Associations Between Depression and Coronary Heart Disease

Alexis Wheeler

School of Psychology
Faculty of Health Sciences
The University of Adelaide
South Australia
Australia

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

December 2014
Table of Contents

Table of Contents ........................................................................................................ i
List of Tables ................................................................................................................. v
List of Figures ................................................................................................................ vi
List of Appendices ......................................................................................................... viii
Abstract ......................................................................................................................... ix
Declaration ..................................................................................................................... xi
List of Publications ....................................................................................................... xii
Acknowledgements ...................................................................................................... xiii
List of Abbreviations .................................................................................................... xiv

CHAPTER ONE: BACKGROUND ............................................................................. 1
PREAMBLE .................................................................................................................... 2

1. DEPRESSION........................................................................................................... 5
   1.1. Key Concepts ...................................................................................................... 5
   1.2. Diagnosis ......................................................................................................... 8
   1.3. Prevalence ...................................................................................................... 9
   1.4. Health Outcomes, Health Status and Quality of Life ..................................... 11
   1.5. Aetiology: Risk and Protective Factors .......................................................... 12
   1.6. Treatment and Prognosis .............................................................................. 18

2. MINDFULNESS-BASED COGNITIVE THERAPY ......................................... 23
   2.1. History of Mindfulness-Based Cognitive Therapy ......................................... 23
   2.2. Mindfulness-Based Cognitive Therapy and Depression Literature ............. 25
   2.3. Mindfulness-Based Cognitive Therapy and Physiology ............................... 26

3. THE HEART .......................................................................................................... 27
   3.1. Structure and Function of the Heart and Arteries ......................................... 27
      3.1.1. Components of the Heart ........................................................................ 27
      3.1.2. Electrical Conduction in the Heart ......................................................... 29
      3.1.3. Coronary Arteries ................................................................................. 32

4. CORONARY HEART DISEASE .......................................................................... 36
   4.1. Prevalence ..................................................................................................... 37
   4.2. Common Symptoms ...................................................................................... 38
   4.3. Pathophysiology .......................................................................................... 40
      4.3.1. Myocardial Ischaemia .......................................................................... 42
4.4. Coronary Angina Syndromes.................................................................43
  4.4.1. Acute Coronary Syndromes .........................................................44
  4.4.2. Chronic Coronary Syndromes ......................................................45
4.5. Diagnosis............................................................................................46
5. NON-OBSTRUCTIVE CORONARY HEART DISEASE..............................49
  5.1. Prevalence..........................................................................................49
  5.2. Prognosis ............................................................................................50
  5.3. Aetiology of Non-Obstructive Coronary Heart Disease.......................50
      5.3.1. Cardiac Aetiology........................................................................52
      5.3.2. Non-Cardiac Aetiology ...............................................................53
6. CORONARY HEART DISEASE AND DEPRESSION.................................56
  6.1. Prevalence..........................................................................................56
  6.2. Aetiology of Depression and Coronary Heart Disease.......................58
      6.2.1. Mechanisms Linking Depression and Coronary Heart Disease .......59
      6.2.2. Relationship Between Depression and Coronary Heart Disease: A
             ‘Causal Network’ ...........................................................................70
7. THE AUTONOMIC NERVOUS SYSTEM.................................................72
  7.1. Structure and Function of the Autonomic Nervous System...............72
  7.2. Autonomic Nervous System Regulation of Heart Rate.......................76
  7.3. Autonomic Dysfunction ....................................................................78
  7.4. Autonomic Mechanisms Linking Depression and Coronary Heart
      Disease.................................................................................................79
      7.4.1. Sympathetic Nervous System Mechanisms ...................................80
      7.4.2. Parasympathetic Nervous System Mechanisms ............................84
  7.5. Measurement of Autonomic Nervous System Activity ........................85
8. HEART RATE VARIABILITY ...................................................................86
  8.1. Heart Rate Variability Definition and Uses ........................................86
  8.2. Heart Rate Variability and the Autonomic Nervous System ...............87
  8.3. Measurement of Heart Rate Variability ..............................................88
      8.3.1. Time Domain Statistical Methods ...............................................88
      8.3.2. Time Domain Geometric Methods ..............................................89
      8.3.3. Frequency Domain Methods .......................................................92
      8.3.4. Non-Linear Methods ...................................................................96
  8.4. Heart Rate Variability in Coronary Heart Disease and Depression .......97
8.5. Influences on Heart Rate Variability .................................................... 98
  8.5.1. Individual Factors ........................................................................ 98
  8.5.2. Environmental Factors ................................................................. 100
  8.5.3. Behavioural Factors ................................................................. 100
  8.5.4. Medical and Psychological Conditions ...................................... 104
  8.5.5. Prescription Medication ............................................................ 106
8.6. Heart Rate Variability and Literature .................................................. 109

