AN EVALUATION OF CARDIOVASCULAR RISK IN EARLY BEREAVEMENT

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CERTIFICATE OF AUTHORSHIP/ORIGINALITY

I certify that the work in this thesis has not been previously submitted for a degree nor has it been submitted as part of requirements for a degree except as fully acknowledged within the text.

I also certify that the thesis has been written by me. Any help I have received in my research work and in the preparation of this thesis itself has been acknowledged. In addition, I certify that all the information sources and literature used are indicated in the thesis.

Signature of candidate

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ABSTRACT

Although bereavement is associated with adverse health, the mechanism is not well understood, in part because early psychological, behavioural and physiological changes remain incompletely characterised. In this thesis, the results of a prospective evaluation of cardiac risk factors in early bereavement are reported. Psychological, behavioural and physical changes associated with cardiac risk are documented with the main focus on physiological changes in the early acute bereavement period. The relationships between physiological risk factor changes observed and psychological state and social support in the early acute bereavement period are also explored.

Bereaved (n=62) spouses and parents were evaluated within two weeks and at six months following loss using the Centre for Epidemiologic Studies-Depression (CES-D), Spielberger State Anxiety and Anger, Social Support Questionnaire (SSQ-6) and a behavioural questionnaire documenting changes in sleep behaviours, appetite, cigarette and alcohol consumption. Evaluation of cortisol, lipids, inflammatory and prothrombotic changes, 24-hour heart rate and blood pressure were also conducted. Bereaved participants were compared to a sample of non-bereaved individuals (n=50).

Compared to non-bereaved, acutely bereaved participants had elevated symptoms of depression (mean 26.7 ±1.7 vs 5.9 ±0.7, $p<0.001$), anxiety (mean 47.4 ±2.0 vs 28.2 ±1.4, $p<0.001$) and anger (median 16.0 vs 15.0, $p<0.001$). Acutely, bereaved participants slept less than non-bereaved (mean 5.9 ±0.2 vs 7.2 ±0.2 hours,

p<0.001) and were more likely to report reduced appetite (p<0.001) and changes to alcohol consumption (p<0.001).

Compared to the non-bereaved, acutely bereaved participants had higher cortisol levels (median 306 vs 266, p=0.003), lower total cholesterol (median 4.9 vs 5.4, p=0.006), lower LDL (median 2.4 vs 2.9, p<0.001), higher neutrophils (median 4.0 vs 3.3, p=0.002), a trend towards higher vWF-ag (127 vs 114, p=0.055), higher 24-hour heart rate (mean 75.5 ± 1.9 vs 70.6 ± 1.2, p=0.008), lower SDNN (median 116 vs 129, p=0.04), and higher daytime blood pressure load (systolic mean load: 39.7 ± 0.03 vs 25.8 ± 0.02, p=0.005 and diastolic mean load 20.1 ± 0.02 vs 13.5 ± 0.02, p=0.008).

At six months, in the bereaved participants, depression, anxiety and anger had reduced significantly (all p<0.001). Appetite had returned to normal and sleep time had increased (p<0.001). Heart rate (p=0.03), diastolic blood pressure load (p=0.03), VWF-ag (p=0.008) and neutrophil (p=0.001) levels were all lower compared to the initial acute assessment. Total cholesterol (p=0.01) and LDL (P=0.003) increased while HDL levels decreased (p=0.04) from the acute assessment to six months. Cortisol, SDNN and systolic blood pressure remained unchanged.

At the acute initial assessment, no significant associations between symptoms of depression and physiological changes acutely were observed. Increased symptoms of anxiety were associated with higher heart rate (r=0.27, p=0.04), total cholesterol (r=0.29, p=0.02) and LDL (r=0.29, p=0.03) levels. Increased anger symptoms were

associated with higher heart rate ($r=0.27$, $p=0.04$), daytime systolic blood pressure ($r=0.28$, $p=0.04$) and LDL levels ($r=0.35$, $p=0.008$).

To determine if levels of social support were associated with lower cardiovascular risk, the relationships between levels of social support and physiological changes observed were described. No significant relationships between social support (availability or satisfaction) and physiological changes acutely were observed.

In conclusion, the results offer insight into the psychological, behavioural and physiological changes that may contribute to health risk in the surviving spouse or parent in early bereavement. The recognition that bereavement is associated with increased cardiac risk should provide an impetus for individuals to act on cardiac symptoms by seeking medical advice and for health care providers to monitor such individuals more closely.

Chapter One – Background to study

1.1 *Risk factors for coronary heart disease*

Coronary heart disease (CHD) is the largest single cause of death in Australia accounting for 18% of all deaths. In 2004 – 2005, CHD affected 3.7 million Australians with an estimated 46,134 heart disease related deaths, mainly acute myocardial infarction (AMI), (Australian Institute of Health and Welfare, 2008). The National Heart Foundation of Australia and the American Heart Association scientific position statements identify risk factors for coronary heart disease (American Heart Association, 2008; National Heart Foundation of Australia, 2008). Often referred to as traditional risk factors for heart disease, older age, male sex and heredity factors are identified as risk factors that cannot be modified or controlled. Risk factors that may be modified, treated or controlled include: tobacco smoking, high blood cholesterol, elevated blood pressure, physical inactivity, obesity and overweight, poor diet and nutrition and diabetes mellitus (American Heart Association, 2008; National Heart Foundation of Australia, 2008).

1.2 *Triggering of acute cardiac events*

Recent advances have lead to greater understanding of the physiological mechanism of acute coronary events and activities that promote acute changes (Bunker et al., 2003; Muller, Abela, Nesto, & Tofler, 1994; Rozanski, Blumenthal, & Kaplan, 1999). Most, but not all, acute coronary occlusions occur as the result of rupture to an unstable atherosclerotic plaque and superimposed thrombus formation (Davies &

Thomas, 1984; Libby, 1995; Servoss, Januzzi, & Muller, 2002). Additionally, myocardial necrosis may occur secondary to coronary vasospasm, with or without thrombus formation (Kloner, 2006).

There is considerable evidence that plaque rupture does not occur in a random fashion but may be "triggered" by external stressors (Muller et al., 1994; Servoss et al., 2002; Tofler, 1997). The term "triggering" refers to physical and/or emotional stressors that promote haemodynamic or prothrombotic responses that, in the presence of an unstable atherosclerotic plaque, may cause plaque disruption and thrombosis (Kloner, 2006; Servoss et al., 2002; Tofler & Muller, 2006).

The evidence surrounding "triggering" stems originally from evidence of a peak in presentations with acute myocardial infarction symptoms and sudden cardiac death in the first half of the day. In the Framingham Heart Study, the risk of sudden cardiac death was 70% higher between 7am and 9am compared with the remainder of the day (Willich et al., 1987). A meta-analysis of the morning excess of acute myocardial infarction and sudden cardiac death estimated that approximately one of every eleven AMIs and one of every fifteen sudden cardiac deaths are attributable to morning excess (Cohen, Rohtla, Lavery, Muller, & Mittleman, 1997). The observed increased morning cardiac risk has been attributed to increases in heart rate and blood pressure, higher circulating prothrombotic factors and increased morning cortisol levels (Kloner, 2006).

In addition to an observed morning peak, Monday has been associated with higher risk of myocardial infarction, primarily in the working population (Willich et al., 1994). This higher risk is presumed to be the result of more physical activity on return to work, and possible emotional burden resulting in increased sympathetic activity (Cohen et al., 1997). Indeed, high pressure work deadlines have been associated with a six fold increased risk of AMI in the prior 24-hours (Moller et al., 1999). Similarly, the Christmas and New Year holiday season has been associated with increased cardiac risk, even after accounting for known seasonal fluctuations (Cohen et al., 1997). In addition to emotional and physical stress associated with the holiday period, it is postulated that the higher seasonal risk may also be the result of increased behavioural risk factors such as dietary and alcohol intake, reduced sleep or delay in seeking health care (Kloner, 2006).

1.3 *Psychological triggers of acute cardiac events*

A pioneering study, known as the Multicenter Investigation of Limitation of Infarct Size (MILIS) study, reported that almost half (48%) of participants, who had suffered an acute myocardial infarction (AMI), identified a possible trigger preceding the event (Tofler et al., 1990). In this study, emotional upset (18%) was the most commonly reported potential precipitant, followed by moderate physical activity (14%), heavy physical activity (9%) and lack of sleep (8%). Of note, 13% of participants reported a combination of 2 or more possible triggers highlighting the complex and potentially interactive nature of triggering activities. Additionally, in the pilot phase of the Triggers and Mechanism of Myocardial Infarction (TRIMM) study, possible acute

triggers were reported by 67% of participants, with 52% reporting emotional stress in the day prior to the AMI, confirming the association between emotional stress and acute cardiac events (Willich et al., 1991).

Since the MILIS study (Tofler et al., 1990), a growing body of evidence suggests that emotional stress is strongly associated with CHD and acute events (Angerer et al., 2000; Bunker et al., 2003; Muller et al., 1994; Rozanski et al., 1999; Steptoe & Whitehead, 2005; Tennant, 1999; Tofler, 1997). An Expert Group of the National Heart Foundation of Australia published a review of systematic reviews of the evidence relating to psychosocial risk factors and their relation to development or progression of CHD, or the occurrence of acute cardiac events. The expert group concluded that the commonly regarded components of stress: depression, social isolation and lack of quality of social support, were strongly and consistently causally associated with cause and progress of CHD (Bunker et al., 2003). The expert group concluded that the increased risk contributed by these psychosocial factors is of similar order to conventional risk factors such as smoking, dyslipidaemia and hypertension.

Depression: Depression has long been associated with increased incidence of cardiac events, although the exact mechanism remains unclear (Kuper, Marmot, & Hemingway, 2002; Rozanski et al., 1999). Major depression is characterised by the presence of depressed mood and decreased interest in all activities persisting for at least two weeks and accompanied by at least four of the following symptoms: changes in appetite, sleep disturbance, fatigue, psychomotor retardation or agitation, feeling of

guilt or worthlessness, problems concentrating, and suicidal thoughts. Both major depression, and the presence of depressive symptoms in the absence of major depression, are associated with increased cardiac risk (Kuper et al., 2002; Rozanski et al., 1999).

