification seems warranted. Therefore, a need exists for recent analysis of depression and chest pain in patients with NoCAD.

The published manuscript featured in Chapter Four examines the association between depression and chest pain, and explores the plausible aetiological explanations for this association in patients with normal coronary arteries (i.e., NoCAD). The results may have implications for the diagnosis and treatment of depression in chest pain patients, as well as aetiological significance.

6. CORONARY HEART DISEASE AND DEPRESSION

In previous sections of this thesis, depression and CHD were independently discussed. This section addresses the main focus of this thesis - the relationship between the two conditions, by discussing the prevalence of comorbidity and various causal pathways underlying the relationship between depression and CHD as an interdependent network.

6.1. Prevalence

As previously discussed, depression and CHD are significant conditions not only in Australia but also worldwide, and both are major contributors to the burden of disease (AIHW, 2008, 2010; Mathers et al., 2008; Murray et al., 2012). Moreover, depression is a significant problem among people with medical illnesses (Carney & Freedland, 2009). On average, between 9.3-23% of individuals with one or more chronic physical diseases have comorbid depression (Moussavi et al., 2007).

Studies of the relationship between depression and CHD have a long history, and scientific evidence of this association dates back at least to the 1930s (Carney & Freedland, 2003). It is now well established that there is a link between depression and CHD (Davidson, 2012; Stapelberg et al., 2011). Importantly, the relationship between depression and CHD appears to be complex and reciprocal; they frequently co-exist and are highly prevalent together (Carney & Freedland, 2009; Lett et al., 2004; Stapelberg et al., 2011). Studies have documented a disproportionately high prevalence of depression in CHD patients relative to the general population. Point prevalence estimates for the population at large range from 4-7% (Ayuso-Mateos et al., 2001; Steffens et al., 2000). Previous research found that one in five patients with newly diagnosed coronary disease had major depression while another one in five had minor depression (Carney, Freedland, Rich, & Jaffe, 1995; Glassman & Shapiro, 1998; Schleifer et al., 1989). An analysis of numerous cross-sectional studies reported point prevalence range of depression from 14% to as high as 47% in CHD patients (Ahto et al., 1997; Gonzalez et al., 1996; Lesperance et al., 2000; Lett et al., 2004; Valkamo et al., 2001). However estimates tend to be lower, at 15-23%, when DSM criteria are used to establish diagnosis (Connerney, Shapiro, McLaughlin, Bagiella, & Sloan, 2001; Gonzalez et al.,

1996). Causal aspects of relationship between depression and CHD are discussed below.

The comorbidity of depression and CHD has received considerable research attention, possibly due to the associated high risk of morbidity and mortality. Self-reports of disability have shown that depression has a significant and persistent effect on physical functioning in patients with CHD (M. D. Sullivan, LaCroix, Spertus, & Hecht, 2000). Moreover, depression appears to not only increase the risk and incidence of ischaemic cardiac events (i.e., CHD) but also ischaemic heart disease (i.e., CAD) in disease-free cohorts (Dekker et al., 2000; Goldston & Baillie, 2008; Penninx et al., 2001), conferring a relative risk of 1.64-1.73 for the subsequent development of CAD (Ferketich, Schwartzbaum, Frid, & Moeschberger, 2000; Rugulies, 2002). Depression also increases the risk of mortality (in disease-free and CHD individuals) (Seymour & Benning, 2009), with a relative risk of 1.6 for minor depression and 3 for major depression (Penninx et al., 2001) in those with cardiac disease. Among disease-free individuals, similar risks were reported; 1.5 for minor depression and 3.9 for major depression (Penninx et al., 2001).

The relationship between obstructive CAD and depression has also been extensively investigated, showing that one in five patients experience depression following AMI (Frasure-Smith, Lesperance, & Talajic, 1993). Depression has also been shown to be predictive of cardiac outcomes, such as increased risk of onset and progression of CAD in disease-free (Lett et al., 2004) and CAD patients (Carney, Rich, Freedland et al., 1988). A relative risk between 1.5-2 was reported for the subsequent development of CAD in disease-free individuals (Lett et al., 2004). Concurrently, CAD increases the risk for depression (Carney, Freedland et al., 1995; Stapelberg et al., 2011). Furthermore, depression increases the risk for morbidity and all-cause and cardiac mortality, especially following AMI (Barefoot & Schroll, 1996; Glassman & Shapiro, 1998). Depressive symptoms are a risk factor for both short-term (Frasure-Smith et al., 1993; Frasure-Smith, Lesperance, & Talajic, 1995) and long-term mortality (Carney et al., 2008; Lesperance, Frasure-Smith, Talajic, & Bourassa, 2002; Pfiffner & Hoffmann, 2004; Welin, Lappas, & Wilhelmsen, 2000). In fact, depression has been linked with a 1.5- to 2.5-fold increase in the risk of recurrent cardiac events and death (Lett et al., 2004), although a later study reported a 3- to 4-fold increase (Schulman &

Shapiro, 2008). Barefoot and colleagues (1996) showed that CAD patients (who were followed for 19.4 years) with moderate to severe depression were at 69% greater risk for cardiac death and 78% greater risk for all-cause death compared to non-depressed controls. Increased risk was not confined to the initial months after hospitalisation.

6.2. Aetiology of Depression and Coronary Heart Disease

Numerous mechanisms have been theorised to explain the relationship of comorbid depression and CHD. Several independent mechanisms have been hypothesised, including behavioural, genetic, immune and autonomic mechanisms, vascular abnormalities and polyunsaturated omega-3 free fatty acid deficiency. These mechanisms have typically been discussed as separate entities in empirical research and many reviews have discussed one or more of these causal mechanisms (Barth, Schumacher, & Herrmann-Lingen, 2004; Goldston & Baillie, 2008; Musselman et al., 1998). Tracey (2002) and Musselman and colleagues (1998), for example, discussed the relationship between autonomic and inflammatory mechanisms linking depression and CHD. Importantly, however, it is believed that considerable overlap and inter-connectivity exists between all mechanisms such that they are best explained and conceptualised as a network of pathogenic determinants (Stapelberg et al., 2011).

Until recently, however, no single comprehensive model had described the causal mechanisms linking depression and CHD. It is thought that these mechanisms may form the nodes in a complex causal network, giving rise to a reciprocal association between the diseases (de Jonge et al., 2010; Stapelberg et al., 2011). A review by de Jonge and colleagues (2010) canvassed the possible mechanisms which linked depression and CHD, identifying the relationship as a complex system or network, and suggesting that the network might usefully be studied using systems biology. This idea was not discussed further, nor did the review provide a topological map of this network or suggest how systems biology might be applied to it. Stapelberg and colleagues (2011) expanded on de Jonge's review (2010) and discussed the key mechanisms linking depression and CHD, constructing a topological map of the causal network to describe the relationship between depression and CHD. These mechanisms may help explain how depression increases the risk for incident coronary disease and for subsequent cardiac morbidity and mortality. It raises the possibility that knowledge of the common mechanisms linking depression and CHD could assist in improving

prevention and treatment for both conditions. The author of this thesis accepts the argument that the mechanisms linking depression and CHD can usefully be conceptualised as a network and topological map, rather than independent entities. Accordingly, reprinted versions of Stapelberg and colleagues' (2011) diagrams are reproduced below to help depict the mechanisms.

6.2.1. Mechanisms Linking Depression and Coronary Heart Disease

Six principal mechanisms have been suggested to explain the link between depression and CHD (Stapelberg et al., 2011): (1) behavioural mechanisms, (2) genetic mechanisms, (3) dysregulation of immune functioning, (4) coagulation abnormalities and vascular endothelial dysfunction, (5) polyunsaturated omega-3 free fatty acid deficiency, and (6) autonomic mechanisms. They are described in turn below, followed by a description of the map proposed by Stapelberg and colleagues (2011).

An additional mechanism that has been proposed as explaining the relationship between depression and CHD is antidepressant cardiotoxicity. However, there is little supporting evidence to suggest this plays a significant role in cardiac morbidity and mortality. Although certain antidepressants (such as TCAs and MAOIs) have cardiotoxic side effects and can increase the incidence of adverse cardiac events in depressed people (Carney et al., 2002), the observed association between depression and CHD long precedes the development of antidepressant medication (Carney et al., 2002). Moreover, cardiotoxic reactions from antidepressants are generally not severe or life threatening, and SSRIs (which have few cardiotoxic side effects), are now the first line of pharmacological therapy for depression (Carney et al., 2002). However, antidepressant cardiotoxicity cannot entirely be excluded, as SSRIs sometimes have cardiac effects. Pacher and Kecskemeti (2004), for example, found that SSRIs produced clinical effects of bradycardia, QT prolongation, decreased T wave amplitude, and effects on the vasomotor centre and blood pressure.

Behavioural Mechanisms

Depression has been associated with several behavioural cardiac risk factors and poor health behaviours as depicted in Figure 9, accounting for higher levels of morbidity and mortality.

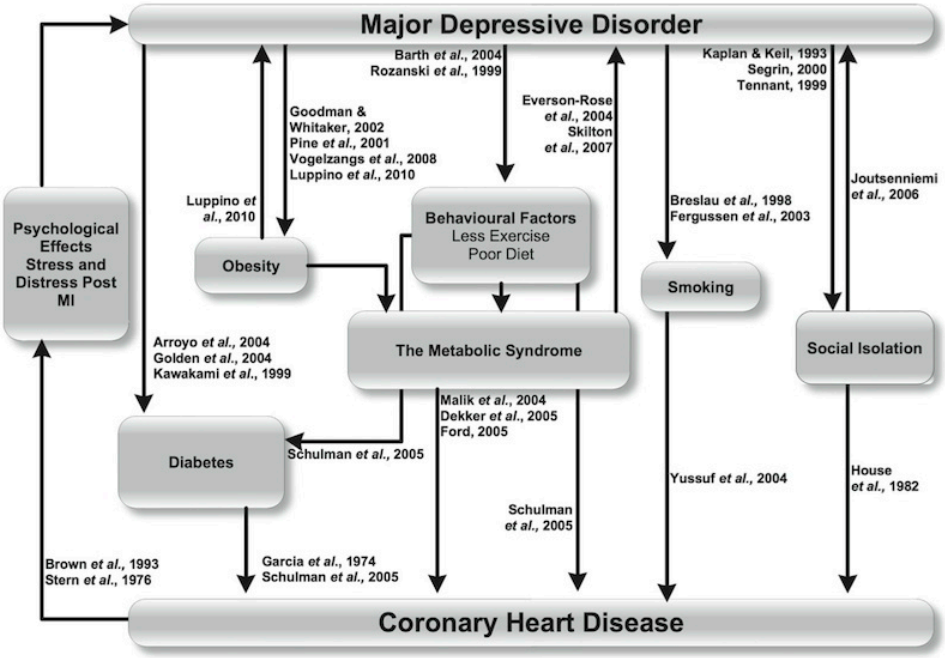

Figure 9. Behavioural mechanisms linking depression and coronary heart disease. Reprinted from "A Topographical Map of the Causal Network of Mechanisms Underlying the Relationship Between Major Depressive Disorder and Coronary Heart Disease", by N. J. C. Stapelberg et al., 2011, *Australian and New Zealand Journal of Psychiatry, 45,* p. 354. Reprinted with permission.

Daily smoking and nicotine dependence are more prevalent among depressed people (Breslau, Peterson, Schultz, Chilcoat, & Andreski, 1998; Fergusson, Goodwin, & Horwood, 2003), and the rate of AMI is almost three times higher in smokers than non-smokers (Yusuf et al., 2004), which may potentially help explain the link between depression and CHD (Stapelberg et al., 2011). In addition to smoking, other risk factors such as low physical activity and poor diet are more prevalent among depression than non-depressed people (Barth et al., 2004; Rozanski, Blumenthal, & Kaplan, 1999). Therefore, depressed people also have higher than average rates of obesity and diabetes, which are also risk factors for cardiac disease (Schulman, Muskin, & Shapiro, 2005). Independently, depression has been identified as a risk factor for diabetes (Arroyo et al., 2004; Golden et al., 2004; Kawakami, Takatsuka, Shimizu, & Ishibashi, 1999) and obesity (Luppino et al., 2010; Pine, Goldstein, Wolk, & Weissman, 2001) and in turn diabetes is a risk factor for CHD (Garcia, McNamara, Gordon, & Kannel, 1974). Obesity has also been found to increase the risk of depression (Luppino et al., 2010).

Metabolic syndromes are conditions that increase the risk of developing CVD and insulin resistance, such as obesity, diabetes and hyperglycaemia, all of which have been associated with depression (Everson-Rose et al., 2004). Independent of age, smoking status, socio-economic status and lifestyle, metabolic syndrome in both men and women has been associated with increased prevalence of depression (Skilton et al., 2007) and increased risk of all-cause and cardiovascular morbidity and mortality (Dekker et al., 2005; Ford, 2005; Malik et al., 2004).

Chronic life stresses, social isolation, poorer social skills and maladaptive coping strategies are more prevalent among depressed people (Kaplan & Keil, 1993; Segrin, 2000; Tennant, 1999). In particular, social isolation is a significant contributor to poor cardiac health and increased cardiac mortality (House, Robbins, & Metzner, 1982). Poor social support networks are associated with a two- to three-fold increase in the incidence of CHD over time, and low emotional support also increases the risk of future adverse cardiac events (Rozanski et al., 1999), especially in those with MI (Berkman, Leo-Summers, & Horwitz, 1992). It is known that depression and social support influence each other (Lakey & Cronin, 2008; Leach et al., 2008), however the direction and explanation for this causality is unclear. Inadequate social support and social isolation may lead to depression, particularly in the context of a significant stressor such as an MI (Joutsenniemi et al., 2006). Depressed people are also less likely to adhere to medical treatment, such as pharmacological or psychological, which contributes to poor health outcomes (Carney et al., 2002; DiMatteo, Lepper, & Croghan, 2000), which may later contribute to mortality.

Psychological distress, low self-esteem and occupational and social functioning impairment are common after MI (Brown, Munford, & Munford, 1993; Stern, Pascale, & Ackerman, 1977). Studies typically discuss psychological distress in conjunction with depression or anxiety, however it is unclear whether distress following MI leads to further deterioration in the form of depression. It is possible that distress and loss of function after MI combined with low social support could directly contribute to an increased risk of depression (Stapelberg et al., 2011).

This discussion identified some links between depression and CHD, mediated by behavioural mechanisms. However when cardiac risk factors (such as smoking

status) are statistically adjusted, an increase in cardiac disease risk in depressed patients still exists. This suggests that behavioural factors alone do not account for the link between the two diseases (Stapelberg et al., 2011).

Genetic Mechanisms

Genetic mechanisms have assisted in partially explaining the link between depression and CHD. Research findings are promising but need to be expanded to fully understand the complex relationship. Given that this field is large, only pertinent findings are discussed (Figure 10).

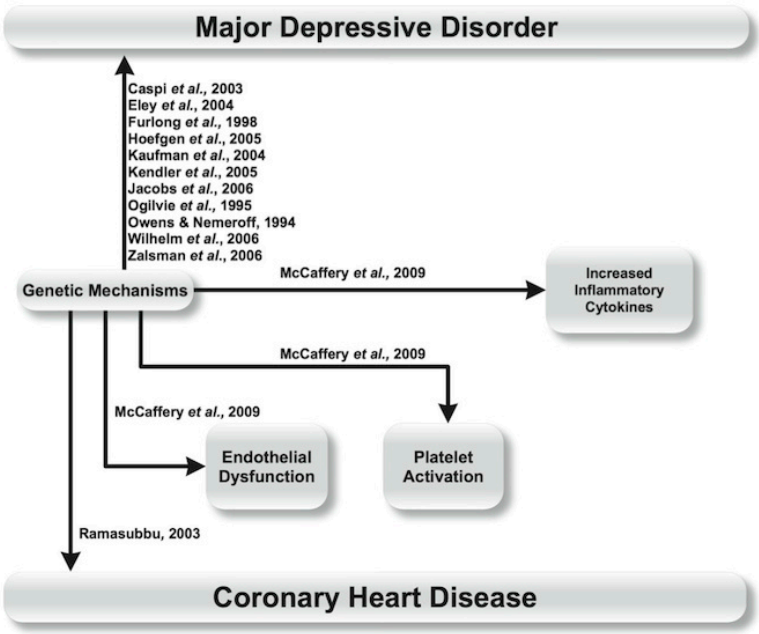

Figure 10. Genetic mechanisms linking depression and coronary heart disease. Reprinted from "A Topographical Map of the Causal Network of Mechanisms Underlying the Relationship Between Major Depressive Disorder and Coronary Heart Disease", by N. J. C. Stapelberg et al., 2011, *Australian and New Zealand Journal of Psychiatry, 45,* p. 355. Reprinted with permission.

Previous research has suggested that genetic polymorphism of the 5-HTT serotonin transporter gene contributes to the pathogenesis of depression (Furlong et al., 1998; Ogilvie et al., 1996; Owens & Nemeroff, 1994). This gene codes for the serotonin transporter protein and facilitates the reuptake of serotonin from the synaptic cleft in serotonergic neurons (Stapelberg et al., 2011). People who possess one or two short alleles of the 5-HTT gene have been found to be more depressed during and after

stressful events than those who have two long alleles of the gene (Caspi et al., 2003; Kendler, Kuhn, Vittum, Prescott, & Riley, 2005; Wilhelm et al., 2006; Zalsman et al., 2006). If an allele is short, the efficiency of gene transcription can be reduced, resulting in reduced expression of the serotonin transporter (Stapelberg et al., 2011). The short allele has also been associated with depression in patients with ACS (Nakatoni et al., 2005). There is a potential link between the short allele and sympathetic nervous activation. Individuals with stable CHD and who were carriers of the short allele have been found to have increased stress levels, increased NE secretion and thus greater risk of depression (Otte, McCaffery, Ali, & Whooley, 2007). The precise mechanism by which possession of the short allele results in depression is still not known (Otte et al., 2007) and therefore more research is needed.

Other researchers have focused on genetic polymorphisms of monoamine systems, including 5-HTT, MAO-A or COMT. It is believed that these genes are candidates for mood disorders (Ramasubbu, 2003), however the serotonin transporter gene functional polymorphism is a candidate for both mood disorders and CVD risk factors (Ramasubbu, 2003). Thus, it has been proposed that the serotonin transporter gene functional polymorphism is associated with depression-related increased CVD morbidity and mortality (Ramasubbu, 2003), however currently little direct research exists. A candidate gene study analysed predictors of depression in CVD patients (McCaffery et al., 2009). This study focused on genes relating to inflammation, platelet aggregation, endothelial function and omega-3 fatty acid metabolism and found that variation in genes relating to endothelial dysfunction and platelet aggregation could contribute to depression in cardiac patients (McCaffery et al., 2009). Genetic mechanisms influencing inflammatory mechanisms, endothelial dysfunction and platelet activation may, therefore play a role in the association between depression and CHD.

Inflammatory Mechanisms

Dysregulation of immune mechanisms includes several factors including increased inflammatory cytokines, atherosclerosis and neuro-inflammatory reflexes. Relationships between these mechanisms are shown in Figure 11.

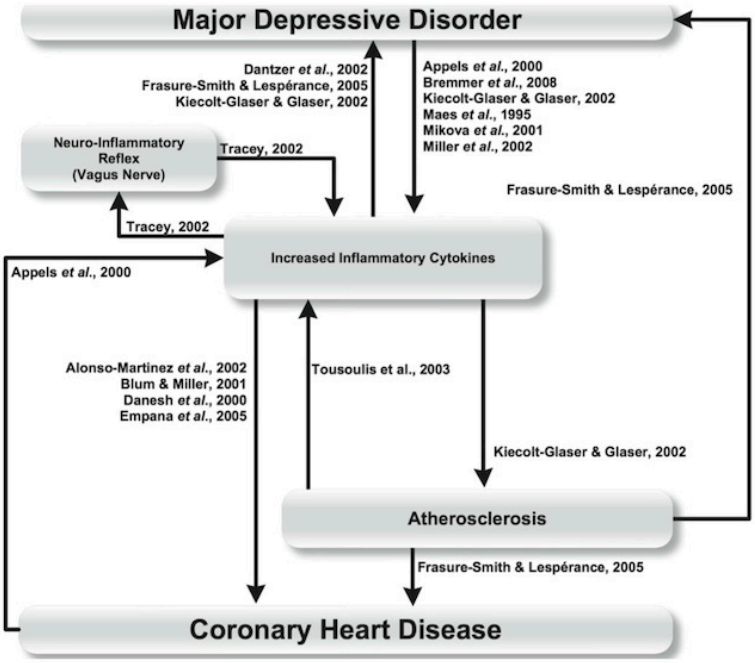

Figure 11. Inflammatory mechanisms linking depression and coronary heart disease. Reprinted from "A topographical map of the causal network of mechanisms underlying the relationship between major depressive disorder and coronary heart disease", by N. J. C. Stapelberg et al., 2011, *Australian and New Zealand Journal of Psychiatry, 45,* p. 356. Reprinted with permission.

Previous research has shown that depressed individuals often exhibit elevated levels of pro-inflammatory cytokines, such as interleukins (ILs) IL-1, IL-2, IL-6, tumour necrosis factor (TNF) and acute phase proteins such as C-reactive protein **(**Appels, Bar, Bar, Bruggeman, & de Baets, 2000; Danesh et al., 2000; Maes et al., 1995; Mikova, Yakimova, Bosmans, Kenis, & Maes, 2001). High levels of these inflammatory markers have also been associated with several cardiac diseases including congestive heart failure, CHD and MI (Appels et al., 2000; Blum & Miller, 2001; Danesh et al., 2000; Empana et al., 2005).

Furthermore, it has been suggested that the development of atherosclerotic lesions can activate a chronic, low-grade immune activation, resulting in increased production of cytokines (Tousoulis et al., 2003). Conversely, inflammation may be linked to an increased rate of atherosclerosis, which in turn increases the risk of adverse cardiac events (Dantzer, Wollman, & Yirmiya, 2002). Thus, atherosclerosis is not only a risk factor for CHD but may also independently influence both depression and cardiac

disease. Previous research has shown that elevated levels of cytokines can cause depressive symptoms such as loss of appetite, fatigue, apathy and social withdrawal (Frasure-Smith & Lesperance, 2005). Results have been inconclusive as to determine whether a cumulative effect occurs in patients with depression and heart disease (Schins et al., 2005; Schulman & Shiparo, 2008). However, if atherosclerosis is a factor involved in both depression and CHD, this may explain such a finding.

Autonomic neural pathways have been postulated as a mechanism linking depression and CHD, whereby the pathways reflexively monitor and adjust the inflammatory response (Tracey, 2002). The review by Tracey (2002) explains the existence of a neuro-inflammatory reflex, stating that sensory pathways (which are activated by inflammatory stimuli) relay information to the hypothalamus, which then activates an anti-inflammatory response. Evidence showed that the neural control of acute inflammation is reflexive and can inhibit the activation of macrophages (disease fighting cells) and the release of cytokines via the vagus nerve. Thus, the inflammatory response can be counteracted by stimulation of the vagus nerve, which inhibits the release of cytokines (Tracey, 2002). Based on this finding, it is possible that vagal dysfunction could cause an increase in inflammatory markers, contributing to CHD (Stapelberg et al., 2011). The function of the vagus nerve is explained further in Section 7.

Despite relationships existing between depression, CHD and the above inflammatory mechanisms, when inflammatory markers were adjusted for, Empana and colleagues (2005) found that depressed mood was still related to CHD. This suggests that inflammatory factors alone do not account for the link between the two diseases (Stapelberg et al., 2011).

Endothelial Dysfunction and Platelet Activation

Endothelial dysfunction is a condition affecting the endothelium (the inner lining of blood vessels), causing an imbalance between vasodilating and vasoconstricting substances produced by or acting on the endothelium. Researchers have suggested that the development or acceleration of atherosclerosis is caused by coagulation abnormalities and vascular endothelium dysfunction in people with depression (Laghrissi-Thode, Wagner, Pollock, Johnson, & Finkel, 1997; Nemeroff &

Musselman, 2000). The mechanisms are raised platelet activation or elevated immune cell levels (Laghrissi-Thode et al., 1997; Nemeroff & Musselman, 2000). Endothelial dysfunction is also related to mental stress. Studies have found that acute psychological or mental stress in healthy people with no CVD risk factors caused transient endothelial dysfunction (Ghiadoni et al., 2000; Spieker et al., 2002), providing evidence for this link between stress and atherogenesis. Furthermore, depression is also associated with endothelial dysfunction (Broadley, Korszun, Jones, & Frenneaux, 2002; Rajagopalan et al., 2001) and individuals with ACS and depression exhibit elevated levels of cellular adhesion molecules such as ICAM-1 (Lesperance, Frasure-Smith, Theroux, & Irwin, 2004). Even in medically healthy people, depression is associated with increased levels of ICAM-1, which predisposes to increased risk of CHD (Empana et al., 2005).

Depression has also been associated with platelet reactivity and activation, resulting in an increased risk of cardiac thrombotic events (Frasure-Smith & Lesperance, 2005). When activated, platelets secrete serotonin, which binds to platelet serotonin receptors. This interaction causes platelet aggregation and vasoconstriction of arteries (Dale et al., 2002; De Clerck, 1991; Schulman & Shapiro, 2008) and helps to regulate homeostasis and blood clotting. In depressed individuals, the serotonin receptors are up-regulated, causing increased density of platelet serotonin receptors (Arora & Meltzer, 1989; Sheline, Bardgett, Jackson, Newcomer, & Csernansky, 1995) and changes in platelet reactivity and activation. Altered platelet activation can cause increased thrombosis, arterial occlusion, vasoconstriction (Musselman et al., 1998), and elevated levels of inflammatory cytokines (Vieweg et al., 2006).

Both immune mechanisms discussed above (endothelial dysfunction and platelet activation) contribute to atherosclerosis and vascular damage in depressed people (Laghrissi-Thode et al., 1997; Nemeroff & Musselman, 2000; Vieweg et al., 2006) and can lead to CHD. In addition, atherosclerosis can compromise cerebral blood supply, causing damage and neuronal loss in areas of the brain that involve mood and cognition, potentially contributing to the development of depression (Alexopoulos et al., 1997; Frasure-Smith & Lesperance, 2005). Endothelial and coagulopathic mechanisms linking depression and CHD are depicted in Figure 12.

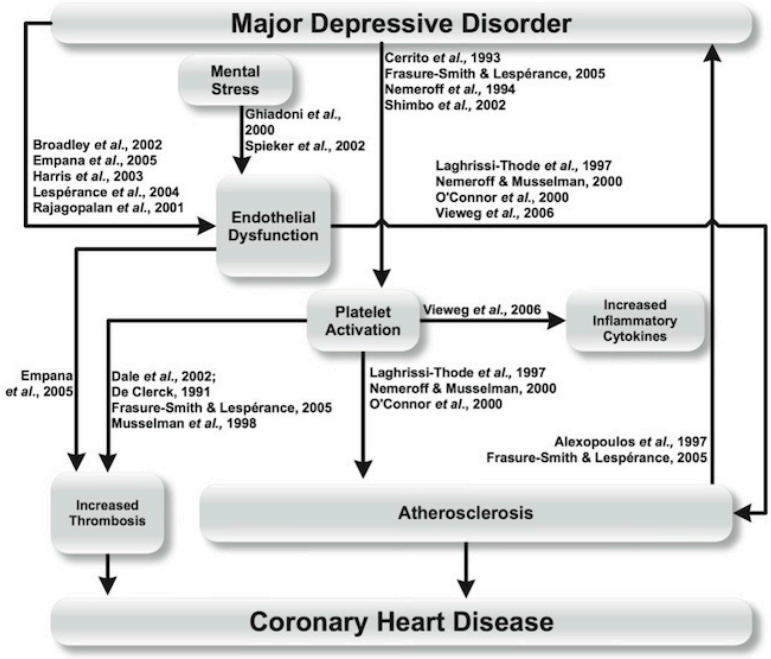

Figure 12. Endothelial and coagulopathic mechanisms linking depression and coronary heart disease. Reprinted from "A Topographical Map of the Causal Network of Mechanisms Underlying the Relationship Between Major Depressive Disorder and Coronary Heart Disease", by N. J. C. Stapelberg et al., 2011, *Australian and New Zealand Journal of Psychiatry, 45,* p. 358. Reprinted with permission.

In addition, endothelium functioning regulates coronary microvascular functions, suggesting that MVD may reflect endothelial dysfunction of the microvessels (Reis et al., 2001). Disturbances in microvascular circulation are common to both depression and CAD. Vaccarino and colleagues (2009) reported a shared genetic pathway between depression and MVD, indicated by common pathophysiological processes (such as ST-segment changes and abnormalities in myocardial reversible perfusion defects) common among patients with chest pain and normal coronary arteries (Bugiardini & Bairey Merz, 2005) and genetic factors common to both depressed and CHD patients. These processes have been suggested to link depression and early atherosclerosis (Bugiardini & Bairey Merz, 2005; Vaccarino et al., 2009). This view is supported by documentation of abnormal coronary blood flow responses to vasoactive stimuli and markers of ischaemia (Buffon et al., 2000; Bugiardini, Pozzati, Ottani, Morgagni, & Puddu, 1993).

Polyunsaturated Omega-3 Free Fatty Acid Deficiency

Previous research has found that comorbid depression and CHD is associated with low serum and low red blood cell levels of omega-3 polyunsaturated fatty acids (PUFAs) (Amin, Menon, Reid, Harris, & Spertus, 2008; Frasure-Smith, Lesperance, & Julien, 2004). However, in the absence of other medical illnesses, omega-3 fatty acid deficiency is independently associated with depression (Locke & Stoll, 2001; Sontrop & Campbell, 2006) and independently with CHD (Kris-Etherton, Harris, & Appel, 2002). Some researchers have shown that depression may be reversed, or antidepressant efficacy enhanced, with eating foods containing PUFAs, such as eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) (Lin & Su, 2007; Peet & Horrobin, 2002). It has been suggested that the risk of death from CHD can be predicted from the 'omega-3 index': red blood cell EPA plus DHA (Harris & Von Schacky, 2004).

Cell membranes are made up of PUFAs. In particular, concentrated levels of EPA and DHA are found at neuronal synapses and play an important role in neurotransmission and receptor function in the human brain (Haag, 2003; Kris-Etherton et al., 2002). This may help explain how omega-3 PUFA deficiency contributes to depression. Furthermore, people with depression and ACS often have decreased omega-3 PUFA plasma levels (Frasure-Smith et al., 2004), possibly suggesting a mechanism which links depression and CHD. Evidence exists showing that a dietary deficiency of PUFAs is associated with an increased risk of inflammation (Iso et al., 2002) and that inadequate intake of PUFAs can exacerbate the effects of hypertension, chronic inflammatory and atherosclerotic disorders (Simopoulos, 2002). Thus, the pathways by which PUFAs link CHD and depression may involve inflammatory mechanisms and atherosclerosis.

The relationships between PUFAs, depression and CHD discussed above are depicted in Figure 13.

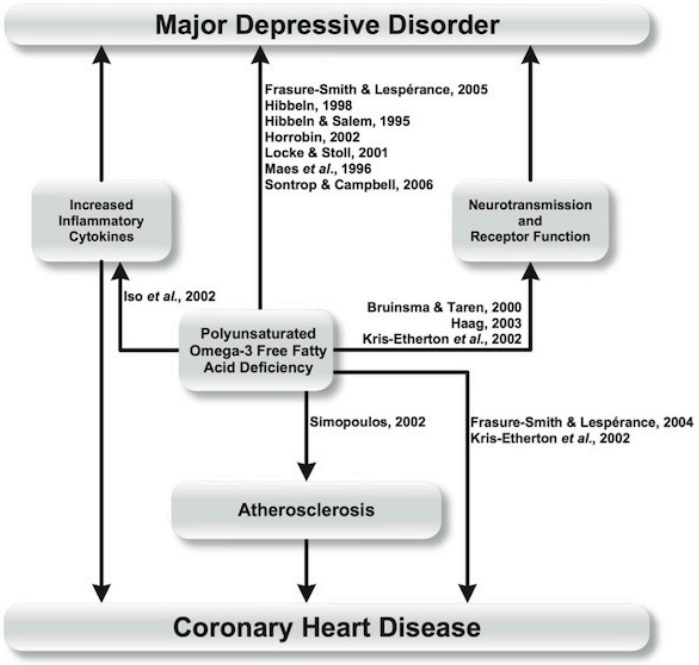

Figure 13. Polyunsaturated omega-3 free fatty acid deficiency linking depression and coronary heart disease. Reprinted from "A Topographical Map of the Causal Network of Mechanisms Underlying the Relationship Between Major Depressive Disorder and Coronary Heart Disease", by N. J. C. Stapelberg et al., 2011, *Australian and New Zealand Journal of Psychiatry, 45,* p. 359. Reprinted with permission.

Autonomic Mechanisms

People with depression often have autonomic dysfunction, and this dysfunction is believed to cause altered function in the sympathetic nervous system (SNS) and parasympathetic nervous system (PNS), as well as activation of the hypothalamic-pituitary-adrenal (HPA) axis in addition to abnormal vagal control. This autonomic dysfunction has been associated with increased risk for CVD, including CHD (Musselman et al., 1998).

Prior to discussion of the linkage between autonomic mechanisms, depression and CHD, it is essential to understand the structure and function of the ANS, including the vagus nerve. This is discussed in the next section (Section 7), followed by theories of autonomic mechanisms linking the two illnesses.

6.2.2. Relationship Between Depression and Coronary Heart Disease: A 'Causal Network'

It is evident from the above review that there are numerous mechanisms associated with both depression and CHD. These mechanisms are typically discussed as separate entities in the relevant literature. However, it is possible that no single mechanism stands alone as the cause for the relationship. Rather than isolated pathways linking depression and CHD it is possible that the mechanisms overlap and are linked via interrelationships which function together to form a causal network (Stapelberg et al., 2011). Due to high inter-connectivity, it is conceivable that there are feedback loops between pathways (Stapelberg et al., 2011). A topological map of the causal network linking mechanisms between depression and CHD is shown in Figure 14. This network conceptualises the mechanisms as a single interconnected system.

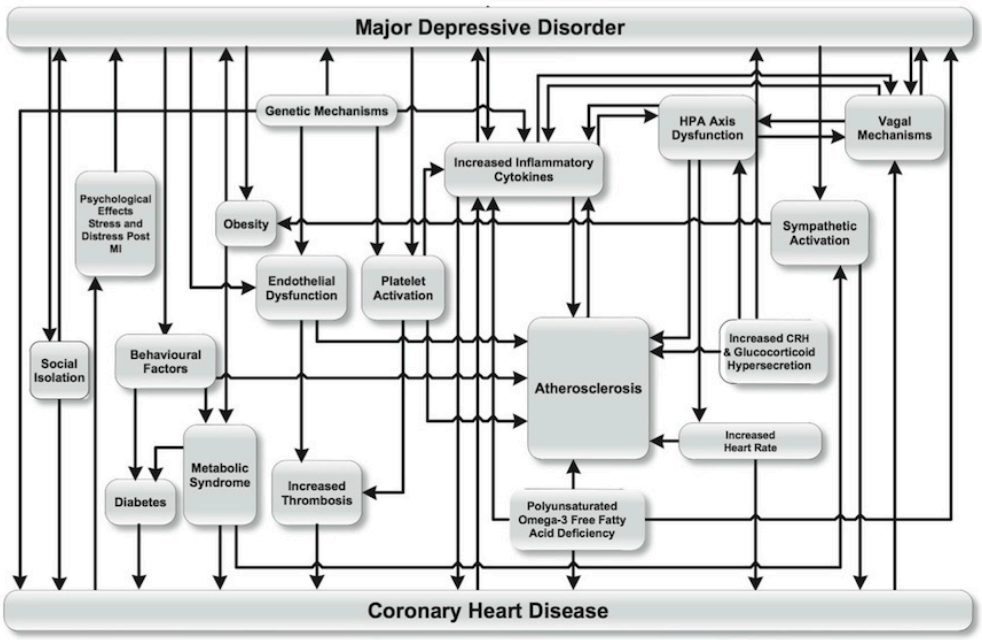

Figure 14. The relationship between depression and coronary heart disease: A topographical map of the causal network. Reprinted from "A Topographical Map of the Causal Network of Mechanisms Underlying the Relationship Between Major Depressive Disorder and Coronary Heart Disease", by N. J. C. Stapelberg et al., 2011, *Australian and New Zealand Journal of Psychiatry, 45,* p. 362. Reprinted with permission.

Quantification of the Causal Network

According to Stapelberg and colleagues (2011), the causal network is best conceptualised as a biological network. They expand on de Jonge and colleagues' (2010) review, by further examining the causal network in terms of systems biology. Systems biology is an emerging approach within biomedical and biological scientific research and involves an integrated analysis of complex interacting biological pathways or networks (Noorbakhsh, Overall, & Power, 2009). It focuses on how these interactions give rise to the function and behaviour of a system, making use of mathematical and computational models to quantify that system. Large numbers of individual elements (such as bio-molecules) or biological sub-systems (such as metabolic pathways) are measured simultaneously and tracked over time and their relationships to each other are elucidated.

Systems biology methods also have application in understanding complex diseases that involve multiple pathogenic determinants (Noorbakhsh et al., 2009), such as comorbid depression and CHD. In systems biology, each mechanism linking depression and CHD can be conceptualised as a node in a causal network. Attempting to quantify each node may help explain which mechanism contributes more or less (in quantitative terms) to exacerbate CHD in depressed patients, or cause depression in CHD patients (Stapelberg et al., 2011). Although it is known that mechanisms between depression and CHD are linked, it is unclear how much each mechanism contributes to the overall relationship in quantitative terms. Establishing quantitative relationships between each pathway in the causal network and thus establishing the topological map in detail will potentially allow each pathway to be measured and ranked (Stapelberg et al., 2011). This may assist in further understanding how the various mechanisms linking depression and CHD are interconnected, and may help in reducing the risk of recurrent cardiac events in depressed CHD patients. According to Stapelberg and colleagues (2011), who provide a starting point to the development of a topological map and analysis of systems biology, extensive future research is needed to further complete the topological map by identifying and establishing all the links and nodes in the causal network (i.e., further mechanisms which may link depression and CHD). More research is also needed to quantify the activity between each node, which will allow significant nodes to be targeted to address disease prevention and treatment. This thesis aimed to contribute to that research endeavour.

7. THE AUTONOMIC NERVOUS SYSTEM

This section introduces and discusses the structure and function of the ANS, including its two branches; the SNS and PNS, and how the two branches regulate HR. Finally, autonomic mechanisms linking depression and CHD are discussed in detail, as is disruptions to the ANS (which can lead to dysregulation), and measurement of ANS activity.

7.1. Structure and Function of the Autonomic Nervous System

The ANS controls automatic bodily functions that are engaged in homeostasis, which is the balancing of biophysiological processes in response to changes in the internal and external environment to achieve a physiological steady state (van Dijk et al., 2013). The ANS is responsible for regulation of internal organs and glands in processes such as perspiration, heart and respiratory rate, digestion, pupil reflexes, salivation, micturition and sexual arousal. Specifically, the ANS is involved in the human stress response (Tortora & Derrickson, 2012; van Dijk et al., 2013).

The ANS comprises two divisions or branches: SNS and the PNS, which typically function independently and in opposition to each other. This natural opposition is better understood as complementary in nature rather than antagonistic. The main function of the SNS is to prepare the human body for action in times of danger or stress, and in response to warning stimuli it activates physiological changes. This system is therefore commonly labelled with the term "fight or flight" (Tortora & Derrickson, 2012). Sympathetic responses, which may occur during physical activity, emotional stress or an emergency, result in increased heart and breathing rates, dilation of the pupils, dry mouth and sweaty but cool skin (Tortora & Derrickson, 2012). In contrast, the PNS regulates the resting state of the body by conserving and restoring energy and replenishing nutrient stores. It is therefore known as the "rest and digest" branch (Tortora & Derrickson, 2012). In brief, one branch of the ANS activates a physiological response (sympathetic) and the other inhibits it (parasympathetic).

The Parasympathetic Nervous System

The PNS controls organs via afferent fibres (the preganglionic fibres) that arise from the oculomotor (III), facial (VII), glossopharyngeal (IX) and vagal (X) cranial

nerves in the brainstem and the second, third and fourth sacral spinal nerves (S1-S3) (Figure 15). For this reason, the parasympathetic division is also called the craniosacral division (Tortora & Derrickson, 2012). The preganglionic fibres of cranial nerves III, VII and IX innervate the postganglionic neurons in local ganglia, which are (in the case of the PNS) located close to the organs they regulate.

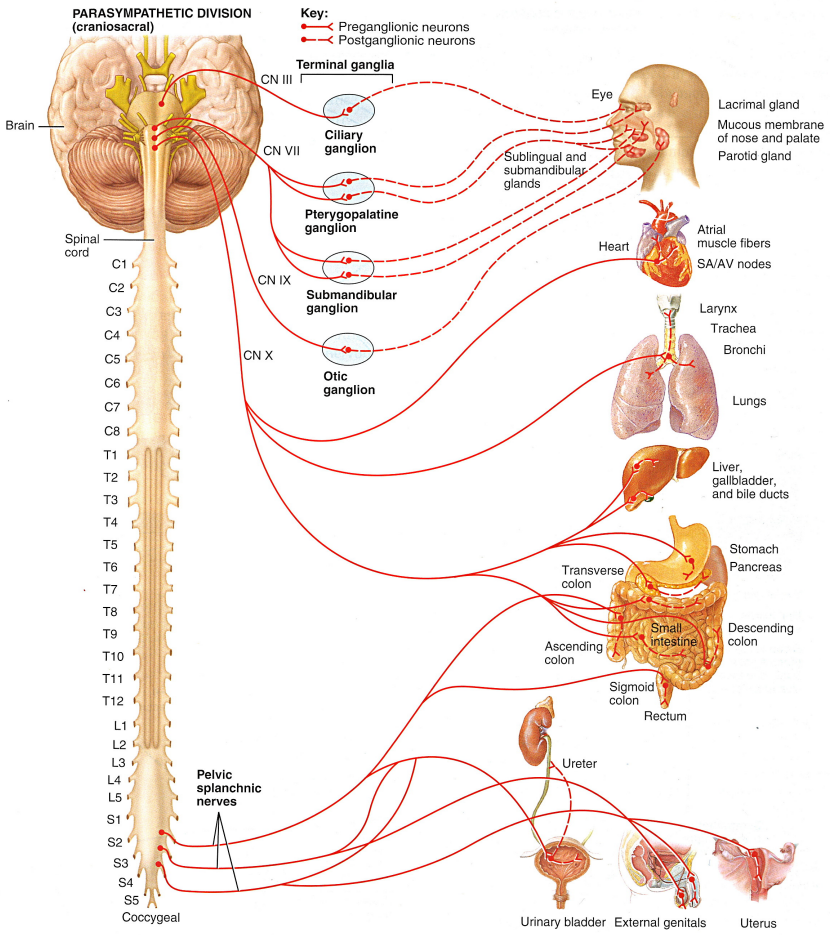

Figure 15. The parasympathetic nervous system. Distribution of parasympathetic innervation of the organs by cranial and sacral nerves. Reprinted from *Principles of Anatomy and Physiology* (13th ed., p. 586), by G. J. Tortora and B. Derrickson, 2012, Hoboken, NJ: Wiley & Sons, Inc. Reprinted with permission.