SUMMARY .............................................................................................................. 115
CHAPTER TWO: THESIS OBJECTIVES .............................................................. 116
1. THESIS OBJECTIVES ................................................................................. 117
  1.1. Gaps Identified in the Literature ..................................................... 117
CHAPTER THREE: STUDY MEASUREMENT ..................................................... 120
1. MEASUREMENT ......................................................................................... 121
  1.1. Validity and Reliability .................................................................... 121
  1.2. Types of Instruments ....................................................................... 125
CHAPTER FOUR: STUDY 1 ............................................................................... 127
1. INSTRUMENTS .......................................................................................... 128
  1.1 Instruments Utilised .......................................................................... 128
    1.1.1. Generic Measure ...................................................................... 128
    1.1.2. Disease-Specific Measure ....................................................... 129
STATEMENT OF AUTHORSHIP ............................................................................ 130

Study 1: Prevalence of Depression in Patients with Chest Pain and Non-Obstructive Coronary Artery Disease .............................................................. 132

CHAPTER FIVE: STUDY 2 .................................................................................. 142
1. SURVIVAL ANALYSIS ................................................................................. 143
  1.1. What is Survival Analysis? ............................................................... 143
  1.2. Components Required ................................................................. 143
  1.3. Censoring ........................................................................................ 144
  1.4. Survival Time Distributions ............................................................ 145
  1.5. Survival Analysis Statistical Methods ............................................ 148
  1.6. Cox Regression Modelling .............................................................. 149
  1.7. Interpretation of Covariates ............................................................ 151
2. INSTRUMENTS ............................................................................................ 153
  2.1. Instruments Utilised .......................................................................... 153
2.1.1. Generic Measure .................................................................................................................. 153
2.1.2. Domain-Specific Measures ............................................................................................... 153
2.1.3. Other Measure .................................................................................................................. 155

STATEMENT OF AUTHORSHIP .................................................................................................. 156

Study 2: Depression and 5-Year Mortality in Patients with Acute Myocardial Infarction: Analysis of the IDACC Database ...................................................................................................... 158
Inclusion of Acute Coronary Syndrome ..................................................................................... 170

CHAPTER SIX: STUDY 3 .............................................................................................................. 174

1. STUDY DESIGN ......................................................................................................................... 175
   1.1. Design .................................................................................................................................. 175
   1.2. Testing Procedure .............................................................................................................. 177
   1.3. Sample: Inclusion and Exclusion ...................................................................................... 178

2. INSTRUMENTS .......................................................................................................................... 180
   2.1. Instruments Utilised ............................................................................................................ 180
      2.1.1. Generic Measure ............................................................................................................ 180
      2.1.2. Domain-Specific Measure ............................................................................................ 180
      2.1.3. Other Measure ............................................................................................................. 180

STATEMENT OF AUTHORSHIP .................................................................................................. 182

Study 3: Investigating the Effect of Mindfulness Training on Heart Rate Variability in Mental Health Outpatients: A Pilot Study .................................................................................. 184

CHAPTER SEVEN: DISCUSSION ................................................................................................ 199

1. DISCUSSION ............................................................................................................................. 200
   1.1. Summary of Findings ......................................................................................................... 201
   1.2. Methodological Strengths and Limitations ....................................................................... 205
   1.3. Clinical Implications and Recommendations for Future Research ......................... 209
   1.4. Summary ............................................................................................................................ 220

REFERENCES .................................................................................................................................. 222

APPENDICES .................................................................................................................................. 305
List of Tables

Table 1. Estimated and projected leading specific cause of disease burden in 2003 and 2010 ........................................... 3
Table 2. DSM-IV major depressive disorder symptoms ................................................. 7
Table 3. Differential diagnosis of chest pain ................................................................. 51
Table 4. Time domain parameters of heart rate variability ............................................ 91
Table 5. Frequency domain parameters of heart rate variability .................................... 95
Table 6. Baseline characteristics of NWAHS healthy controls and chest pain patients ................................................. 138
Table 7. Multivariate predictors of depression in patients with chest pain .................. 139
Table 8. Dummy coding of a categorical covariate ......................................................... 150
Table 9. Univariate baseline characteristics of acute myocardial infarction patients who survived to 5 years and those who died from all-causes ................................................. 164
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 ................................................. 166
Table 11. DSM-IV diagnoses of mental health outpatients ............................................ 189
Table 12. Characteristics of mental health outpatients for the three test times ......... 193
Table 13. Effect sizes (Cohen’s $d$) ................................................................. 195
List of Figures

All figures and diagrams were reproduced with permission from the authors or in accordance with the Creative Commons BY 3.0 (CC-BY 3.0 AU) licence or the 1976 United States Copyright Act (Section 107) doctrine of “fair use”.