In a recent study of nearly 300 patients admitted to hospital with acute coronary syndrome (ACS), the prevalence of discrete time-limited episodes of moderate or severe depressed mood were reported to be 18.2% with 8.3% respectively (Steptoe, Strike, Perkins-Porras, McEwan, & Whitehead, 2006). Using a case-cross over methodology, where the critical time period of two hours prior to symptom onset was compared with control periods on a within-subject basis, the odds of ACS following depressed mood were 2.5 (95% confidence intervals 1.05 to 6.56) relative to the same two hour period 24 hours earlier. Compared to usual levels of depressed mood, the relative risk of ACS onset following depressed mood was 4.33 (confidence intervals 3.39 to 6.11).

Mechanisms proposed include both increased behavioural risk factors and direct biological processes, such as hypercortisolemia, procoagulant state, inflammatory processes and reduced heart rate variability enhancing arrhythmogenic potential (Carney et al., 2001; Rozanski et al., 1999; Steptoe et al., 2006).

Anxiety: A review of ***s***tudies that evaluated anxiety (as distinct from anxiety associated with depression) concluded that anxiety alone is not associated with increased risk of myocardial infarction (Kuper, Marmot, & Hemingway, 2002;

Rozanski, Blumenthal, & Kaplan, 1999). This is echoed by the Expert Group of the National Heart Foundation of Australia who state that there is neither consistent nor strong evidence of a casual association between anxiety and CHD (Bunker et al., 2003). However, Rozanski et al. (1999) in their review of studies highlight a potential dose effect with anxiety with increased levels associated with increased risk of sudden cardiac death.

In one study of over 1600 patients interviewed after AMI, in the two hour period prior to symptom onset, 5% of patients reported anxiety symptoms above the 75th percentile on an anxiety scale (Mittleman et al., 1995). Using the case-crossover methodology, when this time period was compared to a control period, 24 to 26 hours earlier, the relative risk was 1.6 (95% confidence intervals 1.1 to 2.2). In addition to this association between anxiety state and cardiac risk, considerable evidence exists that higher symptoms of anxiety are associated with poorer outcome in patients with prior cardiac disease (Benninghoven et al., 2006; Moser et al., 2007).

Increased sympathetic activation and subsequent occurrence of life threatening arrhythmias has been proposed as the likely mechanism of increased cardiac risk during states of increased anxiety, in addition to possible increased behavioural risk factors (Rogowski et al., 2007).

Anger: Reports of heightened anger state as a trigger of acute cardiac events are fewer than episodes of depression and anxiety. In one study of over 1600 patients who

experienced an AMI, 39 (2.4%) patients reported anger ≥5 on a seven point scale that was associated with a relative risk of 2.3 (95% confidence intervals 1.7 to 3.2) when compared to a control period of usual annual frequency and 4.0 (95% confidence intervals 1.9 to 9.4) when the control period was the same 2-hour period the day before the AMI (Mittleman et al., 1995). This level of anger, corresponded with "very angry, body tense, clenching fists or teeth" up to "furious or enraged" and was reported to have occurred following conflicts with family members (25%), conflicts at work (22%) and legal problems (8%).

The association between anger and AMI risk was confirmed in another study of 700 patients admitted to coronary care units (Moller et al., 1999). Using a similar case-crossover design to that described earlier, the relative risk of AMI was 9.0 (95% confidence intervals 4.4 to 18.2) during and 60 minutes after an episode of anger. In this study, the effect of anger was less pronounced in patients who were more accustomed to outbursts. In another study of almost 13,000 CHD patients, proneness to anger placed normotensive middle-aged men and women at significant risk for cardiovascular morbidity and death independent of established biological risk factors, with a hazards ratio of 2.69 (95% confidence intervals 1.48 to 4.90), (Williams et al., 2000). Interestingly, in this study no significant association was reported between trait anger and CHD incident risk among hypertensive individuals.

Sympathetic activation resulting in elevated cortisol, increased heart rate and blood pressure and prolonged vasoconstriction aggravating endothelial dysfunction

have been proposed as potential mechanisms of increased anger triggering cardiac events (al'Absi & Bongard, 2006; Muller, Abela, Nesto, & Tofler, 1994; Verrier, Hagestad, & Lown, 1987).

Bereavement: The death of a loved one is recognised as one of life's greatest stresses requiring significant psychological adjustment (Maciejewski, Zhang, Block, & Prigerson, 2007; Stroebe, Schut, & Stroebe, 2007; Stroebe, 2001). The response to bereavement, commonly referred to as grief, is a unique psychological stress where acute symptoms of depression, anxiety and anger are frequently reported and may last for several weeks or months and for some may lead to chronic psychological stress (Stroebe et al., 2007; Stroebe, 2001; Stroebe, Stroebe, & Hansson, 1993). Bereavement can be particularly devastating for the surviving spouse, who is often required to deal with simultaneous disruption to living arrangements, financial security and social status (Stroebe, 2001). For some spousal bereavement has the potential to result in social isolation that may have impact on cardiovascular health in the longer term (Bunker et al., 2003). Additionally, the death of a child has been associated with significant symptoms of depression, anxiety and stress (Goodenough, Drew, Higgins, & Trethewie, 2004; Miyabayashi & Yasuda, 2007).

Increased morbidity and mortality has been reported among bereaved people, most notably in surviving spouses (Hart, Hole, Lawlor, Smith, & Lever, 2007; Jagger & Sutton, 1991; Martikainen & Valkonen, 1996; Schaefer, Quesenberry, & Wi, 1995). Coronary heart events appear to account for up to approximately 50% of the increased

deaths during spousal bereavement. (Cottington, Matthews, Talbott, & Kuller, 1980; Hart et al., 2007; Jones, 1987; Parkes, Benjamin, & Fitzgerald, 1969; Ward, 1976).

1.4 *Rationale for the present study*

The National Heart Foundation of Australia position statement on stress and CHD highlights the need for future research on psychosocial risk factors and coronary artery disease (Bunker et al., 2003). Two major reviews of bereavement research in recent times recommend that research priorities focus on the physiological, behavioural and support mechanisms that place bereaved persons at increased risk (Genevro, Marshall, & Miller, 2004; Stroebe, 2001). Additionally, although most deaths occur in health care settings (Genevro, Marshall, & Miller, 2004), few studies have recruited bereaved individuals from the hospital setting, especially in the first few weeks of bereavement.

Despite the fact that bereavement acts as an acute trigger for increased cardiac mortality and morbidity, the exact physiological changes contributing to increased risk remain relatively unexplored. The need to design preventive regimens to provide maximum protection during times of peak risk of myocardial infarction has been suggested (Tofler & Muller, 2006; Willich, Jimenez, Tofler, DeSilva, & Muller, 1992). However, the absence of insight into the impact of bereavement on risk factors in early bereavement results in uncertainty regarding appropriate strategies during this known risk period. This study represents the first prospective evaluation of cardiac risk factors in early bereavement in a sample of spouses and parents of patients who died in the

acute care setting. The results will provide preliminary insights into the physiological response to bereavement that may inform future preventative strategies in early bereavement.

1.5 *Outline of thesis*

In this chapter the association between acute psychological states, such as depression, anxiety and anger, and risk of acute cardiac events have been discussed and potential mechanisms identified. In the second chapter the epidemiological evidence reporting increased cardiovascular and mortality risk in bereavement is reviewed. The strengths and limitations of these studies are discussed. Potential contributing risk factors are identified and related to the present study. A representation of the manner in which bereavement may trigger acute myocardial infarction and sudden cardiac death is presented. The research hypothesis and aims are then presented. In chapter three the study design is described including the eligible research participants and setting, recruitment procedures and tracking of participants through the study. The data collection methods, process and instruments are also detailed. The data analysis methods used to test the primary and secondary study hypotheses are described. Next, the research findings are discussed in chapter four. The study's strengths and limitations, as well as implications for practice and future research, are then discussed. Finally, in chapter six the results and discussion reported in this thesis are summarised.

1.6 *Summary*

Each year in Australia, there are over 46,000 heart disease related deaths. Advances in medical research have lead to greater understanding of the physiological mechanism of acute coronary events and behaviours that promote acute changes in these risk factors. Evidence suggests that many acute cardiac events may be triggered by external stressors that provoke an acute psychological response. Bereavement appears to act as an acute trigger for increased cardiac mortality and morbidity, with coronary heart events accounting for up to approximately half of the increased deaths in early bereavement. However the exact physiological changes contributing to increased risk remain relatively unexplored during this vulnerable time. This thesis reports on a prospective evaluation of cardiac risk factors in early bereavement in a sample of bereaved people recruited from the acute care setting. This study also explores the relationships between physiological risk factor changes, psychological state and social support in the early acute bereavement period.

Chapter Two - Literature Review

2.1 *Introduction*

In this chapter epidemiological evidence reporting increased cardiovascular risk and mortality risk in bereavement is explored. The studies are explored in chronological order and potential contributing risk factors identified and related to the present study. A representation of the manner in which bereavement may trigger acute myocardial infarction and sudden cardiac death is then presented.

2.2 *Bereavement and spousal mortality*: The death of a loved one is generally considered to be one of the most stressful of human experiences. The association between bereavement and increased health risk has been an object of study over the past 50 years, with substantial evidence suggesting increased mortality among surviving spouses. In this review a summary of research on bereavement mortality is presented while known risk factors are identified. Distinctions between bereavement and grief are commonly inconsistent in the literature as well as clinical practice. In this review, bereavement refers to the loss of a loved one by death and grief refers to the distress resulting from bereavement (Stroebe, 2001).

In 1963, a landmark study reported a follow-up of 4,486 widowers of 55 years or older (Young, Benjamin, & Wallis, 1963). The investigators collected data from the British General Register Office for a twelve-month period, reporting 214 deaths within the first six months since spousal death. Death rates were calculated by dividing the

deaths by the mean number of widowers at risk during the time period. A comparison of widowed mortality to that of married men revealed 66 excessive deaths in the bereaved group in the first six months following spousal death, representing an odds ratio of 1.39 with little differential thereafter. The authors concluded that this excessive death rate represented an almost 40% increased mortality rate, compared to married men, in the first six months of bereavement, which fell back to the married men's risk after six months.