The preganglionic fibres release the neurotransmitter acetylcholine (Ach; which is stored in synaptic vesicles), which binds to nicotinic receptors on the postganglionic neurons (Figure 16). ACh is also used by postganglionic fibres innervating the organs via muscarinic receptors (located on the smooth muscle and/or endothelium of organs) (Tortora & Derrickson, 2012). Target organs include salivary glands, lungs, liver, gall bladder, intestines, reproductive organs and the heart.

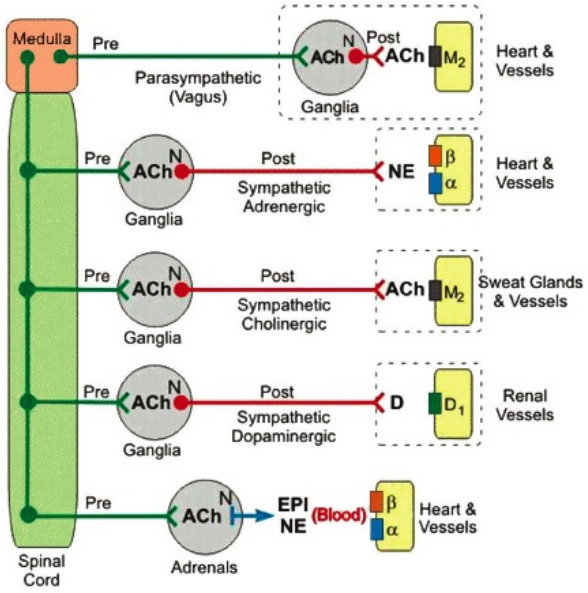

Figure 16. Neurotransmitters and receptors in the innervation of the parasympathetic and sympathetic nervous system. Reprinted from *Cardiovascular Pharmacology Concepts: Autonomic ganglia,* by R. E. Klabunde, 2011, Retrieved from http://www.cvpharmacology.com/autonomic_ganglia.htm. Reprinted with permission.

Within the PNS, the vagus nerve is the principal nerve to innervate the heart. Vagal fibres end on cardiac plexi on the SA node and the AV node (Tortora & Derrickson, 2012). Stimulation of the vagus nerve generally causes a decrease in pacemaker rate, thereby causing a decrease in HR (and often blood pressure) and a parallel increase in HRV (variations in HR frequency) (Acharya, Joseph, Kannathal, Lim, & Suri, 2006). This action contributes to a regulatory balance in physiological autonomic function (Acharya et al., 2006).

The Sympathetic Nervous System

The SNS controls organs via afferent fibres (the preganglionic fibres) that arise from the 12 thoracic segments (T1-T12) and the first two (and sometimes three; L1-L3) lumbar segments of the lumbar spinal cord. For this reason, the sympathetic division is also called the thoracolumbar division (Figure 17) (Tortora & Derrickson, 2012).

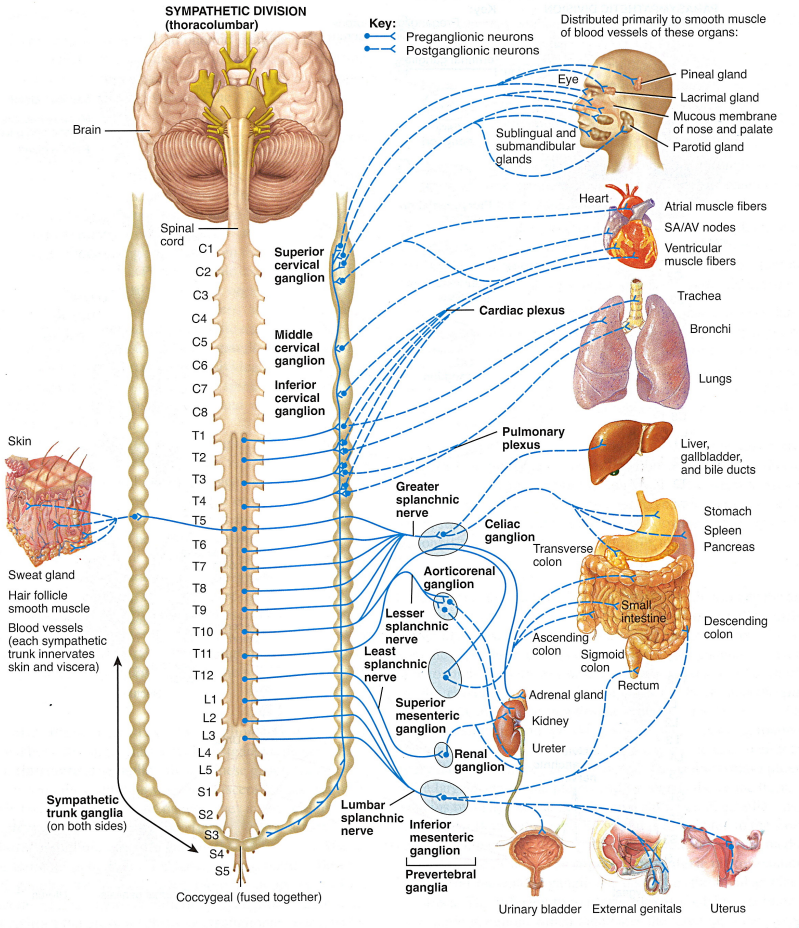

Figure 17. The sympathetic nervous system. Distribution of sympathetic innervation of the organs by thoracic and lumbar nerves. Reprinted from *Principles of Anatomy and Physiology* (13th ed., p. 585), by G. J. Tortora and B. Derrickson, 2012, Hoboken, NJ: Wiley & Sons, Inc. Reprinted with permission.

The preganglionic fibres innervate the postganglionic nerves in the ganglia, which are located close to the spinal cord (in the case of the SNS), by ACh. Unlike the PNS, postganglionic fibres in the SNS release several different neurotransmitters (Tortora & Derrickson, 2012). As shown in Figure 16, ACh innervates sweat glands through muscarinic receptors, dopamine binds to dopamine receptors and innervates renal vessels, and NE binds to α-adrenergic receptors on smooth muscle walls and on blood vessels (e.g., arterioles) and β-adrenergic receptors on the heart (Tortora & Derrickson, 2012). The cardiac sympathetic plexi lie on the ventricles and atria near the SA and AV nodes. Innervation of the α-receptor causes contraction and vasoconstriction, which increases blood flow and pressure, and innervation of the β-receptor increases the SA rate thereby increasing HR (Acharya et al., 2006). In addition,

contractibility of the muscles of the atria and ventricles is increased via direct stimulation.

7.2. Autonomic Nervous System Regulation of Heart Rate

Nervous system regulation of the heart originates in the cardiovascular centre in the medulla oblongata. In this part of the brainstem, input is received from a variety of sensory receptors and also from higher brain centres, such as the limbic system and cerebral cortex (Figure 18) (Tortora & Derrickson, 2012). During anticipation (e.g., in a competitive situation such as sport) the limbic system may send nerve impulses to the cardiovascular centre, causing an anticipatory increase in HR (Tortora & Derrickson, 2012). As a result, three types of sensory receptors send input to the cardiovascular centre. Receptors are beyond the scope of this thesis and are introduced only briefly. As physical activity occurs, the proprioceptors monitor the position of limbs and muscles and send nerve impulses at an increased frequency to the cardiovascular centre. This in turn causes a rapid increase in HR (Tortora & Derrickson, 2012). Chemoreceptors monitor chemical changes in the blood, and baroreceptors monitor the stretching of major arteries and veins caused by the pressures of blood flowing through them (Tortora & Derrickson, 2012). Once the cardiovascular centre has received input, it then directs the appropriate output to the heart by increasing or decreasing the frequency of nerve impulses in both the sympathetic and parasympathetic branches of the ANS (Figure 18) (Tortora & Derrickson, 2012).

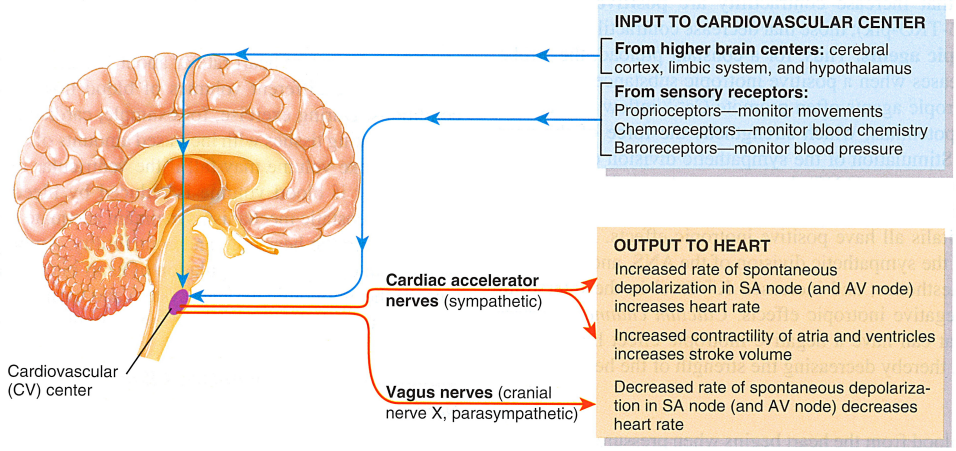

Figure 18. Nervous system control of the heart. Reprinted from *Principles of Anatomy and Physiology* (13th ed., p. 784), by G. J. Tortora and B. Derrickson, 2012, Hoboken, NJ: Wiley & Sons, Inc. Reprinted with permission.

The control of HR is a result of a dynamic equilibrium between opposing sympathetic and parasympathetic influences (Berntson, Cacioppo, & Quigley, 1991). Sympathetic neurons extend from the medulla oblongata into the spinal cord. Sympathetic cardiac accelerator nerves from the thoracic region of the spinal cord extend out to the SA node, AV node and myocardium (Tortora & Derrickson, 2012). Impulses in the cardiac accelerator nerves trigger the release of NE, which binds to β1-adrenergic receptor on cardiac muscle fibres (Tortora & Derrickson, 2012). This causes two separate effects: NE speeds the rate of spontaneous depolarisation in SA and AV node fibres, so that these pace makers fire impulses more quickly and HR increases, and NE enhances Ca^{++} entry through the voltage-gated slow Ca^{++} channels in the contractile fibres (found throughout the atria and ventricles). This increases contractibility and a greater volume blood is ejected during systole (Tortora & Derrickson, 2012).

Impulses from parasympathetic nerves reach the heart via the right and left vagus nerves. Vagal axons terminate in the SA and AV nodes and the atrial myocardium (Tortora & Derrickson, 2012). They release ACh which decreases HR by slowing the rate of spontaneous depolarisation in autorhythmic fibres (Tortora & Derrickson, 2012). In contrast to sympathetic activity, changes in parasympathetic activity have little effect on the contractibility of the ventricles because only a few vagal fibres innervate ventricular muscle (Tortora & Derrickson, 2012).

This continual shift of balance between the sympathetic and parasympathetic stimulation of the heart either increases or decreases HR. However, vagal tone is thought to provide overall control of the equilibrium by acting as a 'brake', counteracting and damping sympathetic drive, resulting in the term cardiac vagal control (CVC) to refer to the balance of both sympathetic and parasympathetic control elements (Rottenberg, 2007). At rest, parasympathetic stimulation predominates and during stress or physical activity sympathetic stimulation dominates (Tortora & Derrickson, 2012). However, other factors such as chemicals influences (e.g., which can decrease or increase pH or lower oxygen levels), hormones (epinephrine and NE from adrenal medullae) and cation imbalances (Ca^{++}, K^{+}, Na^{+} [sodium ion]) can influence both the basic physiology of cardiac muscle and the HR, while age, gender, physical fitness and body temperature can also affect resting HR (Tortora & Derrickson, 2012).

7.3. Autonomic Dysfunction

The normal autonomic integration of cardiovascular, renal, gastrointestinal, and temperature control contributes to the metabolic control directed by the needs of each organ to maintain homeostasis for the entire organism, and also can compensate for circumstances of stress or disease. When the ANS fails to function as it should, significant impairment in function results (Somers, 2012). The term 'dysautonomia' refers to any dysfunction or dysregulation of the ANS, the portion of the nervous system that conveys impulses between the blood vessels, heart, and all the organs in the chest, abdomen, and pelvis and the brain (Somers, 2012). Dysregulation can produce apparent malfunction of the organs it regulates. For this reason, dysautonomia patients often present with numerous, seemingly unrelated maladies. In general, the most common dysautonomias affect the sympathetic system (Somers, 2012). However, the parasympathetic system and conditions of increased or decreased parasympathetic tone are important to understand because they can have significant implications for cardiovascular health (Somers, 2012).

Research has shown that a relationship exists between the ANS and CVD disorders, leading to mortality. Several forms of alteration in autonomic function affecting the cardiovascular system have been demonstrated. Damage to nerves, extrinsic cardiac nerves or intrinsic cardiac nerves (e.g., from viral infections that primarily affect non-cardiac nerves, or from diseases that cause cardiac damage) can result in cardioneuropathy (Rubart & Zipes, 2012; Schwartz & Zipes, 1999). Such neural changes may also cause electrical instability. MI, for example, can interrupt neural transmission and cause sympathetic supersensitivity that may contribute to the development of arrhythmias (Rubart & Zipes, 2012; Schwartz & Zipes, 1999). Mutations in genes encoding cardiac ion channels can cause abnormal firing of neurons (Lehnart et al., 2008; Scornik et al., 2006). This finding may explain why variants of the long QT syndrome causes sudden cardiac death preceded by sympathetic arousal (Rubart & Zipes, 2012).

Alterations in vagal and sympathetic innervation can induce physiological changes, such as the development of arrhythmias and ventricular tachyarrhythmias, which can cause sudden cardiac death (Cao et al., 2000; Liu et al., 2003; Oh et al., 2006; Schwartz & Zipes, 1999). Experimental evidence showing an association between

fatal arrhythmias and either increased sympathetic activity or reduced vagal activity has resulted in the development of quantitative markers of autonomic activity (Task Force, 1996). One of the most promising of these markers is HRV, which is discussed further in the next section (Section 8).

Autonomic dysfunction in psychiatric disorders has gained increased interest over the years, and may play an important role in diagnosis of and recovery from psychiatric conditions, such as depression (Moser et al., 1998). Research has shown that similar to people with CHD and CAD (Rothschild, Rothschild, & Pfeifer, 1988; Saleem, Ullah, & Majeed, 2011; Stein et al., 2000; Wennerblom, Lurje, Tygesen, Vahisalo, & Hjalmarson, 2000), those with depression also have reduced HRV (Kemp et al., 2010; Udupa et al., 2007) and increased HR (Moser et al., 1998; Drago et al., 2007). In particular, in depressed patients, sleep disturbances and changes in appetite indicate autonomic dysfunction (Bicakova-Rocher, Gorceix, Reinberg, Ashkenazi, & Ticher, 1996; Davidson & Turnbull, 1986). Symptoms such as dry mouth or constipation suggest decreased parasympathetic activity in drug-free patients (Davidson & Turnbull, 1986) whereas diarrhoea suggests increased sympathetic activity. Thus, it is believed the ANS plays an important role in the relationship between these two disorders.

7.4. Autonomic Mechanisms Linking Depression and Coronary Heart Disease

The ANS has been suggested as a link between depression and CHD. Currently, research suggests that depression causes autonomic dysfunction, resulting in altered function of the SNS, PNS (including irregularities in vagal control) and HPA axis (Stapelberg et al., 2011). In turn, autonomic dysfunction can increase the risk of CVD (Musselman et al., 1998). Furthermore, increases in sympathetic activation, resting HR and HR responses to physical stressors, as well as impaired baroreflex sensitivity, high variability in ventricular repolarisation, and reduced HRV are common in depressed people (Davydov, Shapiro, Cook, & Goldstein, 2007; De Meersman & Stein, 2007). These changes have been associated with increased mortality and cardiac morbidity (Grippo & Johnson, 2002). The causal pathways are depicted in Figure 19.

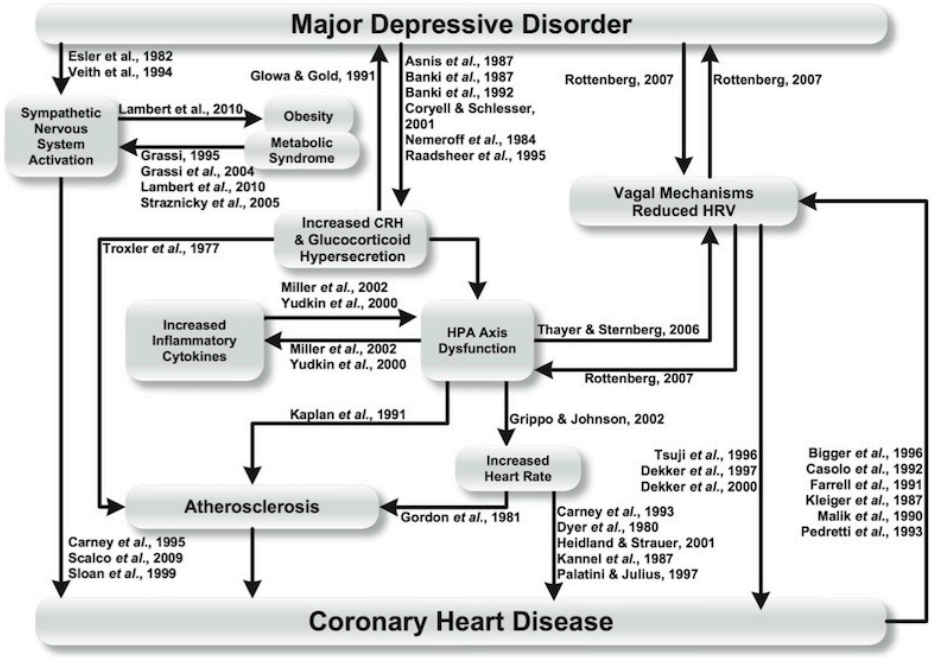

Figure 19. Autonomic mechanisms linking depression and coronary heart disease. Reprinted from "A Topographical Map of the Causal Network of Mechanisms Underlying the Relationship Between Major Depressive Disorder and Coronary Heart Disease", by N. J. C. Stapelberg et al., 2011, *Australian and New Zealand Journal of Psychiatry, 45,* p. 360. Reprinted with permission.

7.4.1. Sympathetic Nervous System Mechanisms

Sympathetic Activation and Activity

Depressed people may have increased SNS activation and SNS hyperactivity (Veith et al., 1994). In these people, hyperactivity has also been associated with increased cardiovascular morbidity and mortality (Carney, Saunders et al., 1995). Furthermore, depressed people have increased levels of sympathetic tone evidenced by elevated NE spill-over (Veith et al., 1994) (discussed further in Section 7.5). Overactivation of cardiac sympathetic outflow can occur under stressful conditions (such as experimental mental stress) and has been associated with severity of symptoms of depression during such stress (Hamer, Tanaka, Okamura, Tsuda, & Steptoe, 2007; Sheffield et al., 1998). As described in Section 7.1, sympathetic nerve activity increases during stress, resulting in an increase in cardiac output, HR and muscular blood flow (Acharya et al., 2006; Tortora & Derrickson, 2012). It has been proposed that the increases in these physiological parameters are causal factors between emotional stress and adverse cardiovascular events (Scalco et al., 2009). In a study analysing

sympathetic outflow, Barton and colleagues (2007) found a bimodal distribution of cardiac and whole body sympathetic nerve activity in a sample of depressed people - one subset showed sympathetic activation whereas others showed low sympathetic activation. These findings indicate that sympathetic regulation in depression is complex (Barton et al., 2007). Previous research has shown that depressed patients exhibit increased cardiac and total sympathetic activity, while muscle sympathetic activity is unchanged or reduced (Barton et al., 2007; Lambert & Schlaich, 2004). Barton and colleagues (2007) suggest that at rest and in response to stressors, the sympathetic nervous activity is regionalised (Esler, Jennings, & Lambert, 1989). Sympathetic outflow to organs such as the heart is preferentially activated, especially during mental stress (Barton et al., 2007; Esler et al., 1989), which in turn, has been associated with an increased risk of CHD (Carney, Saunders et al., 1995).

Obese people and people with metabolic syndrome have also been found to exhibit increased SNS activation (Grassi et al., 2004; Straznicky et al., 2005), with sympathetic outflow changes a significant contributor to this (Lambert, Straznicky, Lambert, Dixon, & Schlaich, 2010). Increased efferent muscle sympathetic nerve activity (Grassi et al., 2004; Straznicky et al., 2005) and noradrenergic spill-over to the blood from kidneys (Vaz et al., 1997) are also associated with obesity. The effects of sympathetic activation in obesity have been associated to CHD and cardiac failure via pathways related to hypertension and renal pathology (Lambert et al., 2010).

Hypothalamic-Pituitary-Adrenal Axis

The HPA axis refers to a set of direct influences by, and feedback interactions between, three endocrine glands: the hypothalamus, the pituitary gland (located below the hypothalamus), and the adrenal glands (located on top of the kidneys) (Tortora & Derrickson, 2012). This physiological system plays a significant role in the stress response, and thus homeostasis (Tortora & Derrickson, 2012).

Under stress (whether physical or psychological), neurons in the hypothalamus release corticotrophin-releasing hormone (CRH) (Tortora & Derrickson, 2012). This hormone is then transported to the pituitary gland and secretes adrenocorticotropic hormone (ACTH). This release stimulates the adrenal cortex (part of the adrenal gland), which in turn, causes the secretion of cortisol and catecholamines, primarily of

epinephrine but also of NE (Tortora & Derrickson, 2012). In addition, as previously discussed (Section 7.1), stress stimulates the SNS resulting in an increase in circulating glucose, HR, and blood pressure (Tortora & Derrickson, 2012). To keep the system in balance, the secretory molecules complete a feedback loop by acting on the three endocrine glands to modulate HPA activity, as depicted in Figure 20 (Tortora & Derrickson, 2012). As blood levels of cortisol increase (from production by the adrenal cortex), cortisol inhibits the hypothalamus and pituitary gland, which in turn reduces the output of CRH and ACTH (Tortora & Derrickson, 2012).

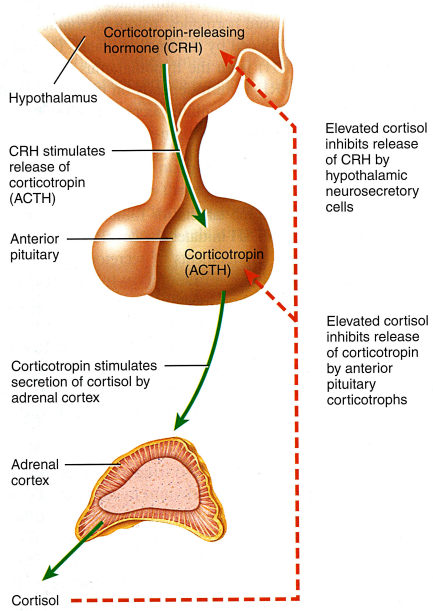

Figure 20. Hypothalamic-pituitary-adrenal axis negative feedback loop. Reprinted from *Principles of Anatomy and Physiology* (13th ed., p. 691), by G. J. Tortora and B. Derrickson, 2012, Hoboken, NJ: Wiley & Sons, Inc. Reprinted with permission.

The relationship between depression and HPA dysfunction has been investigated since the 1970s. In depression, the HPA axis is up-regulated with a down-regulation of its negative feedback controls, resulting in hypersecretion of cortisol (Asnis et al., 1987; Coryell & Schlesser, 2001). Depressed people demonstrate increased levels of CRH, further supporting the hypothesis of an up-regulation of the HPA axis (Banki, Karmacsi, Bissette, & Nemeroff, 1992; Nemeroff et al., 1984).

Adverse cardiovascular events have been associated with HPA dysfunction (Grippo & Johnson, 2002). When CRH increases sympathetic activity, elevated mean HR can result (Brown et al., 1982) in depressed people (Forbes & Chaney, 1980). The

increase in HR has also been found in otherwise healthy depressed people, as well as those with comorbid depression and CHD (Carney, Rich, teVelde et al., 1988). Carney and colleagues (1993), for example, found that people with depression and CHD showed higher mean HRs than non-depressed people with CHD. Elevated mean HR has been found to independently increase the risk of coronary artery plaque rupture (Heidland & Strauer, 2001), thus providing a further mechanism for adverse cardiac events in depressed people. Other adverse events associated with increased mean HR include arrhythmias, sudden death, myocardial ischaemia, cardiac failure (Carney, Freedland, Rich, Smith, & Jaffe, 1993; Palatini & Julius, 1997) and increased arterial wall stress, which has also been linked to atherosclerosis (Gordon, Guyton, & Karnovsky, 1981).

Additionally, both elevated plasma cortisol (Troxler, Sprague, Albanese, Fuchs, & Thompson, 1977) and chronic HPA and sympathoadrenal hyperactivity (Kaplan, Pettersson, Manuck, & Olsson, 1991) have been associated with atherosclerosis. These links may provide further mechanisms to explain the way in which increased plasma cortisol levels increase the risk of CVD (Stapelberg et al., 2011). Furthermore the development of myocardial ischaemia during exercise and mental stress may be caused by sympathetic hyper-responsiveness (Goldberg et al., 1996). Krantz and colleagues (1991) found that people with CAD and increased cardiovascular reactivity also had higher rates of mental stress-induced myocardial ischaemia.

The prefrontal cortex, which is connected to the limbic system, is assumed to play a role in the modulation of autonomic responses to mental stress and emotional stimuli (Davydov et al., 2007). Although controversial, it has been suggested that the prefrontal cortex directly modulates cardiovascular control (Resstel, Fernandes, & Correa, 2004) and is thus important in mood regulation and in cortical control of the HPA and the SNS (Stapelberg et al., 2011). In depression, people have been found to have significantly fewer prefrontal cortex cells (Rajkowska, 2000), which could help explain autonomic instability or dysfunction in depression.

Researchers have also suggested that HPA dysfunction can increase the levels of pro-inflammatory cytokines (Yudkin, Kumari, Hymphries, & Mohamed-Ali, 2000). By moderating endocrine functions, the ANS can play a role in the level of pro-

inflammatory mediators in the body (Berntson, Norman, Hawkley, & Cacioppo, 2008). Adrenergic modulation by the SNS and the HPA axis can cause an increase or decrease of pro-inflammatory cytokines, such as TNF, IL-1. In addition, the HPA axis can be further stimulated by inflammatory cytokines including IL-6, increasing the secretion of cortisol and other hormones (Yudkin et al., 2000). Lastly, HPA dysfunction and reduced CVC (discussed previously in Section 7.2) can result in reduced HRV (Thayer & Sternberg, 2006).

7.4.2. Parasympathetic Nervous System Mechanisms

Vagal Mechanisms and Heart Rate Variability

HRV is discussed in detail in Section 8, but briefly described here to clarify the way in which PNS mechanisms link depression and CHD. In humans, HR varies continuously depending on daily factors (e.g., exercise and stress) and physiological functions (e.g., respiration or blood pressure regulation) (Stein, Bosner, Kleiger, & Conger, 1994). These beat-to-beat variations are termed HRV. Normal variability in HR reflects autonomic neural regulation of the heart and the circulatory system (Saul, 1990) through the balancing actions of the SNS and the PNS branches of the ANS (Acharya et al., 2006). HRV is therefore a valuable tool for investigating the vagal (parasympathetic) influences of the brain on the heart, and vice versa, and may also provide a mechanism linking depression and CHD.

As discussed in Sections 7.1 and 7.2, parasympathetic cardiac control is the principal mechanism for autonomic regulation of the heart and cardiac function and is mediated by the vagus nerve (Tortora & Derrickson, 2012). HR is a result of the dynamic balance between sympathetic and parasympathetic (vagal) influences (Section 7.2). It is this balance that is termed CVC (Rottenberg, 2007). It has been suggested that measures of CVC, such as HRV, reflect vagal activity (Rottenberg, 2007). Changes in vagal tone have been associated with both depression and cardiac disease (Rottenberg, 2007). The level of resting vagal tone is associated to physiological responses to stressful situations (Stapelberg et al., 2011). High baseline levels of CVC indicate appropriate regulation of sympathetic and parasympathetic balance, whereas weak parasympathetic control may reflect poor balance of parasympathetic and sympathetic control (Rottenberg, 2007).

Research has shown that depression and CHD can cause reduced CVC (Carney, Saunders et al., 1995; Rottenberg, 2007), and that low HRV is associated with sudden death and ventricular arrhythmias in people with CHD. Reduced HRV may therefore present a further mechanism for relating these comorbid conditions (Curtis & O'Keefe, 2002; Tsuji et al., 1996). Adverse consequences are associated with HRV. Early changes in HRV are present following MI and are a risk factor for mortality (Bigger et al., 1996; Kleiger, Miller, Bigger, & Moss, 1987; Malik, Farrell, & Camm, 1990). This risk is significantly higher in patients with decreased HRV (Kleiger et al., 1987). Furthermore, reduced HRV increases the risk of MI, coronary insufficiency (insufficient blood flow) (Tsuji et al., 1996), sudden cardiac death (Goldberger, Findley, Blackburn, & Mandell, 1984; Myers et al., 1986) and CVD mortality (Dekker et al., 2000; Dekker et al., 1997). A causal relationship may also exist between CVC and depression, and CVC may be involved in depression maintenance (Rottenberg, 2007).

7.5. Measurement of Autonomic Nervous System Activity

Several methods have been developed over the years to assess autonomic activity. However, ANS activity is commonly measured in three ways: (1) by directly measuring sympathetic neural activity via microelectrode recordings from superficial nerves (van Dijk et al., 2013), (2) by using radiotracer techniques to measure NE spill over via isotope dilution (useful in less accessible sites such as the heart) (Lansdown & Rees, 2012), and (3) by using changes in an organ's response as a proxy for changes in ANS activity (e.g., measuring HR such as in HRV) (van Dijk et al., 2013). Although highly valid, the first two methods are invasive and thus less feasible. Although it is possible to measure NE without using radiolabelled NE, this greatly decreases sensitivity, thus is rarely performed this way (Lansdown & Rees, 2012). Therefore the latter measurement is the preferred option as it is not only highly feasible but is also non-invasive (van Diji et al., 2013). Various laboratory and ambulatory devices exist to measure cardiac autonomic control, such as the ECG. The ECG can be used to determine HRV, a marker of autonomic activity (Task Force, 1996). HRV is discussed next (Section 8).

8. HEART RATE VARIABILITY

It has long been known that a relationship exists between the ANS and cardiovascular disorders such as CHD, as well as with psychiatric disorders such as depression. Experimental evidence showing an association between fatal arrhythmias and either increased sympathetic activity or reduced vagal activity has resulted in the development of quantitative markers of autonomic activity (Task Force, 1996). One of the most promising of these markers is HRV.

In this section HRV is defined, its relationship with the functioning of the ANS (PNS and SNS) and measurement of HRV is explained, and some potential confounding variables for HRV measurement discussed. Finally, some recent research on interventions, which has either aimed to modify HRV or used HRV as an outcome measure, is reviewed.

8.1. Heart Rate Variability Definition and Uses

HRV is defined as beat-to-beat changes in HR, that is, the variation in RR interval (previously discussed in Section 3.1.2; Figure 5), and thus it reflects the modulation of HR by the ANS (Wu & Lo, 2008). HRV is measured non-invasively using an ECG machine or Holter monitor. Indices of HRV have been shown to be stable over 24 hours, and free of placebo effect (Kleiger et al., 1991; Task Force, 1996) in normal (Kleiger et al., 1991, Van Hoogenhuyze et al., 1991) and post-MI people (Kautzner, 1995). Some fragmentary data suggest that stability of HRV measures may persist for months and years (Task Force, 1996). This lack of intra-individual variability over time and individual reproducibility makes HRV suitable for intervention therapy assessment and an excellent tool for studying the status of the ANS and autonomic input to the heart (Kleiger et al., 1991; Task Force, 1996).

The clinical relevance of HRV was first reported by Hon and Lee (1963), who found that foetal distress resulted in changes in interbeat intervals, indicating the possible development of hypoxia. Reduced HRV was subsequently found to correlate with increased mortality in post-MI patients (Wolf, Varigos, Hunt, & Sloman, 1978). Power spectral analysis of HR fluctuations was introduced to quantitatively evaluate beat-to-beat cardiovascular control (Akselrod et al., 1981). These frequency domain

analyses contributed to the understanding of the autonomic background of RR interval fluctuations in HR (Pagani et al., 1986; Pomeranz et al., 1985). The late 1980s and early 1990s saw further recognition of the clinical importance of HRV, when it was confirmed that HRV was a strong independent predictor of mortality after an AMI (Bigger, Fleiss, Rolnitzky, & Steinman, 1993; Bigger et al., 1992; Kleiger et al., 1987; Malik, Farrell, Cripps, & Camm, 1989). HRV was later linked to psychiatric disorders such as depression (Roose, Glassman, & Dalack, 1989; Udupa et al., 2007). Since then, HRV has been used increasingly as a diagnostic method in medicine because of its potential to provide valuable insight into physiological and pathological conditions and to enhance risk stratification (Task Force, 1996).

8.2. Heart Rate Variability and the Autonomic Nervous System

A healthy heart does not always beat in a regular manner. In daily life, many factors influence HR, including sleep, exercise and physical and mental health (Stein et al, 1994). Physiological functions such as respiration, blood pressure regulation, thermoregulation, renin-angiotensin system rhythms may also periodically alter the intervals between normal sinus beats (Stein et al., 1994). The interaction between these systems causes fluctuations, and such periodic rhythms are the source of HRV.

Normal variability in HR is due to autonomic neural regulation of the heart and the circulatory system (Saul, 1990) through the balancing actions of the SNS and the PNS branches of the ANS (Acharya et al., 2006). Low variability in HR suggests abnormality and insufficient adaptability of the ANS and physiological malfunction, that is, excessive SNS or diminished PNS activity, resulting in cardio-acceleration (Acharya et al., 2006; Pumprla, Howorka, Groves, Chester, & Nolan, 2002). Hence, changes and reduction in an individual's HRV pattern can provide an early indication of compromised health and the need for further investigations to determine a specific diagnosis. Low HRV, for example, is an independent predictor of post-MI mortality (Bigger et al., 1992). Conversely, high HRV indicates a healthy individual with good adaptability and well-functioning autonomic control mechanisms, that is, low SNS or high PNS activity, resulting in cardio-deceleration (Acharya et al., 2006; Pumprla et al., 2002).

The degree of variability in HR provides information about the functioning of nervous control on the HR and the heart's ability to respond (Acharya et al., 2006). HRV is therefore a valuable tool for investigating the sympathetic and parasympathetic functions of the ANS both in healthy individuals and in patients with various non-cardiovascular disorders (Task Force, 1996).

8.3. Measurement of Heart Rate Variability

HRV is commonly measured using a recording device; an ECG (previously described in Section 4.5) or Holter monitor (procedure discussed in Chapter Six, Section 1.2) linked by wires to electrodes attached to a person's chest. Depending on the design of the study, the patient lies in a supine position or sits/stands for a set time period while the device records HR, and HRV is then calculated using a computer software program.

Conventional linear HRV analyses include time domain and frequency domain analyses, and both have been reported as prognostic factors for CHD (Bigger et al., 1993; Bigger, Fleiss, Rolnitzky, Steinman, & Schneider, 1991; Task Force, 1996; Tsuji et al., 1996). They are introduced in the following sections. HR fluctuations have been conceptualised as complex behaviours originating from non-linear processes; therefore non-linear methods are also used for the analysis of HRV and these are also described below, with definitions and abbreviations summarised in Tables 4 and 5.

8.3.1. Time Domain Statistical Methods

HR variations can be evaluated by two approaches: time domain or frequency domain. HR is derived from the interval between RR in the ECG (previously described in Sections 3.1.2). Time domain methods use simple statistical analyses (means and variance) to measure the amount of variability present in a pre-specified time period in a continuous ECG (Stein et al., 1994). Non-sinus beats and artefact are first removed, and the normal RR intervals are measured (R is a point corresponding to the peak of the QRS complex of the ECG wave; thus RR is the interval between successive R's, also referred to as normal to normal (NN) intervals.

Statistical Measures

Time domain variables can be classified into two classes: (1) those derived from direct measurements of NN intervals or instantaneous HR (i.e., inter-beat intervals), including SDNN, and (2) those derived from the differences between NN intervals, including RMSSD (Task Force, 1996). These variables may be derived from the total ECG recording or calculated using smaller segments of the recording period (Task Force, 1996). The latter method allows comparison of HRV to be made during varying activities, such as rest or sleep (Task Force, 1996).

The simplest variable to calculate from inter-beat intervals is the standard deviation of NN intervals (SDNN), that is, the square root of variance. Variance is mathematically equal to total power; therefore, SDNN reflects all the cyclic components responsible for variability in the recording. It is a marker of the overall magnitude of variability (Lombardi & Stein, 2011; Task Force, 1996), thus a low value indicates low HRV. Preferably, SDNN is computed on long-term recordings (Lombardi & Stein, 2011). As the period of ECG monitoring decreases, SDNN estimates shorter and shorter cycle lengths, thus, the total variance of HRV increases with longer recordings. SDNN is, therefore, dependent on the length of recording period and recordings of different durations should not be compared (Task Force, 1996). Other variables calculated from segments of the total monitoring period, commonly over five minute durations include SDANN (an estimate of the changes in HR due to cycles longer than 5 minutes) and SDNN index (which measures the variability due to cycles shorter than 5 minutes).

The most commonly used measure from interval differences is RMSSD, the root mean square of successive difference between adjacent NN intervals, which estimates short-term components of HRV (Lombardi & Stein, 2011). Other variables include NN50 and pNN50. All three measurements of short-term variation are highly correlated because they estimate high frequency (HF; discussed further below) and thus reflect vagal/parasympathetic activity (Lombardi & Stein, 2011). RMSSD is, however, the preferred measure because it has better statistical properties (Task Force, 1996).

8.3.2. Time Domain Geometric Methods

An alternative approach to statistical analysis is geometric analysis, whereby NN intervals are converted into a geometric pattern, such as the sample density

distribution of NN interval duration or differences between adjacent NN intervals or a Lorenz plot of NN or RR intervals (Task Force, 1996). A formula is then used to calculate the variability of the geometric and/or graphics properties of the resulting pattern.

Geometric Measures

A commonly measured geometric time domain parameter is the HRV triangular index, which is a measure of overall HRV (Lombardi & Stein, 2011). The HRV triangular index is the integral of the density distribution (that is, the number of all NN intervals) divided by a maximum of the density distribution (Task Force, 1996). The length of NN intervals serves as the x-axis of the plot and the number of each NN interval length serves as the y-axis. The length of the base of the triangle is used and approximated by the main peak of the NN interval frequency distribution diagram (Acharya et al., 2006). Geometric methods are highly advantageous as they are relatively insensitive to the quality of the series of NN intervals (Acharya et al., 2006) and insensitive to artefacts and ectopic beats, because these are left outside the triangle (Malik et al., 1993). This reduces the need for pre-processing of the recorded data (Malik et al., 1989), which is required in statistical time domain methods. The major disadvantage of the geometric method is the need for a reasonable number of NN intervals to construct the geometric pattern. At least 20 minutes of recording is required, with 24 hours preferred (Lombardi & Stein, 2011; Task Force, 1996). This was not an issue in the Study 3 (Chapter Six) as the ECG was monitored for 20 minutes.

Artefact

HRV is extremely sensitive and can be altered due to artefact arising from ectopic beats (additional or skipped heartbeats), arrhythmic events (irregular heartbeat) and missing data (Citi, Brown, & Barbieri, 2012; Task Force, 1996). All time domain indices (statistical and geometric measures) can therefore be affected by artefact, and errors in as little as 2% of the data can result in unwanted biases in HRV calculations (Citi et al., 2012). To ensure accurate results it is critical to manage artefact and RR errors appropriately prior to performing any HRV analyses (Citi et al., 2012). However, if artefact exists, it should carefully be eliminated (Acharya et al., 2006). Preferentially, short-term recordings free of ectopy, arrhythmia and missing data should be used (Task Force, 1996).

The variety of time domain measures of HRV are summarised in Table 4. Since many measures of HRV correlate with each other, it is recommended that time domain parameters SDNN, SDANN, RMSSD and HRV triangular index be used for assessment (Task Force, 1996). For Study 3 (Chapter Six), time domain measures SDNN, RMSSD and triangular index were analysed from the 20 minute ECG recording. As SDANN is an estimate of long-term components of HRV, it was not analysed in Study 3.