<table>
<thead>
<tr>
<th>Figure</th>
<th>Description</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Estimated and projected total burden (DALYs) of major disease groups in 2003 and 2010</td>
<td>3</td>
</tr>
<tr>
<td>2</td>
<td>Structure of the heart</td>
<td>28</td>
</tr>
<tr>
<td>3</td>
<td>Path of blood flow through the heart</td>
<td>29</td>
</tr>
<tr>
<td>4</td>
<td>Conduction system of the heart</td>
<td>30</td>
</tr>
<tr>
<td>5</td>
<td>Normal electrocardiogram</td>
<td>31</td>
</tr>
<tr>
<td>6</td>
<td>Coronary arteries</td>
<td>33</td>
</tr>
<tr>
<td>7</td>
<td>Plaque build-up in an artery</td>
<td>37</td>
</tr>
<tr>
<td>8</td>
<td>Coronary microvascular disease</td>
<td>53</td>
</tr>
<tr>
<td>9</td>
<td>Behavioural mechanisms linking depression and coronary heart disease</td>
<td>60</td>
</tr>
<tr>
<td>10</td>
<td>Genetic mechanisms linking depression and coronary heart disease</td>
<td>62</td>
</tr>
<tr>
<td>11</td>
<td>Inflammatory mechanisms linking depression and coronary heart disease</td>
<td>64</td>
</tr>
<tr>
<td>12</td>
<td>Endothelial and coagulopathic mechanisms linking depression and coronary heart disease</td>
<td>67</td>
</tr>
<tr>
<td>13</td>
<td>Polyunsaturated omega-3 free fatty acid deficiency linking depression and coronary heart disease</td>
<td>69</td>
</tr>
<tr>
<td>14</td>
<td>The relationship between depression and coronary heart disease: A topographical map of the causal network</td>
<td>70</td>
</tr>
<tr>
<td>15</td>
<td>The parasympathetic nervous system</td>
<td>73</td>
</tr>
<tr>
<td>16</td>
<td>Neurotransmitters and receptors in the innervation of the parasympathetic and sympathetic nervous system</td>
<td>74</td>
</tr>
<tr>
<td>17</td>
<td>The sympathetic nervous system</td>
<td>75</td>
</tr>
<tr>
<td>18</td>
<td>Nervous system control of the heart</td>
<td>76</td>
</tr>
<tr>
<td>19</td>
<td>Autonomic mechanisms linking depression and coronary heart disease</td>
<td>80</td>
</tr>
<tr>
<td>20</td>
<td>Hypothalamic-pituitary-adrenal axis negative feedback loop</td>
<td>82</td>
</tr>
<tr>
<td>21</td>
<td>Type III censoring</td>
<td>145</td>
</tr>
<tr>
<td>22</td>
<td>Survival curves</td>
<td>146</td>
</tr>
<tr>
<td>23</td>
<td>Density curves</td>
<td>147</td>
</tr>
</tbody>
</table>
Figure 24. Hazard functions.................................................................................................................... 147
Figure 25. Proportion of patients surviving during 5-year follow-up by presence of depression .................................................................................................................................................. 165
Figure 26. Recruitment flow diagram ........................................................................................................ 192
Figure 27. CES-D (as a continuous variable) by time .................................................................................. 194
# List of Appendices

<table>
<thead>
<tr>
<th>Appendix</th>
<th>Title</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Short Form-36 questionnaire</td>
<td>306</td>
</tr>
<tr>
<td>B</td>
<td>Seattle Angina Questionnaire</td>
<td>309</td>
</tr>
<tr>
<td>C</td>
<td>Center for Epidemiologic Studies Depression Scale</td>
<td>312</td>
</tr>
<tr>
<td>D</td>
<td>Hospital Anxiety and Depression Scale</td>
<td>313</td>
</tr>
<tr>
<td>E</td>
<td>Multidimensional Scale of Perceived Social Support</td>
<td>314</td>
</tr>
<tr>
<td>F</td>
<td>Life Orientation Test-Revised</td>
<td>315</td>
</tr>
<tr>
<td>G</td>
<td>Participant invitation letter</td>
<td>316</td>
</tr>
<tr>
<td>H</td>
<td>Patient information sheet</td>
<td>317</td>
</tr>
<tr>
<td>I</td>
<td>Participation consent form</td>
<td>322</td>
</tr>
<tr>
<td>J</td>
<td>Health and lifestyle questionnaire</td>
<td>323</td>
</tr>
<tr>
<td>K</td>
<td>Participation thank you letter</td>
<td>327</td>
</tr>
<tr>
<td>L</td>
<td>GP information letter</td>
<td>328</td>
</tr>
<tr>
<td>M</td>
<td>Interview questions form</td>
<td>329</td>
</tr>
<tr>
<td>N</td>
<td>Individual results letter</td>
<td>331</td>
</tr>
<tr>
<td>O</td>
<td>SPSS syntax of the detected hazard ratio for cardiac mortality in acute myocardial infarction patients</td>
<td>332</td>
</tr>
<tr>
<td>P</td>
<td>Achieved hazard ratios for predictors of cardiac mortality in acute myocardial infarction patients</td>
<td>333</td>
</tr>
</tbody>
</table>
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.

I give consent to this copy of my thesis when deposited in the University Library, being made available for loan and photocopying, subject to the provisions of the Copyright Act 1968.

The author acknowledges that copyright of published works contained within this thesis resides with the copyright holder(s) of those works.

I also give permission for the digital version of my thesis to be made available on the web, via the University’s digital research repository, the Library Search and also through the web search engines, unless permission has been granted by the University to restrict access for a period of time.

Signature:                      Date: 19/12/2014
List of Publications

Publications are listed in order of appearance in this thesis.


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

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