A nine-year follow-up of these same 4,486 male bereaved subjects revealed that deaths with a diagnosis of "coronary thrombosis and other arteriosclerotic and degenerative heart disease" accounted for 53% of the reported increased mortality (Parkes et al., 1969). Interestingly, 22.5% of deaths were from the same diagnostic group as the spouses' death, considered unlikely to be by chance. One explanation proposed was the tendency of unfit individuals to marry other unfit individuals, as well as the fact that the wife and husband share the same potentially pathogenic environment (dietary and social factors). The authors also suggested that the increased mortality resulted from the possibility that bereaved men may have altered their nutritional or health practices in the absence of their wives, making them more susceptible to cardiac disease (Parkes et al., 1969). While these findings are from secondary evidence from four decades ago and are limited only to widowers over 55 years, it was one of the first large epidemiological studies to demonstrate a relationship between spousal bereavement and increased cardiovascular risk in the surviving spouse.

In Sheffield, United Kingdom, the death rate of 366 bereaved spouses (87 widowers and 279 widows) was recorded for two years following death of their spouse (Ward, 1976). In this study, bereaved spouses were followed up from monitoring of their electoral registration, home visits and monitoring of Housing Department records. The mortality rate of spouses was compared with population-abridged life tables for England and Wales. Analysis revealed that while the widows' deaths were evenly spread over the two year study period, three-quarters of the deaths among the widowers occurred within the first six months after the death of their spouse. A significant relationship was also reported between the place of death of the first spouse and the health of the survivor. While not conclusive evidence, if the first spouse died in hospital, the bereaved spouse was more likely to die themselves shortly afterwards. It is likely that this is the reason the deceased spouse died in hospital, as the surviving spouse was possibly unable to care for the spouse at home. Also of note, there was no difference in spousal survival rates between unexpected versus expected spousal death in this sample. Despite the lack of a control group for comparison, this study did suggest an increased mortality risk for surviving widowers in the first six months, with cardiovascular disease a contributing factor in 20% of the excess deaths.

A study of 81 Caucasian women who died suddenly from arterosclerotic heart disease examined the association of sudden cardiac death and three categories of environmental events, including: death of a significant other, change in living conditions and change in work conditions (Cottington et al., 1980). The subjects had no history of coronary heart disease (CHD), were aged between 25 and 64 years, resided in

Pennsylvania and were of middle socioeconomic background. Subjects were identified from coroners' records and death certificates. The next of kin of the deceased were interviewed within one month of the death regarding medical history, demographics and the preceding life events as described above. Age- and sex-matched controls were recruited from the deceased's immediate neighbours for comparison. Results revealed that, relative to matched controls, subjects were more likely to have experienced death of a significant other, but not changes in living or work conditions. The odds ratio when death of a significant other occurred in the six months preceding their own death was reported to be 6.5 (with an estimated standard error ±4.9). This study is important as it demonstrates a relationship between bereavement and risk of sudden cardiac death in women of middle socioeconomic background. A strength of this study is the matching of bereaved to neighbourhood controls for comparison. In addition the interviews of close relatives were conducted within 1.5 months of death, making recall bias less likely to have occurred. The authors hypothesized that changes to social support and lifestyle, nutritional and sleep pattern changes, increased tobacco and alcohol use, together with pathophysiological processes, such as lymphocyte suppression or rapid sympathetic and parasympathetic shifts secondary to emotional disturbances, may have contributed to this increased risk of sudden death.

A large study of 1,447 American bereaved primary carers explored secondary morbidity and the use of health care services within the first four months of bereavement (Mor, McHorney, & Sherwood, 1986). The sample was mainly Caucasian, 72% female and 55% related to the deceased by marriage. Following the death of their

loved one, six percent of the sample reported increased use of alcohol, 18% reported use of antianxiety medications, 58% consulted a physician (21% more than 3 times) and 21% were hospitalised in the first four months. In comparison to the National Center for Health Statistics, the physician visiting rates of the bereaved were significantly higher than national rates. Using a linear regression model, primary care persons with health limitations or those with depression were found to be more likely to make physician visits. The odds of hospitalisation were 2.1 times greater among bereaved with health limitations. If that person was a spouse of the deceased, they had a 1.6 fold increased risk of hospitalisation compared to other relatives. While men reported increased use of alcohol, the multivariate analysis showed that the surviving spouses were at greater risk for increased alcohol use irrespective of sex. Another important finding in this study was the increased use of antianxiety medications among female spouses of the deceased, especially those reporting depression and those with less social support. This is an important study as it suggests that spousal bereavement may change health status and be associated with increased mortality, while also emphasising the importance of social support during the early grieving period. This study also highlights an increased health risk for bereaved spouses with previous health limitations in the early bereavement period.

The Office of Population Censuses and Surveys (OPCS) Longitudinal Study analysed a sample of individuals in England and Wales following widowhood from 1971 to 1981 (Jones, 1987). Of the 133,007 married men in the 1971 census longitudinal sample, 7,060 suffered widowhood before the end of 1981. In the same

period, 14,900 of the 131,277 married women were widowed. In this study, recorded death from ischaemic heart disease (IHD), compared to expected deaths, was higher in all groups, with the highest risk groups being widows less than 65 years (odds ratio 1.35) and widowers older than 75 years (odds ratio 1.12). Separate analysis of the deaths of ten women that occurred on the same day as their husbands' deaths revealed that six of the deaths were from circulatory diseases and four of these from IHD. While small in number, this was significantly higher than expected from all widows (expected number two). Of eight widowers' deaths that occurred on the same day as their wives deaths, two were from IHD. The authors report a peak of all cause mortality lasting for six months after bereavement in widows consistent with previous research, but a less sharp though visibly more extended period in widowers. This study adds evidence to the suggestion that spousal bereavement is associated with increased mortality risk secondary to IHD. However the effect size is not as large as reported in earlier studies and appears to be confined largely to widows less than 65 years and widowers over 75 years. The increased death from IHD seen in the first 24 hours is also of interest and may be associated with the acute emotional stress associated with bereavement.

A prospective study of 95,647 Finnish widowed persons was reported following analysis of all death certificates between 1972 and 1976 (Kaprio, Koskenvuo, & Rita, 1987). The mortality of the entire cohort was reported to be 6.5% higher than expected for non-bereaved during this four-year period. The study reported standardised mortality ratios (SMRs), which were calculated by dividing the number of cases by expected cases among age groups and sex. For deaths from all natural causes, SMRs

were twofold higher during the first week of bereavement for both men and women. Mortality ratios decreased for women after the first month and decreased for men after the first six months except for older men over 65 years. In the first week of bereavement, a 2.3-fold increase in mortality secondary to IHD for men and a 3.5-fold increase for women was reported. This was almost twice the risk of death from cerebrovascular disease. The increased risk from IHD decreased to population levels after the first month but increased again in the second year for widowers less than 65 years. In summary, this study reported highest risk time in the first week that extended over the first month and remained elevated until six months. In their discussion the authors propose that emotional distress resulting in sleep disturbance may be a significant factor contributing to cardiac mortality. A relationship between lack of sleep and cardiovascular disease had been reported previously, supporting this hypothesis (Partinen, Putkonen, Kaprio, Koskenvuo, & Hilakivi, 1982).

A prospective study exploring the mortality of elderly bereaved, over 75 years of age, reported an increased risk of mortality for approximately six months (Jagger & Sutton, 1991). In total, 1,149 elderly people living in the community were interviewed. From initial data collected, 344 cases (59% male) and their spouses who lived as a couple were followed up for seven years. Over the study period, 32% of cases lost a spouse and 53% of the cases had themselves died. Using a statistical model controlling for known confounders for mortality in this age group, the relative risk for bereavement was considered for spouses. The highest relative risk of mortality was seen among women (odds ration of 3.8) that returned to normal at six months. Of interest, unlike

prior studies, no significant risk was reported among men. The death of an elderly spouse is likely to result in loss of a long-time companion and possible loss of a support person for social and daily life necessities, which may account for the increased mortality seen in elderly widows. A strength of this study is that it prospectively monitored elderly married couples living in the community for spousal death. The findings support previous studies identifying that the first six months of bereavement are the highest risk period for widows.

The hypothesis that increased mortality in the bereaved is the result of a "shared environment" was assessed in a retrospective cohort study of 12,522 married pairs belonging to a health care plan in northern California (Schaefer et al., 1995). The sample of middle income members of the community included couples over 40 years of age. Subjects were identified following a health check-up that included a general physical examination and a self-reporting questionnaire covering medical history, current medical problems, demographic characteristics and health-related behaviours such as alcohol consumption or smoking. Subjects who completed the health check between 1964 and 1973 were screened from the time of their first assessment up to the end of 1987 using a computerised mortality database. Eight couples who died as a result of the same accident were excluded from the study analysis. During the study period, 12% of men and 26% of women were bereaved. Among the bereaved, 30% of men and 15% of women subsequently died. The relative mortality risk for bereaved men was reported as 2.02 fold in the first six months and 1.97 fold in the next six months. This risk reduced to 1.71 in the second year and lowered again to1.33 after 5 years. For

women, the relative mortality risk was reported to be 1.6 in the first six months, 2.24 in the second six months and then dropped off in the second year.

The effects of a shared environment, examined using proportional hazards analysis, revealed that none of the spouses' covariates were significantly associated with risk of mortality. As such, the authors dispelled the possibility that "shared environment" was a contributor to this cohort's increased mortality for the surviving spouse. However the time frame from initial assessment to spousal death was lengthy (minimum 14 years and maximum 23 years). The results of this study, despite the limitations of using secondary sources for follow-up and the fact that this was a health-conscious population, add to the existing evidence of increased mortality risk following spousal bereavement with the highest risk period in the first year. The study also suggests that increased risk cannot be solely attributed to a shared 'pathogenic" environment and that a casual effect of increased mortality during bereavement existed in this population.

A prospective study of 1.58 million Finnish residents for five years investigated the mortality risk of newly-bereaved spouses, controlling for bias from common socioeconomic environmental and common lifestyles, as well as accidents common to spouses (Martikainen & Valkonen, 1996). During the study period the mortality rate among the population was 0.07%, with 83,980 widowed during the follow-up period. Controlling for age, excess mortality among all bereaved men was reported to be 21%, with a 50% excess in the first week that reduced to 20% after six months. Excess

mortality among bereaved women was 9% with an initial excess of 50% in the first week that dropped of to less than 10% at six months. Of significance, after controlling for age, excluding common accidents and standardising for economic environment and lifestyles, increased mortality was evident in the bereaved compared to non-bereaved. The authors imply that the excess mortality seen in the early bereaved period may be attributed to stress and grief and that a casual effect exists, not accounted for by lifestyle or shared environment among spouses.