Table 4

Time Domain Parameters of Heart Rate Variability

Variable	Units	Description
		Statistical Measures
SDNN	ms	Standard deviation of all NN intervals
SDANN	ms	Standard deviation of the averages of NN intervals in all 5 min segments of the entire recording
RMSSD	ms	The square root of the mean of the sum of the squares of differences between adjacent NN intervals
SDNN index	ms	Mean of the standard deviations of all NN intervals for all 5 min segments of the entire recording
SDSD	ms	Standard deviation of differences between adjacent NN intervals
NN50 count		Number of pairs of adjacent NN intervals differing by more than 50ms in the entire recording
pNN50	%	NN50 count divided by the total number of all NN intervals
		Geometric Measures
HRV triangular index		Total number of all NN intervals divided by the height of the histogram of all NN intervals
TINN	ms	Baseline width of the minimum square difference triangular interpolation of the highest peak of the histogram of all NN intervals
Differential index	ms	Difference between the widths of the histogram of differences between adjacent NN intervals measured at selected heights
Logarithmic index		Coefficient of the negative exponential curve which is the best approximation of the histogram of absolute differences between adjacent NN intervals

Note. Adapted from "Heart Rate Variability: Standards of Measurement, Physiological Interpretation, and Clinical Use", by Task Force of The European Society of Cardiology and The North American Society of Pacing and Electrophysiology, 1996, *European Heart Journal, 17,* p. 358. Adapted with permission.

8.3.3. Frequency Domain Methods

Time domain methods are computationally simple, but lack the ability to discriminate between sympathetic and parasympathetic contributions of HRV, whereas frequency domain methods allow for this distinction (Acharya et al., 2006). Frequency domain parameters are analysed by power spectral density (PSD) methods via mathematical algorithms. PSD provides a basis of how power (i.e., variance) distributes as a function of frequency (Task Force, 1996). Methods for the calculation of PSD may be classified as non-parametric (such as Fast Fourier Transformation) and parametric (such as Yule-Walker autoregressive process). In most instances, both methods provide comparable results (Task Force, 1996).

Frequency Domain Measures

The separate rhythmic contributions from sympathetic and parasympathetic autonomic activity modulate the HR (NN) intervals of the QRS complex in the ECG at distinct frequencies (Acharya et al., 2006). Four frequency bands (ULF: ultra low frequency; VLF: very low frequency; LF: low frequency; HF: high frequency) associated with different physiological rhythms can be analysed, depending on whether recording time is short or long (Task Force, 1996).

Short-Term Recordings

Three main spectral components can be calculated from short-term recordings of 2 to 5 minutes (Task Force, 1996): VLF (0.0033-0.04 Hz), LF (0.04-0.15 Hz) and HF (0.15-0.4 Hz). The distribution of the power and the central frequency of LF and HF are not fixed but may vary in relation to changes in autonomic modulations of the heart period (Task Force, 1996). These two parameters are the best understood physiologically. It has long been believed that LF predominantly reflects sympathetic activity, but can also reflect parasympathetic activity (Lombardi & Stein, 2011; Notarius & Floras, 2001; Task Force, 1996). However, the traditional interpretation of LF has recently been questioned, with some researchers arguing that it predominantly reflects the PNS (Goldstein, Bentho, Park & Sharabi, 2011; Reyes del Paso, Langeqitz, Mulder, Roon & Duschek, 2013). Due to the controversial view that LF reflects PNS activity, the former interpretation of LF has been adopted. LF waves correlate, in part, with baroreflex activity, which modulates blood pressure (Bernardi et al., 1994). Baroreflex sensitivity, a measure of the autonomous control of the HR caused by

variations in blood pressure and defined as the altered RR interval following changes in systolic blood pressure (Nesvold et al., 2012), is an independent predictor of poor prognosis in CHD (Bernardi et al., 2001). Baroreflex sensitivity decreases when autonomic balance is dominated by sympathetic activity and increases through parasympathetic dominance (La Rovere, Pinna, & Mortara, 1998). In addition, when respiration rate is 6 breaths per minute (0.1 Hz) or lower or when taking a deep breath, parasympathetic activity is present (Lehrer, Sasaki, & Saito, 1999; Peressutti, Martin-Gonzalez, & Garcia-Manso, 2012). Breathing at this rate causes HF and LF waves in HR to synchronise and merge at a rate of respiration, causing increases in amplitude of respiratory sinus arrhythmia (RSA; discussed below) (Lehrer et al., 1999). Resonance occurs between processes involved in RSA and in those that mediate LF cardiac variability (presumably including baroreflex activity) (Lehrer et al., 1999). Thus, when in a state of relaxation with a slow and even breathing, LF values can be high indicating increased parasympathetic activity, rather than an increase in sympathetic regulation. This can often be observed in meditation with slow breathing (Lehrer et al., 1999). Slow breathing can therefore not only enhance HRV but can also increase baroreflex sensitivity, by synchronising inherent cardiovascular rhythms (Bernardi et al., 2001). In addition, a linear relation exists between the degree of RSA and parasympathetic cardiac control (Katona & Jih, 1975; Kovatchev et al., 2003) making RSA a useful prognostic tool in cardiac patients, such as in MI.

The interpretation of HF is broadly supported as an index of CVC and thus parasympathetic activity (Lombardi & Stein, 2011; Notarius & Floras, 2001; Task Force, 1996). Generally an increase in HF accompanies an increase in HRV. HF is also known as a 'respiratory' band because it corresponds to the NN variations caused by respiration. This phenomenon is known as RSA and is a naturally occurring variation in HR (Ben-Tal, Shamailov, & Paton, 2012; Grossman & Taylor, 2007). The respiratory frequency, however, is not restricted to the HF band. It can be as low as 0.1 hertz during relaxation and as high as 0.7 hertz during intense exercise (Bailon, Laguna, Mainardi, & Sornmo, 2007). During the breathing cycle, inhalation temporarily suppresses vagal activity, causing an immediate increase in HR, and exhalation then decreases HR and causes vagal activity to resume (Ben-Tal et al., 2012; Grossman & Taylor, 2007). On an ECG, RSA is seen as subtle changes in the RR interval synchronised with respiration. The RR interval is shortened during inspiration and prolonged during expiration (Peng

et al., 2004). The LF/HF ratio can also be calculated and is the ratio between the power of LF and HF frequency bands (Task Force, 1996). Similarly to LF, the interpretation of the LF/HF ratio has recently been debated, with researchers suggesting it represents parasympathetic activity (Goldstein et al., 2011; Reyes del Paso et al., 2013). However, since this interpretation is highly controversial, this thesis will adopt the previously accepted view that the LF/HF ratio is a measure of sympathovagal balance, that is, the overall balance between sympathetic and parasympathetic systems (Lombardi & Stein, 2011; Task Force, 1996). Higher values indicate increased sympathetic activity or reduced parasympathetic activity. The physiological process of VLF is much less defined and its attribution to heart period changes is questionable (Task Force, 1996). The major constituent of VLF, the non-harmonic component, does not have coherent properties but is affected by algorithms of baseline or trend removal. VLF is therefore considered a dubious measure for short-term recordings (e.g., ≤5 min) and should be avoided (Task Force, 1996).

In Study 3 (Chapter Six), participants undertook two 20-minute ECG recordings. Frequency domain parameters (LF and HF) were then calculated per 5 minutes intervals.

Frequency parameters ULF, LF and HF are typically measured in absolute values of power; ms^2 (see Table 5). However, LF and HF can also be measured in normalised units; nu (Task Force, 1996), which represent the absolute value of each power component in proportion to the difference between total power and (short-term estimate of the total power of PSD in the range of frequencies between 0 and 0.4 Hz) and VLF. LF and HF nu represent the controlled and balanced behaviour of the two branches of the ANS (Task Force, 1996). LF nu, for example, emphasises changes in sympathetic regulation. In addition, normalisation tends to minimise effects on LF and HF due to changes in total power (Task Force, 1996). However, normative values can suffer from interpretation problems and may be obscured by being reported as proportions (Krygier et al., 2013). If LF decreases enough, for example, HF nu may increase dramatically while spectral power in the HF band decreases. A change in HF nu could be the result of increased HF, decreased LF, or a combination (Krygier et al., 2013). In order to describe the total distribution of power in spectral components, LF nu

and HF nu should never be quoted without the absolute vales of LF and HF (Task Force, 1996).

Long-Term Recordings

Spectral analysis can also be used to analyse the sequence of NN intervals in a 24-hour recording. In addition to VLF, LF and HF, ULF (<0.0033 Hz) may be calculated. The slope of the 24-hour spectrum can also be assessed on a log-log scale by linear fitting the spectral values (Task Force, 1996). The variety of frequency domain measures of HRV are summarised in Table 5.

Table 5

Frequency Domain Parameters of Heart Rate Variability

Variable	**Units**	**Description**
	Analysis of Short-Term Recording	
5 min total power	ms^2	The variance of NN intervals over the temporal segment
VLF	ms^2	Power in very low frequency range
LF	ms^2	Power in low frequency range
LF norm	nu	LF power in normalised units
HF	ms^2	Power in high frequency range
HF norm	nu	HF power in normalised units
LF/HF		Ratio LF/HF
	Analysis of Long-Term Recording	
Total power	ms^2	Variance of all NN intervals
ULF	ms^2	Power in the ultra low frequency range
VLF	ms^2	Power in the very low frequency range
LF	ms^2	Power in the low frequency range
HF	ms^2	Power in the high frequency range
α		Slope of the linear interpolation of the spectrum in a log-log scale

Note. Adapted from "Heart Rate Variability: Standards of Measurement, Physiological Interpretation, and Clinical Use", by Task Force of The European Society of Cardiology and The North American Society of Pacing and Electrophysiology, 1996, *European Heart Journal, 17,* p. 360. Adapted with permission.

However, the interpretation of LF, HF and LF/HF can be controversial from long-term recordings, as environmental factors, physical activity and quality and duration of sleep are major determinants of HRV which vary significantly over time (Lombardi & Stein, 2011). As a result, it has been recommended that these HRV indices should be restricted to short-term recordings under controlled conditions in order to relate them to ANS functioning (Lombardi & Stein, 2011).

8.3.4. Non-Linear Methods

Fluctuations in HR have been recognised as complex behaviours originating from non-linear processes (Goldberger et al., 2002; Lo, Novak, Peng, Liu, & Hu, 2009; Peng, Costa, & Goldberger, 2009). Applying conventional linear algorithms to the irregular and "patchy" patterns of HR may therefore be misleading (Buchman, 2002; Goldberger et al., 2002). In contrast to time and frequency domain measures, which capture the amount of HRV at various time scales, non-linear HRV measures attempt to capture the structure or complexity of the HR time series (Stein, Domitrovich, Huikuri, & Kleiger, 2005). A random, normal or totally periodic series of heartbeats, for example, might each have the exact same standard deviation (SDNN), but their underlying organisation would be completely different (Stein et al., 2005). It has therefore been suggested that non-linear analysis may elicit valuable information for the physiological interpretation of HRV (Task Force, 1996), serve as a more reliable index for such systems in clinical studies (Goldberger et al., 2002; Peng et al., 2009) and provide valuable information for the estimation of the risk of sudden death (Task Force, 1996).

A commonly used non-linear method of analysing HRV is the Poincaré plot. Each data point represents a pair of successive beats; the x-axis is the current RR interval, while the y-axis is the previous RR interval. HRV is quantified by fitting mathematically defined geometric shapes to the data (Brennan, Palaniswami, & Kamen, 2001). Other methods employed include the correlation dimension, Kolmogorov entropy and Lyapunov exponents. As non-linear methods were not used in this research and are therefore outside the scope of this thesis, they will not be discussed further.

8.4. Heart Rate Variability in Coronary Heart Disease and Depression

HRV has become a common tool for investigating physiological changes in a variety of illnesses (Sztajzel, 2004). Both depression and CHD have been associated with decreased HRV (Carney, Saunders et al., 1995; Drago et al., 2007; Kemp et al., 2010; Stein et al., 2000; Udupa et al., 2007). HRV may, therefore, provide a strong link between these two conditions.

Heart Rate Variability and Coronary Heart Disease

Research has shown that early changes in HRV occur following CHD in terms of increased sympathetic activity and decreased parasympathetic activity (Rothschild et al., 1988; Saleem et al., 2011; Stein et al., 2000; Wennerblom et al., 2000), which have been associated to cardiac events and mortality (Bigger et al., 1993; Bigger et al., 1992). HRV has in fact been shown to be an independent predictor of mortality post-MI (Bigger et al., 1992; Kleiger et al., 1987; Malik et al., 1989). HRV significantly improves in the following two months after MI, possibly due to the re-establishment of autonomic cardiac control (Lombardi et al., 1987). Further recovery occurs after 12 months, however HRV remains reduced compared to people without MI (Bigger et al., 1991; Schwartz et al., 1988). Several studies have showed that for periods greater than 1 year, HRV remains lowered post-MI, increasing the risk of mortality (Bigger et al., 1992). In addition, the risk of mortality is significantly higher in CAD and MI survivors with reduced HRV (Kleiger et al., 1987), with adverse consequences including increased risks of MI, coronary insufficiency (insufficient blood flow) (Tsuji et al., 1996) and sudden cardiac death (Goldberger et al., 1984; Myers et al., 1986).

Heart Rate Variability and Depression

In the 1990s, several studies investigated the relationship between depression and HRV. Initially, mixed findings were reported (Agelink, Boz, Ullrich, & Andrich, 2002; Bar et al., 2004), with some studies finding decreased HRV in depressed (compared to non-depressed) people (Dalack & Roose, 1990; Lehofer et al., 1999; Roose et al., 1989), whereas others reported no differences (Jakobsen, Hauksson, & Vestergaar, 1984; Lehofer et al., 1997; O'Connor, Allen, & Kazzniak, 2002; Yeragani et al., 1991). It was later reported that sympathetic activity was increased and parasympathetic activity was decreased in depressed people (Udupa et al., 2007). One study also reported that only severely depressed people showed a reduced HRV and a

lower cardiac vagal activity compared to controls (Agelink et al., 2002). The heterogeneity of these earlier findings is believed to reflect methodological issues such as small sample size, different HRV measures reported, and other confounding factors, including antidepressant medication (Kemp et al., 2010). As a result, a recent meta-analysis (Kemp et al., 2010) attempted to clarify these findings by examining the above methodological issue, finding that depression is indeed associated with decreased HRV. In addition, the severity of depression negatively correlated with HRV; that is, the more severe depression is, the lower the HRV (Kemp et al., 2010). Furthermore, a more recent meta-analysis by Kemp and colleagues (2012) further supported previous findings of reduced HRV in depression.

Heart Rate Variability, Coronary Heart Disease and Depression

Research has shown HRV changes in people with comorbid depression and CHD. Decreased HRV has been found in depressed CAD and AMI patients (Carney et al., 2001; Carney, Saunders et al., 1995; Drago et al., 2007). In addition, increased HR has been reported in people with depression (Moser et al., 1998) and in those with depressed AMI compared to those with AMI without depression (Drago et al., 2007). According to Carney and colleagues (2005), the decrease in HRV associated with depression may help to explain the increased mortality.

8.5. Influences on Heart Rate Variability

Numerous factors can influence HRV and affect the analysis, making interpretation of results difficult. Some of these factors are discussed below.

8.5.1. Individual Factors

Age and Gender

Previous research has found that HRV is influenced by gender and to a greater extent by age (Zhang, 2007). Gender differences in HRV are evident but conflicting and differences appear to be dependent on age and HRV time and frequency domain (Bonnemeier et al., 2003; Umetani, Singer, McCraty, & Atkinson, 1998; Yamasaki et al., 1996). Findings on age differences in HRV are clearer and reflect physiologic and maturational factors. Maturation of the sympathetic and vagal divisions of the ANS results in an increase in HRV with gestational age (van Ravenswaaij-Arts et al., 1991) and during early postnatal life (van Ravenswaaij-Arts et al., 1991). After birth, HRV

decreases with age (Acharya, Kannathal, & Krishnan, 2004; Acharya, Kannathal, Sing, Ping, & Chua, 2004) and this decline starts in childhood (Schwartz, Gibb, & Tran, 1991). Sympathetic activity is high in infants and decreases between the ages of 5 and 10 years (Finley, Nungent, & Hellenbrand, 1987). Between the ages of 20 to 70, in healthy individuals HRV decreases with age with a decline of cardiac vagal modulation (Bonnemeier et al., 2003; Zhang, 2007). It is believed that the significant decrease in HRV results from the post-pubertal growth spurt to adulthood (Zhang, 2007), a decrease in nocturnal parasympathetic activity (Bonnemeier et al., 2003) and possibly also declining in health in the older population and decrease in physical activity (Zhang, 2007). Exercise also impacts HRV. Young people (<30 years) tend to have a higher HRV because of active autonomic modulations. With aging, the HR changes less because of increasingly sedentary lifestyles (Davy, Desouza, Jones, & Seals, 1998; Zhang, 2007). The only proven method to increase HRV, especially for older people (>50 years), is engaging in regular exercise (Davy et al., 1998; Zhang, 2007). Normal HRV in the healthy population is, therefore, strongly affected by two factors: age and exercise (Zhang, 2007).

Pregnancy

Pregnancy is also associated with multiple physiological changes, including changes in the ANS. During pregnancy, the ANS helps the parturient adapt to the different states of pregnancy (Speranza, Verlato, & Albiero, 1998). Data on changes in HRV in the first trimester are controversial, with some studies finding no change in sympathetic activity (Antonazzo, Cetin, Tarricone, Lombardi, & Pardi, 2004; Kuo, Chen, Yang, Lo, & Tsai, 2000) and others showing an increase in sympathetic activity, which continues, and reaches a maximum at the end of the second trimester (Curione et al., 2005; Khlybova, Tsirkin, Dvoryanskii, Markarova, & Trukhin, 2008; Medvedev, Astakova, & Kirsanov, 1989; Walther et al., 2005). In the second and third trimesters of pregnancy, many studies have found that HRV decreases, indicating an increase in sympathetic activity (Khlybova et al., 2008; Tsirkin et al., 2004, Medvedev et al., 1989; Walther et al., 2005). Pregnant women near or at term (compared to non-pregnant women) were found to exhibit a higher HR and overall decreased HRV, as indicated by decreased parasympathetic modulation (reflected by decreased SDNN, RMSSD, pNN50 and HF) (Avery, Wolfe, Amara, Davies, & McGrath, 2001; Chamchad, Horrow, Nakhamchik, & Arkoosh, 2007; Stein et al., 1999). In addition, before delivery,

sympathetic activity is unchanged (Medvedev et al., 1989) or decreased, facilitating a normal delivery (Khlybova et al., 2008; Gudkov, Pomortsev, & Fedorovich, 2001). As summarised by Khlybova and colleagues (2008), numerous explanations have been proposed for the changes in sympathetic activity. However, it is believed that the changes are necessary for activating maternal mechanisms that support foetal growth and development, including inhibition of uterine contractions and increases in the cardiac pump function and blood gas transport (Khlybova et al., 2008).

Maternal depression during pregnancy (compared to healthy controls) is also associated with decreased HRV (as reflected by SDNN and SDANN), as well as a higher HR while asleep (Shea et al., 2008). In addition, the LF/HF ratio during sleeping hours was positively associated with higher depression scores, indicating decreased parasympathetic drive with higher depression scores (Shea et al., 2008). These findings suggest that in the study of HRV, both normal pregnancy and depression during pregnancy confound HRV.

8.5.2. Environmental Factors

Diurnal Range

Individuals' HRV has been found to vary with the time of day at which it is measured (Kim, Yoon, & Cho, 2014; Ramaekers, Ector, Aubert, Rubens, & Van de Werf, 1998; Rao & Bopardikar, 1998). It is therefore recommended that for longitudinal HRV analyses, data collection should be conducted at a similar time of day for each participant.

8.5.3. Behavioural Factors

Smoking

The majority of the published research demonstrates that both acute and chronic smoking affects HRV. Smoking increases HR (Saperova & Dimitriev, 2014; Swarnkar, Kumar, Verma, & Goel, 2013) and reduces HRV. Smokers exhibit increased sympathetic and decreased parasympathetic activity (Acharya et al., 2006; Alyan et al., 2008; Kobayashi et al., 2005; Saperova & Dimitriev, 2014). The decrease in vagal modulation of the heart is particularly apparent during a parasympathetic manoeuvre, that is, the switch from sympathetic to parasympathetic activity, which is required in controlled respiration or after a fright (Barutcu et al., 2005). In addition, smoking

increases ectopic beats and induces ischaemic ST-T changes, and it may increase the vulnerability to arrhythmias or ischaemic heart disease (Swarnkar et al., 2013). As explained by Dinas and colleagues (2013), two main mechanistic pathways have been proposed to explain how smoking disrupts the normal ANS functioning: nicotine and respirable particles. However these are beyond the scope of this thesis and are not further discussed.

Caffeine

The consumption of caffeinated drinks stimulates the ANS (Quinlan, Lane, & Aspinall, 1997), causing both alertness and relaxation (Hibino, Moritani, Kawada, & Fushiki, 1997). The feeling of alertness is due to excitation of the central nervous system, and the relaxation due to the calming of the same system (Hibino et al., 1997). Some parameters of cardiovascular activity, such as blood pressure (James, 2004; Noordzij et al., 2005) and HR, have been extensively investigated. Some studies showed no effect of caffeine on HR (Nishijima et al., 2002; Rauh, Burkert, Siepmann, & Mueck-Weymann, 2006; Richardson et al., 2009; Sondermeijer, van Marle, Kamen, & Krum, 2002) whereas others showed a significant effect (Notarius & Floras, 2012; Waring, Goudsmit, Marwick, Webb, & Maxwell, 2003). Studies on the influence of caffeine on HRV are, however, rare. Recently, Koenig and colleagues (2013) summarised findings in a systematic review, reporting that some studies found caffeine reduced parasympathetic activity (Sondermeijer et al., 2002), although the best evidence suggests an increase in parasympathetic vagally mediated HRV (as indexed by HF) due to a calming effect (Hibino et al., 1997; Monda et al., 2009; Notarius & Floras, 2012**)**. However, due to large between-study variations in the participants, experimental conditions and caffeine consumption, there is as yet no consensus concerning the impact of caffeine on HRV (Koenig et al., 2013).

Caffeine appears to have different effects in people with CHF (Notarius & Floras, 2012) or post-STEMI (Richardson et al., 2009). Notarius & Floras (2012) found an increase in HF and decrease in HR in healthy people, but not in CHF patients, whereas Richardson and colleagues (2009) found that caffeine (compared to a de-caffeinated drink) promoted a significant increase in parasympathetic activity post-STEMI. Furthermore, results differ when HRV is measured at rest or during or after exercise (Karapetian, Engels, Gretebeck, & Gretebeck, 2012, Nishijima et al., 2002,

Waring et al., 2003) or in the supine position (Monda et al., 2009). One study, for example, found a significant increase in HF only during rest (Karapetian et al., 2012), while another study reported increases in HF, LF and total power only during exercise and not during rest (Nishijima et al., 2002). Monda and colleagues (2009) found a caffeine-induced increase in HF when participants were studied supine, but not when studied seated. Explanations relating to differing results between different populations or experimental conditions are explained in Koenig and colleagues' review (2013). Lastly, a dose-dependent relationship was found in one of two studies (Sondermeijer et al., 2002) that compared different caffeine doses (100mg vs. 200mg) (Rauh et al., 2006; Sondermeijer et al., 2002). This study found a significant decrease in SDNN, RMSSD and HF for both groups, but decreases in pNN50 and LF/HF only for the 200mg group. The other study (Rauh et al., 2006) reported no significant differences between the groups. These results may differ because young male habitual caffeine consumers were studied, whereas participants in the study that reported a dose-response relationship were non-habitual caffeine users (Koenig et al., 2013). Although there is a large amount of research focusing on acute (short-term) effects, studies of chronic (long-term) effects are rare. However, some studies have reported that high doses of caffeine can cause tachycardia (Starr et al., 1937), increased plasma epinephrine (Smits, Thien, & van't Laar, 1985), and psychological symptoms of anxiety in people with depression or panic disorder (Lee, Flegel, Greden, & Cameron, 1988).

In people with depression or panic disorder, excessive caffeine intake can cause psychological symptoms of anxiety (Lee et al., 1988). Research has shown that depression, panic disorder and anxiety are all associated with decreased HRV **(**Gorman & Sloan, 2000; Prasko et al., 2011; Udupa et al., 2007; Yeragani et al., 1998), possibly due to decreased cardiac vagal function (Yeragani et al., 1998; Gorman & Sloan, 2000). Findings suggest that caffeine can substantially influence HRV findings and should be avoided under testing conditions.

Alcohol

Research has shown that both acute and chronic alcoholic consumption affects the ANS. The HRV changes associated with chronic use follow a J-shaped curve; such that moderate alcohol consumption (i.e., drinking less frequently or abstaining altogether) confers a protective effect against poor health, whereas heavy consumption

is associated with poorer health (Karpyak, Romanowicz, Schmidt, Lewis, & Bostwick, 2014; Quintana, Guastella, McGregor, Hickie, & Kemp, 2013). Daily low dose (approximately one standard drink in women and two in men) is associated with increased HRV, namely increased RMSSD, SDNN and HF and decreased LF and LF/HF ratio (Janszky et al., 2005; Karpyak et al., 2014). However, as alcohol consumption dosage increases, parameters indicative of reduced HRV and decreased vagal modulation (decrease in pNN50, HF and RMSSD and increase in LF/HF ratio) are reported (Minami et al., 2002; Thayer, Hall, Sollers, & Fischer, 2006). Both acute and chronic alcoholism cause a reduction in HRV, as indicated by increased sympathetic activation and decreased parasympathetic activity (Acharya et al., 2006; Karpyak et al., 2014; Malpas, Whiteside, & Maling, 1991; Romanowicz, Schmidt, Bostwick, Mrazek, & Karpyak, 2011; Rossinen et al., 1997). Additionally, Malpas and colleagues (1991) further showed vagal neuropathy (damage to the vagus nerve) in men with chronic alcohol dependence (using 24-hour HRV analysis). Damage to the vagus nerve can result in sending wrong or weak signals between the body and brain, resulting in an irregular HR, and thus altered HRV.

Illicit Drugs

Illicit drugs, such as marijuana, cocaine and methamphetamines, are highly addictive drugs associated with ANS dysfunction. Research has shown that acute methamphetamine intoxication stimulates the SNS, resulting in increased HR and hypertension (Meredith, Jaffe, Ang-Lee, & Saxon, 2005). Chronic methamphetamine use also induces ANS dysfunction (i.e., vagal abnormalities) linked to cardiovascular pathology (Kaye, McKetin, Duflou, & Darke, 2007), including CAD, MI and cardiomyopathy (Kaye et al., 2007; Swalwell & Davis, 1999). A more recent study found that a methamphetamine-dependent group demonstrated significant reduction in HRV, reduced parasympathetic activity (as demonstrated by reduced RMSSD, pNN50 and HF) and diminished heartbeat complexity compared to drug-free controls (Henry, Minassian & Perry, 2012). In addition, more recent use of methamphetamine was linked with autonomic abnormalities, with greater use in the previous 12 months associated with elevated HR and sympathetic tone, as evidenced by higher LF and LF/HF ratio (Henry et al., 2012).

Like methamphetamine, cocaine is generally assumed to stimulate cardiovascular function but can also cause parasympathetic withdrawal. Research pertaining to cocaine and HRV is rare and much of it focuses on prenatal cocaine exposure. Koenig and colleagues' (2014) recent review reported a common finding in adults of decreased HF, RMSSD and pNN50 after cocaine administration (Irwin et al., 2007; Vongpatanasin, Taylor, & Victor, 2004). Intravenous use of cocaine has shown to produce tachycardia that is mediated by withdrawal of parasympathetic (i.e., vagal) inhibition, as indicated by decreases in cardiac vagal tone (Newlin, 1995; Newlin, Wong, Stapleton, & London, 2000). This decrease in vagal tone was particularly robust with intravenous cocaine given to experienced abusers. Following intravenous cocaine, HR significantly increased at the same time that vagal tone decreased (Newlin, 1995; Newlin et al., 2000). In addition, Newlin and colleagues (1990) reported similar results for smoked marijuana; increased HR due to withdrawal of vagal tone.

8.5.4. Medical and Psychological Conditions

Blood Pressure

Studies of HRV in hypertensive individuals have shown reduced HF nu, SDNN, RMSSD and pNN50 and greater LF nu and LF/HF ratio compared to normotensive controls (Havlicekova et al., 2009; Natarajan, Balakrishnan, & Ukkirapandian, 2014; Piccirillo, Munizzi, Fimognari, & Marigliano, 1996; Urooj, Pillai, Tandon, Sp, & Saha, 2011). These findings suggest sympathetic hyperactivity and decreased vagal tone (Natarajan et al., 2014; Piccirillo et al., 1996), concluding decreased HRV (Schroeder et al., 2003; Virtanen, Jula, Kuusela, Helenius, & Voipio-Pulkki, 2003).

In addition, hypertensive individuals demonstrate structural and functional alterations of the cardiovascular system, which may increase their cardiovascular risk beyond that induced by the blood pressure elevation alone (Acharya et al., 2006). Left ventricular hypertrophy (LVH; thickening of the heart's left ventricle pumping chamber, commonly due to high blood pressure) and strain are associated with increased morbidity and mortality, and HRV is significantly decreased in patients with LVH secondary to hypertension (Acharya et al., 2006).

As previously stated, the activity of the cardiac vagus nerve is influenced by the arterial baroreflex. The amplitude of RSA (a marker of HRV) has been found to

correlate with baroreflex sensitivity, which is reduced in hypertension (Acharya et al., 2006). This reduction in baroreflex sensitivity is also correlated with cardiac LVH (Acharya et al., 2006).

Coronary Heart Disease

CHD is a common medical illness known to significantly affect HRV. As previously mentioned in Section 8.4, cardiac patients exhibit altered HRV in terms of increased sympathetic activity and decreased parasympathetic activity (Bigger et al., 1993; Bigger et al., 1992; Rothschild et al., 1988; Saleem et al., 2011; Stein et al., 2000; Wennerblom et al., 2000). The increase in sympathetic activity and decrease in vagal tone creates cardiac electrical instability. As a result, the ventricular fibrillation threshold is lowered, thus predisposing to ventricular fibrillation (abnormal irregular contractions of the heart's ventricles) and ventricular arrhythmias (La Rovere, 2004; Wharton, Coleman, & Strauss, 1992). In contrast to the adverse effect of sympathetic stimulation in ischaemic heart disease, such as MI, increased vagal activity via stimulation of the vagus nerve (e.g., due to direct neural stimulation or interventions) may have a protective effect from potential arrhythmic events by increasing the fibrillation threshold. This is not always achieved however (La Rovere, 2004; Wharton et al., 1992). Within 24 hours of AMI, excessive vagal stimulation, for example, may cause bradycardia, promoting ventricular arrhythmias (Wharton et al., 1992).

Depression and Anxiety

Besides CHD, several other medical conditions alter HRV, such as diabetes, renal failure, brain damage, depression and anxiety. The relationship between depression and HRV has previously been described in Section 8.4. Although early findings were mixed, it is now known that similar to CHD, depression is associated with reduced HRV (Kemp, Quintana, Felmingham, Matthews, & Jelinek, 2012; Kemp et al., 2010; Udupa et al., 2007) and that HRV is lower in more severe depression (Kemp et al., 2010). Another psychological disorder, anxiety, is also known to significantly alter and decrease HRV (Gorman & Sloan, 2000; Friedman, 2007). Watkins and colleagues (1999) found that vagal control correlated with state anxiety rather than with depression severity in a group of depressed psychiatric patients. As a result, they argued for stronger links between anxiety and HRV than between depression and HRV. However, this study lacked a non-depressed control group and had a small sample, mostly

consisting of women. Research has reported that women are more prone to anxiety and have lower vagal tone than men (Carney, Freedland, & Stein, 2000).

In addition, comorbid anxiety is common in depression (Kaufman & Charney, 2000; Kessler et al., 2005; Merikangas et al., 2003) and depressed CHD people (Tully & Cosh, 2013). Approximately 30-40% of 18-65 year olds with depression also have anxiety (Wittchen & Jacobi, 2005), and in the older population (55-85 year olds) 47.5% of these with depression also meet criteria for at least one anxiety disorder (Beekman et al., 2000). Some researchers have argued that the lower HRV seen in depression is not due to comorbid anxiety but to the rapid breathing related to anxiety-related behaviours (Rottenberg, 2007; Wilhelm, Grossman, & Coyle, 2004). However, even when respiratory rate is controlled for, in such techniques as paced breathing (Wilhelm et al., 2004), an association is still found between depression and HRV. In addition, a recent meta-analysis found that patients with comorbid depression and anxiety displayed the greatest reduction in HRV relative to controls, a large effect size, whereas reduced HRV in depressed patients (relative to controls) was only associated with a medium effect size (Kemp et al., 2012).

8.5.5. Prescription Medication

HRV is significantly influenced by various groups of drugs. In fact, prescription medication is possibly one of the biggest confounder when measuring HRV. Of particular relevance are antidepressant medications used in the treatment of depression, and the cardiac medications used both for cardiac patients and for those with comorbid depression and CHD. It follows that, when undertaking any HRV study or interpreting HRV results, the influence of medication should be considered.

Antidepressant Medication

As described in Section 1.6, one of the oldest classes of medications used in the treatment for depression is TCAs. TCAs suppress HRV in depressed people (Rechlin, 1994; Rechlin, Claus, & Weis, 1994), and have adverse cardiac effects such as anticholinergic effects acting at the SA node (Rottenberg, 2007) and alpha-1 adrenergic effects (Jakobsen et al., 1984), both of which can reduce HRV. Several studies have found reduced HRV only in the depressed group taking TCAs, when compared with unmedicated depressed patients and with healthy controls (Lehofer et al., 1997; Rechlin,

Weis, & Claus, 1994; Kemp et al., 2010). In addition, depressed patients did not exhibit decreased HRV compared to controls prior to TCA therapy, only after TCA therapy commenced (Rechlin, Weis et al., 1994). A recent meta-analysis confirmed a reduction in HRV associated with TCA treatment (Kemp et al., 2010). Some studies have also shown that the effect of TCA is dependent on the length of ECG recording time. Short recordings depict an initial sharp fall in HRV (van Zyl, Hasegawa, & Nagata, 2008) but longer recordings indicate smaller HRV changes, although studies were not consistent with each another (Lederbogen et al., 2001; van Zyl et al., 2008). Although more research is needed to fully understand the effects of TCA on HRV over longer recordings, it is clear that TCAs significantly confound HRV. In addition, tetracyclic antidepressants (Tulen et al., 1996) have been associated with decreased HRV.

Research has been inconsistent in demonstrating the effect of SSRIs on HRV. Some studies found no effect of SSRIs on HRV (Rechlin, 1994; Rechlin, Weis et al., 1994), but others reported an increase (Tucker et al., 1997) or decrease in HRV (Bar et al., 2004; Volkers et al., 2004). Moreover, short duration ECG recordings have shown a small increase in HRV, while longer recordings contradicted this result (van Zyl et al., 2008). A more recent cross-sectional analysis (Licht et al., 2008) concluded that depressed people exhibited lower HRV, however it was suggested that the effects of antidepressant medication rather than depression drove this association. The subsequent meta-analysis by Kemp and colleagues (2010) refuted this finding, and further clarified contradictory results by finding that SSRIs neither increased nor decreased HRV.

Apart from TCAs and SSRIs, some other antidepressant classes such as SNRIs can decrease HRV (Licht, de Geus, van Dyck, & Penninx, 2010). Licht and colleagues (2010) also showed that like SNRIs, TCAs and SSRIs also decreased RSA (which was used as a measure of HRV), possibly even accounting for the lowering of HRV previously attributed to depression. However, these findings have been disputed due to the study design, statistical methods and clinical relevance of small changes in RSA (Kemp, Quintana, & Malhi, 2011).

Other psychotropic medications, such as mood stabilisers, have been associated with altered HRV (Henry, Minassian, Paulus, Geyer, & Perry, 2010; Tomson & Kenneback, 1997). Some participants on lithium showed a decrease in the LF/HF ratio

compared to participants not taking the drug (Henry et al., 2010). Research has shown that different antipsychotic medications have different effects on HRV. Some increase HRV (Cohen, Loewenthal, Matar, & Kotler, 2001), whereas others decrease or have no effect on HRV (Henry et al., 2010). A similar finding was reported for four different types of atypical antipsychotic medications: only one of the four (clozapine) was found to significantly reduce parasympathetic resting tone, and thus HRV (Agelink et al., 2001). However, this sample was small, dosage was fixed and arbitrary, and the cardiovascular effects of the drugs were only observed for 2 weeks (Stapelberg, Hamilton-Craig, Neumann, Shum, & McConnell, 2012). It has, however, long been accepted that antipsychotic drugs alter the QTc interval (the observed QT interval corrected via a mathematical formula). In typical antipsychotic drugs, this has been associated with fatal cardiac arrhythmias (Zareba & Lin, 2003) whereas in atypical antipsychotic drugs QTc is also increased but thus far not clearly associated with arrhythmias (Glassman, 2005).

Cardiac Medication

The most common medication used for CHD is beta-adrenergic blockers, which affects HRV in both normal individuals (Cook et al., 1991) and people with CHD (Bekheit et al., 1990; Lampert, Ickovics, Viscoli, Horwitz, & Lee, 2003), such as MI (Lampert et al., 2003) and cardiac failure (Coumel et al., 1991). In both normal and CHD individuals, it was found that beta-blockers reduced LF, that is, sympathetic activity (Bekheit et al., 1990; Cook et al., 1991), and increased HF, that is, parasympathetic activity (Lampert et al., 2003; Pagani et al., 1986). Thus, in those with CHD, it has been suggested that the long-term use of beta-blockers restores the ANS imbalance by improving parasympathetic tone and reducing sympathetic predominance (Lampert et al., 2003), possibly explaining their therapeutic effect (Acharya et al., 2006). Overall, beta-blockers increase HRV, which has been linked to the protective effects of this drug in CHD (Niemela, Airaksinen, & Huikuri, 1994).

There is less published research for other cardiac medications, and existing findings are contradicting. One study found that the calcium channel blocker diltiazem had no effect on HRV in normal people (Cook et al., 1991), whereas it reduced LF in post-MI patients (Bekheit et al., 1990). HRV effects may be dependent on the specific calcium channel blocker used. Different calcium channel blockers have either shown no

consistent effects on HRV or significant decreases in HRV (Bekheit et al., 1990; Zuanetti, Latini, Neilson, Schwartz, & Ewing, 1991). Other CHD medications, such as angiotensin-converting enzyme inhibitors, were found not to affect HRV but digitalis glycosides significantly increased HF (Kaufman et al., 1993).

Conclusion

Although prescription medication may be one of the biggest confounder of HRV, the available evidence clearly indicates that there are many influencing factors. Although HRV represents a promising marker for the investigation of the effect of HRV on depression and CHD, possibly providing a quantitative elucidation of the network of causal mechanisms linking the two illnesses, confounders should be eliminated in order to allow for a more reliable quantification of the relationship between HRV, depression and CHD.

8.6. Heart Rate Variability and Literature

Research has often focused on the links between decreased HRV, negative emotions and poor physical health, but the converse has also been found: high HRV is related to well-being (Kemp & Quintana, 2013) over and above reductions in negative affect (Boehm & Kubzansky, 2012; Krygier et al., 2013). This has supported research concerning the effect of positive psychological attributes, such as optimism (Dubois et al., 2012), and psychotherapies, on the ANS. A large proportion of HRV research, however, has focused on the impact of CBT, meditation and yoga on the ANS. There is growing evidence that mindfulness meditation is related to cardiac health and the ANS, including HRV and RSA. As yet, however, fewer studies have examined the relationship between mindfulness-based practices, such as MBCT, and HRV.

Heart Rate Variability and Cognitive Behaviour Therapy

The effect of CBT on HRV has been analysed in mental disorders such as panic disorder, chronic fatigue syndrome, posttraumatic stress disorder, depression, as well as other medical illnesses including CHD. In panic disorder patients, a decrease in HR, increase in HRV and overall improvement of neurocardiac control regulation after CBT has been demonstrated (Diveky et al., 2013; Garakani et al., 2009; Prasko et al., 2011). Similar findings were reported for chronic fatigue syndrome (Hansen, Kvale, Stubhaug, & Thayer, 2013) and posttraumatic stress disorder (Nishith et al., 2003). These studies

showed a remission in symptoms following CBT accompanied by a reduction in the HRV indicator of sympathetic predominance LF/HF (Nishith et al., 2003), indicating a shift in sympathovagal balance toward greater vagal activation (Hansen et al., 2013). A similar result was found for depressed patients undergoing CBT. Parasympathetic activity and overall HRV was increased after CBT, as indicated by increases in SDNN, RMSSD and HF (Kim, Lim, Chung, & Woo, 2009).

CBT has further been found to be efficacious in comorbid depression and CHD (Carney, Freedland, Stein et al., 2000; Freedland et al., 2012; Freedland et al., 2009). In the analysis of HRV, HR and daytime RMSSD (reflecting parasympathetic activity) improved significantly in severely depressed patients after CBT treatment, but remained unchanged in mildly depressed and the control patients. Only RMSSD improved to a level comparable to the control patients (Carney, Freedland, Stein et al., 2000). These results suggest that treating depression with CBT may reduce HR and increase short-term HRV. Thus, CBT may have a beneficial effect on a risk factor for mortality in depressed patients with CHD (Carney, Freedland, Stein et al., 2000; Freedland et al., 2012). Finally, because these study results are similar to the effects of beta-blockers on HRV (i.e., reduces sympathetic tone, decreases HR especially during the daytime and increases RMSSD without any significant change in longer-term HRV) in both healthy (Cook et al., 1991) and CAD (Niemela et al., 1994) patients, it has been suggested that CBT may reduce sympathetic predominance and/or may improve daytime vagal tone in patients with moderate to severe depression (Carney, Freedland, Stein et al., 2000).

Heart Rate Variability and Yoga

A substantial amount of research has analysed the effect of yoga on HRV, with the majority of studies finding positive results. Having originated as an Eastern philosophy, yoga (of which there are various types) is frequently presented as a lifestyle intervention to reduce stress and restore ANS balance (Raub, 2002). The National Centre for Complementary and Alternative Medicine refers to yoga as a "mind-body medicine", recommending it as a non-pharmacological tool for managing stress (Cole, 2005; Raub, 2002). Yoga is defined as any movement meditation technique that includes breathing techniques (pranayama) or one or more of the following: physical postures specific to yoga (asanas), meditation or chanting (mantra) (McCall, Ward, Roberts, & Heneghan, 2013). Due to the continuous focus on the body, breathing and

mind, yoga is psychological in character (Papp, Lindfors, Storck, & Wandell, 2013). Many of the slow movements in yoga are thought to support synchronisation between breathing and moving which promotes slower, deeper and more evenly paced breathing (Papp et al., 2013). This, in turn, increases parasympathetic activity and a feeling of relaxation, which can influence HR, blood pressure and breathing pace (Papp et al., 2013).

Multiple studies have confirmed that yoga relaxation and yoga meditation techniques increase parasympathetic activity and reduce sympathetic activity, indicating improved HRV, as commonly indicated by an increase in HF and/or RSA (Bernardi et al., 2001; Khattab, Khattab, Ortak, Richardt, & Bonnemeier, 2007; Markil, Whitehurst, Jacobs, & Zoeller, 2012; Telles et al., 2013; Vempati & Telles, 2002; Yunati, Deshpande, & Yuwanate, 2014). Reductions in blood pressure and HR, improvements in stress and sleep; and a calming effect on the body and mind have also been reported (Cole, 2005; Patra & Telles, 2010; Raub, 2002; Vera et al., 2009; Yunati et al., 2014).

In contrast to the relaxation and meditation techniques in yoga, some strenuous yoga postures have been associated with increased sympathetic activity (Manjunath & Telles, 2003; Sinha, Ray, Pathak, & Selvamurthy, 2004). Practising 12 yoga postures increased HR and respiratory rate (Sinha et al., 2004), and practising the headstand also increased sympathetic activity, reflected in sudomotor (based on skin resistance) and vasomotor (based on finger plethysmogram amplitude) responses (Manjunath & Telles, 2003). Similarly, increased HR and predominantly sympathetic activation occurs during the yoga posture phases of cyclic meditation (a "moving meditation"), whereas parasympathetic dominance increased and HR decreased after the postures (during the guided meditation phase, which typically occurs at the end of a yoga session) (Sarang & Telles, 2006; Telles, Reddy, & Nagendra, 2000). It has been suggested that some yoga postures are a form of mild exercise (Rai & Ram, 1993). Thus, the yoga postures in cyclic meditation may have caused an increase in LF, as the immediate effect of mild exercise (Mourot, Bouhaddi Tordi, Rouillon, & Regnard, 2004). However, performing yoga postures during the day appears to shift sympathovagal balance in favour of parasympathetic activity (and reduce sympathetic activity) during sleep that night (Papp et al., 2013; Patra & Telles, 2010). Yoga may enhance the plasticity of the ANS and

improve the ability to recover after stress (Patra & Telles, 2010). Thus, it appears that meditation and yoga postures have different physiological effects.

Heart Rate Variability and Meditation

Yogic meditation is not the only type of meditation. There is extensive literature examining the physiological effects, such as HRV, of the different forms of meditation, finding positive results. Autonomic activities during meditation are characterised by decreased sympathetic activity and increased parasympathetic activity. Most studies of transcendental meditation (TM) – from the 1970s onwards - reported changes suggestive of increased autonomic stability and sympathetic withdrawal (Orme-Johnson, 1973) and decreased heart and breathing rate (Wallace, 1970; Wallace, Benson, & Wilson, 1971). One study reported increased HRV due to TM, compared with health education in patients with stable CAD (Paul-Labrador et al., 2006). Similar changes indicative of increased HRV including reduced sympathetic and/or increased parasympathetic activity were found during both non-directive meditation (Nesvold et al., 2012) and concentrative meditation (Phongsuphap, Pongsupap, Chandanamattha, & Lursinap, 2008). Similarly, Wu and Lo (2008) found inward-attention meditation pushed the sympathovagal balance to parasympathetic predominance and sympathetic inhibition, as shown by decreases in the LF/HF ratio, LF norm, and increase in the HF nu, during meditation.

Other meditative techniques derived from various Indian and Asian traditions have been investigated, as well as rosary prayer. Studies have found increased parasympathetic activity and decreased sympathetic activity associated with meditation (Takahashi et al., 2005; Tang et al., 2009). However, differential activity in the different subdivision of the ANS has been observed during 'Om' meditation (Telles, Nagarathna, & Nagendra, 1995). There was a simultaneous reduction in HR (possibly related to increased vagal tone with reduced cardiac sympathetic activity) and finger plethysmogram amplitude (decreased sympathetic vasomotor activity) (Telles et al., 1995). In a study of Zazen meditation, an increase was found for both HF (which was attributed to increase in parasympathetic activity) and LF (which was attributed to both parasympathetic and sympathetic arousal mechanism during the Zanmai state of deep Zen meditation for experienced Zen meditators (Hoshiyama & Hoshiyama, 2008). In another study, a significant decrease in respiration rate and a significant increase in

HRV associated with respiration were found among Zen practitioners (Lehrer et al., 1999). Similar changes were observed during rosary prayer, as well as an increase in baroreflex sensitivity during this activity (Bernardi et al., 2001).

Heart Rate Variability and Mindfulness Meditation

The physiological benefits of Buddhist meditation have long been known. Therefore, interest in the effects of meditation practice on health outcomes, specifically mindfulness meditation, has been growing rapidly (Hofmann et al., 2010). In particular, mindfulness meditation-based interventions such as MBSR and MBCT (previously discussed in Section 2.1), are increasingly implemented adjunctively with medical or psychological approaches. However, few studies have examined the relationship between MBCT and ANS markers, such as HRV.

The majority of existing studies have analysed mindfulness meditation and HRV. Telles and colleagues (2005) analysed three different phases of Vipassana, a type of mindfulness meditation. They found a decrease in LF and LF/HF ratio and an increase in HF during the breath awareness phase, but not in the body awareness or philosophical contemplation phases. This suggested a shift in the autonomic balance toward vagal dominance specifically for breath awareness practice (Telles, Mohapatra, & Naveen, 2005). Other studies have suggested that the HRV changes resulting from mindfulness meditation may also improve effectiveness of self-regulatory mechanisms such as attention and emotion processing (Peressutti et al., 2012), and control over HR (Delizonna, Williams, & Langer, 2009). HRV changes have also been associated with years of practice in novice and experienced meditators, and suggest that changes in breathing pattern are associated with the quality and focus of attention (Peressutti, Martin-Gonzalez, Garcia-Manso, & Mesa, 2010).

Research has shown that CBT and meditation both improve HRV. Therefore, it is hypothesised that MBCT (which, as described in Section 2.1, includes aspects of both CBT and mindfulness) would demonstrate similar results. Literature on HRV and MBCT is scarce, however. One study analysed the breathing cycle in body scan meditation (a technique used in MBCT) (Ditto, Eclache, & Goldman, 2006). The authors demonstrated that participants displayed significantly greater increases in RSA while meditating than while engaging in any other relaxation activity. The acute effects

of meditation, however, cannot be entirely reduced to respiratory rate; mindfulness meditation appears to have an effect over and above simple breathing interventions (Krygier et al., 2013). The belief that meditation produced an impact on vagal activity in Ditto and colleagues' (2006) research is strengthened by the fact that a significant effect of meditation on RSA was observed even after correction for respiration rate. More recently, studies demonstrated that meditation training and controlled breathing with MBSR improved cardiac sympathovagal balance measured by HRV (Nijjar et al., 2014a, b). However, the finding that the mean respiration rate during meditation (Nijjar et al., 2014b) was higher compared to other studies (Lehrer et al., 1999; Phongsuphap et al., 2008) may be due to novice meditators only having a few weeks to practise their skills in the study by Nijjar and colleagues. It is likely that more practice may induce lasting changes in HRV (Nijjar et al., 2014b). Nijjar and colleagues (2014a, b) conclude that further studies on the association between MBSR and HRV are warranted, however, MBSR may be a beneficial adjunct in management of conditions with reduced HRV, such as CHD and AMI.

Conclusion

Whether there is an overall reduction in sympathetic activity (as seen in TM) or differential activity in different subdivisions of sympathetic activity (as seen in Om meditation) or reduced sympathetic activity in some phases of meditation (as in Vipassana), there is evidence that meditation is associated with reduced sympathetic activity (in some, if not all sympathetic subdivisions) and increased parasympathetic activity.

There is significant evidence that meditation improves HRV in both depressed and CHD patients. Few studies, however, pertain to the specific effect of MBCT on HRV in normal or mental health patients. As such, this is an area of much needed research. The third study in this thesis (Chapter Six) aimed to broaden the literature base, by increasing understanding of the relationship between depression and HRV and MBCT. It aimed to test whether MBCT would improve parameters of HRV, reduce depressive symptoms and increase QoL. Since several mechanisms link depression and CHD, it is possible that MBCT may also benefit both CHD patients and patients with comorbid depression and CHD.

SUMMARY

This introductory chapter and literature review introduced depression, MBCT, followed by an introductory account of cardiac function, CHD and CAD. The associations between depression and CHD were described, specifically examining autonomic mechanisms and HRV as a measurement of ANS activity. Lastly, HRV and treatment methods were analysed.

A number of gaps in the literature were identified, and the following three published manuscripts address some of these gaps. Prior to presenting the three manuscripts, the thesis objectives are discussed and methodological considerations concerning measurement instruments are briefly reviewed.

CHAPTER TWO: THESIS OBJECTIVES

CHAPTER TWO
THESIS OBJECTIVES

The preceding components of the literature review provided overviews of depression, MBCT, cardiac function, CHD and CAD. Associations between depression and CHD were described, specifically examining the ANS and HRV. The aim of this thesis is to contribute to the existing body of knowledge of depression in CHD patients, and identify factors that contribute to mental health problems and subsequent mortality. Furthermore, it aims to build a platform for future treatment strategies and management of depression in cardiac patients. There are many gaps in this complex literature. Three were selected as amenable to investigation in this thesis, and led to production of the three manuscripts.

1. THESIS OBJECTIVES

1.1. Gaps Identified in the Literature

1. An absence of evidence indicating whether NoCAD patients exhibit higher levels of depressive symptoms than obstructive CAD patients.

Although literature exists to explain why obstructive CAD patients suffer from heightened levels of depression compared to a "normal healthy" population, there is less research on patients with normal coronary arteries (i.e., NoCAD). Furthermore, questions remain surrounding the prevalence rate of depression in obstructive CAD compared to NoCAD patients. Identification of possible differences and explanations between the two groups of cardiac patients needs to be addressed. Some older studies have identified a relationship between depression and NoCAD, but a need exists for updated analysis of this relationship.

This study aimed to examine the relationship between depression and the presence/absence of obstructive CAD in patients undergoing coronary angiography for the evaluation of chest pain. The specific objectives were to: (1) compare the prevalence of depression in patients with chest pain and obstructive CAD or NoCAD, utilising a

healthy control cohort as a reference population; and then (2) determine whether the presence or absence of obstructive CAD is an independent predictor of depression.

2. An absence of evidence indicating whether depression predicts long-term mortality in depressed AMI and ACS patients in the Australian population.

The majority of studies investigating whether depression predicts mortality in MI patients have been conducted internationally. Few studies were found utilising an Australian cohort. Furthermore, whether depression is a risk factor for long-term mortality following MI remains controversial. In addition, changes in the management of MI patient populations, and exposure to newer therapies for CHD, may have modified the impact of depression on long-term mortality.

The aim of this study was to investigate the long-term outcomes of Australians with AMI. Specifically, this study primarily explored whether depression during hospitalisation for AMI predicted all-cause and/or cardiac mortality at 5 years, in an Australian cohort.

The original manuscript was produced with the inclusion of an ACS group, as well as an AMI group. However, at completion of the manuscript, the ACS was removed from the submitted manuscript. Therefore, a secondary analysis of this study includes patients with the more broadly defined ACS.

3. An absence of evidence indicating whether MBCT affects HRV in mental health outpatients with depression.

MBCT is a relatively new therapy for the treatment of depression and anxiety. The majority of research has focused on mental health problems and whether symptoms of these problems decrease following mindfulness therapy. Although HRV is a well-researched area in mental health and in medical patients undergoing yoga, meditation and CBT, to name a few, little research pertains to HRV in depressed patients undergoing MBCT.

The original aim was to explore the potential impact of MBCT on cardiac physiology and on the mental and physical health of mental health outpatients with current depression. Specifically, this study primarily investigated whether MBCT promoted an improvement in HRV. Secondarily, it examined any improvement in depressive symptoms and QoL following MBCT. Due to slower than expected recruitment, study criteria were expanded to include mental health outpatients with a broader range of DSM-IV Axis 1 (mood or anxiety) diagnoses.

CHAPTER THREE: STUDY MEASUREMENT

CHAPTER THREE
STUDY MEASUREMENT

The three studies in this thesis were undertaken using quantitative research methods. The first two projects (Chapters Four and Five) utilised pre-existing data sets whereas the third project (Chapter Six) was designed and conducted specifically for this thesis. Additional information relating to the studies but not described in the manuscripts because of word-limitations (specifically the psychometric instruments utilised in the studies, statistical methods and study design) is now presented, prior to the published manuscripts.

Additional information relating to the quality criteria for measurement instruments is relevant to all three studies and is therefore also presented below.

1. MEASUREMENT

In order to understand why specific psychometric instruments were chosen for research in this thesis, it is important to understand the concepts of validity and reliability. Given that this thesis is based on the fields of psychology, psychiatry and medicine, and that some readers may be less familiar with psychometric criteria for validity and reliability due to their disciplinary backgrounds, these concepts are described.

1.1. Validity and Reliability

A number of psychometric instruments were administered during the course of this research. Psychometric methods provide well-established scientific techniques for measuring subjective judgments on numerical scales and for evaluating the rigour of measurement scales against reliability and validity requirements (Schroter & Lamping, 2004). The questionnaires utilised in the three studies in this thesis were chosen for their quality. The following section introduces the quality criteria for measurement properties, namely validity and reliability.

Validity

Validity is concerned with the meaning and interpretation of the instrument (Bowling, 2001). In quantitative research, validity determines whether the research truly measures what it is intended to measure (Bowling, 2001). There are three main types of validity: content, criterion and construct validity.

When evaluating an instrument, content validity is often the first to be examined. Content is a non-statistical type of validity, and focuses on the content of the instrument. It is the extent to which the instrument items adequately measure all facets of a given construct (e.g., depression) (Bowling, 2001). A questionnaire will typically contain a number of questions intended to measure a construct. To rate the content validity of a questionnaire, the author must provide a succinct and easily readable description of the facets, the aim of the questionnaire, and the target population for which the questionnaire was developed, which is short and simple to understand and read (Terwee et al., 2007). A panel of experts then reviews the instrument to determine whether it has content validity (Terwee et al., 2007).

Evaluation continues with the use of statistical methods to determine criterion validity. This is defined as the degree to which scores on an instrument highly correlate with a gold standard (the best accepted) measure of the same construct (Terwee et al., 2007). If a gold standard does not exist, as is the case for HRQoL, sometimes a specific target for an HRQoL measure exists and is treated as a gold standard (Guyatt et al., 1993). When this occurs, criterion validity is assessed by evaluating if the instrument correlates highly with a gold standard measure of the same theme. On occasion, a simpler, shorter version of an already full-length established measure is developed and sampled on an appropriate population (Guyatt et al., 1993). Correlation analysis is then used as an indicator of agreement to determine whether the results of the new instrument compare to an established one, and whether they agree sufficiently so that one instrument can confidently be used as a surrogate of the other without consequentially altering the research findings (Bland & Altman, 1986).

Where there is a gold standard clinical test, criterion validation can be further extended to diagnose a particular disease. In doing so, a threshold or cut-off score on an instrument is developed to identify respondents as diseased or non-diseased (Parikh,

Mathai, Parikh, Chandra Sekhar, & Thomas, 2008), for example, depressed and non-depressed. From this, two attributes are of significance: sensitivity and specificity. Sensitivity is the ability of a test to correctly identify all patients with the disease, whereas specificity is the ability of the test to correctly identify all patients without the disease (Parikh et al., 2008). Different threshold scores will result in different estimates of sensitivity and specificity for a test. Sensitivity and specificity are typically inversely proportional, meaning that as sensitivity increases, specificity decreases, and vice versa (Parikh et al., 2008). Receiver operator characteristic (ROC) curves are commonly used to visualise and select threshold scores based on their performance by plotting the sensitivity (true-positive probability) against 1-specificity (false-positive probability) for all possible cut-off points (Lalkhen & McCluskey, 2008). The area under the ROC curve represents the overall accuracy of a test to correctly classify those with and without disease, with a value approaching 1.0 indicating high sensitivity and specificity (Lalkhen & McCluskey, 2008).

Construct validity is important when gold standard measures do not exist, such as in the measurement of pain. It refers to the degree to which the instrument measures the concept of interest (Guyatt et al., 1993), and involves comparisons between measures and examination of the logical relations that should exist between a measure and characteristics of patients and patient groups (Guyatt et al., 1993) Construct validity is the most complex approach to validity as it is based on different types of validity, including content and criterion validity (Gaberson, 1997). To determine whether an instrument has construct validity, a definition of the concept to be measured should first be defined and many items should be developed to adequately represent the concept. Understanding the concept allows hypotheses or predictions about how the instrument being tested should relate to other measures (Guyatt et al., 1993). A number of instruments are then administered to a population and the data is examined. Validity is strengthened or weakened when the hypotheses are confirmed or refuted (Guyatt et al., 1993). Alternatively, correlation evidence or factor analysis can be used to determine construct validity (McDowell & Newell, 1996).

Reliability

Validity is often discussed in conjunction with errors in measurement, known as reliability. More specifically, reliability is the extent to which test results are consistent

and stable over time (i.e., across repeated applications of the measure) and an accurate representation of the total population under study (Bowling, 2001). Reliable measurement results are reproducible and generalisable to other measurement occasions (Gaberson, 1997). Traditionally, reliability has been categorised into several different subtypes, including stability, internal consistency and equivalence.

Stability is the degree to which the same results are obtained from a respondent on repeated testing over a period of time. This is often assessed using the test-retest procedure, that is, administration of the instrument on different occasions to the same people (Bowling, 2001). This reliability is only meaningful when the construct being measured is expected to be stable over time (Gaberson, 1997). Scores from the two sets of readings are analysed using the Pearson correlation coefficient to assess the degree of relationship between the sets of data (Bowling, 2001). Although the test-retest procedure is an essential part of reliability, brief intervals between assessments may produce error due to practice effects, that is, memory of earlier practice. The respondent may have remembered what they answered the first time and simply repeated their answer the second time (Giuffre, 1995).

Internal consistency involves testing for homogeneity, that is, the extent to which each item on the instrument measures the construct of interest, and thus assesses the consistency of the results (Bowling, 2001). Tests assess the extent to which individual items are inter-correlated and the extent to which they correlate with overall instrument scores (Bowling, 2001). Internal consistency is most frequently measured with Cronbach's coefficient, alpha (Cronbach, 1951). However, Cronbach (2004) more recently developed the complex generalisability theory and claimed that it is a more appropriate way to examine data.

Equivalence is very similar to stability, but instead of the same instrument being tested, in the case of equivalence two or more versions of an instrument are tested, usually at the same time (Giuffre, 1995). Both forms of the test are administered to the same people, and the resulting scores are correlated to determine whether the instruments measure the construct equally well (Gaberson, 1997). However, a limitation of this type of reliability is that many research instruments lack equivalent forms. Equivalence can also be analysed when different raters assess an instrument to

determine whether they obtain the same result, introducing what is called inter-rater reliability (Giuffre, 1995). To test inter-rater reliability, the researcher will assess the difference in scores across raters and determine the degree of agreement or correlation between the observations (Giuffre, 1995). If the scale is categorical, Cohen's Kappa Test of Concordance (Cohen, 1960, 1968) is generally used, whereas Pearson's product-moment correlation is used for comparing continuous scores (Bowling, 2001).

Although an instrument may be proven to be reliable, it may not be valid, and vice versa. Therefore, evaluating the validity and reliability of an instrument is an important and necessary step in selecting appropriate research instruments.

1.2. Types of Instruments

The measurement of health outcomes has now become of increasing interest (Dougherty et al., 1998). Health status instruments, such as those used to measure HRQoL, are well suited for use in studies involving depressed and CHD patients because many interventions are directed toward improving QoL rather than extending survival (Dougherty et al., 1998).

Two types of instruments are available to measure HRQoL: generic instruments and disease-specific instruments. Generic scales measure the health status of the patient in general rather than addressing a specific disease/condition. They can, therefore, be used to compare the HRQoL of patient groups across diseases, across different treatments or interventions, and across different groups of patients (McSweeny & Creer, 1995; Patrick & Deyo, 1989). Conversely, disease-specific scales focus on the complaints that are attributable to a specific diagnosis/disease or patient population (McSweeny & Creer, 1995; Patrick & Deyo 1989). These instruments detect responsiveness or clinically significant changes in a particular group (such as patients' levels of severity), and are therefore more sensitive to treatment effects (McSweeny & Creer, 1995). However, disease-specific scales have been criticised as being too narrow in focus, while neglecting the measurement of important outcomes and modifying variables, such as depression, social support, coping and self-esteem (Bowling, 2001). Therefore, domain-specific scales are often used when the area is of particular relevance to the study and its hypothesis, and when generic and disease-specific scales neglect that area (Bowling, 2001).

The research conducted for this thesis utilised both a generic instrument and disease-specific instrument, along with three domain-specific scales, and a personality and cognitive measure (Appendices A-F). These questionnaires are critically reviewed in the relevant chapters.

CHAPTER FOUR: STUDY 1

CHAPTER FOUR
STUDY 1

The study "Prevalence of depression in patients with chest pain and non-obstructive coronary artery disease" (presented in this chapter, abbreviated to 'NoCAD study') utilised one generic HRQoL measure and one disease-specific angina questionnaire.

1. INSTRUMENTS

1.1. Instruments Utilised

1.1.1. Generic Measure

Short Form-36

Designed for use in population surveys and evaluative studies of health policy, the SF-36 (Ware & Sherbourne, 1992; Appendix A) is the most well-known and widely used generic measure of HRQoL. This self-administered questionnaire takes approximately 10-15 minutes to complete and consists of 36 questions grouped into eight subscales that are relevant to functional status and well-being: physical functioning, physical role functioning, bodily pain, general health, vitality, social functioning, emotional role functioning, and mental health. The eight domains can be grouped into two component summary scales of physical and mental health, allowing differentiation between physical and mental health outcomes (Ware, Kosinski, & Keller, 1994). Scale scores on the SF-36 are derived by summing the items together within each scale, dividing by the range of scores and then transforming raw scores to a 0 to 100 scale. The two component summary scales are derived by standardising each of the eight subscales scores based on the general US population (mean score 50, standard deviation 10) (Ware, Snow, Kosinski, & Gandek, 1993). However, the SF-36 can be scored using the method of Tucker and colleagues (2010), which was utilised in each of the three studies in this thesis. This method allows for the correlation between physical and mental health in producing factor score weights for the component summary scores. The traditional method by Ware and Sherbourne (1992) is based on an exploratory factor analysis with an orthogonal rotation, and does not allow for a correlation between

physical and mental health. That is, the traditional scoring approach tries to break down health into independent (orthogonal/uncorrelated) physical and mental health components. This results in inconsistencies between the various subscales and the component summaries. The method of Tucker and colleagues (2010) corrects these inconsistencies. Lower scores equate to poorer health status, and 100 represents the best health state. The SF-36 has excellent psychometric properties, as demonstrated in the general population (Ware & Gandek, 1998), CHD specific samples (Cronbach, 1951; Failde & Ramos, 2000; McHorney, Ware, Lu, & Sherbourne, 1994) and Australian settings (McCallum, 1995).

More recently, however, a study (Tavella et al., 2010) defined a threshold value on the mental component summary score of the SF-36 that identified depressed cardiac patients as measured by the depression questionnaire CES-D (discussed in Section 2.1.2 of Chapter Five). The diagnosis of depression for the following study (Study 1) was based on the previously validated method using the SF-36 mental summary score.

1.1.2. Disease-Specific Measure

Seattle Angina Questionnaire

The Seattle Angina Questionnaire (SAQ; Spertus et al., 1995; Appendix B) is a self-administered disease-specific questionnaire designed to measure functional status of patients with CAD. The 19 items are grouped into five domains: physical limitation (9 items), angina stability (1 item), angina frequency (2 items), treatment satisfaction (4 items), and disease perception (3 items). Each item is answered using 5- or 6-point Likert scales. The scale is scored by assigning a value of 1 to responses that indicate the lowest level of functioning, and then summing across the items within each of the 3 domains. Each domain score is transformed to a scale of 0-100 by subtracting the lowest possible score, divided by the scale range and multiplying by 100. A score of 100 represents the best outcome. All SAQ domains are psychometrically sound, and its high sensitivity makes it suitable for detecting changes relevant to angina (Spertus et al., 1995).

STATEMENT OF AUTHORSHIP

Title of Paper	Prevalence of depression in patients with chest pain and non-obstructive coronary artery disease
Publication Status	Published
Publication Details	Wheeler, A., Schrader, G., Tucker, G., Adams, R., Tavella, R., & Beltrame, J. F. (2013). Prevalence of depression in patients with chest pain and non-obstructive coronary artery disease. *American Journal of Cardiology, 112*(5), 656-659. doi: 10.1016/j.amjcard.2013.04.042

Author Contributions

By signing the Statement of Authorship, each author certifies that their stated contribution to the publication is accurate and that permission is granted for the publication to be included in the cardidate's thesis.

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Contribution to the Paper	Study conception and design, statistical analysis, management and interpretation of the data, manuscript preparation, critical review and revision of the manuscript		
Signature		**Date**	4.11.13

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Contribution to the Paper	Supervised development of the work, manuscript preparation and critical review		
Signature		**Date**	18.11.13

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Contribution to the Paper	Provided expert advice on statistical analysis and data interpretation, critical review of the manuscript		
Signature		**Date**	6.11.13

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Contribution to the Paper	Provided data for the study, critical review of the manuscript		
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Signature		**Date**	6.11.13

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Signature		**Date**	6.11.13

STUDY 1

Prevalence of Depression in Patients with Chest Pain and Non-Obstructive Coronary Artery Disease

This results chapter is reproduced in the exact form as it appears in the manuscript:

Wheeler, A., Schrader, G., Tucker, G., Adams, R., Tavella, R., & Beltrame, J. F. (2013). Prevalence of depression in patients with chest pain and non-obstructive coronary artery disease. *American Journal of Cardiology*, *112*(5), 656-659. doi: 10.1016/j.amjcard.2013.04.042

In keeping with the style of this thesis, the tables have been re-numbered, the references reformatted and incorporated into the thesis master reference list, and the manuscript repaginated.

Many studies have demonstrated the prevalence of depression in patients with coronary artery disease (CAD), but few have examined this relation in those with chest pain who do not have obstructive CAD on angiography. The aim of this study was to compare the prevalence of depression amongst patients with chest pain in the presence or absence of obstructive CAD and a healthy control group without chest pain. This prospectively designed, observational cohort study used 2 independent data sets: (1) The Queen Elizabeth Hospital Coronary Angiogram Database (n = 1,144), consisting of 819 patients with obstructive CAD and 325 patients with nonobstructive CAD (NoCAD), all of whom had chest pain and (2) the North West Adelaide Health Study (NWAHS; n = 3,168), a population-based biomedical cohort, from which patients with chest pain were excluded. The presence of depression was determined by a previously validated method using the Short Form 36. The prevalence of depression differed among the 3 groups, with 63% in those with NoCAD, 53% in those with CAD, and only 24% in the healthy NWAHS cohort. Analysis of the angiography cohort revealed age, gender, antidepressant medication, previous myocardial infarction, previous airway disease, Short Form 36 physical summary score, Seattle Angina Questionnaire physical limitation score, and NoCAD on angiography to be independent predictors of depression. In conclusion, these findings highlight the importance of screening for depression in patients with NoCAD.

Depression is reported to occur in 10% to 40% of patients with coronary artery disease (CAD) (Ruo et al., 2003; Sheps & Sheffield, 2001) and is an independent predictor of mortality in those who experience acute myocardial infarctions (AMIs) (Frasure-Smith, Lesperance, & Talajic, 1993; Wheeler et al., 2012). Coronary angiography is the benchmark investigation for the evaluation of CAD and enables the distinction between patients who have obstructive CAD and those who do not have significant CAD, that is, nonobstructive CAD (NoCAD). Patients with NoCAD constitute a puzzling cohort for clinicians, because symptoms are often indistinguishable from those with obstructive CAD (Bugiardini & Bairey Merz, 2005), yet the causes of the chest pain may be diverse, including cardiac (coronary spasm and microvascular dysfunction) and noncardiac (esophageal reflux, musculoskeletal, and psychiatric) disorders (Brims, Davies, & Lee, 2010; Bugiardini & Bairey Merz, 2005; Watson, 2006). Although many studies have focused on the prevalence of depression in patients with obstructive CAD, few have investigated its prevalence in those with NoCAD, despite psychiatric conditions' potentially contributing to the associated chest pain. In the present study, we examined the relation between depression and the presence or absence of obstructive CAD by (1) comparing the prevalence of depression in patients with chest pain and obstructive CAD or NoCAD, using a healthy control cohort as a reference population and (2) determining if the presence or absence of obstructive CAD is an independent predictor of depression.

Method

This prospectively designed cohort study used 2 independent data sets to evaluate 3 study groups: (1) a healthy control group derived from the North West Adelaide Health Study (NWAHS) and (2) patients with chest pain with or without obstructive CAD on angiography obtained from The Queen Elizabeth Hospital (TQEH) Coronary Angiogram Database. The 2 data sets recruited patients from the same geographic region, the northwestern districts of Adelaide.

Details of the design used in the NWAHS have been previously reported (Grant et al., 2006; Grant et al., 2009). In brief, the NWAHS is a population-based biomedical cohort study investigating the prevalence of chronic conditions and health-related risk factors. Households within the northwestern districts of Adelaide with telephone numbers in the electronic directory were randomly selected and invited to participate in

the study. Analysis of bias in the study showed no differences in self-reported general health status and social demographics compared with the general population (Taylor et al., 2006). Those recruited underwent telephone interviews to ascertain their health problems and completed health status questionnaires (Grant et al., 2006; Grant et al., 2009). The original NWAHS consisted of 4,060 participants. For this study, those with histories of chest pain or cardiac disorders or who had missing cardiovascular data were excluded from the analysis, thereby resulting in a "healthy cohort" of 3,168 participants (mean age 52 ± 15 years, 54% women).

The coronary angiography cohort included patients who underwent angiography for the evaluation of chest pain at TQEH from 2003 to 2007. This hospital provided cardiac catheterization facilities for the northwestern districts of Adelaide. The database was established to determine the clinical characteristics, health status, and subsequent outcomes of patients who underwent coronary angiography for the evaluation of chest pain. On the basis of the subsequent coronary angiographic findings, patients were grouped into those with obstructive CAD (i.e., coronary artery stenosis ≥50%) and those with NoCAD (i.e., normal coronary angiographic results or minor lesions [<50%]). Of the 1,268 patients recruited to TQEH Coronary Angiogram Database, 124 had alternative cardiac causes of their chest pain (e.g., severe aortic stenosis) and were excluded from the analysis. Of the remaining 1,144 patients, 819 had obstructive CAD (mean age 62 ± 11 years, 26% women), and 325 had NoCAD (mean age 57 ± 12 years, 57% women).

Variables recorded in the NWAHS and TQEH Coronary Angiogram Database included (1) demographics (age, gender, the Socio-Economic Indexes for Areas Index of Relative Socioeconomic Disadvantage (IRSD)) (ABS, 2008b), (2) cardiac-associated risk factors (smoking status, hypertension, hypercholesterolemia, diabetes mellitus, family history of CAD, number of risk factors, acute or stable chest pain pattern at angiography presentation, previous AMI, angina pectoris, heart failure, stroke or transient ischemic attack, airway disease, and musculoskeletal disease), (3) depression-associated risk factors (antidepressant medication), and (4) psychometric data obtained from the Short Form 36 (SF-36) mental and physical summary scores and Seattle Angina Questionnaire domains. The IRSD quintiles are produced by the Australian Bureau of Statistics (2008b) to measure socioeconomic status by postal code. IRSD

scores are grouped into quintiles (highest, high, middle, low, and lowest) for analysis, where the highest quintile represents postal codes with the highest IRSD scores (most advantaged areas) and the lowest quintile represents postcodes with the lowest IRSD scores (most disadvantaged areas) (ABS, 2008b). Of relevance, most TQEH Coronary Angiogram Database patients completed questionnaires before the coronary angiographic study, so that patients and clinicians were unaware of the diagnosis of obstructive CAD or NoCAD.

The diagnosis of depression for this study was based on a previously validated method using the SF-36 mental summary score (Tavella et al., 2010). The SF-36 was scored using the method of Tucker et al (Tucker, Adams, & Wilson, 2010), which allows for the correlation between physical and mental health in producing factor score weights for the component summary scores. Using a threshold mental summary score value of ≤45, this method has 93% sensitivity and 64% specificity for the diagnosis of depression (Tavella et al., 2010). On the basis of this method, patients were classified as depressed or not depressed at the time of study recruitment.

Statistical analyses were performed using SPSS version 17 (SPSS, Inc., Chicago, Illinois). In the univariate analyses, ambiguous responses to categorical variables (e.g. "not sure," "not asked," "not stated") were recoded as missing values. Patients with missing SF-36 mental summary scores were excluded from analyses. Descriptive statistics for the study cohorts are expressed as mean ± *SD* for continuous data and as percentages for categorical data. Baseline characteristics were compared using Student's *t* tests and chi-square tests for the respective data. The primary end point (prevalence of depression) was compared among the 3 study groups using binary logistic regression. On the basis of the available data from the angiography database and the prespecified depression definition (SF-36 mental summary score ≤45), the study had 76% power to detect an odds ratio (OR) of 1.44 for the prevalence of depression at the 0.05 significance level for NoCAD compared with obstructive CAD.

To determine if the presence or absence of CAD on angiography was an independent determinant of depression, a multivariate binary logistic regression model was developed. Comparisons between the angiographic groups for potential univariate predictors of depression were undertaken as described earlier. A significance level of *p*

≤0.25 in the univariate analyses was used as a criterion for entry into the multivariate analysis. The categorical form of SF-36 mental summary score was used as the dependent variable (i.e., depressed or not depressed), to determine the ORs (exp [ß]) and 95% confidence intervals (CIs) of predictor variables. Missing and "not sure," "not asked," or "not stated" responses (≥10 cases) for the categorical covariates were combined into a valid category to include the maximum number of records possible in the analysis and to mitigate bias. The identified variables from the univariate analyses were entered into the regression model and the best predictors selected using the backward elimination of nonsignificant terms. Covariates were removed from the regression model 1 by 1 according to the significance criterion specified (p = 0.05) using the log likelihood test. The best fit model of non-nested alternatives was determined using the Akaike information criterion. The significance level for predictors of depression in the final model was defined as p <0.05.

Results

The clinical and psychometric characteristics of the healthy NWAHS patients compared with those with chest pain (obstructive and NoCAD) are summarized in Table 6. Compared with the healthy controls, the chest pain (angiography) population was older with more cardiovascular risk factors and had a poorer quality of life. Unadjusted analyses demonstrated a significant difference in the prevalence of depression among the 3 groups. Compared with the NWAHS healthy control cohort, the OR was higher for the obstructive CAD (OR 3.483, 95% CI 2.947 to 4.117, p <0.001) and NoCAD (OR 5.359, 95% CI 4.166 to 6.895, p <0.001) patients. Furthermore, depression was more prevalent in those with NoCAD (OR 1.539, 95% CI 1.166 to 2.030, p = 0.002) relative to those with obstructive CAD.

Table 6

Baseline Characteristics of NWAHS Healthy Controls and Chest Pain Patients

Characteristic	Healthy Controls (*n* = 3,168)	Obstructive CAD	
		Yes (*n* = 819)	No (*n* = 325)
Age (yrs)* †	52 ± 15	62 ± 11	57 ± 12
Women*†	1,714 (54%)	215 (26%)	185 (57%)
Hypertension*†	622 (22%)	533 (66%)	182 (58%)
Hypercholesterolemia*†	1,600 (56%)	589 (75%)	184 (60%)
Diabetes mellitus*†	217 (8%)	263 (33%)	58 (18%)
Number of risk factors*†			
0	1,096 (35%)	58 (7%)	54 (16%)
1	1,308 (41%)	219 (27%)	113 (35%)
2	644 (20%)	315 (38%)	110 (34%)
3	110 (3.5%)	198 (24%)	43 (13%)
4	10 (0.5%)	29 (4%)	5 (2%)
Family history of CAD*†	1,554 (54%)	418 (55%)	189 (62%)
Smoking status*†			
Ex-smoker	1,052 (37%)	340 (43%)	102 (32%)
Current smoker	527 (18%)	174 (22%)	58 (18%)
Angiogram presentation*			
Stable chest pain pattern	-	505 (62%)	253 (78%)
Previous AMI*	-	250 (31%)	20 (6%)
Previous angina pectoris	-	360 (44%)	134 (41%)
Previous airway disease	-	139 (18%)	69 (22%)
Previous heart failure*	-	18 (2%)	0 (0%)
Previous musculoskeletal disease	-	107 (14%)	57 (18%)
Previous stroke/transient ischemic attack	-	46 (6%)	25 (8%)
Antidepressant medication	-	91 (11%)	47 (15%)
Health/psychological indexes			
SAQ angina frequency	-	63 ± 28	65 ± 24
SAQ angina stability	-	41 ± 33	44 ± 31
SAQ physical limitation	-	58 ± 24	60 ± 25
SAQ quality of life	-	43 ± 22	44 ± 22
SF-36 physical summary score*†	49 ± 10	36 ± 10	38 ± 11
SF-36 mental summary score*†	51 ± 10	43 ± 11	41 ± 11
Depression*†	697 (24%)	394 (53%)	186 (63%)

Data are expressed as mean ± *SD* or number (percentage). Values may not add up to the total, because of missing cases.
SAQ = Seattle Angina Questionnaire.
*p <0.05, obstructive CAD versus NoCAD.
†p <0.05 among healthy controls, obstructive CAD, and NoCAD.

Univariate analyses of the TQEH angiography cohort revealed the following as significant potential predictors of depression: age (continuous and categorical), gender, hypertension, hypercholesterolemia, diabetes mellitus, number of risk factors, smoking status, family history of CAD, antidepressant medication, angiographic presentation, previous AMI, airway disease, heart failure, musculoskeletal disease, stroke or transient ischemic attack, SF-36 physical summary score, and Seattle Angina Questionnaire physical limitation and angina stability scores. Multivariate analyses using the Akaike information criterion to determine the model of best fit among non-nested alternatives (continuous vs categorical age predictors) identified 8 factors as significant independent predictors of depression in chest pain patients, including the presence of NoCAD (Table 7).

Table 7

Multivariate Predictors of Depression in Patients with Chest Pain

Predictor	**OR (95% CI)**	***p* Value**
NoCAD	1.44 (1.03-2.03)	0.03
Age	0.97 (0.96-0.99)	<0.001
Female gender	1.69 (1.23-2.32)	<0.001
Antidepressant medication	2.58 (1.57-4.25)	<0.001
Prior acute myocardial infarct	1.64 (1.17-2.30)	0.004
Prior airways disease	1.48 (1.01-2.17)	0.045
SF-36 physical summary score	1.03 (1.01-1.05)	0.009
Seattle Angina Questionnaire physical summary score	0.97 (0.96-0.98)	<0.001

Discussion

The major finding of this study is that depression is more prevalent in patients with chest pain with NoCAD than either those with obstructive CAD or healthy controls. Moreover, NoCAD is an independent predictor of depression in patients who undergo coronary angiography for the evaluation of chest pain. These observations have important implications in the pathogenesis and treatment of patients with chest pain referred for coronary angiography.

We used SF-36 mental summary scores to identify depressed patients in healthy control and chest pain cohorts. The method has been previously validated in similar cohorts using a well-established depression scale (the Center for Epidemiologic Studies

Depression Scale) (Tavella et al., 2010), and the findings of the present study provide further face validity for this method. First, consistent with previous studies of depression, there was a 2-fold greater probability of depression in patients with obstructive CAD compared with healthy controls (Egede, 2007). Second, the use of antidepressants was a strong predictor of the SF-36 score-derived depression category (Table 7), suggesting that it was comparable with clinician-diagnosed and clinician-treated depression. Third, other well-characterized predictors of depression, including previous AMI (Frasure-Smith et al., 1993), airway disease (Lacasse, Rousseau, & Maltais, 2001), and impaired physical activity (Cole & Dendukuri, 2003), were independent predictors. Given the consistencies in the study findings with the established research on depression, the novel methodologic approach is verified, so that attention to the unique findings of this study can be addressed.

Patients with NoCAD constitute a heterogeneous clinical group, with multiple causes for the chest pain prompting angiography. One study reported that 25% had psychiatric disorders, 25% microvascular angina, 25% esophageal disorders, and the remaining a variety of other medical conditions responsible for the chest pain prompting angiography referral (Beitman et al., 1989). However, this is an oversimplification, because these disorders may coexist or be difficult to delineate. Cardiac syndrome X, for example, is characterized by normal angiographic findings despite positive results on exercise stress testing and has been associated with a high prevalence of depression (Asbury, Creed, & Collins, 2004; Ketterer et al., 1996; Piegza, Pudlo, Badura-Brzoza, & Hese, 2009). These findings can be explained by 3 plausible alternative mechanisms. First, the exercise test finding is a "false-positive," and the source of the chest pain is depression or some other noncardiac disorder (e.g., esophageal reflux). Second, the patient has a coronary microvascular disorder resulting in myocardial ischemia producing chest pain and positive stress test results, with depression ensuing from the suboptimal therapies available for this disabling disorder. Third, depression and coronary microvascular disorders have a common pathophysiologic or genetic pathway, so that the disorders coexist (Vaccarino et al., 2009). It may therefore be difficult to identify the primary cause for the chest pain in patients with NoCAD, although the presence of causative or contributory disorders such as depression can be quantified.

However, whether treatment of the depressive illness improves the presenting chest pain symptoms can be more readily addressed.