The short-term and long-term effects of spousal bereavement were evaluated using a prospective case controlled sample of 1,993 sets of twins and 35,860 married individuals from the Swedish Twin Registry, born between 1886 and 1958 (Lichtenstein, Gatz, & Berg, 1998). Married and widowed individuals were monitored for survival over a twelve-year period. The bereaved sample contained almost three times more women than men, as has been reported in similar studies. Age-adjusted relative hazards of death were calculated controlling for smoking status, excessive alcohol drinking, education, body mass index, cardiovascular or respiratory disease. These covariates were measured in the sample by questionnaires at the beginning of the study with a 90% response rate reported. After controlling for covariates, surviving male spouses less than 70 years of age, compared to married males, had a higher risk of death with relative hazards of 3.36 in the first six months that dropped to 1.38 in the next six months. A similar relationship was seen with surviving female spouses less than 70 years of age, with the highest risk period in the first six months (hazards ratio 2.92). Surprisingly, this relationship was not seen in males over 70 years of age with a

reported hazards ratio 0.82 in the first six months and 1.2 in the second six months, which then returned close to that of married controls after twelve months. However, surviving female spouses over 70 years had a similar hazards ratio to younger females (1.74 in the first six months that reduced to 0.83 in the second six months). Also of note: bereaved women under 70 years who had a pattern of increased mortality risk during the early bereavement period had markedly decreased risk if they survived four years after bereavement (hazards ratio 0.64 after four years).

Separate analysis of bereaved twins compared to their still married co-twin was also reported. There were similar hazards ratio patterns to the sample as a whole with the highest hazards ratio for bereaved females under 70 years (hazards ratio 8.0). Interestingly, females under 70 years of age at time of bereavement who survived the first year, were less likely to die themselves (hazards ratio 0.48 after four years), (Lichtenstein et al., 1998). This report is important for several reasons. The results are consistent with previous studies demonstrating an association between bereavement and surviving spouses' mortality in the early bereavement period (first six months), even when controlling for measured risk factors. The study methodology utilised good case-matching as twins were matched for age, genetic propensities (in the case of identical twins), sex (if same sex) and a strong likelihood that they shared background variables such as childhood environment. This method of case-matching may also have controlled for other unknown confounding variables not measured in analysis of the population at large. Bereaved widows under 70 years age had a pattern of increased mortality risk during the early bereavement period, but also a markedly decreased risk if they survived

four years after bereavement, as compared to married women. The decreased risk long-term for women would suggest that if females survive the acute phase of bereavement then their risk is greatly reduced and bereavement may actually have a protective effect in later years.

Christakis and Iwashyna (2003) hypothesised that support at the time of death would influence the mortality of their surviving spouses. This matched retrospective cohort study compared mortality risk among 30,838 couples where the deceased used hospice care and an equal number of couples where the deceased did not utilise hospice care. In this study, hospice care was described as including nursing services, physician visits, homemaker assistance, social assistance and bereavement counselling. The exact services hospice users utilised is not stated, but deaths in both study groups were from the same twelve most common primary diagnoses. Mortality rates were identified for eighteen months after spousal death from US Medicare claims, reported to be a reliable and accurate method in this health care system. Eighty percent of the surviving spouses were female and 93% Caucasian, with a mean age of 75 years. Analysis of spousal mortality revealed that bereaved spouses whose deceased partners had used hospice services, compared to “control bereaved” subjects who did not, were less likely to die themselves in the first eighteen months of bereavement, with an adjusted odds ratio of 0.92 for widows and 0.95 for widowers. This study highlights the possible protective influence of social support on spousal outcome.

A study conducted among Israeli adults explored the influence of duration of bereavement, sex, age, education, ethnic origin and number of children on surviving spousal mortality (Manor & Eisenbach, 2003). The study was based on a 20% population sample from the 1983 census, with death records for the subsequent nine and a half years and data on demographic and socioeconomic variables. In total 4,402 men and 11,114 women (9% and 27% of the population, respectively) were bereaved during the follow-up period. Similar to previous studies, across all age groups the relative risk of mortality among widowers was reported to be 1.38 and for widows 1.48 in the first six months, when compared to married subjects. Consistent with prior studies, the risk of mortality decreased after this six-month period for both sexes. When analysed in five-year age groups, the effect of spousal loss was greatest among 50 to 54 year old men (odds ratio 3.06) but distributed more evenly across female age groups. Household size was not a significant factor among either sex, although women with one to three children had the lowest risk among the sample studied. This suggests that having no children results in less support and having more than three children may add to strain and mortality risk. Adjustment for ethnicity or education resulted in minimal changes to the relative risk among all bereaved. These results are consistent with previous studies suggesting that a shared pathogenic environment does not account for increased mortality among surviving spouses and that social support may be an important protective factor for some.

A recently published study, conducted in Scotland, prospectively monitored a cohort of individuals participating in the Renfrew/ Paisley study since enrolment

between 1972 and 1976 (Hart et al., 2007) . Participants at this time completed a health screen and follow up mortality was screened via the National Health Service Central registry to the end of March 2004. Throughout the thirty-year study period, nearly 70% of men and almost 50% of women who became bereaved since enrolment, died in the subsequent follow-up period giving a relative risk of 1.27 compared to married individuals. When the time after bereavement was subdivided into the first five years and greater then five years, there was a tendency for higher deaths from cardiovascular disease (CVD) or coronary heart disease (CHD) in the first five years, whereas deaths from stroke or cancers were higher after five years. When divided into smaller time intervals, after adjusting for known cardiac risk factors, all cause mortality was highest in the first six months (RR 1.31) and reduced in the next six months (RR 1.09). Risk of death from CVD or CHD were highest in the initial six months following bereavement (RR 1.21 and 1.31 respectively), even after adjustment for known individual cardiac risk factors.

Despite the limitation of controlling for traditional cardiovascular risk factors measured several years prior to bereavement, this recent study confirms earlier findings of increased risk of mortality in early bereavement with the risk of cardiovascular related events highest in the first six months, consistent with previous studies in the past half decade.

2.3 *Summary*

In this review the findings from key epidemiological studies since 1963 were discussed, in which bereavement is identified as a significant risk factor for cardiac mortality and morbidity. While some studies included all family members in their samples, the majority focused analysis on bereaved spousal health risk, perhaps because of the ability to monitor spousal bereavement via public records. The studies reviewed have employed differing methodologies and have consistently demonstrated an increased risk of mortality and morbidity among surviving spouses (Table 1).

Table 1 Summary of studies discussed demonstrating mortality risk during bereavement

Authors	**Methods and sample**	**Key results**
Young et al., 1963	Review of General Register Office register of 4,486 widowers older than 55 years old.	Excessive deaths among widowers (40% increased risk) within the first six months following the death of their spouse.
Parkes et al., 1969	National Health Service central register follow-up of same 4,486 widowers from Young, Benjamin and Wallis (1963) study.	CHD responsible for 53% of increased mortality. 22.5% of widowed deaths were from same diagnostic group as the deceased spouse.
Ward, 1976	Prospective follow-up of 366 bereaved spouses for two years (87 men and 279 women).	Equal number of deaths among men as women. First six months was the highest mortality risk period for widowers. Deaths among widowers were spread across two- year period. Cardiovascular disease accounted for 20% of excess deaths. No difference between expected deaths and unexpected deaths for surviving spouse mortality risk. In hospital death a possible risk factor for surviving spouse.
Cottington et al., 1980	Retrospective case matched comparison of 81 Caucasian female sudden deaths from arteriosclerotic heart disease.	The odds ratio when death of a significant other was present in the six months prior to death was reported to be 6.5 (compared to neighbourhood controls).
Mor et al., 1986	Analysis from quasi-experimental study exploring the impact of hospice care on quality of life. Included 1,447 primary care givers. One third of sample were female.	The odds of hospitalisation were 2.1 times greater among bereaved with health limitations, and if that person was a spouse of the deceased, they had a 1.6 increased risk of hospitalisation compared to other relatives. Alcohol use increase reported following bereavement, more so in men and the potential protective role of social support highlighted. 21% of bereaved were hospitalised in the first four months of bereavement.

Jones, 1987	Ten-year analysis from population census in United Kingdom identifying mortality among surviving spouses.	Deaths from IHD were higher among all surviving bereaved spouses. Highest risk of IHD among widows < 65 years and widowers >75 years. Unusual high number of same day deaths from IHD in widows. Highest risk period for widows was in the first six months, less sharp and more extended in widowers. Spousal mortality risk higher after unexpected death of spouse.
Kaprio et al., 1987	Prospective study of 95,647 Finnish widows.	Cohort mortality was 6.5% higher among bereaved. Standardised mortality ratios were 2-fold higher in the first week for both men and women and decreased after one month in women and after six months in men. There was a 2.3-fold increased risk from IHD in women and 3.5-fold increase in men compared to population levels.
Jagger & Sutton, 1991	Prospective study of 344 elderly couples over a seven year time period.	Reported a 3.8-fold increased risk of spousal mortality in women that retuned to normal levels after six months. No significant risk reported among men.
Schaefer et al., 1995	Retrospective cohort study of 12,522 middle income married couples.	The relative risk of mortality was higher for both men and women in first year after spousal death; higher for men in first six months and highest for women in second six months that lowered after twelve months. No evidence that shared environment influenced surviving spouse mortality risk.
Martikainen & Valkonen, 1996	Prospective study of 1.58 million Finnish residents for five years.	Highest risk period for men and women was in the first week that reduced to 20% at six months for men and 9% for women. Increased mortality was still evident after controlling for economic environment and common lifestyles of couples.