In a landmark study, Cannon et al (1994) recruited 60 consecutive patients with NoCAD and subjected them to systematic assessment, reporting that 22% had abnormal exercise test results, 41% had abnormal esophageal motility testing, and 63% had ≥1 psychiatric disorder. Furthermore, using a randomized, double-blind, placebo-controlled study design, they demonstrated that imipramine therapy reduced chest pain episodes by 52 ± 25%. Because the prevalence of depression and other psychiatric disorders were matched between the treatment groups, the treatment effect was attributed to the pain sensitivity-altering properties of imipramine, although an antidepressant effect cannot be excluded.

The present study highlights the importance of screening for depression in patients who undergo coronary angiography for the evaluation of chest pain. This is particularly pertinent considering (1) the high prevalence of depression in this population, especially in comparison with other published studies that have undertaken screening studies after AMI, general cardiac admissions (Wade, Cheok, Schrader, Hordacre, & Marker, 2005), and cardiac outpatients (Ruo et al., 2003) and (2) the availability of potential therapies to and improve quality of life (Keitner et al., 2009; Reed et al., 2009; Skevington & Wright, 2001). In conclusion, depression is prevalent in patients who undergo coronary angiography for the evaluation of chest pain, and those with NoCAD should be particularly targeted for assessment.

Disclosures

The authors have no conflicts of interest to disclose.

CHAPTER FIVE: STUDY 2

CHAPTER FIVE
STUDY 2

The statistical method 'survival analysis' was utilised in the study "Depression and 5-year mortality in patients with acute myocardial infarction: Analysis of the IDACC database" (Identifying Depression as a Comorbid Condition, abbreviated to 'IDACC study'). Survival analysis is not a commonly performed statistical method in psychology. This section discusses survival analysis, what it is used for and how it is conducted, before presenting the published manuscript.

1. SURVIVAL ANALYSIS

1.1. What is Survival Analysis?

Time-to-event analysis involves estimating the probability that an event will occur at different points in time (Lang & Secic, 2006). One of the most common applications of time-to-event analysis is survival analysis, which can be broadly defined as the time to the occurrence of a given event (Lee & Wang, 2003). Survival analysis estimates the probability of survival as a function of time from a starting point (Lang & Secic, 2006). Much of the survival research has focused on predicting the probability of response, survival, or mean lifetime, comparing the survival distributions of experimental animals or of human patients, and in identification of risk and/or prognostic factors relating to response, survival and the development of a disease (Lee & Wang, 2003). However, survival analysis can be used across many fields, for example to estimate the probability of a felon's time to parole (criminology), duration of first marriage or divorce (sociology), length of magazine subscription (marketing), lifetime of electronic devices (reliability engineering) or most commonly in the field of medicine to estimate the probably of relapse into disease, development of symptoms, or treatment to response, or time to death (Lang & Secic, 2006; Lee & Wang, 2003).

1.2. Components Required

Two main features are important in survival analysis: the event of interest and survival time (Le, 1997). The event of interest is the endpoint/outcome event that the researcher is interested in, whereas survival time is the time to reach the event of

interest (Le, 1997). To calculate survival time, three basic components are required (Le, 1997): (1) starting point, (2) ending event of interest, and (3) measurement scale for the passage of time.

In the analysis of the IDACC database, survival time was calculated from the participants' date of entry into the original IDACC study (starting point) to date of death (ending event of interest) in days (measurement scale). The event of interest was 5-year mortality, so survival times were calculated with an event cut-off of 1825 days (5 years excluding leap years).

When calculating survival time, it is important to take into account those participants who do not complete the study. When the event of interest has occurred, and the interval between the starting time and the event is known, the data are said to be uncensored and "complete" (Lang & Secic, 2006). However, in survival analysis, many participants may not experience the event of interest at the end of the study or time of analysis, having dropped out or be lost to follow-up. The data is then said to be censored and "incomplete" (Lang & Secic, 2006). In this case, one of three types of censoring occurs (Lee & Wang, 2003).

1.3. Censoring

Types I and II censoring typically occur in animal studies. Type I censoring occurs when a fixed number of animals undergo treatment/s (Lee & Wang, 2003). Due to time and/or cost limitations, researchers may not be able to wait for the death of all animals. One method to counter this problem is to sacrifice the animals after a certain period of time (Lee & Wang, 2003). With type II censoring, researchers may wait until a fixed proportion of the animals have died, after which the survivors are sacrificed (Lee & Wang, 2003). As the IDACC study analysed human rather than animal participants, types I and II censoring were not relevant and type III censoring was utilised.

Type III censoring is often used in clinical and epidemiologic studies with a fixed study period during which participants enter the study at different times (Lee & Wang, 2003). The survival times of patients who died before the end of the study are recorded from time of entry into the study until death. These are called uncensored

observations (Lee & Wang, 2003). The survival times of patients still alive by the end of the study are recorded from entry to the end of the study. These are censored observations (Lee & Wang, 2003). If patients are lost to follow-up, or withdraw before the end of the study, the survival times are recorded from time of entry into the study to last contact. These are also censored observations (Lee & Wang, 2003). Figure 21 shows an example of type III censoring.

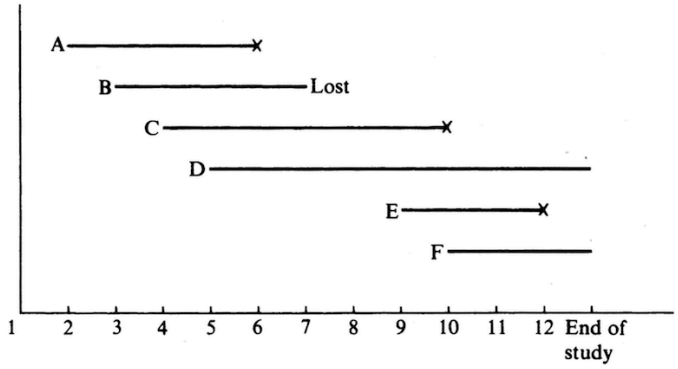

Figure 21. Type III censoring. Reprinted from *Statistical Methods for Survival Data Analysis* (3rd ed., p. 4), by E. T. Lee and J. W. Wang, 2003, Hoboken, NJ: John Wiley and Sons, Inc. Reprinted with permission.

In Figure 21, patients A to F entered the 12-month study at different times. Patients A, C and E died at 6, 10 and 12 months (uncensored observations, with death denoted by "x"). Patient B was lost to follow-up during the study, and patients D and F remained alive at the end of the study (all 3 being censored observations) (Lee & Wang, 2003).

Patients entered the IDACC study at different times between 2000 and 2002. The follow-up date was 31 August 2007. If patients died during the study period, they were said to have uncensored observations. If they withdrew or were lost during the course of the IDACC study or remained alive at the end of follow-up, they had censored observations.

1.4. Survival Time Distributions

After survival time has been calculated, with censoring taken into account, the survival times can be plotted against time. The distribution can then be analysed and

interpreted. The distributions of survival times are usually characterised by three functions, which are the survival function, the density function and the hazard function.

Survival Function

The survival function, S(*t*), is the probability that an individual survives longer than *t* units of time (Lee & Wang, 2003). The course of survival can be plotted to show the survival rates of one or more groups (Lee & Wang, 2003). The survival function is represented by a downward sloping curve, which may reach 0% probability of survival by a certain final time (Garson, 2009). A steep curve represents low survival rate or short survival time, as shown in Figure 22, diagram (a), and a gradual or flat curve represents high survival rate or long survival time, as demonstrated in Figure 22, diagram (b).

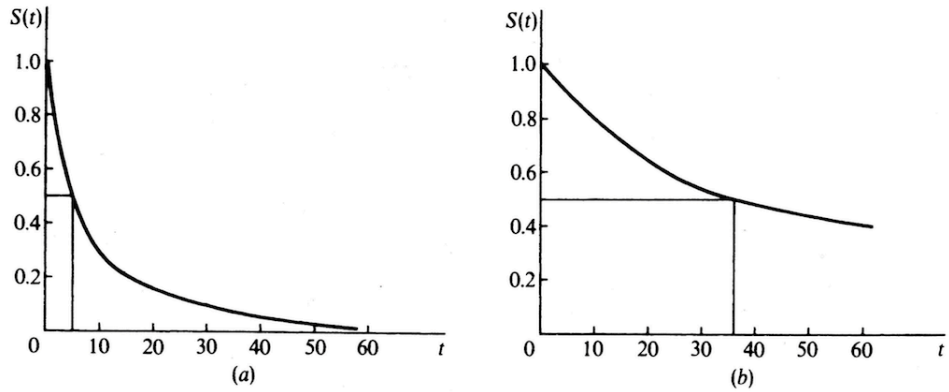

Figure 22. Survival curves. Reprinted from *Statistical Methods for Survival Data Analysis* (3rd ed., p. 9), by E. T. Lee and J. W. Wang, 2003, Hoboken, NJ: John Wiley and Sons, Inc. Reprinted with permission.

Density Function

Density function, f(*t*), can be defined as the unconditional (not conditioned on covariates) instantaneous (at any instant *t*) probability that an individual has experienced the event, that is, the failure rate (Garson, 2009). It is the probability of failure in a small interval per unit time (Lee & Wang, 2003). The density function, therefore, is also called the unconditional failure rate. This function can be expressed in a graphic plot, where the probability is represented by the area under the curve at any point on the x-axis (Figure 23, diagrams a and b). Figure 23, diagram (a) shows a high failure rate at the beginning of the study, which decreases as time progresses. Figure 23,

diagram (b) shows the peak of high failure at 1.7 units of time. The shaded area between 1 and 2 units of time represents the proportion of individuals that failed (experienced the event).

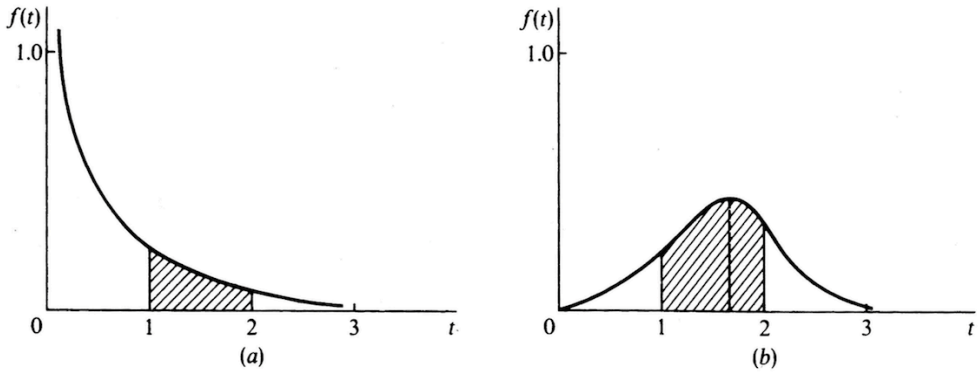

Figure 23. Density curves. Reprinted from *Statistical Methods for Survival Data Analysis* (3rd ed., p. 10), by E. T. Lee and J. W. Wang, 2003, Hoboken, NJ: John Wiley and Sons, Inc. Reprinted with permission.

Hazard Function

The hazard function, h(*t*), is defined as the probability of failure during a very small time interval, assuming that the individual has survived to the beginning of the interval (Lee & Wang, 2003). The hazard function is thus also known as the conditional failure rate. The hazard function may increase, decrease, remain constant or indicate a more complicated process (Lee & Wang, 2003), as shown in Figure 24 below.

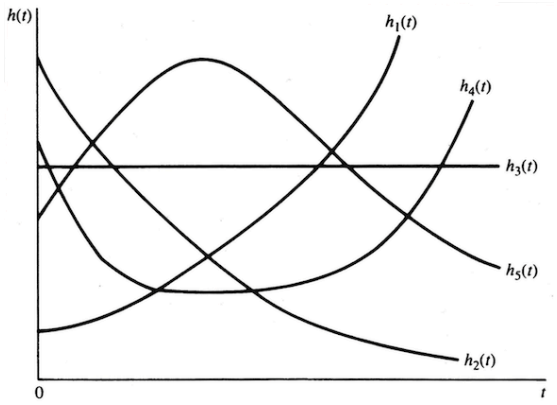

Figure 24. Hazard functions. Reprinted from *Statistical Methods for Survival Data Analysis* (3rd ed., p. 12), by E. T. Lee and J. W. Wang, 2003, Hoboken, NJ: John Wiley and Sons, Inc. Reprinted with permission.

Cancer patients who do not respond to treatment, for example, have an increasing hazard rate ($h_1(t)$), whereas a decreasing hazard rate may be represented by wounded soldiers undergoing surgery ($h_2(t)$). The surgery is at first dangerous, but this risk decreases if surgery is successful. A constant hazard rate ($h_3(t)$) may represent healthy individuals aged between 18-40, whose main risks of death are accidents. The process of human life may exemplify the bathtub curve, as shown in $h_4(t)$. Initially, risk is high due to high infant mortality. As life proceeds, risk remains constant until a certain time when it begins to increases due to wear-out failures. Finally, cancer patients have a high and increasing risk until successful treatment, after which risk decreases, as in $h_5(t)$ (Lee & Wang, 2008).

1.5. Survival Analysis Statistical Methods

After an initial analysis of survival time and plotting of the curve, the data can be analysed. Several statistical methods are available for analysing survival data, such as the Kaplan-Meier method, the Life Table method (non-parametric models), the Weisbull method (parametric model) or the Cox regression method (semi-parametric model), which implements the proportional hazards model (Garson, 2009; Lang & Secic, 2006). In the IDACC study, both the Kaplan-Meier and Cox regression methods were selected for the reasons described below. Therefore, the Life Table and Weisbull methods will not be discussed.

Non-Parametric Models

The Kaplan-Meier method is a non-parametric model. Unlike parametric models, non-parametric models do not require the researcher to make assumptions about the shape of the hazard function or how covariates affect it (Garson, 2009). This may eliminate parameter estimate bias, especially if the incorrect shape of the hazard function is specified (Garson, 2009). Instead, the Kaplan-Meier method estimates the change over time of the hazard function from empirical data. It is a descriptive method to generate tables and plots to describe these functions (Garson, 2009). The effect of covariate variables is shown only by stratifying the data into groups (e.g., by gender) to plot and contrast separate hazard functions for each group. However, non-parametric models can only compare a very limited number of groups and cannot be used for continuous data (Garson, 2009). Kaplan-Meier survival curves are therefore most useful when describing the effect of a single covariate on time. In the IDACC study, the

Kaplan-Meier method was used to describe change over time in depression (as a dichotomous variable) in patients hospitalised for AMI.

Semi-Parametric Models

If the effect of more than one covariate on time is of interest, a method to handle several covariates is required. In the IDACC study the semi-parametric Cox regression model was utilised because it is designed to analyse the time until an event has occurred (Garson, 2009) and can include several covariates. One or more predictor variables, covariates, are placed in the model to predict the status (event) variable (Garson, 2009). In the IDACC study, the status was mortality. The covariates are eliminated from the model one by one if not statistically significant. The primary output is the hazard ratio, which measures the risk associated with each covariate (Garson, 2009). Similar to non-parametric models, this model also makes no assumptions about the shape of the hazard function. However, it does make assumptions about how covariates affect the function (Garson, 2009), in that hazard rates are assumed to be proportional between groups over time (Garson, 2009). In SPSS (Statistical Package for the Social Sciences), this assumption can be tested using partial residuals.

1.6. Cox Regression Modelling

Numerous components are essential to construct a Cox model. These include the status (event) variable, covariates and the method.

Status Variable

The status (event variable) is the dependent variable that is analysed in relation to the survival time variable (Garson, 2009). In the IDACC study, survival time to mortality at 5 years was used as the dependent variable to determine the hazard rates.

Covariates

Covariates are the independent predictor variables expected to predict survival time (Garson, 2009). Both continuous and categorical variables were analysed in the IDACC study. In a Cox regression model, it is important to include the maximum number of records (i.e., data) in the analysis, in order to mitigate bias (which might result from excluding large numbers of missing records). This is achieved by combining the missing and 'not sure/not asked/not stated' responses for categorical variables into a

valid category. Table 8 shows a valid category 'not stated' for the categorical variable 'cigarette smoking status'. Based on the quantity of missing/ambiguous responses, the researcher decides when to assign a valid category for a categorical variable (Garson, 2009). A small number of such responses may induce little bias and hence can be excluded from the model. The greater the number of missing or ambiguous responses that are present, the more bias incorporated into the model. In the IDACC study, a valid category was assigned for any categorical variable with 10 or more missing or ambiguous responses.

After all covariates of interest have been entered into the Cox model, SPSS (which was used for analysis in the IDACC study) will automatically convert the categorical variables into a set of dummy variables, each with its own regression coefficient. In doing so, one category of each categorical variable is omitted and turned into a reference category, as in Table 8. In SPSS, this is the last category by default but the reference can be manual specified. For categorical variables in the IDACC study, the first category was manually specified as the reference category, allowing for more logical interpretation of the covariate.

Table 8

Dummy Coding of a Categorical Covariate

Cigarette Smoking Status
Never smoked (reference)
Currently smokes
Ex-smoker
Not stated

The interpretation of the regression coefficient depends on the type of coding scheme chosen, which in turn depends on the comparisons the researcher requires: coding schemes are selected so that the resulting comparisons are the most meaningful for testing study hypotheses. The coding scheme is based on a set of equations that enable comparisons to be made (Garson, 2009). Numerous coding schemes are available: simple, deviation, difference, Helmert, repeated, polynomial and indicator (Garson, 2009; SPSS, 2008). Indicator coding scheme was chosen for all categorical variables in the IDACC study for ease of interpretation. Indicator coding is similar to

simple coding, but uses less complex equations for comparisons. In indicator schemes, dummy coding allows the regression coefficient to compare the effect of the dummy with the reference category (Garson, 2009). Each category (except the reference category) is compared to the reference category. Table 8 shows an example of the categorical variable 'cigarette smoking status', where 'never smoked' has been omitted and designated as the reference category. The dummies 'currently smokes, ex-smoker' and 'not stated' are compared to the reference 'never smoked'.

Method

Variables can be processed and entered into the model in four ways: enter, forward, stepwise and backward (SPSS, 2008). Backward elimination was utilised in the IDACC study to avoid potential problems with forward or stepwise selection methods. In forward and stepwise methods, when a predictor is entered into a model, the predictor chosen is the one that best explains the residual variation in the current model. Accordingly, new predictors added are not chosen for their predictive ability in regard to the dependent variable, but rather for their ability to explain the residual variation of the model with the incorporated current predictors. Backwards elimination of predictor variables avoids this problem. In the backward method, all covariates are entered into the model at the beginning and the non-significant covariates are manually removed sequentially according to the significant criterion specified (Lee & Wang, 2003), which is the probability for entry into and removal of covariates from the model. In the IDACC study, the entry criterion was 0.05 and removal was 0.06. Once the significance levels are set, the model is run and the parameters that define the model and coefficients of all covariates are estimated. The Wald test examines each covariate, and the least significant covariate not meeting the specified alpha level for staying in the model is removed. Once a covariate has been manually removed from the model, it is never re-added. This procedure is repeated until all covariates that remain in the model meet the significance level for staying in the model (Lee & Wang, 2003).

1.7. Interpretation of Covariates

After all non-significant covariates have been removed, the final model will be limited to significant independent covariates. The output of interest is the hazard ratio (sometimes referred to as odds ratio [OR]) and is characterised in the output by Exp. β. The hazard ratio measures the risk associated with each explanatory variable (Garson,

2009) and is the amount of change in the hazard of the event (i.e., increased risk) for every unit or level increase in the explanatory variable (Lang & Secic, 2006). For categorical variables, a hazard ratio greater than 1 indicates an increased risk for those with that characteristic and less than 1 indicates a decreased risk (Lang & Secic, 2006). If the hazard ratio equals 1, this indicates that the characteristic of that variable neither promotes nor protects against the event (Lang & Secic, 2006). For continuous variables, the hazard ratio indicates a unit change in the event for every unit change in the variable. Confidence intervals (CIs) should be attached to the hazard ratio, and indicate the precision of the estimated ratio. The narrower the CIs, the more precise are the estimates (Lang & Secic, 2006).

By conducting a Cox regression in the IDACC study, the independent predictors of mortality at five years in patients with AMI were determined. The results and discussion of this study are presented in the manuscript following Section 2 below.

2. INSTRUMENTS

The IDACC study presented in this chapter utilised several psychometric instruments, including a generic HRQoL measure, three domain-specific measures (depression, anxiety and social support), and a trait personality questionnaire.

2.1. Instruments Utilised

2.1.1. Generic Measure

Short Form-36

The administration of the SF-36 (Appendix A) was previously described in Section 1.1.1 of Chapter Four.

2.1.2. Domain-Specific Measures

Center for Epidemiologic Studies Depression Scale

The CES-D (Radloff, 1977; Appendix C) is a freely available and widely used 20-item self-report scale designed to measure the frequency and severity of depressive symptoms in the general population. It includes the major components of depression, with an emphasis on affective components: depressed mood, feelings of guilt, worthlessness and helplessness, psychomotor retardation, loss of appetite and sleep disorder (Radloff, 1977). The scale is a valuable tool in identifying symptoms of depression, high-risk groups or those in need of treatment.

Respondents are instructed to indicate how often each symptom was experienced during the past week, on a 4-point Likert scale ranging from 'rarely or none of the time' to 'most or all of the time'. Scores range from 0 to 60, with higher scores indicating an increased level of depressive symptoms. Scores can be divided into 3 categories according to standard threshold scores (Ensel, 1986; Zich, Attkisson, & Greenfield, 1990): not depressed 0-15, mild depression 16-26, moderate to severe depression 27-60. A score of 27 has been found to be more useful as a cut-off for screening depression in medical patients than the standard threshold score of 16 (Zich et al., 1990).

The validity of the CES-D as a measure of depression has been confirmed in primary care populations (Zich et al., 1990), clinically depressed patients (Morin et al., 2011), and in the general population; and in different ethnic groups (Vera et al., 1991) and older populations (Himmelfarb & Murrell, 1983; Zich et al., 1990). It has also been extensively used in large studies, including among CHD patients (Cheok, Schrader, Banham, Marker, & Hordacre, 2003; Penninx et al., 2001). The questionnaire has high internal consistency, adequate test-retest reliability, excellent concurrent validity by clinical and self-report criteria (Ensel, 1986; Radloff, 1977) and substantial construct validity (Weissman, Sholomskas, Pottenger, Prusoff, & Locke, 1977).

Hospital Anxiety and Depression Scale

The Hospital Anxiety and Depression Scale (HADS; Zigmond & Snaith, 1983; Appendix D) is a self-report questionnaire designed and widely used to measure depression and anxiety in physically ill patients. Items relate to feelings during the preceding week. The questionnaire excludes somatic symptoms, which could indicate physical rather than psychological morbidity, thereby avoiding potential confounds. The scale consists of 14 items (7 for depression and 7 for anxiety) comprising two subscales and ratings are made on a 4-point Likert scale. Items are summed on each of the two subscales, with higher scores indicating greater psychological distress. Scores on each independent subscale can also be interpreted in ranges: normal (0-7), mild (8-10), moderate (11-14) and severe (15-21) (Snaith, 2003). HADS has been validated as a measure of depression and anxiety in patients with MI (Johnston, Pollard, & Hennessey, 2000; Roberts, Bonnici, & Mackinnon, 2001) and primary care patients (Wilkinson & Barczak, 1988). Its high test-retest reliability makes it suitable for monitoring these symptoms.

Multidimensional Scale of Perceived Social Support

The Multidimensional Scale of Perceived Social Support (MSPSS; Zimet, Dahlem, Zimet, & Farley, 1988; Appendix E) is a 12-item instrument designed to measure an individual's subjective assessment of social support adequacy from three sources: family, friends and significant other. Respondents are asked to answer each statement on a 7-point Likert scale, ranging from 'very strongly disagree' to 'very strongly agree'. The items are divided into three different factor groups relating to the

source of support, with scores being summed for the level of support, ranging from 7-28. The level of overall perceived social support is the sum of all 12 items, with scores ranging from 7-84. High scores indicate high levels of perceived support. The MSPSS is psychometrically sound (Zimet et al., 1988) and strong test-retest reliability, internal reliability and validity have been demonstrated (Zimet et al., 1988). The MSPSS has also been validated in psychiatric patients (Kazarian & McCabe 1991).

2.1.3. Other Measure

Life Orientation Test-Revised

The Life Orientation Test (LOT) was developed by Scheier and Carver in 1985 to measure the personality trait of dispositional optimism. However, they found that two of the 12 items were measuring an individual's method of coping rather than generalised expectancies. In an attempt to improve the internal characteristics of the LOT, it was revised in 1994 (LOT-R; Scheier, Carver, & Bridges, 1994; Appendix F), to focus more on respondents' expectations for the future. The revised inventory contains 10 items: 4 filler items and 6 scale items (3 positively worded and 3 negatively worded), which are used for scoring. The three negative items are reverse-scored before calculating the overall score. The remaining four items are filler items intended to conceal the purpose of the inventory. Respondents are asked to answer the 10 statements about themselves and their future, indicating the extent of agreement, on a 5-point Likert scale, ranging from 'strongly agree' to 'strongly disagree'. Scores are calculated by summing the 6 scale items, resulting in a score range from 0-24. Higher scores represent greater optimism. Several studies have reported adequate measures of internal consistency and test-retest reliability (Hirsch, Britton, & Connor, 2010; Majer, Jason, & Olson, 2004; Scheier et al., 1994).

STATEMENT OF AUTHORSHIP

Title of Paper	Depression and 5-year mortality in patients with acute myocardial infarction: Analysis of the IDACC database
Publication Status	Published
Publication Details	Wheeler, A., Beltrame, J., Tucker, G., Air, T., Ling, L-H., & Schrader, G. (2012). Depression and 5-year mortality in patients with acute myocardial infarction: Analysis of the IDACC database. *Australian and New Zealand Journal of Psychiatry, 46*(7), 669-675. doi: 10.1177/0004867412449875

Author Contributions

By signing the Statement of Authorship, each author certifies that their stated contribution to the publication is accurate and that permission is granted for the publication to be included in the cardidate's thesis.

Name of Principal Author (Candidate)	Alexis Wheeler		
Contribution to the Paper	Study conception and design, statistical analysis, management and interpretation of the data, manuscript preparation, critical review and revision of the manuscript		
Signature		**Date**	4.11.13

Name of Co-Author	John Beltrame		
Contribution to the Paper	Supervised development of the work, manuscript preparation and critical review		
Signature		**Date**	6.11.13

Name of Co-Author	Graeme Tucker		
Contribution to the Paper	Provided expert advice on statistical analysis and data interpretation, critical review of the manuscript		
Signature		**Date**	6.11.13

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Contribution to the Paper	Provided expert advice on statistical analysis and data interpretation, critical review of the manuscript		
Signature		**Date**	8.11.13

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Contribution to the Paper	Data categorisation prior to analysis		
Signature		**Date**	6.11.13

Name of Co-Author	Geoffrey Schrader		
Contribution to the Paper	Assisted with the study inception and design, supervised development of the work, manuscript preparation and critical review		
Signature		**Date**	18.11.13

STUDY 2

Depression and 5-year Mortality in Patients with Acute Myocardial Infarction: Analysis of the IDACC Database

This results chapter is reproduced in the exact form as it appears in the manuscript:

Wheeler, A., Beltrame, J., Tucker, G., Air, T., Ling, L-H., & Schrader, G. (2012). Depression and 5-year mortality in patients with acute myocardial infarction: Analysis of the IDACC database. *Australian and New Zealand Journal of Psychiatry*, *46*(7), 669-675. doi: 10.1177/0004867412449875

In keeping with the style of this thesis[2], the tables and figure have been re-numbered, the references incorporated into the thesis master reference list, and the manuscript repaginated.

[2] In the published manuscript reporting Study 2 (in the Australian and New Zealand Journal of Psychiatry) hazard ratio was abbreviated to HR. Throughout this thesis, however, to prevent confusion, the abbreviation HR is used only for heart rate, and hazard ratio has not been abbreviated. Accordingly, within the manuscript presented below the abbreviation HR has been replaced with hazard ratio.

Abstract

Objective: Symptoms of depression are highly prevalent and persistent following myocardial infarction (MI). Whether depression is a risk factor for long-term mortality following MI remains controversial. The present study aimed to determine whether depression during hospitalisation for acute MI (AMI) predicted 5-year all-cause or cardiac mortality.

Method: This study utilised the Identifying Depression as a Comorbid Condition (IDACC) database of 337 hospitalised patients with AMI. Depressive symptoms were assessed using the Center for Epidemiologic Studies Depression scale (CES-D). Data were linked to a government administrative death registry to determine 5-year mortality. Survival data were analysed using Cox's proportional hazards model.

Results: The mean age during AMI hospitalisation was 59 years ± 12, 74% of patients were men and depression (CES-D ≥ 16) was present in 132 patients (39.3%). The 5-year all-cause mortality rate was 10.4% (35 deaths) and the cardiac mortality rate was 6.5% (22 deaths). When depression was defined as a dichotomous variable, moderate to severe depression (defined by CES-D ≥ 27) at the time of AMI was associated with all-cause mortality (hazard ratio 2.54, 95% confidence interval 1.03 to 6.28; p = 0.04) but not cardiac mortality. However, when depression was defined by three categories (no depression CES-D < 16, mild depression CES-D 16–26, moderate to severe depression CES-D ≥ 27), it was not found to predict mortality. In addition, perceived social support was a predictor of all-cause and cardiac mortality in AMI patients.

Conclusions: Our results indicate that the relationship between mortality and depression severity is not linear and that the association only becomes evident when the severity reaches a threshold level of CES-D ≥ 27, consistent with major depression. Low power may have influenced the finding of a lack of association between depression and cardiac mortality.

Keywords

Depression, mortality, myocardial infarction

Introduction

According to the World Health Organization, by 2020 depression will be the second leading cause of disability-adjusted life years lost – with ischaemic heart disease being the first (Murray and Lopez, 1996). Previous research has established that one in five patients experience depressive symptoms after myocardial infarction (MI) (Frasure-Smith et al., 1993) and that these symptoms are a risk factor for short-term mortality (Frasure-Smith et al., 1995). However, whether depression is a risk factor for mortality ≥ 5 years post-MI remains controversial, with some studies reporting that depression predicts mortality in MI patients (Carney et al., 2008; Lesperance et al., 2002; Pfiffner and Hoffmann, 2004; Welin et al., 2000) while more recent reports have failed to detect an association (Dickens et al., 2007; Parakh et al., 2008). The present study was conducted to determine whether depression was associated with mortality 5 years after initial hospitalisation for acute MI (AMI) in a local Australian cardiac population. Analyses were undertaken on a well-characterised cohort of patients hospitalised for a range of cardiac conditions from the Identifying Depression as a Comorbid Condition (IDACC) (Schrader et al., 2005) database in terms of demographic, socioeconomic, psychological and cardiac factors. Predictors of all-cause and cardiac mortality were examined in a subset of patients hospitalised for AMI.

Method

Design

Details of the design of the IDACC study have been previously reported (Cheok et al., 2003) but, in brief, patients admitted to South Australian hospitals with a range of cardiac diagnoses were recruited between 2000 and 2002. Patients were screened for depression with clinical outcomes followed for 12 months following discharge (Cheok et al., 2003). Depression was diagnosed by the Center for Epidemiologic Studies Depression scale (CES-D) with scores being divided into three categories according to standard threshold scores (Ensel, 1986; Zich et al., 1990): not depressed < 16; mildly depressed 16–26, indicative of minor depression; and moderately to severely depressed ≥ 27, indicative of major depression (Cheok et al., 2003).

Patients with an admission diagnosis of AMI in the initial IDACC study were included in the present study. Mortality data, including cause of death, were obtained from the South Australian Government death register. Patients in the IDACC database

were subsequently linked to the register. Patients who were initially admitted into hospital with AMI were then categorised after 5 years as being alive or deceased. Mortality was categorised as all-cause or cardiac by a cardiac clinician, who was blind to the depression status.

The study was approved by the North Western Adelaide Health Service Human Research Ethics Committee and the SA Health Ethics Committee for access to the administrative mortality database. All IDACC participants gave written informed consent.

Participants

Details of the number of patients meeting enrolment criteria and patients excluded in the IDACC study have been previously reported (Schrader et al., 2005). The IDACC database consisted of 1541 patients. The IDACC study recruited 337 patients with an admission diagnosis of AMI (aged 23–84 years, 74% males), who formed the target population in the present prospectively designed, long-term, follow-up study.

Measures

Details of the measures collected in the IDACC study have been previously reported (Cheok et al., 2003). Variables included (a) patient demographics (age, sex, marital status and index of relative socioeconomic disadvantage); (b) cardiac risk factors (body mass index (BMI), length of stay in hospital, family history of heart disease, cigarette smoking status, prior high blood pressure/high cholesterol, prior diabetes and prior heart condition/heart procedure); (c) depression risk factors (prior emotional problem and persistent depression (defined as being depressed at both baseline and 12 months); and (d) psychometric data, including (i) quantitative depression questionnaires (CES-D) (Radloff, 1977) and Hospital Anxiety and Depression Scale (HADS) anxiety score (Zigmond and Snaith, 1983), (ii) a generic quality of life questionnaire (Short Form-36 (SF-36) mental and physical component summary score) (Ware &Sherbourne, 1992), and (iii) life event and social support questionnaires (Life Orientation Test-Revised (LOT-R)) (Scheier et al., 1994) and Perceived Social Support Scale (PSSS) (Zimet et al., 1988).

Statistical Analyses

Statistical analyses were performed using the SPSS statistical software package version 11.0.4 (SPSS for Mac OS X; Chicago, IL: SPSS Inc., 2005). In the univariate analyses, ambiguous responses to categorical variables (e.g. 'not sure/not asked/not stated') were recoded and managed as missing values. Descriptive statistics were reported as means ± standard deviation and percentages. Initially, categorical data were analysed with the chi-squared statistic, and continuous variables with *t*-tests, to identify associations between the outcome of mortality at 5 years and potential predictor variables. Baseline clinical features analysed as possible predictors of mortality were based on previous literature (Carney et al., 2008; Lesperance et al., 2002; Parakh et al., 2008; Pfiffner and Hoffmann, 2004; Welin et al., 2000). Baseline variables assessed in univariate analyses included (a) demographic data, (b) cardiac risk factors, (c) depression risk factors, and (d) questionnaire scores (CES-D, HADS, SF-36, LOT-R and PSSS). Analyses were performed on both continuous and categorical CES-D scores. In addition to the primary analysis, the prediction model was tested with depression defined as (1) CES-D ≥ 16 and (2) CES-D ≥ 27. Based upon the available data from the IDACC study and considering the prevalence of moderate to severe depression (CES-D ≥ 27) in the cohort, a power calculation for this investigation was performed. The study had 75% power to detect a hazard ratio of 2.5 at the $p < 0.05$ significance level for all-cause mortality and a 61% power for cardiac mortality.

In accordance with the recommendations of Hosmer and Lemeshow (1999), a significance level of $p \leq 0.15$ in the univariate analyses was used as a criterion for entry into the multivariate analysis. A multivariate Cox proportional hazards model was developed to test the association between covariates and all-cause and cardiac mortality at 5 years. The survival time in AMI patients at 5 years was used as the dependent variable to determine the hazard ratio (exp β) and 95% confidence interval (CI) of predictor variables. Missing and 'not sure/not asked/not stated' responses (≥ 10 cases) for the categorical covariates were combined into a valid category to include the maximum number of records possible in the analysis and to mitigate bias. The significant variables from chi-squared and *t* tests were entered into the Cox model and the best predictors selected using backward elimination of non-significant terms. Models were fit separately using either continuous or categorical versions of the CES-D. Covariates were removed from the survival model one by one according to the

significant criterion specified (entry = 0.05, removal = 0.06) and the model assessed at each step using the log likelihood test. The best-fit model of all the variations was determined using Akaike's Information Criterion (AIC). The significance level for predictors of mortality in the final model was defined as $p < 0.05$. The accuracy of the proportional hazards assumption was tested graphically and using partial residuals.

Results

Of the 337 AMI patients, depression at baseline (defined as CES-D ≥ 16) was evident in 132 patients (39.3%) (mild depression in 76 (22.6%); moderate to severe depression in 56 (16.7%) patients), while 204 patients (60.7%) were not depressed. One case was missing depression data, and was not included in the analysis.

Vital status was determined for all patients at 5 years. There were 35 (10.4%) all-cause deaths and 22 (6.5%) cardiac deaths. Of those dying from non-cardiac causes, six died from cancer, three from respiratory failure, two from sepsis and two from renal failure. Tables 9 and 10 summarise the clinical and psychometric characteristics for all-cause and cardiac mortality, respectively.

All-Cause Mortality

In the univariate analyses for all-cause mortality in AMI patients (Table 9), both the continuous and categorical CES-D (with three categories) variables were significant potential predictors of all-cause mortality at 5 years. Other potential predictors included age, SF-36 physical summary score, perceived social support, prior emotional problem, prior high blood pressure/high cholesterol, HADS anxiety score, prior cardiac condition/procedure and CES-D ≥ 27.

Table 9

Univariate Baseline Characteristics of Acute Myocardial Infarction Patients Who Survived to 5 Years and Those Who Died From All-Causes

Characteristic	**Survivors (*n* = 302)**	**Fatalities (*n* = 35)**	***p*-value**
Demographics			
Age, years	58 ± 12	69 ± 11	<0.001
Risk factors			
Prior high blood pressure/high cholesterol	142 (59.4%)	21 (77.8%)	0.06
Prior cardiac condition/procedure	101 (42.8%)	21 (75.0%)	0.001
Health/psychological indices			
CES-D depression	15 ± 11	19 ± 12	0.05
SF-36 physical summary score	39 ± 11	34 ± 8	0.01
PSSS perceived social support	5.8 ± 1.2	5.4 ± 1.0	0.08
CES-D depression			0.05
Not depressed	186 (61.8%)	18 (51.4%)	
Mildly depressed	70 (23.3%)	6 (17.1%)	
Moderately to severely depressed	45 (15.0%)	11 (31.4%)	
CES-D depression (≥ 27)			0.01
Not depressed	256 (85.0%)	24 (68.6%)	
Depressed	45 (15.0%)	11 (31.4%)	
HADS anxiety	125 (41.4%)	19 (54.3%)	0.14
Prior emotional problem	54 (21.4%)	10 (34.5%)	0.11

Values expressed as number (per cent) or mean ± *SD*.

Values may not add up to the total owing to missing cases.

CES-D, Center for Epidemiologic Studies Depression scale; HADS, Hospital Anxiety and Depression Scale; PSSS, Perceived Social Support Scale; SF-36, Short Form-36.

In the multivariate analysis, AIC was used to determine the model of best fit. Models using both categorical (with three categories) and continuous CES-D were analysed. CES-D was removed from both of the final models, as it was not found to be a significant predictor of all-cause mortality. However, age (hazard ratio 1.09, 95% CI 1.05 to 1.13; $p < 0.001$) and perceived social support (hazard ratio 0.70, 95% CI 0.54 to 0.90; $p = 0.006$) were significant independent predictors. Using CES-D as a continuous or categorical variable (with three categories) did not affect the result. However, when the CES-D score was divided into two categories (not depressed 0–26, depressed ≥ 27) depression was associated with all-cause mortality in the unadjusted model (Figure 25) and multivariate model (hazard ratio 2.54, 95% CI 1.03 to 6.28; $p = 0.043$). Other

predictors in this model included age (hazard ratio 1.10, 95% CI 1.06 to 1.15; $p < 0.001$) and perceived social support (hazard ratio 0.68, 95% CI 0.50 to 0.94; $p = 0.019$).

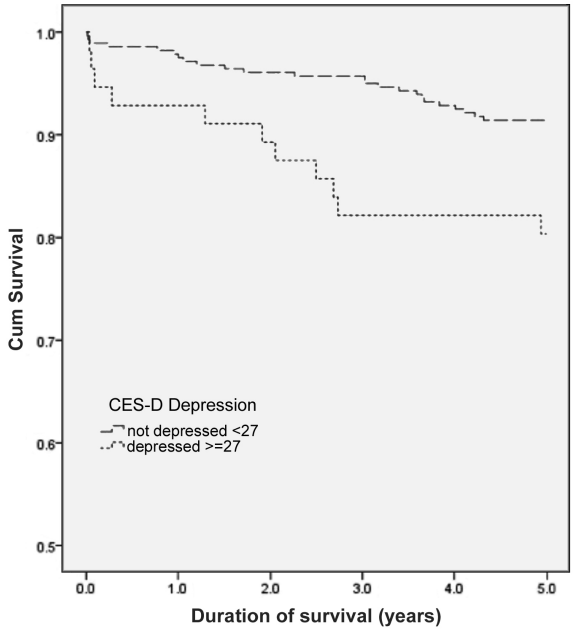

Figure 25. Proportion of patients surviving during 5-year follow-up by presence of depression. Kaplan-Meier survival curves are shown for patients with and without depression during the initial hospitalisation for AMI. There was a significant difference in survival between the two groups.

Cardiac Mortality

Table 10 summarises the characteristics of those experiencing a cardiac cause of death within 5 years of hospital admission for AMI. Compared with the survivors/fatalities from non-cardiac causes, patients who died of a cardiac cause were older, had more risk factors and were more likely to have a prior cardiac condition. They were also more depressed and had a poorer quality of life at the time of study recruitment (Table 10).

When cardiac death was analysed in AMI patients, univariate analyses showed that age, SF-36 physical summary score, perceived social support, prior emotional problem, prior high blood pressure/high cholesterol, prior diabetes, HADS anxiety score, prior cardiac condition/procedure, categorical CES-D (with three categories) and CES-D ≥ 27 were potential predictors of cardiac mortality in AMI patients (Table 10).