Lichtenstein et al., 1998	Prospective study of 1993 pairs of twins discordant for marital status and 35,860 married individuals from the Swedish Twin Registry.	Spousal bereavement was a risk factor for mortality for both men and women using the still married co-twin as a control, after controlling for earlier health status and risk factors. The mortality risk was higher for under 70-year-old females in early bereavement
Nicholas, Christakis & Iwashyna, 2003	Matched retrospective cohort study of 30,838 couples where the deceased used hospice care compared to an equal number of couples where the deceased did not.	Bereaved spouses, whose deceased partner used hospice services, compared to bereaved that didn't, were less likely to die themselves in the first eighteen months of bereavement with an adjusted odds ratio of 0.92 for widows and 0.95 for widowers.
Manor & Eisenbach, 2003	Longitudinal mortality study conducted in Israel. Included 20% sample of the country's population (90,830 people)	Across all age groups the relative risk of mortality among widowers was reported to be 1.38-fold and for widows 1.48 in the first six months when compared to married subjects. Women with 1-3 children had the lowest risk among the sample studied. Adjustment for ethnicity and education resulted in minimal changes to the relative risk among all bereaved.
Hart et al., 2007	Prospective cohort study in Renfrew and Paisley in Scotland of 4395 married couples from 1972 to 2004.	All cause mortality was highest in the first six months (RR 1.31) and reduced in the next six months (RR 1.09). Risk of death from CVD or CHD was highest in the initial six months following bereavement (RR 1.21 and 1.31 respectively), even after adjustment for known individual cardiac risk factors.

Time of greatest risk: For the surviving spouse, the risk of mortality appears to be greater in the immediate weeks following bereavement and remain elevated for the first six months (Nicholas, Christakis & Iwashyna, 2003; Cottington et al., 1980; Hart et al., 2007; Jagger & Sutton, 1991; Jones, 1987; Kaprio et al., 1987; Manor & Eisenbach, 2003; Martikainen & Valkonen, 1996; Ward, 1976).

Age and sex: Not surprisingly, spousal bereavement is mainly a female phenomenon, in keeping with the fact that women live longer (Charlton, Sheahan, Smith, & Campbell, 2001). Several studies that included both sexes in the analysis suggest that men may be more at risk following spousal death, especially in the initial six month period (Jones, 1987; Kaprio et al., 1987; Manor & Eisenbach, 2003; Martikainen & Valkonen, 1996; Schaefer et al., 1995; Ward, 1976). Increased risk appears to be across all age groups although younger men (less than 54 years) and older men (over 75 years) have been identified as possibly most at risk (Jones, 1987; Manor & Eisenbach, 2003). Mortality risk appears to be distributed across all female age groups (Manor & Eisenbach, 2003), although two studies suggest that women under 75 years may be most at risk of death from CHD related events (Jones, 1987; Lichtenstein et al., 1998).

The role of social support: Social support appears to be an important factor to consider in light of evidence of the relationship between decreased social support and increased risk of CHD (Angerer et al., 2000; Tennant, 1999). It is likely that loss of a spouse will result in changes in social support. Although not conclusive, some evidence

exists to support that higher levels of social support at the time of the partner's death may reduce mortality risk (Nicholas, Christakis & Iwashyna, 2003; Manor & Eisenbach, 2003).

Bereavement and cardiovascular disease: Coronary heart events appear to account for a substantial amount of the increased deaths during spousal bereavement, ranging from between 20-53% of excess deaths (Cottington et al., 1980; Hart et al., 2007; Jones, 1987; Parkes et al., 1969; Ward, 1976). In one study of widowers who died suddenly of IHD, subjects were 6.5 times more likely to have lost a significant other in the six months preceding their own death (Cottington et al., 1980). The relationship between IHD and bereavement was also reported in a subsection of the Onset study where the death of a significant other increased the relative risk of acute myocardial infarction by up to 14.3-fold in the first week that slowly reduced to 4.8-fold at one month following bereavement (Mittleman, 2001). This study is consistent with a prior report of excess deaths in the first 24 hours following spousal death (Jones, 1987), and would suggest that acute stress effects may be responsible for the increased mortality seen early in bereavement.

Despite the growing evidence of increased mortality among surviving spouses, the exact physiological mechanisms resulting from acute bereavement are not fully understood. Several theories discussed in the literature include: the tendency of unfit to marry unfit; shared pathogenic environment (dietary and social factors); physiological effects of emotional grief (acute emotional disturbances resulting in a physiological

stress response) and alterations to sleep, alcohol consumption or other drugs and altered dietary behaviours (Cottington et al., 1980; Genevro et al., 2004; Martikainen & Valkonen, 1996; Parkes et al., 1969; Stroebe, 2001). However, studies that controlled for shared environments and shared lifestyle behaviours suggest that the excess deaths seen in surviving spouses may not be totally attributed to these factors alone (Martikainen & Valkonen, 1996; Schaefer et al., 1995).

A representation of the manner in which bereavement may trigger acute myocardial infarction and sudden cardiac death is presented in Figure 1 (Adapted from Muller at al., 1994).

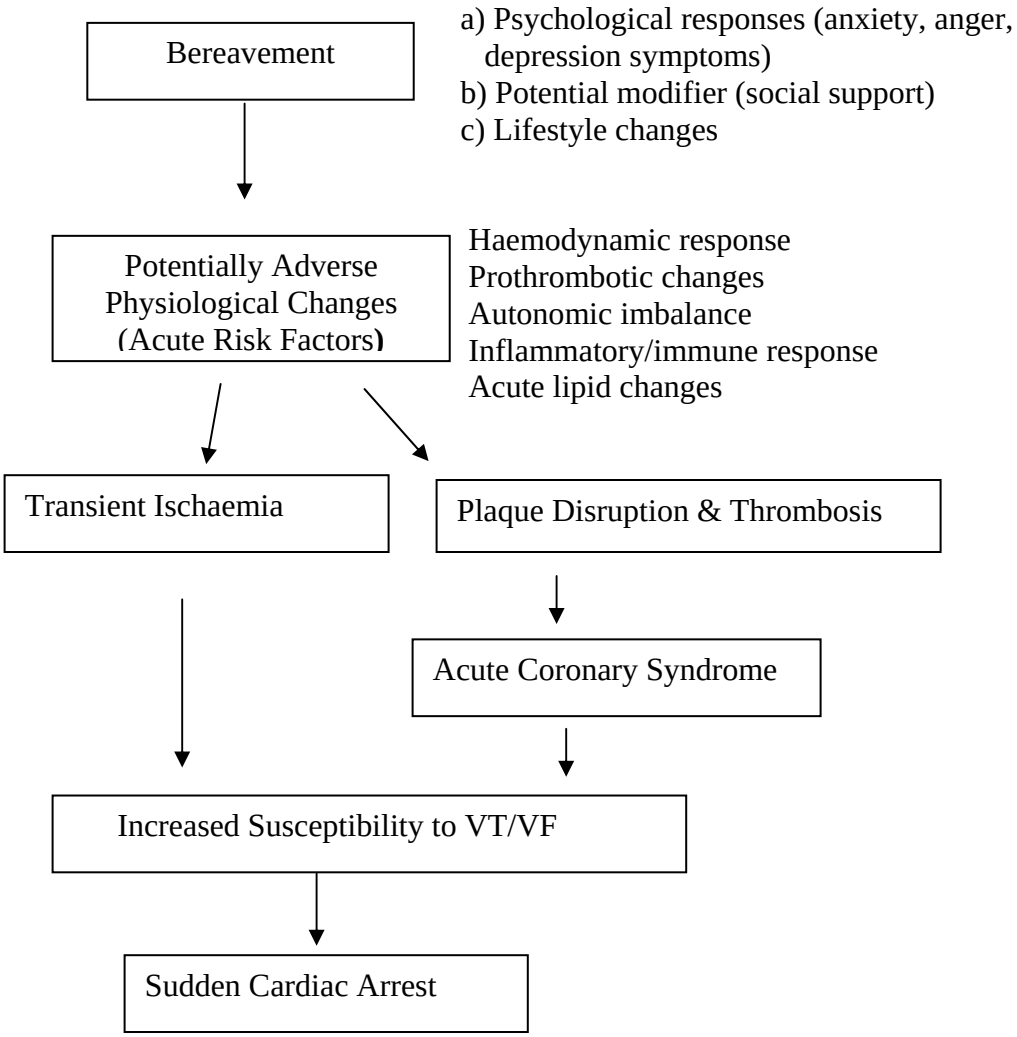


Figure 1: Representation of the manner in which bereavement may trigger acute myocardial infarction and sudden cardiac death.

2.4 *Study aims*

The aim of this study was to identify adverse physiological responses to bereavement as potential acute risk factors for AMI and sudden cardiac death using innovative techniques. The study concentrated on evaluating the effects of bereavement on known physiological pathways that have been postulated to precipitate plaque rupture, thrombosis and arrhythmia. The primary endpoints included fibrinogen levels,

blood pressure and heart rate analysis. Relationships between the psychosocial response and the psychological responses to the bereavement and physiological changes observed were explored, as understanding the nature of such relationships during the complex response to bereavement will aid in designing future preventative therapies to those most at risk.

2.5 *Research Hypothesis*

The primary hypothesis was that bereaved participants, compared to non-bereaved participants, would have increased risk factors for myocardial infarction or sudden cardiac death. Risk factors were categorised as follows:

Psychological: symptoms of depression, anxiety and anger

Behavioural: eating, alcohol, tobacco smoking and sleep behaviours

Physical: waist circumference and BMI

Physiological: cortisol, blood lipids, inflammatory cells, prothrombotic factors, heart rate, heart rate variability and blood pressure.

The secondary hypothesis (1) was that compared to the acute bereavement period, at six months following bereavement there would be a lowering of the cardiovascular risk. This was tested by measuring the above variables six months following bereavement, in addition to the acute measurements.

The secondary hypothesis (2) was that physiological changes associated with bereavement would be associated with higher psychological grief reactions (symptoms of depression, anger and anxiety) and lower levels of social support.

Chapter Three - Methods

3.1 *Introduction*

In this chapter the study design is described. The eligible research participants and setting, recruitment procedures and tracking of participants through the study are detailed. The data collection methods, process and instruments are also described. Finally, data analysis methods used to test the primary and secondary study hypotheses are described.

3.2 *Research Design*

To address the primary research hypothesis that bereaved participants would have increased risk factors for myocardial infarction or sudden cardiac death, the study utilised a descriptive comparative design in which evaluation of psychosocial, behavioural and physiological risk factors in bereaved individuals were compared to a reference group of non-bereaved individuals. To address the secondary hypothesis that compared to the acute bereavement period, at six months following bereavement there would be a lowering of the cardiovascular risk, a longitudinal evaluation of psychosocial, behavioural and physiological risk factors was conducted in bereaved participants. The six-month assessment was postulated to reflect a time of lower cardiovascular risk compared to the initial weeks of bereavement.

3.3 *Subjects and setting*

Bereaved: Sixty two bereaved participants (58 spouses or partners and four parents) were recruited from the critical care units of five hospitals in the Sydney metropolitan area between February 2005 and July 2007. Bereaved participants were eligible for inclusion in the study if they were spouses, partners or parents of deceased patients who died in participating units. Participants were recruited from the hospital adult intensive care and coronary care units following the death of their family member. All participants were adult and no upper age limit was set.

Eligible bereaved participants were identified by either a social worker or designated nursing staff and referred to the investigator for possible inclusion in the study. All identified bereaved spouses or parents of deceased patients who met eligibility criteria at the participating institutions were informed of the study, by either the social worker or investigator at the hospital or by telephone within the first two weeks following bereavement, to enquire of their possible interest in the study. Interested participants were given or mailed a study information sheet (Appendix A) and an appointment was made to conduct the acute assessment in their home. Acute assessments were conducted on day eleven on average (range 4-16 days) following the death of their partner/child. Of those who met the inclusion criteria, 60% agreed to participate. Approximately half of the refusals were from bereaved spouses, while the others were from family members who requested that the researchers not approach the bereaved spouse or parent in person.

Eleven bereaved participants were recruited in the summer months (December to February), 12 during Autumn (March to May), 15 during Winter (June to August) and 13 during Spring (September to November). The flow of subjects from identification to completion including participant withdrawals, are presented in Figure 2.

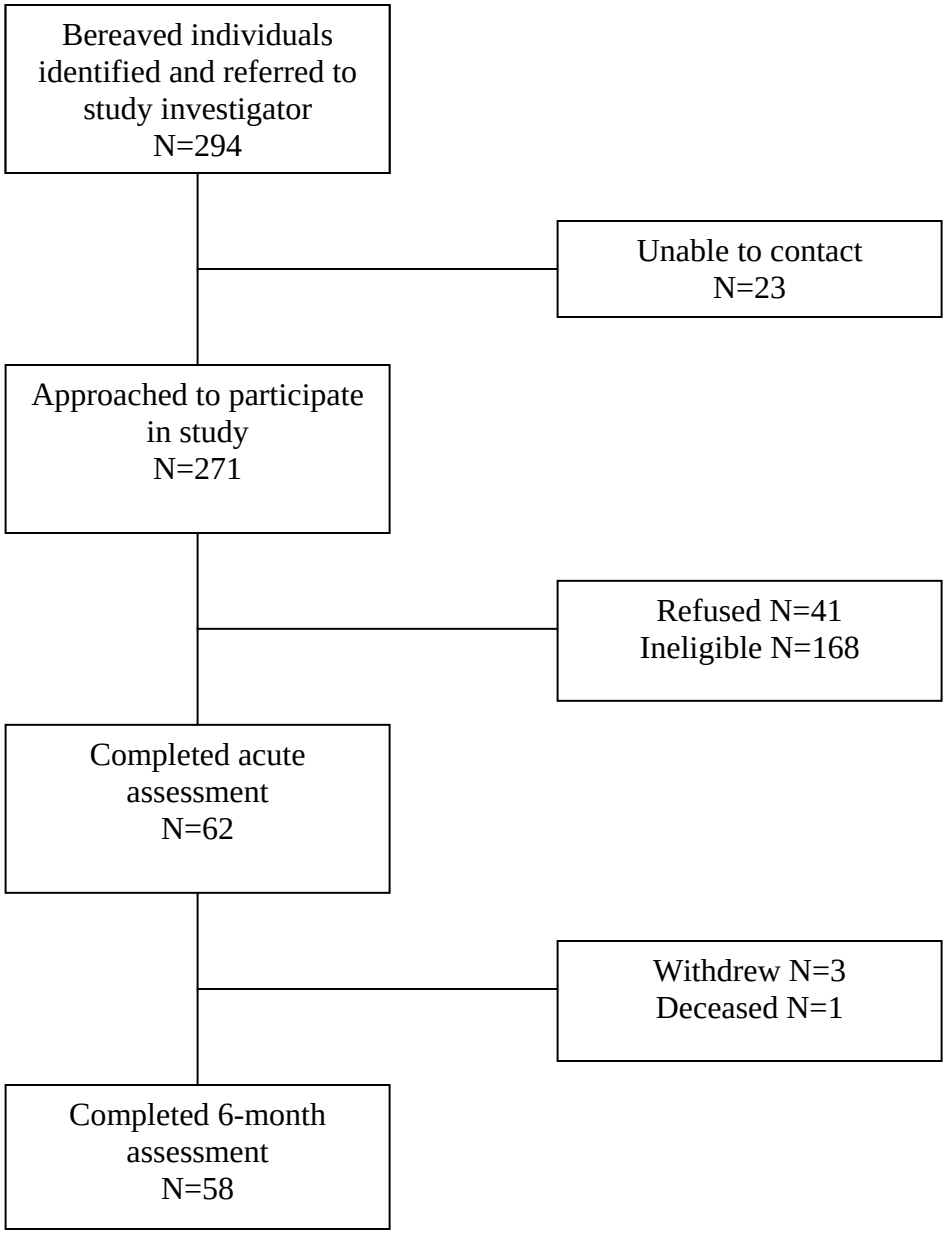


Figure 2. Flow of bereaved subjects from identification, recruitment withdrawals and completions

***Non-bereaved*:** A non-bereaved group was recruited to represent a comparison sample of hospital users who were unlikely to be experiencing major stress related to their family member's hospitalisation. Family members of patients who presented for elective surgery and were discharged from the study hospitals, with no residual complications were identified by the investigator or another research nurse. A study information sheet (Appendix B) was given to family members of patients who consecutively attended the orthopaedic, gastrointestinal or day surgical departments at study sites. Those family members expressing interest in the study were contacted again by the investigator by phone and an appointment made in their home once their relative had recovered from their surgery (approximately one month following surgery).

Ten non-bereaved participants were recruited during the Summer months (December to February), 12 during Autumn (March to May), 15 during Winter (June to August) and thirteen during Spring (September to November), which was not significantly different to recruitment of the bereaved participants, X^2, p=0.80 (Figure 3).

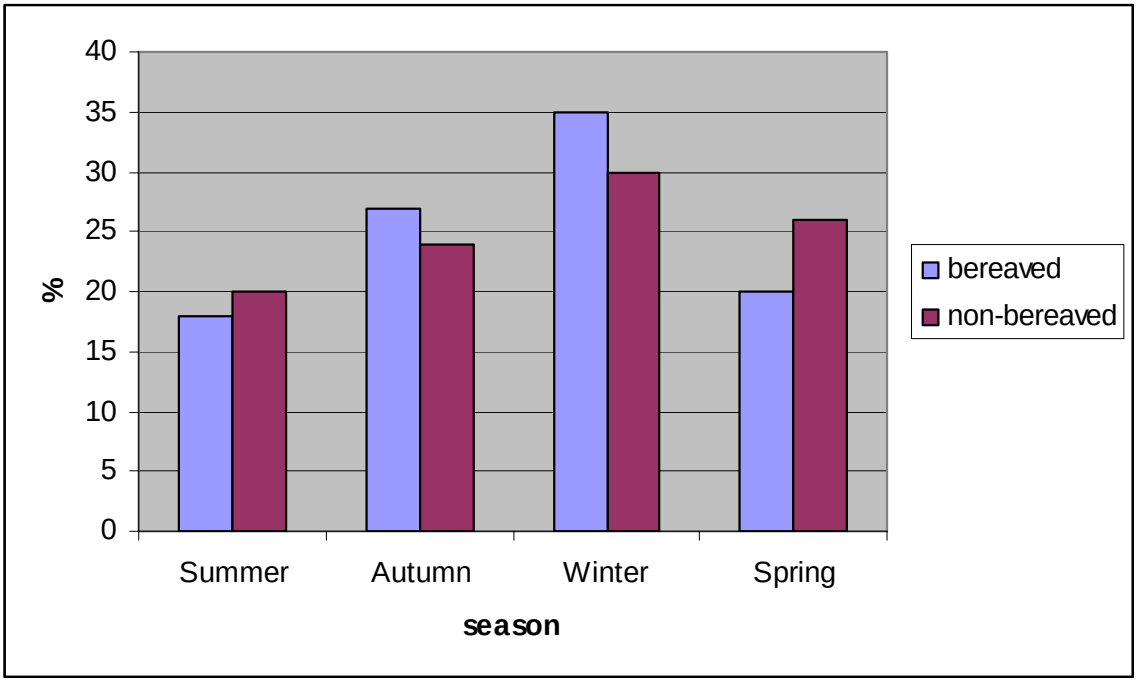


Figure 3 Recruitment by season across study period

Exclusion criteria: Bereaved and non-bereaved subjects were excluded if they had the following conditions: active malignancy, severe illness (respiratory, heart, liver or renal failure), history of coagulopathy, thrombocytopenia, cognitive impairment, psychotic illness, immunosuppressive illness or taking immunosuppressive drugs, residents in nursing homes or unable to speak and read English. In addition, for the non-bereaved group, people who had experienced the death of a close family member or friend in the previous two years were excluded. Of the bereaved participants studied, only one had experienced a second close bereavement in the two years prior to enrolment. In addition all participants who lived more than 60 minutes driving time from the hospital were ineligible. This was necessary because of laboratory requirements for time from collection to storage and analysis of collected blood samples.

3.4 *Sample size and power calculations*

The sample size for the study reported in this thesis was based on the feasibility of participant recruitment and data collection within the University time frame to complete the degree and to allow for a valid statistical analysis. Sixty-two bereaved and 50 non-bereaved participants were studied within the University time frame. Sample size calculations were made for plasma fibrinogen, blood pressure load and heart rate variability prior to commencement of recruitment.

Plasma fibrinogen: Fibrinogen was estimated in other studies to have a standard deviation of around 80mg/100ml. Assuming that a shift of half of this would be significant, a sample size of 80 in each group was calculated to give a power of 88% (2-sample t-test of independent groups).

24-hour Ambulatory Blood Pressure Load (ABP): The BP load is defined as the percentage of ambulatory systolic and diastolic pressures respectively exceeding 140mmHg and 90mmHg during wake time, and 120mmHg and 80mmHg during sleep. A sample size of 80 subjects per group was estimated to give 83.5% power to observe a significant difference ($p<0.05$) assuming a 25% higher ABP load in bereaved versus non-bereaved participants.