Table 10

Univariate Baseline Characteristics of Acute Myocardial Infarction Patients Who Died From Non-Cardiac Causes or Survived to 5 Years and Those Who Died From Cardiac Causes

Characteristic	**Survivors/Fatalities From Non-Cardiac Causes (*n* = 315)**	**Fatalities (*n* = 22)**	***p*-value**
Demographics			
Age, years	58 ± 12	70 ± 9	<0.001
Risk factors			
Prior high blood pressure/high cholesterol	149 (59.6%)	14 (87.5%)	0.03
Prior diabetes	43 (17.8%)	5 (33.3%)	0.14
Prior cardiac condition/procedure	108 (43.9%)	14 (77.8%)	0.01
Health/psychological indices			
SF-36 physical summary score	39 ± 10	33 ± 7	0.01
PSSS perceived social support	5.8 ± 1.2	5.3 ± 1.2	0.12
CES-D depression			0.02
Not depressed	192 (61.1%)	12 (54.5%)	
Mildly depressed	74 (23.6%)	2 (9.1%)	
Moderately to severely depressed	48 (15.3%)	8 (36.4%)	
CES-D depression (≥ 27)			0.01
Not depressed	266 (84.7%)	14 (63.6%)	
Depressed	48 (15.3%)	8 (36.4%)	
HADS anxiety	131 (41.6%)	13 (59.1%)	0.11
Prior emotional problem	57 (21.8%)	7 (36.8%)	0.13

Values expressed as number (per cent) or mean ± *SD*.

Values may not add up to the total owing to missing cases.

CES-D, Center for Epidemiologic Studies Depression scale; HADS, Hospital Anxiety and Depression Scale; PSSS, Perceived Social Support Scale; SF-36, Short Form-36.

However, in the multivariate model, depression was not significantly associated with 5-year cardiac mortality. Other predictors of increased mortality included age (hazard ratio 1.10, 95% CI 1.05 to 1.15; $p < 0.001$) and perceived social support (hazard ratio 0.67, 95% CI 0.49 to 0.93; $p = 0.016$). Results did not change when CES-D was divided into two categories: not depressed 0–26 and depressed ≥ 27.

Discussion

The major finding of this study was that moderate to severe depression (defined as CES-D ≥ 27) predicted all-cause but not cardiac 5-year mortality in AMI patients. However, when the cut-off for depression was lowered (i.e. CES-D ≥ 16), that is, when patients with milder depression were also included in the analyses, depression was not found to be predictive of either all-cause or cardiac mortality. We did not find that depression was associated with either all-cause or cardiac mortality when CES-D was analysed as a continuous variable. This may indicate that the relationship between mortality and depression severity is not linear and that the association only becomes evident when the severity reaches a threshold level (e.g. CES-D ≥ 27), consistent with major depression. The findings of this study are similar to others in reporting an association between depression and long-term mortality (Carney et al., 2008; Lesperance et al., 2002; Pfiffner and Hoffmann, 2004; Welin et al., 2000), while different from those who failed to find an association (Dickens et al., 2007; Parakh et al., 2008).

Previous Studies of Depression and Long-Term Mortality in AMI Patients

The population studied was similar with respect to depression prevalence (CES-D ≥ 16) to that of Drago et al.'s study (2007) (Beck Depression Inventory (BDI) ≥ 10). The prevalence of moderately to severely depressed AMI patients in our study was also similar to that of the major depressive disorder (MDD) prevalence in Drago et al.'s study (2007). However, they reported an increased risk of mortality in patients with MDD compared with those who had mild to moderate depression, as assessed by the BDI (Drago et al., 2007). This suggests a direct correlation between the severity of depression and its influence on prognosis. Similarly, Carney et al. (2008) reported that both minor and major depression were predictive of 5-year all-cause mortality in AMI patients; however, the hazard was higher for major depression than for minor depression. It may be that the CES-D scale we used to measure depression included less severely depressed patients in its mild depression category than the BDI used by Drago et al. (2007) and Carney et al. (2008). This may explain our finding that CES-D ≥ 16 did not predict mortality.

Our finding that perceived social support is associated with all-cause and cardiac mortality is consistent with others who have found that social isolation is associated

with a worse prognosis and mortality after MI (Welin et al., 2000). Furthermore, Pfiffner and Hoffmann (2004) found that the lack of a partner predicted mortality. The mechanisms underlying this association have not been well explained. It may be that people lacking social support are less capable of controlling their cardiovascular risk factors or they may respond later to premonitory symptoms (Welin et al., 2000). Although perceived social support was an independent predictor of mortality in AMI patients, this does not preclude there being a relationship between perceived social support and depression.

Why moderate to severe depression was related to all-cause and not cardiac-specific mortality in AMI patients is unclear from our study. In part it may be related to an insufficient sample size, thus requiring a larger cohort for the more specific cardiac mortality endpoint. In our study, similar to others (Dickens et al., 2007; Parakh et al., 2008; Pfiffner and Hoffmann, 2004; Welin et al., 2000), cigarette smoking status, BMI, family history of heart disease, prior high blood pressure/high cholesterol or diabetes were not predictors of all-cause or cardiac mortality in AMI patients. However, psychosocial factors have been reported to be predictive of the development and prognosis of cardiovascular disease (Bunker et al., 2003; Everson-Rose and Lewis, 2005).

Discrepancies between the findings of the present study and other studies (Carney et al., 2008; Lesperance et al., 2002; Pfiffner and Hoffmann, 2004; Welin et al., 2000) may be related to differences in the management of the AMI patient populations, which have occurred over the last few decades. The 5-year death rates in our study were lower than in earlier studies examining the impact of depression on mortality in MI patients (Carney et al., 2008; Lesperance et al., 2002), which may possibly be due to the greater efficacy of contemporary therapies for coronary heart disease (Lamy et al., 2011). Exposure to newer therapies may have modified the impact of depression on long-term mortality. The IDACC cohort was recruited from 2000 to 2002, and subsequently exposed to newer, more effective cardiac interventions, compared with earlier cohorts where depression emerged more clearly as a predictor of mortality. Of note, no association between depression and mortality was found in Parakh et al.'s recent study (2008). However, their study (Parakh et al., 2008) analysed a higher risk population in terms of co-morbidities than the cohort we examined.

Study Limitations

This study had several limitations. A baseline self-rated measure of depression was used in this study, and patients did not undergo diagnostic interviews by clinicians. Information on whether the depressed patients in hospital were still depressed at the time of their death or up to 5 years was also not available. Length of stay in the index hospital was used as a proxy for severity of AMI, as severity risk factors were not available, and long-term antidepressant medication usage was not collected. Information relating to the use of antipsychotic drugs, multiple medical comorbidities and level of physical activity was also not collected. Despite these limitations, data analysed in this report came from a multicentre study with a large patient population, where patients were exposed to more recent therapeutic advances. The analyses were also broken down into all-cause and cardiac mortality, while many studies are limited to one or the other (Carney et al., 2008; Dickens et al., 2007; Drago et al., 2007; Lesperance et al., 2002; Parakh et al., 2008).

The present findings highlight the complexity of the association between depression and long-term mortality after AMI. Nonetheless, we found an association between moderate to severe depression (measured by self-report during hospital admission for AMI) and all-cause mortality over the subsequent 5-year period in a cohort of patients exposed to contemporary cardiac care. This finding may have implications for the routine use of screening depression in patients admitted to hospital for AMI. Future research designed to establish causal relationships by analysing longitudinal data combining repeated measurements of depression and pathophysiological mechanisms would be beneficial (Lesperance et al., 2002).

Funding

AW was funded by a Queen Elizabeth Hospital Post Graduate Scholarship.

Declaration of Interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

Inclusion of Acute Coronary Syndrome

The study "Depression and 5-year mortality in patients with acute myocardial infarction: Analysis of the IDACC database'" was originally produced with the inclusion of an ACS group, as well as an AMI group. However, at completion of the manuscript it was decided to exclude the ACS analysis from the submitted manuscript, as the AMI group was a more homogenous and specific population than the heterogeneous ACS. The additional unpublished results of the IDACC follow-up are presented.

A further analysis of this study included patients from IDACC with the more broadly defined ACS. An ACS was defined as a hospital admission diagnosis of either UA and/or AMI.

Method

Participants

In the present prospectively-designed, long-term, follow-up study, there were 1116 ACS patients (337 AMI and 779 UA) aged between 23 and 84; of whom 762 (68.3%) were male. Depression (CES-D ≥ 16) was evident in 483 patients (43.5%) (mild depression in 271 (24.4%); moderate to severe depression in 212 (19.1%) patients), while 628 (56.5%) were not depressed by CES-D criteria.

Results

Vital status was determined for all patients at 5 years. Follow-up of the 1116 ACS patients at 5 years found 152 (13.6%) all-cause deaths and 78 (7.0%) cardiac deaths.

All-Cause Mortality

In the univariate analyses for all-cause mortality in ACS patients, both the continuous and categorical CES-D (with 3 categories) variables were potential predictors of all-cause mortality at 5 years. Other significant predictors were age, body mass index (BMI; continuous and categorical), length of stay in index hospital, SF-36 physical summary score, previous diagnosis of diabetes, cigarette smoking status, previous cardiac condition/procedure, persistent depression, CES-D ≥ 16 and CES-D ≥ 27.

In the multivariate analysis, Akaike's Information Criterion (AIC) was used to determine the model of best fit. Models using both categorical and continuous CES-D were analysed. CES-D was removed from both of the final models as it was not found to be a significant predictor of all-cause mortality. However, age (hazard ratio 1.08, 95% CI 1.06 to 1.10, $p < 0.001$), SF-36 physical summary score (hazard ratio 0.95, 95% CI 0.93 to 0.97, $p < 0.001$) and cigarette smoking status ($p = 0.002$); never smoked (reference category); currently smoking (hazard ratio 2.54, 95% CI 1.31 to 4.92, $p = 0.006$); ex smoker (hazard ratio 2.22, 95% CI 1.37 to 3.59, $p = 0.001$) were significant

independent predictors in the multivariate model. Using CES-D as a continuous or categorical variable did not affect the result. Similarly, when the CES-D score was divided into variables with two categories (not depressed 0-15, depressed ≥ 16, or not depressed 0-26, depressed ≥ 27), results did not change.

Cardiac Mortality

When cardiac death was analysed in the ACS cohort, univariate analyses showed that age, BMI (continuous and categorical), SF-36 physical summary score, previous diagnosis of diabetes, cigarette smoking status, previous cardiac condition/procedure, categorical CES-D (with 3 categories) and CES-D ≥ 27 were significant potential predictors in ACS patients.

However, in the multivariate model, depression was not significantly associated with 5-year cardiac mortality. Age (hazard ratio 1.05, 95% CI 1.02 to 1.08, $p < 0.001$), SF-36 physical summary score (hazard ratio 0.96, 95% CI 0.93 to 0.98, $p < 0.001$), cigarette smoking status ($p = 0.043$); never smoked (reference category); current smoker (hazard ratio 2.42, 95% CI 0.94 to 6.25, $p = 0.068$); ex smoker (hazard ratio 2.22, 95% CI 1.11 to 4.43, $p = 0.024$) and previous cardiac condition/procedure ($p = 0.032$); no (reference category); yes (hazard ratio 3.62, 95% CI 1.28 to 10.23, $p = 0.015$) were significant independent predictors of cardiac mortality in ACS patients. Results did not change when the CES-D score was divided into 2 categories: not depressed 0-26, depressed ≥ 27.

Discussion

In considering the broader ACS cohort (i.e. UA and AMI), depression was found to be a univariate predictor of 5-year all-cause and cardiac mortality, but not an independent predictor for either of these endpoints in multivariate analyses. This suggests that for this group, other factors in the model explained the variation in survival time better than depression.

Previous Studies of Depression and Long-Term Mortality in ACS Patients

Few studies that have examined the relationship between depression at the time of diagnosis of ACS and mortality ≥ 5 years. Although an association between depression and 5-year mortality in ACS patients was not found in this study, Grace and

colleagues (2005) found that depressive symptomatology (defined by BDI ≥ 10) during hospitalisation was a significant predictor of all-cause mortality at 5 years (Grace et al., 2005). The discrepancy between these findings may reflect the differences in ACS cohorts. In this study, 70% of the ACS population consisted of UA patients, compared to 52% in Grace and colleagues' study. Furthermore, the diagnosis of UA and AMI in the IDACC study was made on the basis of clinical presentation, ECG findings and the serial cardiac enzyme findings (serum creatine kinase) and not troponin assays, which may have influenced the categorisation of patients. The less specific and sensitive creatine kinase sometimes failed to detect small myocardial infarcts or incorrectly classify them as UA. AMI has since been redefined (Alpert et al., 2000; The Joint European Society of Cardiology/American College of Cardiology Committee, 2000), and based on troponin levels, which has increased the number of myocardial infarcts identified.

Of note, Vaccarino and colleagues (2009) recently reported evidence for a shared genetic pathway between depression and MVD, indicating that common pathophysiological processes may link depression and early atherosclerosis. Since depression was found to be a predictor in AMI patients but and not in the ACS group (which had over two thirds UA patients), it is possible that the pathophysiological processes of depressed MI patients leads to a greater risk of mortality compared to those with UA.

CHAPTER SIX: STUDY 3

CHAPTER SIX
STUDY 3

Due to word limit constraints, the published manuscript "The effect of mindfulness on heart rate variability in mental health outpatients: A pilot study" (presented in this chapter; abbreviated to 'HRV study') provided only a brief explanation of the design and implementation of the study. Accordingly, this section introduces the protocol utilised in the HRV study in more detail.

1. STUDY DESIGN

1.1. Design

The effect of MBCT on HRV was examined in an 8-week pilot study. Participants were tested three times 8 weeks apart (twice before MBCT and once after) in an attempt to limit any change in outcome measures due to chance or time.

A meeting was first arranged with the treating psychiatrist at the Centre for Treatment of Anxiety and Depression (CTAD), a public mental health outpatient clinic in Adelaide, South Australia, to discuss the study design, methodology and recruitment. The study protocol received approval from the Central Northern Adelaide Health Service Ethics of Human Research Ethics Committee.

Given the nature of the sample required for this study, the effort required of participants, and the lack of any funding incentives for participation, recruitment to the study was difficult. Initially, only patients meeting DSM-IV Axis I Major Depressive Episode (APA, 1994) were targeted. However, during the course of the study, recruitment was slower and more difficult than expected. Therefore, study criteria were extended to include participants meeting criteria for any Axis I mood or anxiety disorder. Nevertheless, recruitment to the study was prolonged and a long data-collection period was needed to achieve the minimum sample size for adequate study power.

Participants meeting criteria for a DSM-IV Axis I disorder (APA, 1994) were referred to CTAD by their treating psychologist, psychiatrist or general practitioner. A long waiting list exists for MBCT groups. Due to the specific timing and lengthy recruitment process, all patients on the waiting list had not been confirmed into the program before inviting them into the study. Patients on the waiting list for MBCT at CTAD were recruited between May 2010 to August 2012 and invited to participate in the study via an introductory cover letter (Appendix G) sent with a patient information sheet (Appendix H), consent form (Appendix I) and two questionnaires (Health/Lifestyle questionnaire; Appendix J, and the CES-D; Appendix C) and a reply paid envelope. The Health/Lifestyle questionnaire was specifically designed for this study, and included questions relating to conditions that affect the study or HRV. Thus, this questionnaire listed exclusion criteria. Participants were given the opportunity and time to discuss the study with family, friends, psychologist/psychiatrist/general practitioner, or to contact the study coordinator. If no consent form was returned within 1-2 weeks, a phone call was made to the potential participant, to determine if they would like to be involved.

If a patient consented, but did not satisfy the study criteria from the Health/Lifestyle questionnaire or criteria for attendance in MBCT, a letter was sent thanking them and explaining that they were no longer required to participate (Appendix K). Patients fulfilling the study criteria were contacted via a telephone call to arrange an appointment to attend TQEH, a public hospital in Adelaide, South Australia. Participants were met and greeted by the study coordinator and taken to the testing room, where they underwent physical measurements and completed psychometric questionnaires and electrocardiographic monitoring. A letter was sent to each participant's general practitioner explaining that they had volunteered in a study of HRV (Appendix L).

A follow-up appointment was made by phone or mobile text message for a second HRV appointment 8 weeks after the first appointment. Participants then underwent 8 weeks of MBCT and attended a third HRV appointment immediately post-treatment. A reminder phone call or mobile text message was made several days prior to each appointment. At follow-up appointments, the physical measurements,

questionnaires (with the addition of the Health/Lifestyle Questionnaire and CES-D), and electrocardiographic monitoring were repeated.

1.2. Testing Procedure

Heart Rate Variability Appointment

Participants were asked general questions about their mental health (Appendix M) and physical measurements (height, weight and waist circumference) were taken. Waist circumference was measured in accordance with Yakemchuk (2005). A tape measure was placed horizontally around the participant's waist at the narrowest part of the torso, with the tape measure parallel to the floor. For obese people, the waist was measured at the umbilicus. The measurement was taken at the end of a relaxed expiration (Yakemchuk, 2005). Questionnaires and electrocardiographic monitoring followed, during which HRV was determined.

Electrocardiographic Monitoring

Participants were required to abstain from substances known to affect HRV for a minimum of 4 hours before each appointment: alcohol, illicit substances, caffeine and nicotine. Although some research **(**Henry et al., 2010; Licht et al., 2010; Tucker et al., 1997; Volkers et al., 2004**)** suggests that antidepressant medication can affect HRV, participants were not prevented from taking their usual medications (i.e., they continued TAU) for ethical reasons and because of difficulty in recruitment.

12-Lead Resting Electrocardiogram

Participants were examined in a quiet room and were instructed to relax in the supine position while undergoing a one-off 12-lead resting ECG (performed at their first appointment only). The ECG recording was analysed by a cardiologist at TQEH. In the case of an abnormal ECG, the cardiologist met with the participant on the third (and last) appointment to explain their ECG, and the participant was given a copy of their ECG. In the case of a normal ECG, following completion of the study, a copy of the ECG and a letter explaining the result was sent to the participant (Appendix N).

Holter Monitor Electrocardiogram

Participants either removed or raised their shirt to enable electrocardiographic monitoring and determine HRV via a Holter monitor. An area of skin where an electrode was placed was sandpapered for proper adhesion, and 7 electrodes were attached to the participant's chest. Participants were rested for 5 minutes to stabilise HR (and exclude a potential stress effect) prior to 20 minutes of electrocardiographic testing in the supine position. Recording was stopped and participants sat up to undergo the Stroop Color and Word Test (SCWT; which was used as a stressor). The administration process of the Stroop is described in Section 2.1.3 of this chapter. After completion of the SCWT, a second Holter recording occurred immediately for 20 minutes, in the supine position. This ECG recording aimed to examine any stress effect of the SCWT on HRV. To avoid any effect of diurnal variation on HRV, ECG monitoring was repeated at a similar time for each appointment, for each participant.

At the end of the second Holter recording, participants once again removed or raised their shirt, the electrodes were removed and the patient disconnected from the Holter monitor. Participants were then requested to complete the SF-36, thanked for their time and advised that they would be required for further testing in 8 weeks.

1.3. Sample: Inclusion and Exclusion

Inclusion and exclusion occurred in two parts. Participants on the MBCT waiting list were first required to meet the study criteria listed below, and secondly, the CTAD criteria for MBCT treatment.

Participants were ineligible to participate in this study if they had conditions that might affect HRV or their ability to complete questionnaires, such as:

- Cardiac conditions (e.g., heart failure, atrial fibrillation/flutter), irregular heartbeats (frequent ectopic beats, ventricular bigeminy) or a pacemaker
- Respiratory and neurological disorders
- Pregnancy or lactation
- Caffeine, alcohol or illicit substance abuse
- Colour blindness or difficulties in English speaking, reading or writing

Other factors influencing HRV (previously discussed in Chapter One, Section 8.5), such as age and gender, were also considered as possible exclusion criteria. However, due to the expected difficulty in recruiting, it was decided that limiting these factors would further decrease sample size and prolong recruitment. An initial measurement of baseline blood pressure for each participant for exclusion purposes was planned. However, due to the lengthy testing time of approximately 1½ - 2 hours it was believed that a longer period may deter participation, and therefore this measure was not utilised.

During the course of the study, any self-reported changes in medication, caffeine alcohol or illicit substance usage were discussed with the CTAD psychiatrist and TQEH cardiologist to determine whether that participant should then be excluded. The CTAD psychiatrist also confirmed a primary diagnosis adhering to DSM-IV Axis 1 criteria (mood or anxiety disorder) (APA, 1994).

Potential participants were also excluded from the study if they were diagnosed with a psychiatric condition rendering them ineligible for the CTAD MBCT program (such as a primary diagnosis of posttraumatic stress disorder). Participants met with the psychiatrist at CTAD a few weeks before MBCT commenced to determine suitability for the program (i.e., after their first HRV appointment in this study). Consequently two potential participants were found to be ineligible for the MBCT program after their first HRV appointment had occurred.

2. INSTRUMENTS

The HRV study utilised several psychometric instruments, including a generic HRQoL measure, a domain-specific depression measure and a cognitive questionnaire.

2.1. Instruments Utilised

2.1.1. Generic Measure

Short Form-36

The administration of the SF-36 (Appendix A) was previously described in Section 1.1.1 of Chapter Four.

2.1.2. Domain-Specific Measure

Center for Epidemiologic Studies Depression Scale

The administration of the CES-D (Appendix C) was previously described in Section 2.1.2 of Chapter Five.

2.1.3. Other Measure

Stroop Color and Word Test

The "Stroop effect" was first described in 1935 (Stroop, 1935). In order to further study executive functioning, the SCWT was developed. Subsequently, numerous versions of the test have been developed. A version of the test very similar to Stroop's original version, produced by the C.H. Stoelting Company, manufacturers of psychological laboratory equipment, was utilised in this study. Due to copyright protection, this test is not included in the appendices. The SCWT was designed to test cognitive flexibility, taking advantage of literate adults' ability to read words more quickly and automatically than they can name colours, and of the interference effect of printing colour names in different colours (Golden & Freshwater, 1998).

The test has an alternative use as a psychological or cognitive stressor task (Renaud & Blondin, 1997). In this HRV study, it was used only as a cognitive stressor task. The questionnaire takes approximately 5 minutes to administer and consists of 3 pages. Each page has 100 items, presented in 5 columns of 20 items. Page 1, the Word page, consists of the words "red", "green" and "blue" arranged randomly and printed in

black ink. Page 2, the Color page, consists of 100 items, all written as XXXX, printed in either red, green or blue ink. The last page, the Color-Word page consists of the words from the Word page printed in the colours from the Color page. Item 1 from the Word page is printed in the colour of item 1 from the colour page to produce item 1 on the Color-Word page, and so on. In no case do the word and the colour in which it is printed match. The participant has 45 seconds per page to read down the columns aloud and as quickly as possible. If all columns are completed before the instructor says "stop" then the participant returns to the first column and continues reading. If a mistake is made, the instructor says "No" and the participant corrects the error and continues reading.

The SCWT yields three basic scores: the raw Word score is the number of items completed on the Word page, the raw Color score is the number of items completed on the Color page and the raw Color-Word score is the number of items completed on the Color-Word page. Errors are not counted, although they will result in a lower overall score because the participant is made to repeat the item until correct. The *t*-scores and the interference Color-Word score are derived by adjusting the raw scores by age and education (tables available in the SCWT Manual; Golden & Freshwater, 1998). Test-retest reliability of SCWT scores has been found to be highly consistent across different versions of the test (Golden, 1975).

STATEMENT OF AUTHORSHIP

Title of Paper	Investigating the effect of mindfulness training on heart rate variability in mental health outpatients: A pilot study
Publication Status	Published
Publication Details	Wheeler, A., Denson, L., Neil, C., Tucker, G., Kenny, M., Beltrame, J. F., Schrader, G., & Proeve, M. (2014). Investigating the effect of mindfulness training on heart rate variability in mental health outpatients: A pilot study. *Behaviour Change, 31*(3), 175-188. doi: 10.1017/bec.2014.14

Author Contributions

By signing the Statement of Authorship, each author certifies that their stated contribution to the publication is accurate and that permission is granted for the publication to be included in the cardidate's thesis.

Name of Principal Author (Candidate)	Alexis Wheeler		
Contribution to the Paper	Study conception and design, participant recruitment and follow-up, data collection, statistical analysis, management and interpretation of the data, manuscript preparation, critical review and revision of the manuscript		
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STUDY 3

Investigating the Effect of Mindfulness Training on Heart Rate Variability in Mental Health Outpatients: A Pilot Study

This results chapter is reproduced in the exact form as it appears in the manuscript:

Wheeler, A., Denson, L., Neil, C., Tucker, G., Kenny, M., Beltrame, J. F., Schrader, G., & Proeve, M. (2014). Investigating the effect of mindfulness training on heart rate variability in mental health outpatients: A pilot study. *Behaviour Change*, *31*(3), 175-188. doi: 10.1017/bec.2014.14

In keeping with the style of this thesis, the tables and figures have been re-numbered, the references incorporated into the thesis master reference list, and the manuscript repaginated.

Depression is associated with increased cardiac morbidity and mortality in people with and without cardiac risk factors, and this relationship is, in part, mediated by heart rate variability (HRV). Increased heart rate and reduced HRV are common in depressed patients, which may explain their higher cardiac risk. This pilot study investigated whether mindfulness-based cognitive therapy (MBCT) promoted objective changes in (1) HRV, and (2) depressive symptoms and quality of life, in mental health outpatients. Twenty-seven adults meeting criteria for DSM-IV Axis I disorders completed an 8-week MBCT program. Data were collected on three occasions, 8 weeks apart; twice before and once after MBCT. Participants completed the Short Form-36 and the Center for Epidemiological Studies Depression Scale (CES-D) at each test period. Heart rate and HRV were measured during electrocardiographic monitoring before and after a cognitive stressor. At baseline, 78% of participants met criteria for depression (CES-D ≥16). Multivariate analyses revealed a significant treatment effect for SF-36 physical summary score and depression (as a dichotomous variable), but not for HRV. This pilot study highlights the immediate psychological and health benefits of MBCT. Low power may have influenced the lack of a finding of an association between HRV and MBCT. How- ever, the feasibility of the study design has been established, and supports the need for larger and longer-term studies of the potential physiological benefits of MBCT for cardiac health.

Keywords: mindfulness, heart rate variability, depression, quality of life, anxiety, psychiatric

Over the years, autonomic dysfunctions associated with psychiatric disorders have attracted increasing interest (Lehofer et al., 1997). Heart rate variability (HRV), one of the most promising markers for the measurement of autonomic function (Task Force, 1996), refers to beat-to-beat fluctuations in heart rate. Used to assess cardiac autonomic function, HRV is related to outcomes following cardiac events (Kleiger, Miller, Bigger & Moss, 1987; La Rovere, Bigger, Marcus, Mortara, & Schwartz, 1998). Changes in HRV pattern can be an indicator of compromised health (Pumprla, Howorka, Groves, Chester, & Nolan, 2002). High HRV indicates good adaptability, implying a healthy individual with well-functioning autonomic control (Pumprla et al., 2002). Low HRV reflects excessive sympathetic and/or inadequate parasympathetic tone (Task Force, 1996) and an abnormal and insufficient adaptability of the ANS (Pumprla et al., 2002).

HRV can be evaluated using two approaches: time domain or frequency domain. Time domain methods use simple statistical analyses (means and variance) to measure the amount of variability present in a prespecified time period in a continuous ECG, whereas frequency domain methods analyse the presence of underlying rhythms (Task Force, 1996). In the frequency approach, periodic oscillations of heart rate at various frequencies are measured in order to determine the overall variance in heart rate (Task Force, 1996).

Increased cardiac morbidity and mortality have been associated with depression among persons with and without cardiac risk factors (Penninx et al., 2001), and this relationship is, in part, mediated by reductions in HRV (Carney et al., 2005; Grippo & Johnson, 2002; Thayer & Lane, 2007). Investigation of the relationship between HRV and depression has generally been conducted in cardiac patient samples (Carney et al., 2005; Carney et al., 1995; Drago et al., 2007); however, there is some evidence that depressed patients exhibit decreased HRV (Agelink, Boz, Ullrich, & Andrich, 2002; Nahshoni et al., 2004; Udupa et al., 2007).

Mindfulness-based cognitive therapy (MBCT), a relatively new therapy initially designed for the treatment of relapse in depression, has also been applied to the treatment of active depression and anxiety (Evans et al., 2008; Kenny & Williams, 2007; Teasdale et al., 2000; van Aalderen et al., 2012). MBCT is designed to improve

awareness and non-reactive acceptance of negative thoughts and feelings (Teasdale et al., 2000): teaching participants to disengage from habitual and repetitive negative thinking patterns (e.g., rumination and worry) that are thought to increase vulnerability to depression (Teasdale et al., 2000), and instead purposefully attend to the present moment with friendly interest and in a non-judgmental manner (Baer, 2003; Kabat-Zinn, 1990). It is hypothesised that this reduces rumination and promotes more adaptive responding.

Most evaluations of MBCT have focused on mental health symptoms, and whether they decrease following MBCT programs. MBCT is demonstrably efficacious in reducing depressive symptoms in people with current and recurrent depression (Barnhofer et al., 2009; Finucane & Mercer, 2006; Kenny & Williams, 2007; Kingston, Dooley, Bates, Lawlor, & Malone, 2007; van Aalderen et al., 2012) and in preventing relapses (Godfrin & van Herringen, 2010; Kuyken et al., 2008; Ma & Teasdale, 2004; Teasdale et al., 2000). Furthermore, MBCT improves quality of life (QoL) in both depressed clinical (Godfrin & van Herringen, 2010; Kuyken et al., 2008), non-clinical (Kaviani, Hatami, & Shafiabadi, 2009; Kaviani, Javaheri, & Hatami, 2011), and sub-clinical populations (Kaviani, Hatami, & Javaheri, 2012) and among patients with both medical and mental health problems (Roth & Robbins, 2004).

Although several types of meditation have been shown to be associated with HRV improvements (Phongsuphap, Pongsupap, Chandanamattha, & Lursinap, 2008; Telles, Mohapatra, & Naveen, 2005; Telles et al., 2013; Wu & Lo, 2008), few researchers have explored relationships between MBCT and HRV (Delizonna, Williams, & Langer, 2009; Ditto, Erlache, & Goldman, 2006; Peressutti, Martin-Gonzalez, & Garcia-Manso, 2012; Peressutti, Martin-Gonzalez, Garcia-Manso, & Mesa, 2010). These studies emphasised concentrative techniques and involved intensive practice, suggesting that the HRV changes resulting from MBCT-associated practices supports the premise that mindfulness may improve the effectiveness of self-regulatory mechanisms such as attention and emotion processing (Peressutti et al., 2012), and control over heart rate (Delizonna et al., 2009). Peressutti and colleagues (2010) found that the HRV changes were coherent with years of practice from novice to experienced meditators, and inferred that changes in breathing pattern were associated with the quality and focus of attention. Similarly, Ditto and colleagues (2006) analysed the

breathing cycle in body scan meditation (a technique used in MBCT) and demonstrated that respiratory sinus arrhythmia (an index of parasympathetic control) increased among meditating participants.

The present study aimed to pilot a method for examining the relationship between depression and HRV in mental health outpatients undergoing MBCT. Specifically, the study examined whether MBCT treatment over an 8-week period was associated with objective changes in (a) time and frequency domain HRV, and (b) depressive symptoms and quality of life.

Method

Design

Adults referred for MBCT with a current DSM-IV Axis I diagnosis and a previous history of anxiety and/or depression, were recruited between May 2010 and August 2012 at the Centre for Treatment of Anxiety and Depression (CTAD), a public mental health outpatient clinic in Adelaide, an Australian city. Participants underwent physical measurements, psychometric questionnaires, and electrocardiographic monitoring to determine HRV. The assessment was repeated twice before the commencement of the mindfulness program, and once after, with 8 weeks between each appointment. The three testing sessions occurred at a similar time of day for each participant, to avoid diurnal variations. The project received approval from the Central Northern Adelaide Health Service and the University of Adelaide Human Research Ethics Committees.

Electrocardiographic Monitoring

Participants rested for 5 minutes in a quiet room to stabilise heart rate (and exclude potential stress effects) prior to 20 minutes of electrocardiographic testing in the supine position. Following administration of the Stroop Color and Word Test (used as a stressor; Golden & Freshwater, 1998), participants undertook a second 20-minutes of ECG recording (including the 5 minutes of rest) to analyse any stress effect.

Participants

Participants were referred to CTAD for MBCT by their treating psychologist, psychiatrist or general practitioner, and were accepted into the study once a CTAD

psychiatrist confirmed a primary diagnosis adhering to DSM-IV Axis I criteria (APA, 1994) and satisfying the inclusion and exclusion criteria. Excluded from the study were people with cardiac, respiratory or neurological diagnoses, or an inability to complete psychometric measures (due to language difficulties or colour blindness). Pregnant or lactating women and substance abusers were also excluded. Finally, people were excluded if their psychiatric diagnosis rendered them ineligible for the MBCT program. Throughout the study, any reported changes in participants' medication, caffeine, alcohol or substance use were discussed with the CTAD psychiatrist and a cardiologist, in light of the exclusion criteria.

Participants were 27 volunteers (M age = 47, *SD* = 13, 63% female), with a primary diagnosis of either a mood (current or in remission) or anxiety disorder, and a range of comorbid conditions (Table 11). Participants gave written consent to participate in the study with full knowledge of the experimental nature of the research, and were instructed to abstain from alcohol, illicit substances, caffeine and nicotine for a minimum of 4 hours prior to testing.

Table 11

DSM-IV Diagnoses of Mental Health Outpatients

Primary Diagnosis (*n* = 27)	**Secondary Diagnosis (*n* = 27)**
Mood disorder (20)	
MDD (14)	No secondary diagnosis (8)
	GAD (4)
	Panic disorder (1)
	GAD and panic disorder (1)
Bipolar disorder (3)	No secondary diagnosis (2)
	Chronic depression and anxiety (1)
Dysthymia (3)	GAD (3)
Anxiety disorder (4)	
GAD (4)	No secondary diagnosis (1)
	Dysthymia (3)
No current disorder (3)	-
MDD in remission (3)	No secondary diagnosis (3)

Note: Expressed as diagnosis (number). GAD, generalised anxiety disorder; MDD, major depressive disorder.

Measures

Variables measured in this study included (a) patient demographics (age and gender), (b) physical measurements (weight, height, waist circumference and HRV) and (c) cardiac risk factors (body mass index, cigarette smoking status, alcohol and illicit substance usage, hypertension, hypercholesterolemia, diabetes mellitus, cardiac condition and prescription medication). Psychometric measures included the Short Form-36 version 1 (SF-36; Tucker, Adams, & Wilson, 2010; Ware & Sherbourne, 1992), Stroop Color and Word Test (Golden & Freshwater, 1998) and Center for Epidemiologic Studies Depression scale (CES-D; Radloff, 1977). Participants were classified according to standard CES-D threshold scores (Ensel, 1986; Zich, Attkisson, & Greenfield, 1990) as not depressed <16; mildly depressed 16–26 (indicative of minor depression); or moderately to severely depressed ≥27 (indicative of major depression; Cheok, Schrader, Banham, Marker, & Hordacre, 2003).

To determine HRV, power spectral analysis of the beat-to-beat time series of RR (commonly called normal-to-normal; NN) intervals was performed using the Holter LX Analysis program (NorthEast Monitoring, 2009). Three time domain measures were analysed: SDNN (standard deviation of NN intervals) as a marker of the overall magnitude of variability; RMSSD (square root of the mean squared difference of successive NNs), an estimate of short-term components of HRV; and HRV triangular index (the number of NN intervals divided by the maximum of the density distribution), an estimate of overall HRV. Two frequency bands associated with different physiological rhythms were analysed: low frequency band (LF: 0.04–0.15 Hz), which is determined by both parasympathetic and sympathetic activity; and high frequency band (HF: 0.15–0.4Hz), reflecting mainly respiratory sinus arrhythmia as an index of CVC. The time points of LF and HF were averaged to obtain the raw frequency domain score.

Statistical Analyses

Statistical analyses were performed using SPSS statistical software version 17 (SPSS, 2008) and Stata version 12 (StataCorp, 2011). In the univariate analyses, descriptive statistics were reported as means and standard deviations for continuous data and as percentages for categorical data. The primary endpoint (treatment effect) for HRV parameters and SF-36 physical summary score was analysed as panel data utilising a repeated measures model. The Hausman test indicated whether a fixed or

random effects model was preferred. Depression was analysed as a dichotomous variable (CES-D depressed/not depressed). The percentage of participants in each CES-D depression category remained the same at test times 1 and 2, providing only two outcomes for this variable. Therefore, a population-averaged estimate of the treatment effect was produced and analysed using logistic regression. Probabilities of $p < .05$ were considered significant. Effect sizes were calculated using Cohen's *d,* where a *d* value of 0.2 indicates a small effect, 0.5 a medium effect, and 0.8 a large effect (Cohen, 1988).

Power analysis using GPower software indicated that for an effect size of 0.25, *p* value of .05 and 80% power, this pilot study required a total sample size of 28. Importantly, this power analysis examined the chance of detecting an overall time effect in the repeated measures/logistic regression tests. However, this study was also testing for a treatment effect over and above the linear trend with time. Based on the collected data (with test times 1 and 2 averaged), this study had an effect size of 0.34 and 97% power to detect a time effect for the CES-D score, but at most, a 0.07 effect size and 11% power to detect a time effect for the HRV parameters in the analysis.

Results

Of the 96 people invited into the study, 33 accepted. Two participants withdrew before their first appointment, and during the course of the study another four were excluded, withdrawn or lost to follow-up, resulting in a final sample size of 27 (Figure 26).

The clinical and psychometric characteristics of study participants are summarised in Table 12. With CES-D scores of 16 or higher, the majority of participants were classified as depressed at baseline, but scores decreased over the three testing periods. The SF-36 mental and physical summary scores both increased from test time 1 to test time 3, suggesting improved QoL. More than half of the sample was taking prescription medication for their mental health disorders.

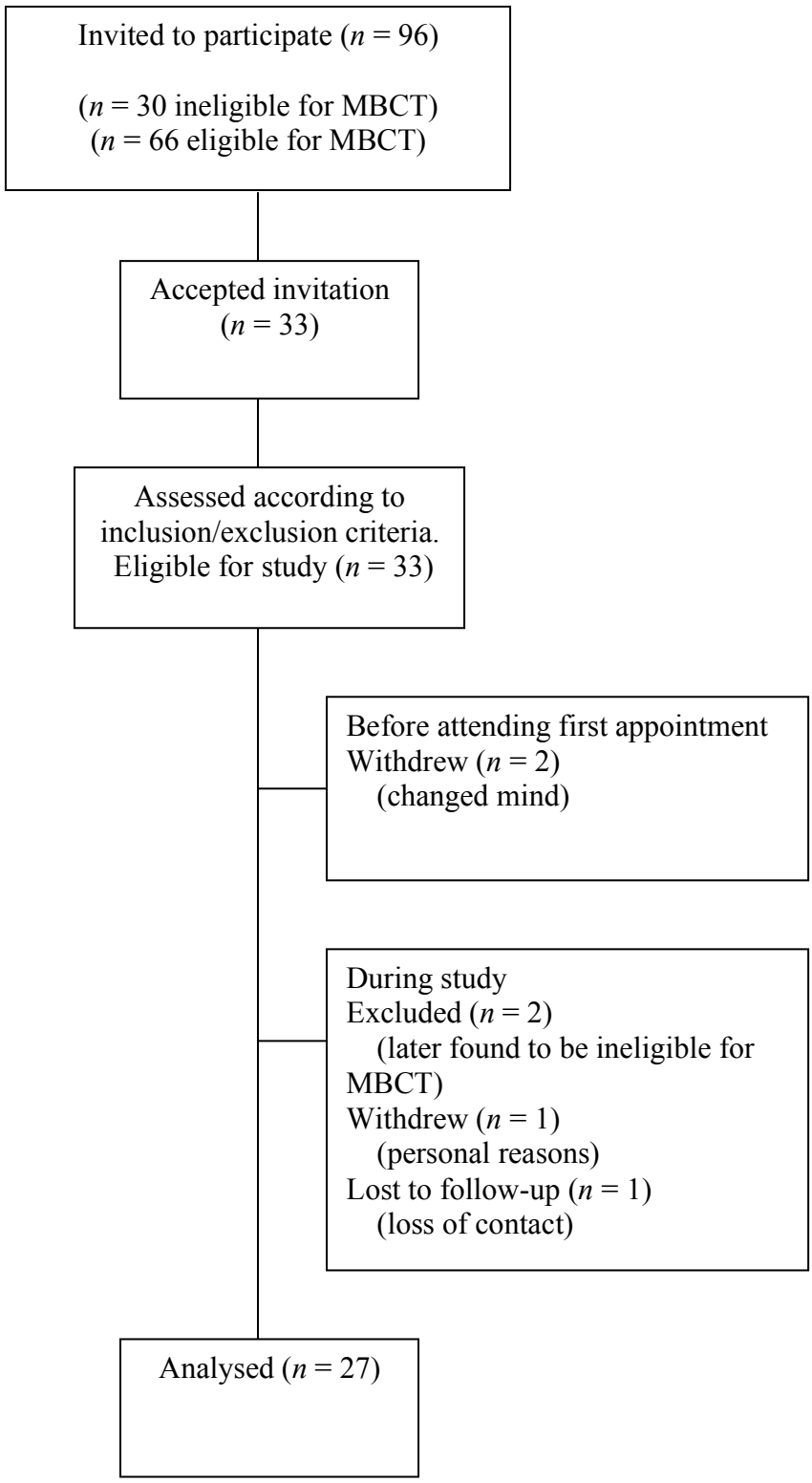

Figure 26. Recruitment flow diagram.