24-hour Heart Rate Variability: The standard deviation of RR intervals over a 24 hour period (SDNN) was the primary measure of heart rate variability. It was hypothesized that differences in the bereaved versus the non-bereaved group would be

comparable to that observed in patients with chronic coronary disease versus healthy middle aged persons (Bigger et al., 1996). In this study by Bigger et al. (1996) with mean SDNN of 120msec versus 141msec and a standard deviation for both groups of 40msec, a sample of 80 was estimated to have a power of over 91% to detect a significant difference ($p<0.05$).

3.5 *Ethical considerations*

Ethics approval was granted by the Human Research Ethics Committees of Northern Sydney Central Coast Health and the University of Technology, Sydney. The main ethical considerations were participant consent, privacy and confidentiality, access to information and potential distress from participation in the study. The investigators recognised the need for great sensitivity in approaching bereaved family members and every effort was made not to increase distress.

As soon as results became available, all assessment data was assessed by the investigator and a cardiologist. Copies of all results were sent to participants upon completion of the study. An advisory committee (social work, pastoral care, nursing and medical staff) established a procedure to refer abnormal results to the person's family doctor if required. This applied to bereaved and non-bereaved participants. Two bereaved participants were referred for bereavement counselling following the six month assessment.

Participants were provided with written information about the study prior to obtaining written consent (Appendix C). The initial and six-month assessments were carried out in participants' homes to avoid increasing bereaved participant's anxiety by visiting the hospital again. Confidentiality was maintained with all participants' data and questionnaire sheets coded with a study number and stored in a locked filing cabinet. The master sheet with study numbers and participants identifying information was locked in a separate filing cabinet. Data entered on the computer were accessible only to the investigators with the use of a password. Participants were advised that they could withdraw their consent at any time during the study without any effect on their relationship with the hospital.

3.6 *Data collection and instruments*

Sociodemographic characteristics and clinical history: On entry to the study, sociodemographic data recorded were: sex, age, origin of birth, education, income, number of people living at home and availability of, and satisfaction with social support. For the bereaved individuals, date of the death, specifics of the terminal illness, cause of death, time from diagnosis of condition that lead to the death and how prepared participants were for the death were obtained (Appendix D).

Personal clinical history was recorded by asking participants a series of questions regarding their previous cardiac history, current medications and eating, smoking and alcohol behaviours (Appendix E). Participants also completed a twenty-

four hour activity diary while undergoing heart rate and blood pressure monitoring documenting physical activity, time to bed and awakening (Appendix F).

Social support: To quantify the availability of, and satisfaction with social support at the initial acute assessment, participants completed the Social Support Scale (SSQ-6), (Radloff, 1977; Sarason, Sarason, Potter, & Antoni, 1985; Sarason, Shearin, Shearin, & Pierce, 1987), Appendix G. This instrument comprises of two fundamental elements of social support: 1) the perception that a sufficient number of others is available to whom a person can turn to during times of need, and 2) the degree of satisfaction with the support available.

The SSQ-6 is a seven item questionnaire, each requiring a two-part answer. Subjects were asked to 1) list the people to whom they could turn and on whom they can rely in particular sets of circumstances (availability) and 2) rate how satisfied they were with the available support (satisfaction). In the questions related to social support availability, the maximal score that was attributed to each individual support question was nine. The overall social support availability score was calculated as the mean of the number of support persons with a possible range of zero to nine. The social support satisfaction score was based on a scale for each item ranging from "very satisfied", scored as one, to "very dissatisfied," scored as six. The overall social support satisfaction score was the mean of the seven satisfaction question scores with a possible range of one to seven. Reliability of this instrument has been previously reported

(Packham & Hall, 2002) and the present study revealed high internal consistency with Cronbach's alpha of 0.96.

Symptoms of depression: Bereaved participants completed the Centre for Epidemiological Studies-Depression (CES-D) questionnaire (Radloff, 1977) at both acute and six-month assessments and non-bereaved on entry to the study (Appendix H**)**. This instrument was developed by the Centres for Disease Control and measures the degree to which people are experiencing symptoms of depression. The instrument comprises of 20 questions related to how the participant felt and behaved in the previous week. Response choices range from "rarely or none of the time (<1 day)" scored as zero, to "most or all of the time (5-7 days)", scored as three. Individual questions that participants did not give a response to were entered as a mean score of all other questions provided there were not more than four missing answers. Scores were added to give a possible score between 0-60. A score of 16 or more is considered to be indicative of clinically significant levels of depression (Breslau, 1985). This self-rating instrument for the measurement of depressive symptoms has revealed good internal consistency in prior studies (Fountoulakis et al., 2001) and in this study Cronbach's alpha at the acute assessment was 0.86 and at six months was 0.91.

Symptoms of Anxiety and Anger: Bereaved participants completed the Spielberger State Anxiety and Anger scales (Spielberger 1983; Spielberger, 1988) at both acute and six-month assessments and non-bereaved on entry to the study (Appendix I). The state anxiety scale consists of 20 items that ask how a person feels

now, and reflects situational factors that may influence anxiety levels at the time of testing. Answers to individual questions range from “not at all”, scored as one, to “very much so”, scored as four. Scores are added giving a range from 20 to 80 with higher scores reflecting greater levels of anxiety. Scores of 30 or greater are considered to be indicative of clinically significant anxiety. Reliability and validity of this scale have been previously reported (Spielberger 1983; Spielberger, 1988) and in this study there was good internal consistency evident with Cronbach’s alpha of 0.96 at the initial acute assessment and 0.95 at the six-month assessment.

The state anger scale relates to the experience of anger at the time of assessment. The questionnaire consists of 15 items that ask how a person feels “right now”. Responses to individual questions range from “not at all”, scored as one, to “very much so”, scored as four. Scores are added giving a range from 15-60 with higher scores reflecting greater anger state. Reliability and validity of this scale have been previously reported (Spielberger 1983; Spielberger, 1988); in the study reported here internal consistency (Cronbach’s alpha) at each assessment was 0.89 at the acute assessment and 0.71 at six months.

Behavioural assessment: Participants completed a questionnaire exploring appetite, alcohol consumption, tobacco smoking and sleeping behaviours in the week prior to their assessment (Appendix J).

Physical assessment: Weight was measured using an electronic scale and recorded to the nearest 0.1kg. Height was measured to the nearest 5mm using a fixed tape measure while participants stood wearing no shoes. Waist circumference was measured at the umbilicus level at end expiration.

Blood analysis: Collection and analysis of blood samples were carried out using standard protocols. Venous blood samples were taken from the antecubital fossa using a butterfly needle (size 0.8 x 19mm) into pre-suctioned blood bottles with minimal use of a tourniquet. Following blood taking, samples were transported in a cool transport box ensuring samples were not in direct contact with the cooling ice block. The mean transport time, from collection to laboratory delivery, was 40 minutes (range 10-60). Participants were asked to refrain from breakfast prior to blood collection. Those who were unable to remain fasting pre-assessment were asked to have a light breakfast on the morning of assessment. A light breakfast was defined as a cup of tea or coffee and slice of toast only. There was no difference between bereaved and non-bereaved in those fasting prior to the initial acute assessment (45% vs 48%, p=0.237). Haematological and biochemistry studies included the following: total cholesterol, LDL-cholesterol, HDL-cholesterol, triglycerides, full blood count (total white cell, neutrophil, monocyte and lymphocyte counts); haemostatic and inflammatory markers: C-Reactive Protein (CRP), fibrinogen, von Willbrand factor antigen (vWF-ag) and Factor VIII; and as a marker of neuroendocrine activation: morning plasma cortisol levels. Analyses were conducted at Royal North Shore Hospital using standard

laboratory techniques by staff blinded to study outcomes and participant group. A summary of the laboratory methods used is presented in Table 2.

Haemodynamic assessment: The following assessments were performed on bereaved participants at the initial acute and six month assessments and on non-bereaved participants on entry to the study: 24-hour heart rate monitoring, resting (clinic) blood pressure, 24-hour ambulatory blood pressure (ABP) recording.

Electrocardiogram (ECG) Holter monitoring was performed using the Medtel Digital System, and analysed using the Medilog Optima reporting system (Oxford Instruments Medical Systems Division). The primary endpoints were 24-hour mean heart rate and the standard deviation of all filtered RR intervals (SDNN) over the analysis. Analyses were conducted by the investigator and a Holter technician under the supervision of a cardiologist with autonomic function expertise who was blinded to group. Attention was paid to the accurate and consistent detection and labelling of beats and erroneous beats were manually labelled. Periods of unreadable cardiac beats were excluded from the analysis.

Ambulatory blood pressure was performed using the Takeda A&D TM-2430, which uses an oscillometric method and received Grade A/A under the British Hypertension Society for measuring both systolic and diastolic blood pressures. Intervals were pre-set to measure BP every 30 minutes during the day (from 6am to 8pm) and every 60 min at night (from 8pm to 6am) to minimize inconvenience during

the monitoring period. Participants kept a diary in which they recorded their activity at the time of individual recordings and time at which they went to bed and when they got out of bed in the morning. Ambulatory blood pressure load, the primary blood pressure endpoint, was defined as the percentage of systolic and diastolic pressures exceeding 140mmHg and 90mmHg respectively while awake (and not in bed), and 120mmHg and 80mmHg during sleep. Attention was paid to exclude artefact readings associated with activity, such as driving, using the participants' diary as a guide. Analyses were conducted by a doctorally trained blood pressure specialist blinded to group.

The cardiovascular risk factors assessed in bereaved and non-bereaved participants at the acute assessment, and in bereaved participants at the six-month assessment are summarized in Table 2.