Table 12

Characteristics of Mental Health Outpatients for the Three Test Times

Characteristic	Time 1 (*n* = 27)	Time 2 (*n* = 27)	Time 3 (*n* = 27)
Demographics			
Age (years)	47 (13)		
Female gender	17 (63%)		
Risk factors			
BMI	28 (7)		
Underweight/normal	7 (26%)		
Overweight/obese	20 (74%)		
Waist circumference	101 (17)		
Palpitations	10 (37%)		
Hypercholesterolemia	6 (22%)		
Hypertension	6 (22%)		
Smoker	2 (7%)		
Medication			
Mental health medication	17 (63%)		
Antidepressants	14 (52%)		
Benzodiazepines	3 (11%)		
Antipsychotics	5 (19%)		
Health/psychological indices			
Undertaking other therapy	10 (37%)		
CES-D Depression	24 (13)	21 (11)	15 (11)
Not depressed	6 (22%)	6 (22%)	16 (59%)
Depressed	21 (78%)	21 (78%)	11 (41%)
Mildly depressed	10 (37%)	12 (45%)	6 (22%)
Moderately-severely depressed	11 (41%)	9 (33%)	5 (19%)
SF-36 physical summary score	39 (13)	39 (13)	45 (11)
SF-36 mental summary score	34 (13)	36 (13)	41 (13)
HRV parameters (before Stroop Test)			
Heart rate	70 (11)	71 (12)	70 (11)
SDNN	53.95 (23)	49.55 (27)	48.22 (21)
RMSSD	27.23 (13)	27.30 (17)	29.13 (15)
Triangular index	12.84 (5)	12.02 (6)	12.99 (9)
Low frequency	0.06 (0.06)	0.07 (0.09)	0.07 (0.08)
High frequency	0.03 (0.03)	0.03 (0.04)	0.03 (0.03)
HRV parameters (after Stroop Test)			
Heart rate	68 (10)	69 (11)	69 (10)
SDNN	60.04 (23)	62.58 (26)	62.81 (26)
RMSSD	28.31 (12)	33.71 (19)	31 (14)
Triangular index	13.32 (6)	13.94 (6)	13.76 (5)
Low frequency	0.08 (0.08)	0.08 (0.11)	0.08 (0.08)
High frequency	0.02 (0.02)	0.03 (0.03)	0.03 (0.03)

Note: Values expressed as number (per cent) or mean *(SD)*. CES-D, Center for Epidemiologic Studies Depression, RMSSD = root mean square of successive RR intervals, SF-36 = Short Form-36, SDNN = standard deviation of normal to normal RR interval. SDNN, RMSSD in ms; LF, HF in sec^2/Hz.

Multivariate analyses revealed significant treatment effects for SF-36 physical summary score (5.35, 95% CI 1.40–9.31, $p = .008$) and for depression as a dichotomous variable (0.20, 95% CI 0.05–0.74, $p = .016$). A linear effect (rather than treatment effect) was detected for depression as a continuous variable (Figure 27). Subgroup analyses were considered (those classified as moderately to severely depressed at baseline, and those primarily diagnosed with generalised anxiety disorder), but these groups were too small for meaningful analyses. No significant change was observed for any time or frequency domain parameter with or without the stressor test. Effect sizes for each parameter are shown in Table 13.

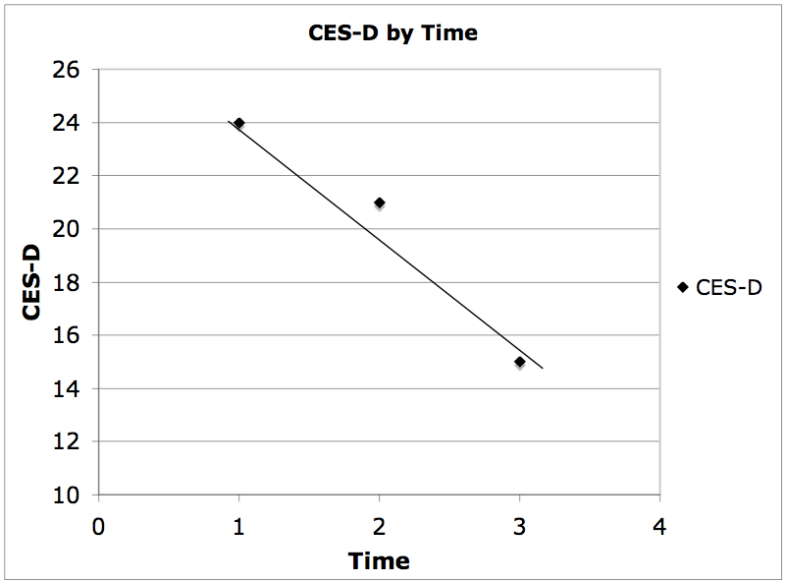

Figure 27. CES-D (as a continuous variable) by time. Mean CES-D scores are shown for each test occasion. There was a linear time effect on depression scores.

Table 13

Effect Sizes (Cohen's d)

Characteristic	Times 1-2	Times 1-3	Times 2-3
Health/psychological indices			
CES-D depression	0.30	0.78	0.52
SF-36 physical summary score	0.02	0.49	0.46
SF-36 mental summary score	0.16	0.53	0.37
HRV parameters (before Stroop Test)			
Heart rate	0.10	0.01	0.10
SDNN	0.18	0.26	0.06
RMSSD	0.004	0.13	0.12
Triangular index	0.15	0.02	0.08
Low frequency	0.08	0.07	0.01
High frequency	0.003	0.09	0.08
HRV parameters (after Stroop Test)			
Heart rate	0.03	0.01	0.02
SDNN	0.10	0.11	0.01
RMSSD	0.34	0.17	0.18
Triangular index	0.10	0.08	0.03
Low frequency	0.03	0.06	0.02
High frequency	0.19	0.18	0.01

Note: CES-D = Center for Epidemiologic Studies Depression, RMSSD = root mean square of successive RR intervals, SF-36 = Short Form-36, SDNN = standard deviation of normal to normal RR interval.

Discussion

This pilot study primarily aimed to examine whether group-based MBCT influenced HRV in mental health outpatients. Results showed no change in heart rate or in time and frequency HRV parameters with or without administration of the stressor (Stroop Color and Word Test). Nevertheless, MBCT was found to promote a significant improvement in health-related QoL as measured by the SF-36 physical summary score, and a reduction in self-reported depressive symptoms. Although underpowered to detect any difference in HRV, this exploratory pilot study provides a basis for future investigation into the relationship between HRV and MBCT.

When CES-D was analysed as a continuous variable, no treatment effect was evident. The majority of variation in the data was explained by a linear time effect (Figure 27). Depression scores decreased linearly from the first baseline test occasion to the post-treatment test occasion. However, when CES-D was analysed as a dichotomous

variable, a large difference in variation was found between the depressed and not depressed categories, resulting in a significant treatment effect. Given that the percentage of depressed patients (as classified by the CES-D) was stable across the 8 weeks for test times 1 and 2, and decreased by half after MBCT, CES-D as a categorical variable provided a clinically meaningful method of analysis. It is notable that during the course of this study some of the participants were receiving additional long-term psychotherapy (psychologist and/or psychiatrist). It is unlikely that this influenced the above findings, because participants were referred to the MBCT course due to a lack of or only partial response to their current therapy.

Validity of Study Findings

Consistent with the established literature (Barnhofer et al., 2009; Godfrin & van Herringen, 2010; Kenny & Williams, 2007; Roth & Robbins, 2004; van Aalderen et al., 2012), our findings provide further evidence for the effectiveness of MBCT for depressive symptoms and QoL. Furthermore, our study showed benefits for a heterogeneous sample of mental health outpatients, similar to those referred to many community mental health providers, treated in mixed rather than diagnosis-specific group sessions. However, given the study's limitations, results must be interpreted with caution. The design was quasi-experimental and did not include a control group, comparison therapy, or any form of randomisation.

Previous Studies of Depression and HRV

This study is believed to be one of the first to investigate the effect of MBCT on HRV. As we noted in the introduction, previous studies examining mindfulness and HRV differed from the MBCT program undertaken in this study in the emphasis of concentrative techniques or intensiveness of practice (Delizonna et al., 2009; Peressutti et al., 2012; Peressutti et al., 2010). Results are therefore not easily comparable. However, Ditto and colleagues (2006) examined the short-term autonomic and cardiovascular effects of one MBCT technique, body scan meditation. They reported an increase in respiratory sinus arrhythmia (an index of parasympathetic control) among meditating participants.

We did not find a significant change in either time or frequency domain HRV parameters with or without administration of the stressor test, but our findings have a

number of potential explanations. First, in terms of final sample size, the study was underpowered to detect either a time or treatment effect in HRV. Second, Agelink and colleagues (2002) found that only severely depressed patients showed reduced HRV and significantly lower modulation of cardiac vagal activity compared to non-depressed controls. In our study, 41% of participants were moderately to severely depressed at baseline and statistically this subgroup was too small for meaningful analyses. In addition, we attempted to compare the HRV parameters in our study with those in other studies (Udupa et al., 2007; Udupa et al., 2011), but the large variability in scores between studies prevented meaningful interpretation. Third, some studies analysing depression and HRV selectively recruited drug-naıve participants (Chang et al., 2012; Lehofer et al., 1997; Moser et al., 1998; Udupa et al., 2007), whereas 63% of our participants were using psychiatric medications. Although consistent with treatment as usual, this may have influenced findings. Selective serotonin reuptake inhibitors (SSRIs) have been reported to either increase (Tucker et al., 1997) or decrease (Bar et al., 2004; Volkers et al., 2004) HRV, and serotonergic and noradrenaline reuptake inhibitors (SNRIs; Licht, de Geus, van Dyck, & Penninx, 2010) and mood stabilisers (Henry, Minassian, Paulus, Geyer, & Perry, 2010) also influence HRV. Moreover, short duration cardiac recordings have shown a small increase in HRV, while longer recordings contradicted this result (van Zyl, Hasegawa, & Nagata, 2008). Finally, several studies of depression and HRV recruited only patients with major depressive disorder (Chang et al., 2012; Udupa et al., 2007). Our study was naturalistic and our sample more heterogeneous. Anxiety is known to affect HRV (Friedman, 2007; Gorman & Sloan, 2000); indeed, Watkins and colleagues (1999) argued for stronger links between anxiety and HRV than depression and HRV. Comorbid anxiety may, therefore, have been a significant confound in our exploration of HRV in mental health outpatients.

It has been suggested that mindfulness is not a self-relaxation technique (Baer, 2003), but rather a form of mental training that facilitates more adaptive responses to stress (Bishop, 2002). Accordingly, it is possible that meditation emphasising concentrative techniques may have a greater impact on HRV. However, it is also possible that the absence of an HRV effect in our study reflects the need for longer-term mindfulness practice and experience, as found in studies of experienced meditators (Peressutti et al., 2012; Phongsuphap et al., 2008). Although our participants' mood,

attitudes and QoL may have changed during the 8-week MBCT program, longer-term follow-up studies of MBCT are essential to document any physiological changes. It should also be noted that HRV was not analysed using non-linear techniques, which may be more sensitive to depression effects (Kemp et al., 2010).

Conclusion

This pilot establishes the feasibility of the study design and highlights the psychological and health-related QoL benefits of MBCT in a naturalistic outpatient sample. Despite the absence of measurable improvements in HRV, the study represents an important extension to knowledge of the population and methodology required in order to examine this relationship. Future studies may, by eliminating confounders, permit more reliable quantification of the contributions of autonomic function to the causal network surrounding depression. To increase sample size, studies could include multicentre sites for recruitment and implement randomised controlled trials. Our study highlights the immediate psychological and QoL value of mindfulness training, and support larger and longer-term studies of its potential physiological benefits on cardiac health.

Acknowledgments

The authors wish to thank the ECG technicians at The Queen Elizabeth Hospital, the CTAD staff and all participants who volunteered for the study.

CHAPTER SEVEN: DISCUSSION

CHAPTER SEVEN
DISCUSSION

1. DISCUSSION

This thesis outlines the findings of three independent but related Australian studies, investigating actual and potential associations between depression and CHD. The research projects, spanning discipline boundaries and supervised by a multidisciplinary academic and clinical panel, aimed firstly to increase understanding of depression and subsequent mortality in adult patients presenting for cardiac investigation and treatments (Studies 1 and 2); and secondly to contribute directly to evidence-based practice with a preliminary investigation of whether a psychological intervention targeting depression might have potential benefits at the level of cardiac physiology (Study 3). These projects contribute to the epidemiological literature by providing empirical support for the relationships between depression and NoCAD, and depression and mortality; and contribute to evidence-based practice by reporting pilot data and methodological considerations concerning evaluation of the potential impact of MBCT on HRV. All three studies have broader implications for future research and clinical practice.

Specific study objectives aimed to: (1) compare the prevalence of depression in patients with chest pain and obstructive CAD or NoCAD, utilising a healthy control cohort as a reference population; and then (2) determine if the presence or absence of obstructive CAD is an independent predictor of depression; (3) investigate whether incident depression during hospitalisation for cardiac conditions predicted all-cause and/or cardiac mortality at 5 years; and (4) explore the potential impact of a depression treatment (MBCT) on HRV, depressive symptoms and QoL, in a sample of mental health outpatients.

A combination of quantitative research methodologies was employed to meet these objectives, including analysis of pre-existing data sets (Studies 1 and 2) and a clinical research study (Study 3). The key findings of the three studies are summarised in this chapter, followed by a discussion of the methodological strengths and

weaknesses of each study. Finally, the broader clinical and research implications of the project findings and future directions for research into depression and CHD are discussed.

1.1. Summary of Findings

Study 1: NoCAD Study

The first study (Chapter Four) was a prospectively-designed observational cohort study utilising two independent data sets. These included: (1) TQEH Coronary Angiogram Database consisting of 819 patients with obstructive CAD and 325 patients with NoCAD, all of whom had chest pain, and (2) the NWAHS, a community study from which individuals with chest pain were excluded. This study compared the prevalence of depression among patients with chest pain in the presence or absence of obstructive CAD and a healthy control group without chest pain; and investigated whether the presence or absence of obstructive CAD independently predicted depression. Consistent with previous findings, depression was more prevalent in NoCAD patients with chest pain than in either obstructive CAD patients with chest pain (OR 1.539, 95% CI 1.166-2.030, $p = 0.002$) (Carney et al., 1990; Channer et al., 1985; Katon et al., 1988; Ketterer et al., 1996; Lantinga et al., 1988) or healthy controls without chest pain (OR 5.359, 95% CI 4.166-6.895, $p < 0.001$) (Ketterer et al., 1996). In addition, NoCAD was established as an independent predictor of depression within the study sample of patients undergoing coronary angiography for the evaluation of chest pain (OR 1.44, 95% CI 1.03-2.03, $p = 0.03$). These findings are of interest, given the presumably lesser extent of gross cardiac pathology among NoCAD patients compared to CAD patients.

Reasons for Association

Study findings do not indicate why NoCAD patients exhibit higher levels of depression than obstructive CAD. However, in the manuscript presented in Chapter Four, three explanations were proposed for the association between depression and NoCAD. Firstly, symptoms experienced by NoCAD patients may be predominantly psychiatric or non-cardiac rather than cardiac in nature. It follows that their chest pain may reflect psychological distress or other non-cardiac causes. Secondly, the patient may have a coronary MVD resulting in myocardial ischaemia producing chest pain, so that their depression may be a response to the suboptimal therapies available for this

disabling disorder and the resulting effect on QoL. Thirdly, depression and coronary MVD may share common pathophysiologic or genetic pathways, so that the disorders coexist (Vaccarino et al., 2009).

An additional explanation may also be postulated: that a lack of diagnosis of a disorder and patients' distress about the lack of diagnosis, and thus lack of treatment may explain the association between NoCAD and depression. Patients with NoCAD are often reassured when they do not have heart disease but are offered no explanation for their symptoms or treatment (Bugiardini & Bairey Merz, 2005; Panza, 2002). As Potts and Bass (1995) found, patients who did not respond to reassurance about their illness experienced continued chest pain and functional incapacity. This explanation is unlikely to explain the results of Study 1, however because the majority of patients in this study were unaware of their formal diagnosis at the time of angiography and completion of psychometric questionnaires.

Study 2: IDACC Study

The second study (Chapter Five) examined whether depression during hospitalisation for AMI predicted 5-year all-cause or cardiac mortality. The pre-existing IDACC data set of 337 AMI patients was utilised and these data were linked to a government death registry to determine 5-year mortality. The major finding of this study was that moderate to severe depression (defined as CES-D $\geq$ 27) at the time of AMI was associated with 5-year all-cause mortality (hazard ratio 2.54, 95% CI 1.03-6.28, $p = 0.04$) but not cardiac mortality. Low power resulting from a low death rate from cardiac causes may have influenced the lack of association between depression and cardiac mortality. However, when the cut-off for depression was lowered (to CES-D $\geq$ 16), that is, when patients with milder depression were also included in the analysis, depression was not found to be predictive of either all-cause or cardiac mortality. Similarly, when CES-D was analysed as a continuous variable, no association was found between depression and mortality. This pattern of results suggests that the relationship between mortality and depression severity is not linear and that the association only becomes evident when the severity of depression reaches a threshold level (e.g., CES-D $\geq$ 27), indicative of major depression. In support of these findings, researchers have reported an association between mortality and major depression

(Agelink et al., 2002; Carney et al., 2008; Drago et al., 2007), suggesting a direct correlation between severity of depression and its influence on prognosis.

These results are consistent with previous studies reporting an association between depression and long-term mortality (Carney et al., 2008; Lesperance et al., 2002; Pfiffner & Hoffmann, 2004; Welin et al., 2000), and they add to the evidence for a long-term detrimental effect of depression on AMI patients. However, the association between depression and long-term mortality is complex and findings remain controversial, as others have failed to find a relationship between depression and mortality (Dickens et al., 2007; Parakh, Thombs, Fauerbach, Bush, & Ziegelstein, 2008), indicating a need for more research. Future research into the pathophysiological mechanisms underpinning this association would also be beneficial, and is further discussed in the 'Implications' section of the Discussion.

Reasons for Lack of Association

The reason why depression independently predicted all-cause and not cardiac mortality at 5 years was unclear in this study. The small proportion of deaths from cardiac causes resulted in low power, possibly contributing to a lack of association between depression and cardiac mortality. Conversely, the lack of association may reflect a lower number of deaths due to cardiac mortality as a result of improved clinical management of AMI patients over the years, due to the greater efficacy of contemporary therapies for CHD (Lamy, Natarajan, & Yusuf, 2011). The cardiac population in this study had experienced more recent and effective cardiac interventions, compared with earlier cohorts. In addition, use of antidepressant and antipsychotic medication was not recorded and thus, it is impossible to determine whether this may have played a role in the lack of association between depression and cardiac mortality.

Study 3: HRV Study

The clinical pilot study (Study 3) detailed in Chapter Six was initially designed to investigate pathophysiological mechanisms underlying depression, by examining changes in HRV in a sample of outpatients undergoing a group-based 8-week MBCT program for depression. However, a lower than anticipated recruitment rate necessitated broadening the study to include a more naturalistic sample of 27 adults with DSM-IV

Axis I mood or anxiety disorder. In this study HRV, depressive symptoms and QoL were measured. Consistent with previous findings, the results of Study 3 indicated that MBCT had immediate benefits for this population, contributing to significant and large treatment gains in individuals' depressed mood (0.20, 95% CI 0.05-0.74, $p = 0.016$), as also found by other researchers (Barnhofer et al., 2009; Finucane & Mercer, 2006; Kingston et al., 2007; van Aalderen et al., 2012) and also gains in QoL (5.35, 95% CI 1.40-9.31, $p = 0.008$), as others found (Godfrin & van Herringen, 2010; Kuyken et al., 2008). However, there was no measurable improvement in HRV following the MBCT program. Low power and/or differences in patient population compared to previous studies may have contributed to the negative finding regarding HRV. This pilot study, however, established the feasibility of the study design and extended current knowledge about the population and methodology required in order to examine this relationship. Study findings highlight the immediate psychological value of mindfulness training and support the case for larger and longer-term studies of its potential physiological benefits on cardiac health.

Reasons for Lack of Association

It is unclear why study findings found no improvement in HRV post-therapy. As described in the manuscript presented in Chapter Six, five explanations were theorised. Firstly, in terms of final sample size, the study was underpowered to detect either a time or treatment effect in HRV. Secondly, it is possible that only severely depressed patients (and not mildly depressed) exhibit reduced HRV (Agelink et al., 2002), thus the prevalence of 41% severely depressed patients in the study was insufficient to find an association. Thirdly, previous research has found that antidepressant medication and mood stabilisers affect HRV (Bar et al., 2004; Henry et al., 2010; Licht et al., 2010; Tucker et al., 1997; Volkers et al., 2004), thus the presence of these medications may have influenced findings. As a result, other studies have recruited drug-naïve participants (Chang et al., 2012; Kikuchi et al., 2009; Lehofer et al., 1997; Moser et al., 1998; Udupa et al., 2007). Fourthly, anxiety is known to affect HRV (Friedman, 2007; Gorman & Sloan, 2000) and some studies have therefore only recruited patients with MDD disorder (Chang et al., 2012; Udupa et al., 2007). Anxiety may, therefore, have been a significant confound in our exploration of HRV in mental health outpatients.

Lastly, it has been suggested that mindfulness is not a self-relaxation technique (Baer, 2003) but rather a form of mental training that facilitates more adaptive responses to stress (Bishop, 2002). It is therefore possible that meditation approaches which emphasise relaxation and breathing to a great extent may have a greater impact on HRV. However, it is also possible that the absence of an HRV effect in this study reflects the need for longer-term mindfulness practice and experience, as found in studies of experienced meditators (Peressutti et al., 2012; Phongsuphap et al., 2008).

1.2. Methodological Strengths and Limitations

Although the three studies presented in this thesis attempted to minimise methodological problems, there were a number of limitations in study design, implementation and/or evaluation that could not be overcome. Two of the three studies utilised pre-existing data sets, thus incorporating the methodological limitations of the parent studies. These limitations are discussed below. This research was undertaken as part of a Doctor of Philosophy (PhD) degree program, and time constraints and lack of research funding resulted in further limitations, particularly in the clinical pilot study (Study 3). Despite the limitations, each study possesses its own strengths.

Study 1

This study provided a multivariate quantitative evaluation of depression in NoCAD patients. Although previous studies have investigated the prevalence of depression in CAD and NoCAD populations in univariate analyses (Carney et al., 1990; Channer et al., 1985; Katon et al., 1988; Ketterer et al., 1996; Lantinga et al., 1988), this study is believed to be one of the first to examine whether NoCAD independently predicts depression in a multivariate analysis. This study was conducted in local Australian healthy and cardiac populations, providing depression prevalences in both CAD and NoCAD groups, which may help inform Australian practices of the severity of this comorbid condition. The NoCAD population is widely understudied and this study therefore represents an important contribution to the fields of psychology, psychiatry and medicine, by specifically examining a common mental health disorder in an understudied cardiac population.

However, like most studies utilising pre-existing data sets, this study had limitations. At baseline a self-report measure of depression had been used, and patients

did not undergo diagnostic interviews by clinicians. Nevertheless, the SF-36 mental summary score has been validated for measuring depression in depressed patients (Tavella et al., 2010). Missing information with potential explanatory value included details of some other illnesses which are prominent in depressed patients experiencing chest pain, such as mitral valve prolapse, Prinzmetal angina, small coronary artery spasm or oesophageal disease. Despite these limitations, the data analysed came from a large, well-characterised cardiac population, in terms of demographic, socio-economic, psychological and cardiac variables.

Study 2

This study has several strengths. Many studies analysing the association between depression and mortality are internationally based (Carney et al., 2008; Dickens et al., 2007; Lesperance et al., 2002; Parakh et al., 2008; Pfiffner & Hoffmann, 2004; Welin et al., 2000), whereas this study was conducted in a local Australian cardiac population. It is important for mortality analyses to be conducted across different countries in order to increase confidence in the accuracy and generalisability of the available findings to the cardiac population at large (Elliott & Kennedy, 2004). However local projects are also important, providing better, more effective mortality data to inform Australian practice. Over the last few decades, worldwide clinical management of AMI patients has dramatically changed and improved, reflecting the efficacy of contemporary therapies for CHD (Lamy et al., 2011). Accordingly, the cardiac population analysed in this study had experienced more recent and effective cardiac interventions, compared with cohorts reported earlier. Hence, results of this study expand on current literature by analysing the rate of depression in a population that has potentially benefited from improvements in cardiac care. In addition, the data were derived from a multicentre study with a large patient population, providing a cardiac sample which was well-characterised in terms of demographic, socio-economic, psychological and cardiac variables. Both all-cause and cardiac mortality outcomes were also analysed, whereas many studies are limited to one or the other (Carney et al., 2008; Drago et al., 2007; Dickens et al., 2007; Lesperance et al., 2002; Parakh et al., 2008).

Despite these strengths, as described in the manuscript presented in Chapter Five, the study had inherent limitations. Although the BDI was collected during this

study, this variable was excluded from analyses due to the large amount of missing data or responses such as 'not asked/not stated'. As a result, the CES-D was used as the baseline measure of depression. However, the CES-D was self-rated rather than a gold standard diagnostic interview by a clinician. Information regarding patients' depression status at any point during the follow-up (up to and including 5 years or at the time of death) was not available. Although the data set was well-characterised in terms of the variables previously mentioned, several other potentially useful explanatory variables had not been collected during the initial study, and therefore were unavailable for analysis. Severity of AMI had to be estimated based on length of stay in the index hospital because severity information was not available, nor was information relating to multiple medical comorbidities, long-term antidepressant or antipsychotic medication or level of physical activity available. The relationship between depression and CHD is partly mediated by physical inactivity, therefore it is possible that physical activity may have eliminated the effect of depression, rather than physical acivity being a confounder. Previous research has shown that sedentary behaviour may partially account for the relation between depression and increased cardiovascular events (Whooley et al., 2008) and depression and mortality (Brummett et al., 2003; Kurdyak, Chong, Gnam, Goering, & Alter, 2011). Moreover, study power was problematic, as demonstrated by the post-hoc power analysis. Perhaps due to improvements in prevention and care, the small proportion of deaths from cardiac causes within the current study meant that it was underpowered to detect a statistically significant association between depression and cardiac mortality if it existed. In future studies investigating this association, samples will need to be significantly larger in order to capture enough cardiac deaths. In recognition of this current study's limited statistical power for this analysis subsequent to publication, the effect of depression (as a dichotomous variable defined by CES-D $\geq$ 27) as a predictor of cardiac mortality was subsequently evaluated by the calculation of a detectable hazard ratio. Based on the sample size of AMI patients in the IDACC database (n = 336), a hazard ratio of 3.26 could have been detected (Appendix O). However, the achieved hazard ratio of depression (that was measured by the model) was 2.819 (Appendix P). As the achieved hazard ratio was much lower than the detected hazard ratio, the chance of detecting a statistically significant result was low.

Study 3

The major contribution of this study is that it is one of the earliest clinical studies to examine the effect of MBCT on HRV. Although previous research has explored the relationship between mindfulness and HRV (Delizonna et al., 2009; Peressutti et al., 2012; Peressutti et al., 2010; Telles et al., 2005), more studies primarily emphasised more concentrative techniques and/or involved more intensive meditation practice than the clinical MBCT treatment program evaluated in this study. This study helps to bridge the gap between research and clinical practice by extending knowledge of the population and methodology required in order to examine the relationship between HRV and MBCT, which is an empirically-supported and widely-used clinical intervention for mental health outpatients.

As mentioned in the manuscript presented in Chapter Six, Study 3 had several limitations. The design was quasi-experimental and did not include a control group, comparison therapy, any form of randomisation, or long-term follow-up. Although these methodological flaws present a threat to validity, it can be argued that less robust study designs can still make a clinical contribution to psychological research (Andrews, 1989; Schwartz, Trask, Shanmugham, & Townsend, 2004), because pilot studies, despite offering lower levels of evidence, still inform research and practice. The behavioural intervention studies by Glueckauf and Quittner (1992) and Perry and colleagues (2010), for example, provided follow-up assessment from 6 to 9 months post-intervention, and although data were only available for participants who underwent treatment, the studies provided valuable information about the longer-term efficacy of the intervention. Thus, although randomised controlled trials and long-term follow-ups are desirable, the design utilised in Study 3 is an acceptable method for a pilot study initially exploring relationships between HRV and MBCT.

Additional limitations of Study 3 further highlight the complexities of formally evaluating interventions in a 'real world' setting. Ultimately, when recruitment ceased in this time-limited project, the accrued sample was still too small, leading to inadequate statistical power to detect either a time or treatment effect on the primary outcome measure - HRV. This was confirmed by a post-hoc power calculation. Considerable attempts had been made to increase recruitment and participation, but lack of funding for this PhD project precluded financial incentives for participation. In

recognition of the study's limited statistical power, impact of the intervention on HRV was therefore further evaluated by the calculation of Cohen's *d* effect sizes (Cohen, 1988; Cumming, Fidler, Kalinowski, & Lai, 2012). Consequently, the resulting *d* values of the HRV time and frequency parameters were very small, suggesting no meaningful effect of MBCT on HRV. The decision to optimise recruitment by expanding the initial inclusion criteria beyond major depression meant that, although naturalistic, the sample studied was also heterogeneous. Outpatients at all depression levels, who were taking psychiatric medication, with a primary DSM-IV Axis I mood or anxiety disorder, were recruited. Those variables may have been confounders in this study. In a previous study concerning HRV, Agelink and colleagues (2002) found that only severely depressed patients showed reduced HRV. Other studies have limited their recruitment to patients with depression alone (Chang et al., 2012; Udupa et al., 2007), because anxiety is known to affect HRV (Friedman, 2007; Gorman & Sloan, 2000). In addition, several studies only recruited drug-naïve participants (Chang et al., 2012; Kikuchi et al., 2009; Moser et al., 1998; Udupa et al., 2007) because of potential effects of antidepressant medication on HRV (Bar et al., 2004; Henry et al., 2010; Licht et al., 2010; Tucker et al., 1997). Lastly, it has been suggested that non-linear measures of HRV may be more sensitive to depression effects (Kemp et al., 2010). As this study was conducted in a clinical setting and was limited by available software and resources, the required software to undertake non-linear techniques was unavailable.

1.3. Clinical Implications and Recommendations for Future Research

The present findings contribute to the epidemiological literature by providing empirical support for the relationships between depression and NoCAD and depression and mortality, and to research and evidence-based practice by reporting pilot data and methodological considerations concerning evaluation of the potential impact of MBCT on HRV. All three studies have broader implications for future research and clinical practice.

Study 1

Previous research has shown that depression is a predictor of obstructive CAD development and prognosis (Rozanski et al., 1999), by decreasing QoL (Frasure-Smith et al., 1995; Ruo et al., 2003) and increasing the risk of cardiovascular events and mortality (Frasure-Smith et al., 1995; Potts & Bass, 1995; Ruo et al., 2003). Less is

known about the heterogeneous clinical group that is labelled as NoCAD, as chest pain symptoms can reflect either cardiac or non-cardiac causes, and symptoms are often indistinguishable from those of obstructive CAD (Bugiardini & Bairey Merz, 2005). Therefore establishing the prevalence of depression in patients with NoCAD is an important step towards determining appropriate clinical services for this challenging cardiac population.

Screening

The results of Study 1, that the prevalence of depression was higher among the NoCAD patients than among obstructive CAD patients or healthy controls, and that NoCAD status independently predicted depression, have implications for clinical cardiac practice. In addition, approximately half of the obstructive CAD patients undergoing angiography for chest pain had depression. This is a higher prevalence rate than those found in other cardiac samples, such as patients screened for depression following AMI or on admission for cardiac conditions (Wade, Cheok, Schrader, Hordacre, & Marker, 2005), or at cardiac outpatient clinics (Ruo et al., 2003). Although clinicians may be aware of the relationship between depression and CAD, NoCAD patients are not always followed up in a similar way although results of Study 1 suggest that they may be more depressed. Currently, patients hospitalised for chest pain complaints are examined and treated on the basis of their chest pain symptoms but are not necessarily screened for depression. The current findings provide support for routine depression screening in patients undergoing coronary angiography for the evaluation of chest pain, especially in those with less gross pathology, such as NoCAD. Results also highlight contact with cardiac services (inpatient, outpatient or emergency) as a potential marker for underlying and undiagnosed depression.

It is possible that without systematic screening and further evaluation, NoCAD patients with treatable depression will be overlooked. Given the potential health consequences of untreated depression, such as impaired general functioning, decreased QoL and mortality (Cuijpers & Smit, 2002; Cuijpers et al., 2013; IsHak et al., 2011; Lenox-Smith et al., 2013), accurate identification of depression should be a high clinical priority. Findings therefore also have implications for the treatment of this population, which may potentially assist in the reduction in somatisation.

Screening questionnaires for depression are cheap and easy to obtain, with some being readily available online in the public domain. They are easy to understand, quick to administer and complete (often between 5-10 minutes) and require little time or training for scoring and interpretation. These tools could be the first-line waiting-room strategy for identifying cardiac patients with depression in a range of clinical settings. Screening tools such as the CES-D (Radloff, 1977) or Patient Health Questionnaire-9 (Kroenke, Spitzer, & Williams, 2001) are effective for identifying patients with elevated depressive symptoms or MDD (Haddad et al., 2013; Kroenke, Spitzer et al., 2001; Morin et al., 2011), and arguably should be included in the evaluation of all new patients presenting to cardiac services. However, to prevent inadequate treatment of CHD patients with depression identified by screening, or overtreatment of depression which may occur due to implementation of standard treatment after routine screening (e.g., administration of prescription antidepressant medications), positive screens should be followed up by diagnostic interviews. In the case of a positive screen and interview, the patient should be referred to a relevant health care professional who can educate the patient and provide knowledge of available treatments. Follow-up of the patient and monitoring of treatment adherence could then follow the initial appointment. It may also be beneficial to have close contact with a psychiatrist or psychologist who can provide supervision and advice to both the patient and health care professional when needed, both elements being similar to collaborative care.

Screening for depression in patients complaining of chest pain, or with known or suspected cardiac disorders and risk factors should not be limited to hospitals but should also be routine in other health care settings such as general practices. Furthermore, it could perhaps be argued that in a similar way mental health professionals should also routinely consider their patients' physical health, and consider cardiac and other risk factors when conducting initial mental health assessments, because of the comorbidity of depression and cardiac problems. This project highlights a need and responsibility for psychologists, psychiatrists and other mental health practitioners (such as cardiovascular care providers) to be aware of the symptoms of both depression and CHD and links between these comorbid conditions. In addition, the development of closer clinical relationships with the mental health professions listed above may be desirable in order to better assist the patient. More broadly in terms of training, it supports the importance, for all health professionals working with chronic physical or

mental illnesses, of having a current and comprehensive understanding of the physiological and interpersonal consequences of illnesses and their interactions, and also of the biological bases of their aetiology and treatment. Without this, patients may receive suboptimal care.

Diagnosis

This study highlights the importance of screening for depression in chest pain patients. A patient complaining of chest pain requires an explanation of their symptoms, because symptoms often persist (Potts & Bass, 1995) and can lead to depression. It is further suggested that all patients admitted to hospital with chest pain complaints undertake a depression screening tool and a thorough physical examination to determine any non-cardiac cause.

Chest pain can have multiple causes (previously described in Chapter One, Section 5.3) and accurate identification is necessary to determine diagnosis and the best form of treatment. If chest pain is attributable to non-coronary disorders or non-cardiac disorders (arising from, for example, the oesophageal, musculoskeletal or respiratory systems), treating the issue and relieving chest pain may reduce stress and uncertainty. If the chest pain has a strong psychological component, treating the underlying psychiatric disorder may reduce or eliminate it (Carney et al., 1990). For pain which is cardiac in nature, appropriate medical treatment (Bugiardini & Bairey Merz, 2005) and/or exercise training (Thompson, 2012) may relieve both chest pain and depressive symptoms.

If depressive symptoms persist after diagnosis and treatment, psychological therapies such as MBCT (Kenny & Williams, 2007; Teasdale et al., 2000; van Aalderen et al., 2012) or CBT (Freedland et al., 2012; Huntley et al., 2012; Mann, 2005; Weersing & Gonzalez, 2009) are available and have good efficacy in the treatment of depression. Cardiac rehabilitation, a medically supervised program incorporating prescribed exercise, education and counselling to patients with obstructive CAD (Thompson, 2012), may be beneficial either independently or in conjunction with depression treatment. In NoCAD patients, medical therapy and symptom management including aspirin, beta-blockers, statins, angiotensin-converting enzyme inhibitors, antidepressants, and exercise training, are beneficial in the reduction of chest pain and

depressive symptoms (Bugiardini & Bairey-Merz, 2005) Other strategies such as oestrogen replacement therapy may reduce frequency of chest pain in post-menopausal women with NoCAD, presumably by improving endothelium-dependent coronary vasodilation (Knuuti et al., 2007). Although numerous studies have investigated various therapeutic agents, there is a lack of data regarding optimal treatment for NoCAD patients, and few large-scale randomised controlled trials. For those patients with negative angiograms (such as in NoCAD), treatment may decrease depressive and chest pain symptoms (Cannon et al., 1994; Potts, Lewin, Fox, & Johnstone, 1999), improve QoL and prevent progression to acute cardiac disease or mortality (Klimes, Mayou, Pearce, Coles, & Fagg, 1990).

Research Implications

Study 1 has implications for ongoing research in psychology, psychiatry and medicine. NoCAD is commonly under-investigated and untreated, but this study suggests that the prognosis of NoCAD patients is not as benign as previously assumed (Bugiardini & Bairey Merz, 2005) as NoCAD patients were at higher risk for depression than CAD patients. This indicates that this commonly understudied population requires further research to better understand the association between depression and NoCAD. Other variables (which are prominent in depressed patients experiencing chest pain) such as mitral valve prolapse, Prinzmetal angina, small coronary artery spasm or oesophageal disease, need to be explored as this may help explain the occurrence of depression in chest pain patients with normal coronary arteries and contribute to developing appropriate treatment for these patients.

Study 2

The finding of Study 2 that depression independently predicts mortality in MI patients at 5 years, offers an extension to the results of Study 1. Not only does this finding confirm that screening for depression is important, but also suggests that without it, depression may be overlooked and may contribute to long-term detrimental consequences, including morbidity and mortality. Screening and intervention therefore may be seen as life saving. Treatment in patients with a positive angiogram may, for example, decrease morbidity and mortality (Ketterer, 1993).

Clinical and Research Implications

Given the advances in therapies for CHD, future studies are needed to examine the association between depression and cardiac mortality. There is a need for researchers to retrospectively compare patients who have and have not received contemporary therapies for CHD and compare their long-term cardiac mortality rates using meta-analyses. In future studies, patients should also be recruited from multiple centres (even more so than in this study) to increase sample size, thus reducing the risk of low power for some outcomes and analyses. This will enable analysis of both all-cause and cardiac mortality. Many of the studies which identified depression more clearly as a predictor of mortality utilised earlier cohorts (Carney et al., 2008; Lesperance et al., 2002; Pfiffner & Hoffmann, 2004; Welin et al., 2000) and thus the discrepancies between this study and others may be related to differences in the management of the AMI population over time. It seems prudent to continue to analyse both all-cause and cardiac mortality over both short-term and long-term periods.

Clinical interviews and self-reported questionnaires should be conducted concurrently at baseline to determine whether patients are classified as depressed. Funded research should measure depression (both incidence and severity) at regular intervals, not only at baseline. Variables associated with depression such as antidepressant/antipsychotic medication, level of physical activity, severity of AMI, and presence of comorbid conditions should also be measured for their potential explanatory value when interpreting and comparing mortality rates.

The Screening Debate

Taken in isolation the findings of Studies 1 and 2 lend support to screening for depression among cardiac patients, both in primary care and in hospital settings. However, these findings need to be considered within the context of a broader ongoing debate.

Many clinicians and researchers have debated whether screening either decreases the prevalence of depression or improves quality of care for people with depression (Gilbody, House, & Sheldon, 2001; Gilbody, Sheldon, & House, 2008; Thombs et al., 2008; Thombs et al., 2013; Thombs & Ziegelstein, 2013; Thombs & Ziegelstein, 2014; Ziegelstein, Thombs, Coyne, & de Jonge, 2009). Reporting two

systematic reviews (Thombs et al., 2008; Thombs et al., 2013), Thombs and colleagues have highlighted the absence of any positive evidence from randomised controlled trials of screening, and have accordingly challenged the effectiveness of depression screening within cardiovascular care settings. Other systematic reviewers have analysed randomised controlled trials in other health care settings (Gilbody et al., 2001; Gilbody et al., 2008), and concluded that if used alone, screening questionnaires for depression appear to have little or no impact on the detection and management of depression by clinicians. Thus, in terms of a cost-benefit analysis, screening alone does not lead to an improvement in depression outcomes and may lead to greater resource consumption (Thombs & Ziegelstein, 2014), such as following up on positive screens, inappropriate labelling or treatment, impractical overuse of scarce health care resources, and costs of inappropriate treatment (Thombs et al., 2013; Ziegelstein et al., 2009).

Recent guidelines developed by the National Heart Foundation of Australia (NHFA) (Colquhoun et al., 2013) which recommend screening for depression in cardiac settings have been further criticised (Thombs et al., 2012; Thombs et al., 2013; Thombs & Ziegelstein, 2013; Thombs & Ziegelstein, 2014), on the grounds that (1) such guidelines are not based on high-level evidence and (2) screening is useful only if it improves patient outcomes beyond those of standard care and demonstrates sufficiently positive results to justify the additional costs and associated potential harms (Thombs et al., 2012). Thombs and colleagues assert that the potential harms of screening are rarely made explicit, but can include a small risk of unnecessary diagnostic testing or treatment (e.g., medication and/or psychotherapy) of depression in patients who are incorrectly identified as having the disorder or adverse effects of inappropriate treatment with medication to some patients who would not otherwise have been exposed, due to false-positive results of screening, and the diversion of scarce resources to screening from other endeavours, such as ensuring better care for patients already identified as having depression (Thombs et al., 2012; Thombs et al., 2013; Thombs & Ziegelstein, 2014). Similarly, Tully and Higgins (2014) suggest that a likely result of screening would be an increase in referrals for treatment by psychologists in hospitals, community centres or private practice (often publicly-funded).

The authors of the NHFA guidelines have suggested that screening cardiac patients for depression could be beneficial (Colquhoun et al., 2013). They further

speculated that screening might be sufficiently beneficial to justify the scarce resources that would be consumed by screening and the potential harm to some patients who would not be otherwise exposed (Tatoulis, 2014). Nevertheless others argue that basing guidelines on speculation is unacceptable, and that formal guidelines and recommendations should rely solely on systematic reviews and high-level evidence in order to benefit patients and prevent unnecessary costs and adverse effects of medical care (Thombs & Ziegelstein, 2014). Protocols based on lower levels of evidence (such as expert opinion or preference) have the potential to increase service usage without improving patient outcomes (Shaneyfelt, 2012). For routine screening to be recommended, there must be sufficient evidence that it does not lead to significant harms that outweigh potential benefits (Ziegelstein et al., 2009). Hence, the growing consensus is that guidelines need to be reformed so that they address patient needs but avoid interventions that consume recourses without proven benefit (Shaneyfelt, 2012; Tilburt & Cassel, 2013).

Two reviews (Gilbody et al., 2001; Gilbody et al., 2008) which were critical of screening focused on screening strategies alone and did not include studies in which screening was embedded within wider enhanced-care programs, such as collaborative care or psychotherapy. Screening, when combined with another intervention, has shown improvements in depression outcomes and QoL in both primary and cardiovascular care settings (Davidson et al., 2010; Freedland et al., 2009; Gilbody, Bower, Fletcher, Richards, & Sutton, 2006; Katon et al., 2012; Williams et al., 2007).

Katon and Unutzer (2006) have defined collaborative care as including two essential elements: a depression care manager (an allied health professional, preferably with a mental health background) to educate patients, provide close follow-up, and monitor treatment adherence, and a psychiatrist to provide case load supervision for depression care managers and clinical advice to primary care providers. Collaborative care for depression has been found to improve depression outcomes (Gilbody, Bower, & Whitty, 2006; Gilbody, Whitty, Grimshaw, & Thomas, 2003). However, several studies have found that screening only improved depression when combined with a collaborative care program (Dietrich et al., 2004; Gilbody, Bower, Fletcher et al., 2006; Pignone et al., 2002; Unutzer et al., 2002; Williams et al., 2007). In theory, patients with CHD should be at least as likely as primary care patients to benefit from

depression screening in the context of a collaborative care treatment program. The few studies that have analysed this in the cardiovascular care setting found positive results (Katon et al., 2012; Rollman et al., 2009; Rollman & Belnap, 2011). Collaborative care interventions typically take 3 to 6 months (Simon, Ludman, Tutty, Operskalski, & Von Korff, 2004; Williams et al., 2007) and although screening can lead to interventions that are associated with increased financial cost in the short-term (Gilbody, Bower, & Whitty, 2006), they are cost effective and probably cost-saving in the longer term (Unutzer et al., 2008; Katon et al., 2005; Katon et al., 2012). Tully and Higgins (2014) suggest that psychologists can intervene effectively to reduce depression in cardiac patients, and CBT and problem-solving therapy should be viewed as frontline treatment options and alternatives to pharmacotherapy.

Clinical Implications

The value of screening for depression in cardiac settings is both an important topic for debate and an urgent priority for future research. Randomised controlled trials to test the effectiveness of depression screening for improving cardiovascular outcomes in cardiovascular care settings are needed. Meanwhile, in the absence of gold standard randomised controlled trial evidence, the value of screening remains an open question. As Altman and Bland (1995) observe, where public health is concerned, the absence of firm evidence does not always justify inaction. On the basis of results of Studies 1 and 2, it can be argued that routine screening for depression in patients with obstructive CAD and NoCAD should take place; that screening should be incorporated into usual clinical practice; and that patients with positive screening results may require further evaluation (Colquhoun et al., 2013). Other research indicates that in this context, coordination and a close relationship between health care providers (i.e., collaborative care) are essential if screening is to improve patient outcomes (Katon & Unutzer, 2006).

Study 3

Depression is associated with increased cardiac morbidity and mortality in people with and without cardiac risk factors (Lett et al., 2004; Penninx et al., 2001), and this relationship is, in part, mediated by HRV (Carney et al., 2005; Grippo & Johnson, 2002). This study offers an extension to the results of Studies 1 and 2, by examining a psychotherapy intervention that may improve depression symptoms, QoL and HRV, and possibly reduce future mortality.

Increased HR and reduced HRV are common in both depressed and cardiac patients, which may explain their higher cardiac risk. Several types of meditation have been shown to be associated with HRV improvements (Phongsuphap et al., 2008; Telles et al., 2013; Wu & Lo, 2008). Some researchers have explored relationships between mindfulness and HRV (Delizonna et al., 2009; Peressutti et al., 2012; Peressutti et al., 2010; Telles et al., 2005) but few have studied either MBCT or MBSR (Ditto et al., 2006; Nijjar et al., 2014a, b). Establishing whether MBCT improves HRV will expand insights into the role of the ANS in depression and into treatment methods for this condition.

Clinical Implications

The findings of Study 3 that MBCT reduced depressive symptoms and improved QoL post-therapy have implications for research and clinical practice. These findings, while consistent with previous literature (Barnhofer et al., 2009; Godfrin & van Herringen, 2010; Kenny & Williams, 2007; van Aalderen et al., 2012), provide further evidence for the effectiveness of MBCT for depressive symptoms and QoL in an Australian community clinic and suggest that the treatment is beneficial for both mildly and severely depressed individuals. Since both cardiac and depressed patients can exhibit decreased HRV, the hypothesised effect of MBCT on HRV may prove to be of benefit to cardiac patients who suffer from depression. However, no significant association was demonstrated between HRV and MBCT.

Research Implications

Although no significant association was found between HRV and MBCT in Study 3, a recent study demonstrated that MBSR improved cardiac sympathovagal balance measured by HRV (Nijjar et al., 2014a, b). The authors concluded that although further studies are warranted, mindfulness training may be a beneficial adjunct in management of conditions with reduced HRV, such as CHD and AMI. The results of Study 3, therefore, have broader implications for clinical practice and future research in the treatment of mental health patients with altered HRV, and may thus contribute to future reductions in depression and mortality. This study has provided empirical support for the practical feasibility of a study design evaluating potential impact of MBCT (or other psychotherapies) on HRV and represents a useful extension to knowledge of the population and methodology required in order to examine this relationship.

Sample size could be increased by including multicentre sites in recruitment, which would increase study power and the ability to detect any measurable improvement in HRV. The implementation of randomised controlled trials, such as control or comparison treatment groups would be beneficial by providing a gold standard study design. This could be achieved by analysing, for example, the effect of MBCT on HRV compared to the effect of TAU (e.g., psychologist/psychiatrist) on HRV.

Future studies may, by eliminating confounders, permit more reliable quantification of the contributions of autonomic function to the occurrence of depression. Future research analysing whether MBCT promotes a change in HRV should aim to recruit patients with either depression or anxiety, in preference to a mixed sample of both disorders. In addition, it would be beneficial to study HRV in two subsets of depressed patients: those with mild depression and those with severe depression, to determine whether the finding of Agelink and colleagues (2002), that only severely depressed patients showed reduced HRV, is replicated. This may contribute to a better understanding of who is at greater risk, and appropriate treatment plans. Although difficult, prescription medication should be limited when studying HRV. Research shows that antidepressant medication (Bar et al., 2004; Henry et al., 2010; Tucker et al., 1997; Volkers et al., 2004) and cardiac medication (Bekheit et al., 1990; Cook et al., 1991; Lampert et al., 2003) are confounders of HRV. Thus, recruiting drug-naïve patients will be beneficial**.** Furthermore, age, gender, diurnal range, caffeine, smoking, alcohol, illicit drugs, blood pressure and comorbid medical conditions have been found to influence HRV (discussed in Section 8.5 of Chapter One) and should be measured and considered when analysing HRV.

Although in this study, participants' mood, attitudes and QoL may have changed during the 8-week MBCT program, longer-term follow-up studies of MBCT are necessary to document any physiological changes. It is possible that patients who continue to undertake mindfulness practices long-term after the MBCT program may exhibit changes in HRV, as has been observed in experienced meditators (Peressutti et al., 2012; Phongsuphap et al., 2008). In addition, studies of HRV should utilise both linear and non-linear techniques, as non-linear techniques are more sensitive to depression effects (Kemp et al., 2010).

Depression and coronary MVD (e.g., NoCAD) share a common pathophysiologic or genetic pathway, so that the disorders coexist (Vaccarino et al., 2009). Depression and CHD patients also exhibit decreased HRV (Drago et al., 2007; Kemp et al., 2010; Udupa et al., 2007). It is therefore possible that CHD and CAD patients with lower HRV may benefit physiologically from MBCT. This is yet to be determined and future research will be advantageous in this area. Furthermore, as Sullivan and colleagues (2009) found in CHF patients undergoing a mindfulness-based intervention, it is also likely that depressed CHD patients will benefit physiologically from MBCT in terms of decreasing depressive symptoms and improving QoL. Considering NoCAD patients exhibit greater levels of depression symptoms than obstructive patients (findings of Study 1), MBCT may be an ideal treatment for this patient group, especially if their chest pain is psychiatric in nature. Treating the disorder (i.e., depression) may also treat the symptoms (i.e., chest pain). MBCT may therefore be used as a possible psychotherapy alternative for both obstructive and non-obstructive CAD.

1.4. Summary

The quote: "Depression is bad for my heart, and my heart is bad for my depression. How depressing is that!" (Bellas & Harvard News Office, 2006) highlights the reciprocal relationship between depression and CHD that has inspired this work.

The three independent studies detailed in this thesis support the premise that both depression and CHD are significant problems. The findings of Studies 1 and 2 provide support for screening CHD patients for depression, as they highlight the prevalence and increased risk of depression in obstructive and NoCAD patients (Study 1), and demonstrate the relevance of depression for mortality (Study 2). Consistent with previous studies, the findings of Study 3 provide further evidence of the effectiveness of MBCT for depressive symptoms and QoL in mental health outpatients. The study also underpins the importance of research into the role of the ANS in both depression and CHD by exploring the feasibility of addressing HRV with a mindfulness intervention (MBCT) in future studies.

Importantly, the combined studies addressed areas that lacked sufficient research: (1) depression in patients with normal coronary arteries and chest pain (i.e.,

NoCAD), (2) predictors of mortality in an Australian population, and (3) MBCT and HRV. Findings of the studies contribute and expand knowledge in the fields of psychology, psychiatry and medicine, and have the potential to decrease depression among CHD patients, which may subsequently reduce mortality. Further large-scale and longer-term research on depression, CHD, MBCT and HRV will help to translate the findings of this research into clinical practice.

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APPENDICES

Appendix A

Short Form-36 Questionnaire

SHORT FORM-36
(SF-36)

INSTRUCTIONS: This questionnaire asks for your views about your health, how you feel and how well you are able to do your usual activities.

Answer every question by marking the answer as indicated. If you are unsure about how to answer a question, please give the best answer you can.

1. In general, would you say your health is: (circle one)

Excellent Very good Good Fair Poor

2. <u>Compared to one year ago</u>, how would you rate your health in general <u>now</u>? (circle one)

Much better now than one year ago

Somewhat better now than one year ago

About the same as one year ago

Somewhat worse than one year ago

Much worse than one year ago

3. The following questions are about activities you might do during a typical day. Does <u>your health now limit you</u> in these activities? If so, how much? (Mark each answer with an X)

<u>ACTIVITIES</u>	**Yes, Limited A Lot**	**Yes, Limited A Little**	**No, Not Limited At All**
a. Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports			
b. Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf			
c. Lifting or carrying groceries			
d. Climbing several flights of stairs			
e. Climbing one flight of stairs			
f. Bending, kneeling or stooping			
g. Walking more than one kilometre			
h. Walking half a kilometre			
i. Walking 100 metres			
j. Bathing or dressing yourself			

Test Phase __ Patient Number __ __

4. During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of your physical health? (Mark each answer with an X)

	YES	NO
a. Cut down on the amount of time you spent on work or other activities		
b. Accomplished less than you would like		
c. Were limited in the kind of work or other activities		
d. Had difficulty performing the work or other activities (for example, it took extra effort)		

5. During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)? (Mark each answer with an X)

	YES	NO
a. Cut down the amount of time you spent on work or other activities		
b. Accomplished less than you would like		
c. Didn't do work or other activities as carefully as usual		

6. During the past 4 weeks, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups? (circle one)

Not at all Slightly Moderately Quite a bit Extremely

7. How much bodily pain have you had during the past 4 weeks? (circle one)

None Very mild Mild Moderate Severe Very severe

8. During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?

Not at all A little bit Moderately Quite a bit Extremely

Test Phase __ Patient Number __ __

9. These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the past 4 weeks. (Mark each answer with an X)

	All of the Time	Most of the Time	A Good Bit of the Time	Some of the Time	A Little of the Time	None of the Time
a. Did you feel full of life?						
b. Have you been a very nervous person?						
c. Have you felt so down in the dumps that nothing could cheer you up?						
d. Have you felt calm and peaceful?						
e. Did you have a lot of energy?						
f. Have you felt downhearted and blue?						
g. Did you feel worn out?						
h. Have you been a happy person?						
i. Did you feel tired?						

10. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting with friends, relatives, etc)? (circle one)

All of the time Most of the time Some of the time A little of the time None of the time

11. How TRUE or FALSE is each of the following statements for you? (Mark each answer with an X)

	Definitely True	Mostly True	Don't Know	Mostly False	Definitely False
a. I seem to get sick a little easier than other people					
b. I am as healthy as anybody I know					
c. I expect my health to get worse					
d. My health is excellent					

Test Phase __ Patient Number __ __

Appendix B

Seattle Angina Questionnaire

SEATTLE ANGINA QUESTIONNAIRE

Although for some people with several medical problems, it is difficult to determine what it is that limits them, please go over the activities listed below and indicate how much limitation you have had due ***to chest pain, chest tightness, or angina over the past 4 weeks.***

1.	*(Mark one box only for each statement)*	**Extremely limited**	**Quite a bit limited**	**Moderately limited**	**Slightly limited**	**Not Limited at all**	**Limited or did not do for other reasons**
A	Dressing yourself	☐	☐	☐	☐	☐	☐
B	Walking indoors on level ground	☐	☐	☐	☐	☐	☐
C	Showering	☐	☐	☐	☐	☐	☐
D	Climbing a hill or a flight of stairs without stopping	☐	☐	☐	☐	☐	☐
E	Gardening, vacuuming or carrying groceries	☐	☐	☐	☐	☐	☐
F	Walking more than a 100m at a brisk pace	☐	☐	☐	☐	☐	☐
G	Running or jogging	☐	☐	☐	☐	☐	☐
H	Lifting or moving heavy objects (eg. furniture, children)	☐	☐	☐	☐	☐	☐
I	Participating in strenuous sports (eg. drinking, tennis)	☐	☐	☐	☐	☐	☐

2. **Compared with 4 weeks ago**, how often do you have chest pain, chest tightness or angina when doing your most strenuous activity?

Much more often	**Slightly more often**	**About the same**	**Slightly less often**	**Much less often**	**I have had No chest pain over the last 4 weeks**
☐	☐	☐	☐	☐	☐

3. Over the **past 4 weeks**, on average, how many times have you had chest pain, chest tightness, or anginal attacks?

4 or more times per day	1-3 times per day	3 or more times per week but not every day	1-2 times per week	Less than once a week	None over the past 4 weeks
☐	☐	☐	☐	☐	☐

4. Over the **past 4 weeks**, on average, how many times have you had to use nitrolingual spray an anginine, or Isordil tablet under the tongue to relieve chest pain, chest tightness or anginal attacks?
I have used them….

4 or more times per day	1-3 times per day	3 or more times per week but not every day	1-2 times per week	Less than once a week	None over the past 4 weeks
☐	☐	☐	☐	☐	☐

5. How bothersome is it for you to take your pills for chest pain, chest tightness or anginal attacks ?

Extremely bothersome	Quite a bit bothersome	Moderately bothersome	Slighty bothersome	Not bothersome at all	My doctor has not prescribed pills
☐	☐	☐	☐	☐	☐

6. How satisfied are you that everything possible is being done to treat your chest pain, chest tightness, or anginal attacks?

Not satisfied at all	Mostly dissatisfied	Somewhat satisfied	Mostly satisfied	Completely satisfied
☐	☐	☐	☐	☐

7. How satisfied are you with the explanations your doctor has given you about your chest pain, chest tightness, or anginal attacks?

Not satisfied at all	Mostly dissatisfied	Somewhat satisfied	Mostly satisfied	Completely satisfied
☐	☐	☐	☐	☐

8. Overall, how satisfied are you with the current treatment of your chest pain, chest tightness, or anginal attacks?

Not satisfied at all	Moderately dissatisfied	Somewhat satisfied	Mostly satisfied	Highly satisfied
☐	☐	☐	☐	☐

9. Over the **past 4 weeks**, how much has your chest pain, chest tightness or anginal attacks interfered with your enjoyment of life?

It has extremely limited my enjoyment of life	It has limited my enjoyment of life quite a bit	It has moderately limited my enjoyment of life	It has slightly limited my enjoyment of life	It has not limited my enjoyment of life
☐	☐	☐	☐	☐

10. If you had to spend the rest of your life with your chest pain, chest tightness, or angina attacks the way it is at the moment, how would you feel about this?

Not satisfied at all	Moderately dissatisfied	Somewhat satisfied	Mostly satisfied	Highly satisfied
☐	☐	☐	☐	☐

11. How often do you worry that you may have a heart attack or die suddenly?

I think or worry about it all the time	I often think or worry about it	I occasionally think or worry about it	I rarely think or worry about it	I never think or worry about it
☐	☐	☐	☐	☐

Appendix C

Center for Epidemiologic Studies Depression Scale

CENTER FOR EPIDEMIOLOGIC STUDIES DEPRESSION SCALE (CES-D)

Tick the box for each statement that best describes how often you felt this way **during the past week.**

During the past week:	**Rarely or none of the time (0-1 day)**	**Some or a little of the time (1-2 days)**	**Occasionally or a moderate amount of the time (3-4 days)**	**Most or all of the time (5-7 days)**
1) I was bothered by things that usually don't bother me	☐	☐	☐	☐
2) I did not feel like eating; my appetite was poor	☐	☐	☐	☐
3) I felt that I could not shake off the blues even with help from my family and friends	☐	☐	☐	☐
4) I felt that I was just as good as other people	☐	☐	☐	☐
5) I had trouble keeping my mind on what I was doing	☐	☐	☐	☐
6) I felt depressed	☐	☐	☐	☐
7) I felt that everything I did was an effort	☐	☐	☐	☐
8) I felt hopeful about the future	☐	☐	☐	☐
9) I thought my life had been a failure	☐	☐	☐	☐
10) I felt fearful	☐	☐	☐	☐
11) My sleep was restless	☐	☐	☐	☐
12) I was happy	☐	☐	☐	☐
13) I talked less than usual	☐	☐	☐	☐
14) I felt lonely	☐	☐	☐	☐
15) People were unfriendly	☐	☐	☐	☐
16) I enjoyed life	☐	☐	☐	☐
17) I had crying spells	☐	☐	☐	☐
18) I felt sad	☐	☐	☐	☐
19) I felt that people disliked me	☐	☐	☐	☐
20) I could not "get going"	☐	☐	☐	☐

Test Phase __ Patient Number __ __

Appendix D

Hospital Anxiety and Depression Scale

HOSPITAL ANXIETY AND DEPRESSION SCALE (HADS)

Please read each item below and place an "X" on the answer that best describes how you have been feeling **during the past week**. Don't take too long over your replies; spontaneous answers are more important. Mark only one answer for each question.

1. I feel tense or 'wound up':
- Most of the time ☐
- A lot of the time ☐
- From time to time, occasionally ☐
- Not at all ☐

2. I still enjoy the things I used to enjoy:
- Definitely as much ☐
- Not quite so much ☐
- Only a little ☐
- Hardly at all ☐

3. I get a sort of frightened feeling as if something awful is about to happen:
- Very definitely and quite badly ☐
- Yes, but not too badly ☐
- A little, but it doesn't worry me ☐
- Not at all ☐

4. I can laugh and see the funny side of things:
- As much as I always could ☐
- Not quite as much now ☐
- Definitely not so much now ☐
- Not at all ☐

5. Worrying thoughts go through my mind:
- A great deal of the time ☐
- A lot of the time ☐
- From time to time, but not too often ☐
- Only occasionally ☐

6. I feel cheerful:
- Not at all ☐
- Not often ☐
- Sometimes ☐
- Most of the time ☐

7. I can sit at ease and feel relaxed:
- Definitely ☐
- Usually ☐
- Not often ☐
- Not at all ☐

8. I feel as if I am slowed down:
- Nearly all the time ☐
- Very often ☐
- Sometimes ☐
- Not at all ☐

9. I get a sort of frightened feeling like 'butterflies' in the stomach:
- Not at all ☐
- Occasionally ☐
- Quite often ☐
- Very often ☐

10. I have lost interest in my appearance:
- Definitely ☐
- I don't take so much care as I should ☐
- I may not take quite as much care ☐
- I take just as much care as ever ☐

11. I feel restless as if I have to be on the move:
- Very much indeed ☐
- Quite a lot ☐
- Not very much ☐
- Not at all ☐

12. I look forward with enjoyment to things:
- As much as I ever did ☐
- Rather less than I used to ☐
- Definitely less than I used to ☐
- Hardly at all ☐

13. I get sudden feelings of panic:
- Very often indeed ☐
- Quite often ☐
- Not very often ☐
- Not at all ☐

14. I can enjoy a good book or radio or TV programme:
- Often ☐
- Sometimes ☐
- Not often ☐
- Very seldom ☐

Appendix E

Multidimensional Scale of Perceived Social Support

MULTIDIMENSIONAL SCALE OF PERCEIVED SOCIAL SUPPORT (MSPSS)

INSTRUCTIONS:

We are interested in how you feel about the following statements. Please read each statement carefully and indicate how you feel about each statement using the scale below.

1=Very strongly disagree
2=Strongly agree
3=Mildly disagree
4=Neutral
5=Mildly agree
6=Strongly agree
7=Very strongly agree

Place the appropriate number on the blank line beside each statement.

1. There is a special person who is around when I am in need. _____
2. There is a special person with whom I can share my joys and sorrows. _____
3. My family really tries to help me. _____
4. I get the emotional help and support I need from my family. _____
5. I have a special person who is a real source of comfort to me. _____
6. My friends really try to help me. _____
7. I can count on my friends when things go wrong. _____
8. I can talk about my problems with my family. _____
9. I have friends with whom I can share my joys and sorrows. _____
10. There is a special person in my life who cares about my feelings. _____
11. My family is willing to help me make decisions. _____
12. I can talk about my problems with my friends. _____

Appendix F

Life Orientation Test-Revised

LIFE ORIENTATION TEST-REVISED

(LOT-R)

INSTRUCTIONS:

Please answer the following statements about yourself by indicating the extent of your agreement using the scale below. Please be an honest and accurate as you can, and try not to let your response to one question influence your response to other questions. There are no right or wrong answers.

0=Strongly disagree

1=Disagree

2=Neutral

3=Agree

4=Strongly agree

Place the appropriate number on the blank line beside each statement.

1. In uncertain times, I usually expect the best. _____
2. It's easy for me to relax. _____
3. If something can go wrong for me, it will. _____
4. I'm always optimistic about my future. _____
5. I enjoy my friends a lot. _____
6. It's important for me to keep busy. _____
7. I hardly ever expect things to go my way. _____
8. I don't get upset too easily. _____
9. I rarely count on good things happening to me. _____
10. Overall, I expect more good things to happen to me than bad. _____

Appendix G

Participant Invitation Letter

Government of South Australia
Central Northern Adelaide Health Service

CENTRAL NORTHERN ADELAIDE HEALTH SERVICE
The Queen Elizabeth Hospital & Lyell McEwin Hospital

INVITATION

……../……../……..

Dear ……..…….

The cardiology and psychiatry departments at The Queen Elizabeth Hospital in conjunction with the Centre for Treatment of Anxiety and Depression (CTAD) are undertaking a study entitled 'The effect of mindfulness on heart rate variability in a group of depressed patients'.

This study aims to determine whether mindfulness can improve heart rate variability, increase quality of life and reduce depressive symptoms. Patients undertaking mindfulness therapy at CTAD in Thebarton are invited to participate.

Please find enclosed a patient information sheet, outlining the background, purpose and method of the study, a consent form and two questionnaires. If you wish to participate in this study, please complete the enclosed consent form, Health/Lifestyle and CES-D questionnaire, and return it in the reply-paid envelope provided.

Thank you for your time.

Yours sincerely

Alexis Wheeler
PhD Candidate

Appendix H

Patient Information Sheet

Government of South Australia
Central Northern Adelaide Health Service

CENTRAL NORTHERN ADELAIDE HEALTH SERVICE
The Queen Elizabeth Hospital & Lyell McEwin Hospital

PATIENT INFORMATION SHEET

Title: The Effect of Mindfulness on Heart Rate Variability in a Group of Depressed Patients.

INVITATION TO PARTICIPATE
We invite you to participate in a research project which we believe is of potential importance.
However, before you decide whether or not you wish to participate, we need to be sure that you understand

why we are doing it, and
what it would involve if you agreed.

We are therefore providing you with the following information.
Please read it carefully and be sure to ask any questions you have.
The Doctor conducting the research will be happy to discuss it with you and answer any questions that you may have.
You are also free to discuss it with outsiders if you wish (ie family, friends and / or your local Doctor)
You do not have to make an immediate decision.
Your participation is purely voluntary.
Should you agree to enter the trial, you may change your mind and withdraw at any stage.

PARTICIPATION IS VOLUNTARY
Participation in any research project is voluntary. If you do not wish to take part, you are not obliged to. If you decide to take part and later change your mind, you are free to withdraw from the project at any stage without providing a reason.

Your decision to take part, not to take part or to withdraw will not affect your routine treatment, your relationship with those treating you, or your relationship with The Queen Elizabeth Hospital.

BACKGROUND TO THE STUDY
- *What is the research about?*

This study aims to determine whether mindfulness can improve heart rate variability, increase quality of life and reduce depressive symptoms.

- *Why is the research being done?*

Research has shown that heart rate variability (the beat to beat changes in heart rate) can be a good indicator of some illnesses. It has been investigated in depressed people undergoing meditation, yoga and tai chi, but not significantly in conjunction with mindfulness. Results from these studies have shown that it is possible to promote a

change in heart rate variability. It is also well known that depression can be a significant problem, sometimes with adverse health consequences, and the potential for an altered quality of life.

- *Who is sponsoring it, and are they paying the researcher or his/her department to do the research?*

This research is not being sponsored.

- *How and why have I been chosen as a possible participant in the research?*

Patients undertaking mindfulness sessions at the Centre for Treatment of Anxiety and Depression (CTAD) in Thebarton will be invited to participate in this study.

- *How many other people have been asked to consider participating?*

Approximately 34 people will be asked to participate in this study.

PROCEDURES AND TREATMENT

- *Will I have to come back to the clinic more often or remain in hospital for longer than would normally be the case?*

You will have three appointments at The Queen Elizabeth Hospital in Woodville, eight weeks apart. Each appointment will be approximately 1 ½ hours in duration. You do not need to stay in hospital for any of these appointments.

1st appointment: 9 weeks preceding your first mindfulness session
2nd appointment: the week preceding your first mindfulness session
----No Appointment, Mindfulness Sessions for 8 weeks---
3rd appointment: the week following your last mindfulness session

- *What will I be asked to do at each visit?*

During your visits you will you be asked to undertake physical measurements (weight, height and waist measurements), an electrocardiogram (ECG) and complete two short questionnaires; one about your quality of life and the other on your attentional capacity. On your second and third visits, you will be required to complete an additional two questionnaires; the Health/Lifestyle questionnaire and CES-D (the same questionnaires you completed 8 weeks prior).
*You will be required to withdrawal from eating/drinking caffeinated products, alcohol, illicit drugs and smoking for 4 hours prior to each visit to the QEH.

- *How long will my participation in the study last?*

You will be involved in the study for approximately 20 weeks.

- *What procedures will I be asked to submit to including exposure to radiation and what will be the likely effects?*

Your heart rate will be recorded using an electrocardiogram (ECG). An ECG is non-invasive and painless, and works using electrodes (small sensors) that stick onto the surface of your skin (small areas may need to be shaved for proper adhesion). While being recorded by the ECG, you will lie flat on a bed in a quiet room for 30 minutes. You will be then asked to complete a questionnaire for 5 minutes, and then rest for another 20 minutes, while still being connected to the ECG. (There will be no exposure to radiation in this study).

- *What treatment will I get if I do take part? Will this be different from the treatment I would get otherwise? If so, how and in what ways?*

If you take part you will undergo an ECG. Your usual treatment at CTAD will continue as usual.

- *If I decide not to take part what other treatments are available to me?*

If you decide not to take part, your usual treatment will continue.

- *Will the decisions about my treatment be made by my usual doctor or by someone else?*

Decisions about your treatment will be made by your usual doctor.

- *Are there any factors, which would exclude me from participating, like pre-existing illness, the possibility of becoming pregnant or other drugs being taken?*

You will be unable to participate if you have a pace maker, certain cardiovascular diseases, an irregular heart beat, or are taking beta or calcium channel blockers. If you change your medications, or substantially change your alcohol, caffeine or drug usage during the study, your participation may not be required any further.

PATIENT MANAGEMENT

- *What would happen if I were to feel severe discomfort or pain?*

If you were to feel severe discomfort of pain, which is extremely unlikely in this study you should contact Alexis Wheeler on 0406 561 096, or your GP.

MEDICINES AND DRUGS

- *What are the names and amounts of the drugs which I will be given?*

This study does not involve the use or administration of any type of medicine or drug.

DISCOMFORTS, RISKS AND SIDE EFFECTS

- *Will there be any discomforts, such as additional needles, biopsies, or pain?*

The research procedures, questionnaires and use of the ECG monitor, are completely non-invasive and painless, and should not cause any discomfort during or after the study. The ECG monitor is a recording only device and does not send out electricity, therefore does not pose any harm.

- *Are there likely to be side effects from the research procedures, and if so what are they?*

There are no known side effects for the testing procedures associated with this study.

- *Who should I contact if I am worried about any effects that I experience?*

You should contact Alexis Wheeler on 0406 561 096.

- *Would I be withdrawn from the study if my condition became worse or if any extra risks came to light during the course of it?*

If this were to happen you would be withdrawn from the study.

- *Are there any activities I should refrain from during and in the period following the research and for how long, eg. blood donations, taking other medication, sexual activity (with or without attempting to achieve a pregnancy) exposure to sunlight, driving, taking part in other studies?*

There are no activities which should be avoided during or after completion of the study.

- *To what extent is the radiation additional to normal treatment and what extra risks are involved?*

No radiation exposure is involved in this study.

PREGNANCY

- *If the protocol requires participants to refrain from becoming pregnant, please include the potential risks involved, the methods of contraception recommended, and the duration for which such methods should be used both during, and after participation.*

There are no risks associated with becoming pregnant during the study.

WHAT WILL HAPPEN TO THE INFORMATION COLLECTED?

- *How will my confidentiality be protected – will the information and results be de-identified?*

All participant data will be identified with a unique code rather than using the participant name. This information will be placed into a file and stored confidentially. Only the chief investigator will have access to the file. The data that will be used for analysis will also be identified by the unique code.

- *Will I be informed about the results of the study?*

Participants will be informed of the outcome of the study when the study has been completed and the results analysed.

- *How long will my information be stored for?*

Your information will be safely stored for a period of 15 years after completion of the study.

WHAT ARE MY RIGHTS?

If you become injured during this study, and your injury is a direct result of the effects of study procedures, The Queen Elizabeth Hospital will provide reasonable medical treatment. Your participation in this study shall not affect any other right to compensation you may have under common law.

- *How can I obtain more information?*

You can obtain more information by contacting Alexis Wheeler on XXXX XXX XXX.

IS THERE ANY PAYMENT FOR PARTICIPATION?

- *Will I be paid for my participation? (Including reimbursement for time, travel, procedures or medications)*

No reimbursement for time, travel or participation is possible in this study.

BENEFITS OF THE RESEARCH

- *Is there any chance that the proposed research will be of benefit to me personally, or to future patients with the same condition?*

This study may not benefit you personally but future patients may benefit from the findings of the study, specifically those with altered heart rate variability.

- *Were the new treatment to be of benefit to me, could I continue with the treatment after the trial?*

The study does not involve a new treatment. However, if you find mindfulness therapy helpful there are groups available where you can continue to practice mindfulness.

- *If not, what medical care and follow up will I receive after the trial?*

Your care will continue at CTAD.

WHAT IF I HAVE A QUESTION ABOUT THE STUDY?

- *How can I obtain more information about this study?*

You can obtain more information by contacting Alexis Wheeler on XXXX XXX XXX.

The Central Northern Adelaide Health Service Ethics of Human Research Committee (TQEH & LMH) has approved this study.
Should you wish to speak to a person not directly involved in the study in relation to

- matters concerning policies,
- information about the conduct of the study
- your rights as a participant, or

should you wish to make a confidential complaint, you may contact The Executive Officer of this Committee, on (08) 8222 6841

Appendix I

Participation Consent Form

Government of South Australia
Central Northern Adelaide Health Service

CENTRAL NORTHERN ADELAIDE HEALTH SERVICE
The Queen Elizabeth Hospital & Lyell McEwin Hospital

CONSENT FORM

Title: The Effect of Mindfulness on Heart Rate Variability in a Group of Depressed Patients.

I, the undersigned .....

hereby consent to my involvement in the research project explained above.

- I have read the information sheet, and I understand the reasons for this study. The research worker has explained the ways in which it will affect me. My questions have been answered to my satisfaction. My consent is given voluntarily.

- I understand that the purpose of this research project is to improve the quality of medical care, but my involvement may not be of benefit to me.

- The details of the research project have been explained to me, including:
  - The expected time it will take
  - The nature of any procedures being performed, and the number of times they will be performed
  - Any discomfort which I may experience

- I have been given the opportunity to have a member of family or a friend present while the project was explained to me.
- My identity will be kept confidential, and nothing will be published which could possibly reveal my identity.
- My involvement in the study will not affect my relationship with my medical advisers. I understand that I am able to withdraw from the study at any stage without having to give a reason, and that by withdrawing it will not affect my treatment at this hospital in the future.

PATIENT SIGNATURE ..... **DATE** ……/……./…….

WITNESS: ..... **DATE** ……/……./…….

INVESTIGATOR ..... **DATE** ……/……./…….

Appendix J

Health and Lifestyle Questionnaire

HEALTH/LIFESTYLE QUESTIONNAIRE and CES-D QUESTIONNAIRE

If you wish to participate in this study, please complete the enclosed *consent form*, *Health/Lifestyle* and *CES-D questionnaire*, and return it in the reply-paid envelope provided.

This *Health/Lifestyle questionnaire* contains questions about your health and lifestyle. The *CES-D questionnaire* contains questions about how you felt during the past week.

Please read the instructions above each question very carefully and then tick each box that applies to you.

There are no right or wrong answers, but your honest answer is important for the accuracy of my study. The answers you give in the survey will remain strictly confidential, and your privacy will be protected at all times.

In a study, sometimes questions arise which require further explanation. If you need help to answer any questions, or have any queries regarding this questionnaire, you are welcome to call me on XXXX XXX XXX.

Thank you for taking part in this study.

Alexis
PhD Candidate

HEALTH AND LIFESTYLE QUESTIONNAIRE

Age ……..…..

Gender Male / Female (Please circle one)

Have you ever had any of the following? (Please tick one box for each question)	Yes	No	If 'yes', what age did you first have the condition?
a. Heart attack (also known as myocardial infarction)	❑	❑	
b. Angina	❑	❑	
c. Heart failure	❑	❑	
d. Palpitations (unusual/irregular heart beats)	❑	❑	
e. Atrial fibrillation	❑	❑	
f. Atrial flutter	❑	❑	
g. Left/right bundle branch block	❑	❑	
h. Cardiomyopathy	❑	❑	
i. A pacemaker	❑	❑	
j. High blood pressure	❑	❑	
k. Low blood pressure	❑	❑	
l. High cholesterol (high blood fats)	❑	❑	
m. Mini-stroke (TIA) or stroke	❑	❑	

Are you colour blind? (Please tick one box only)

Yes	❑
No	❑

Which of the following best describes your smoking status (Please tick one box only)

I've never smoked	❑
I smoke daily	❑
I smoke occasionally	❑
I don't smoke now, but I used to	❑
I've tried it a few times but never smoked regularly	❑

How often do you take illicit drugs? (Please tick one box only)

I don't take illicit drugs	❑
Less than once a week	❑
1, 2, or 3 days a week	❑
4, 5 or 6 days a week	❑
Every day	❑

Test Phase __ Patient Number __ __

How often do you usually drink alcohol? (Please tick one box only)

I don't drink alcohol	❑
Less than once a week	❑
1, 2, or 3 days a week	❑
4, 5 or 6 days a week	❑
Every day	❑

On a day that you drink, how many alcoholic drinks do you usually have? (A standard drink is equivalent to a schooner or midi of beer, a glass of wine or a nip of sprits) (Please tick one box only)

1 to 2 drinks	❑
3 to 4 drinks	❑
5 to 8 drinks	❑
9 to 12 drinks	❑
13 to 20 drinks	❑
21 or more	❑

How often do you usually drink caffeinated products? (eg coffee, soft drink) (Please tick one box only)

I don't drink caffeine	❑
Less than once a week	❑
1, 2, or 3 days a week	❑
4, 5 or 6 days a week	❑
Every day	❑

On a day that you drink, how many caffeinated drinks do you usually have? (Please tick one box only)

1 to 2 drinks	❑
3 to 4 drinks	❑
5 to 8 drinks	❑
9 to 12 drinks	❑
13 to 20 drinks	❑
21 or more	❑

Please list any prescription medication you are currently taking, and how long you have been taking it for. (It is vital to list any anti-depressant medication)

Name of medication	How long

Test Phase __ Patient Number __ __

Has your doctor told you he/she is changing your anti-depressant medication, or are you planning on requesting a change in the near future? (Please tick one box only)

Yes	❑
No	❑
Not sure	❑

Test Phase __ Patient Number __ __

Appendix K

Participation Thank You Letter

Government of South Australia
Central Northern Adelaide Health Service

CENTRAL NORTHERN ADELAIDE HEALTH SERVICE
The Queen Elizabeth Hospital & Lyell McEwin Hospital

THANK YOU

Title: The Effect of Mindfulness on Heart Rate Variability in a Group of Depressed Patients.

Dear ……..…….

Thank you for consenting to take part in this study, and taking the time to complete the questionnaire.

You are not required for any further aspects of this study but you are thanked for your participation.

Many thanks again for your involvement. I wish you all the best for the future.

Yours sincerely

Alexis Wheeler

PhD Candidate

Appendix L

GP Information Letter

Government of South Australia
Central Northern Adelaide Health Service

CENTRAL NORTHERN ADELAIDE HEALTH SERVICE
The Queen Elizabeth Hospital & Lyell McEwin Hospital

GP INFORMATION SHEET

……../……../……..

Dear Doctor

I am writing to inform you that your patient ……..…… of ……..... has volunteered to participant in a study analysing the effect of mindfulness on heart rate variability in a group of depressed patients.

In brief, this study requires participants to attend The Queen Elizabeth Hospital to undergo ECG monitoring, and answer several questionnaires.

If you have any concerns regarding your patient's involvement or queries regarding the study please do not hesitate to contact me on XXXX XXX XXX.

Yours sincerely

Alexis Wheeler
PhD Candidate

Appendix M

Interview Questions Form

INTERVIEW QUESTIONS

1st APPOINTMENT

GP Information

Name of Doctor:

Medical Centre:

Address:

Will you be attending the mindfulness course for depression, anxiety, both or other?

Are you currently undertaking any other psychotherapy? (e.g. psychologist, psychiatrist, counsellor, cognitive behaviour therapy, meditation/yoga)

Test Phase __ Patient Number __ __

1st, 2nd and 3rd APPOINTMENT
In the last 4 hours…

	1st appointment	2nd appointment	3rd appointment
Alcohol			
Smoked			
Caffeine			
Illicit drugs			
Food			

(if yes to food, inform participant to eat a similar meal at similar time before each appointment)

	1st appointment	2nd appointment	3rd appointment
Height (cm)			
Weight (kg)			
Waist circumference (cm)			

2nd and 3rd APPOINTMENT
Are you still planning on attending the mindfulness course?

Have you changed (started any new or stopped) any of your psychotherapy?

Have you changed doses, started any new or stopped any of your prescription medication?

3rd APPOINTMENT
Did you attend all of your mindfulness course sessions?

Test Phase __ Patient Number __ __

Appendix N

Individual Results Letter

Government of South Australia
Central Northern Adelaide Health Service

CENTRAL NORTHERN ADELAIDE HEALTH SERVICE
The Queen Elizabeth Hospital & Lyell McEwin Hospital

……../……../……..

Dear ……..…….

Thank you for your participation in my study analysing 'The Effect of Mindfulness on Heart Rate Variability in a Group of Depressed Patients'. Your time and effort was greatly appreciated.

Enclosed is a copy of your electrocardiograph (ECG). We suggest you give this to your general practitioner for inclusion in your clinical files. This is a useful baseline recording for future comparisons, if necessary. For your interest, your enclosed ECG shows normal heartbeat (referred to as sinus rhythm) and no evidence of a previous heart attack.

If you have any questions or would like further explanation please feel free to call me on XXXX XXX XXX.

Again, thank you for your time. I wish you all the best in the future.

Kind regards

Alexis Wheeler

PhD Candidate

Appendix O

SPSS Syntax of the Detected Hazard Ratio for Cardiac Mortality in Acute Myocardial Infarction Patients

```
. stpower logrank .857, n(336) power(.8) p1(.1667)

Estimated hazard ratio for two-sample comparison of survivor functions
Log-rank test, Freedman method
Ho: S1(t) = S2(t)

Input parameters:

      alpha =    0.0500  (two sided)
         s1 =    0.8570
         s2 =    0.9538
          N =       336
      power =    0.8000
         p1 =    0.1667

Estimated number of events and hazard ratio:

          E =        21
     hratio =    0.3066

. display 1/0.3066
3.2615786
```

Appendix P

Achieved Hazard Ratios for Predictors of Cardiac Mortality in Acute Myocardial Infarction Patients

Predictor	**Hazard ratio (95% CI)**	***p*-value**
Age, years	1.11 (1.06-1.17)	<0.001
PSSS perceived social support	0.65 (0.43-0.99)	0.04
CES-D depression (≥ 27)	2.82 (0.88-9.03)	0.08