Table 2 Summary of cardiovascular risk factors assessed and instruments used

	Variable assessed	Instrument/ technique
Psychological	Symptoms of depression	CES-D questionnaire
	State anxiety and anger	Spielberger state anxiety and anger scales
	Social support (availability and satisfaction)	Social Support Scale (SSQ-6)
Behavioural	Appetite, alcohol intake, tobacco use and sleep behaviours	Behavioural questionnaire
Physical	Weight	Electronic scales Recorded to the nearest 0.1kg.
	Height	Fixed tape measure Measured to the nearest 5mm
	Waist circumference	Umbilicus level at end expiration
Blood analysis	Lipids	Modular P.P. Roche Diagnostics Enzymatic colorimetric test
	CRP	Modular P.P. Roche Diagnostics Particle-enhanced immunotubometric assay
	Morning cortisol	Immulite 2000 analyzer
	FBC	Beckam Coulter LH750 Analyser
	Fibrinogen	Diagnostica Stago STA-R analyser Clauss method
	vWF-ag	Diagnostica Stago STA-R analyser vWF immunoturbidimetric method
	Factor VIII	Diagnostica Stago STA-R analyser FVIII functional assay, APTT clot based assay
Heart rate	24-hour HR and SDNN	Medtel Digital System Medilog Optima reporting system
Blood pressure	Systolic and diastolic blood pressure load	Takeda A&D TM-2430 Oscillometric method

3.7 *Data entry*

Data were entered into a computer from the data collection sheets and laboratory reports on a weekly basis. A Microsoft Office Access database was used for storage and management of multiple data entries. Data were transferred to SPSS (Version 14) for analysis.

3.8 *Missing data*

Participant data lost to follow up was treated as missing data. The valid numbers for each set of variables tested are presented in Appendix K. Missing responses to individual questions within the psychological questionnaires were substituted with the mean value for that scale or subscale as appropriate, provided these questions were not more than half the total scale. There were few missing answers on any scales as the questionnaires were checked for completion by the investigator at the time of data collection.

Seventeen (10%) of the total 170 digitalised Holter recordings were not able to be analysed for heart rate variability due to technical malfunction at the time of download (disc error or inadequate recording quality). These missing data were considered to be random and were substituted by the mean or median value as appropriate from their group (bereaved or non-bereaved) at that assessment time (Altman & Bland, 2007).

Four (6%) of bereaved participants chose not to wear the 24-hour blood pressure monitor during day or night-time at the first assessment and five (9%) chose not to wear the monitor at the six-month assessment. Twelve (19%) of the bereaved participants chose not to wear the blood pressure monitor at night-time during both the initial acute and six-month assessments, but did complete the day-time blood pressure monitoring. Substitution of missing data was not conducted as the decision not to wear the blood pressure monitor was likely to not be random.

3.9 *Data Analysis*

Descriptive statistics were used to characterise the sample. Equivalence of the two groups' baseline characteristics was tested using t-test for interval data and chi-square test (X^2) for categorical data.

The primary analysis involved comparison of bereaved to non-bereaved participants at the initial acute assessment. This was conducted using parametric and nonparametric analysis between groups as appropriate. Log transformation was performed on skewed interval data and parametric analysis applied using Student's t-test. Skewed data unsuccessfully transformed using log transformation were analysed using the Mann-Whitney U test. To analyse BP load, logit transformation was conducted on proportional data prior to analysis.

The secondary hypothesis (1) was that compared to the acute bereavement period, at six months following bereavement there would be a lowering of the

cardiovascular risk. This was tested utilising paired analysis techniques comparing the bereaved acutely to six months. Normally distributed interval data were analysed using a Student's paired t-test. Skewed data unsuccessfully transformed using log transformation were analysed using the Student's t-test non-parametric equivalent McNemar test. Wilcoxon signed-rank test was utilized to compare dichotomous variables from the initial acute assessment to six months.

The secondary hypothesis (2) was that physiological changes associated with bereavement would be associated with higher grief reactions (depression, anxiety and anger) and lower levels of social support. The relationship between the physiological variables and symptoms of depression and anxiety were described using Pearson's product moment correlation and the relationship with anger using Spearman's rank-order correlation due to the non-normal distribution of anger scores. The relationships between physiological variables and social support availability scores were described using Pearson's product moment correlation and the relationship with social support satisfaction using Spearman's rank-order correlation due to the non-normal distribution of satisfaction scores.

Chapter 4 - Results

4.1 *Introduction*

In this chapter, firstly there is a description of the sociodemographic characteristics and clinical history of the bereaved study participants. The bereaved group then are compared to the non-bereaved group at baseline for sociodemographic characteristics, clinical history and social support. The primary analysis for each group of study variables (psychological, behavioural, physical and physiological) are presented comparing the bereaved group at the first acute assessment to non-bereaved and then the bereaved group acutely to the results of their six-month assessment. Relationships between psychological state (symptoms of depression, anxiety and anger) and physiological differences between groups at the first acute assessment are described. Additionally relationships between social support availability and satisfaction, and physiological differences at the initial acute assessment are explored and described. Data related to the primary and secondary hypotheses are presented in tables.

4.2 *Bereaved participants sample characteristics*

Sociodemographic characteristics: The average age of bereaved participants was 65.2 years (range 33-84) and 66% were born in Australia. Not surprisingly, 68% of the sample were female in keeping with the fact that women live longer (Charlton et al., 2001). Fifty-eight (94%) of the sample were spouses or partners of the deceased and four (6%) were parents. Parents were on average 4.3 years older than spouses (67.7 vs 63.4 years) and consisted of two females and two males. For bereaved spouses, the

mean number of years together as a couple ranged from 3-62 years (mean 37.12). Seventy-six percent of the sample reported that the death was “unexpected” and the time from diagnosis of the condition that lead to the death ranged from the same day to 16.85 years (median 13 days). The mean number of support persons reported on the SSQ-6 was 4.5 and 55% were living alone at the time of initial assessment, following the death of their loved one.

Clinical history: Sixteen percent of bereaved participants reported a history of myocardial infarction, 8% stroke and 6% diabetes. Thirty-nine percent were taking anti-hypertensive medications, 22% aspirin and 29% cholesterol lowering medication. Fourteen percent reported a history of snoring or sleep apnoea and 8% a prior history of depression, with less than half of these participants (3%) taking antidepressant medications. Mean body mass index (BMI) was 26.2 (kg/m^2) at time of first acute assessment.

4.3 *Comparison of groups at baseline*

The bereaved and non-bereaved participants did not differ in sociodemographic characteristics, as reported in Table 3. Bereaved participants were more likely to be living alone at the time of the first assessment than the non-bereaved ($p=0.001$), which may be expected in a sample compromising mainly of bereaved spouses. The two groups reported similar numbers of available social support persons and satisfaction with that support as shown by responses to the SSQ-6 (Table 3). There were no

significant differences between the groups' clinical characteristics, medical history, prescribed medications or BMI (Table 4).

Table 3 Sociodemographic characteristics in participants recently bereaved compared to non-bereaved

	Bereaved (n=62)		Non-bereaved (n=50)		p*
	Number		Number		
Age in years mean (range)	65.2	(33-84)	61.6	(36-87)	0.14
Female	42	68%	32	64%	0.41
Born in Australia	38	66%	27	54%	0.16
Education (highest level)					
High school	24	39%	20	40%	
Technical	23	37%	13	26%	
University	13	21%	16	32%	
Did not state	2	3%	0	0%	0.32
Household income					
<$20,000	12	21%	9	18%	
$20,001-60,000	15	26%	16	33%	
>$60,000	16	27%	15	31%	
Did not state	15	26%	9	18%	0.76
Living alone (at time of assessment)	34	55%	5	10%	<0.001
	Mean	SE	Mean	SE	
Number of support persons (SSQ-6) possible range 0-9	4.5 Range 1-9	(0.3)	3.9 Range 0.1-9	(0.21)	0.21
Social support satisfaction (SSQ-6) possible range 1-6	5.6 (median) Range 1-6		5.3 (median) Range1-6		0.28

*t-test or Mann-Whitney U for interval data, X^2 for categorical data

Table 4 Clinical history measured in participants recently bereaved compared to non-bereaved participants

	Bereaved (n=62)		Non-bereaved (n=50)		p*
	Number		Number		
Medical history					
History of myocardial infarction or angina	10	16%	4	8%	0.42
History of diabetes	4	6%	4	8%	0.36
History of stroke	5	8%	3	6%	0.60
History of chronic sleep problems (snoring or sleep apnoea)	9	14%	8	16%	0.60
History of depression	5	8%	6	12%	0.38
History of anxiety disorder	2	3%	3	6%	0.41
Medications					
Heart rate lowering drugs	6	10%	3	6%	0.36
Anti-hypertensive drugs	24	39%	13	26%	0.11
Cholesterol lowering drugs	18	29%	12	24%	0.54
Aspirin	14	22%	10	20%	0.46
Antidepressant drugs	2	3%	3	6%	0.40
Antibiotic drugs	2	3%	3	6%	0.53
Warfarin	2	3%	1	2%	0.58
Physical assessment	Mean	SE	Mean	SE	
Body Mass Index (BMI) kg/m^2	26.2	0.7	26.7	0.7	0.60
	Range 15.5- 41.2		Range 17.3 - 40.2		

*t-test for interval data, X^2 for categorical data

4.4 *Psychological assessment*

The results of assessment of depression, anxiety and anger symptoms are summarised in Table 5. Depression, anxiety and anger symptoms were all elevated acutely in the bereaved compared to non-bereaved participants. Although depression and anxiety symptoms reduced over time in the bereavement group, they remained elevated at six months. Acutely, 84% of bereaved participants reported depression symptoms higher than the recognised cut-off point for clinically significant depression symptoms (16 on the CES-D), compared to 61% at the six-month assessment. Similarly, 82% of bereaved participants reported anxiety symptoms higher than the recognised cut-off point for clinically significant anxiety symptoms (30 on the Spielberger State Anxiety Inventory), compared to 53% at the six-month assessment. Bereaved participants had higher anger scores acutely in the first two weeks that were reduced at six months. However, scores for anger were generally very low.

Table 5 Symptoms of depression, anxiety and anger in bereaved participants acutely and at six months.

Variable	Bereaved (B)		Non-bereaved (NB)		
	Acute	6-months		p B vs NB Acute	p B acute to 6 months
Depression mean (SE) (possible range 0-60)	26.7 (1.7)	16.8 (6.2)	5.9 (0.7)	<0.001	<0.001
Anxiety mean (SE) (possible range 20-80)	47.4 (2.0)	37.2 (2.1)	28.2 (1.4)	<0.001	<0.001
Anger median (IQR) (possible range 15-60)	16.0 (16.0-37.0)	15.0 (15.0-16.0)	15.0 (15.0-15.0)*	<0.001	0.001

SE: Standard error of mean IQR: interquartile range
*88% of non-bereaved participants reported a score of 15 therefore no interquartile range

4.5 *Assessment of appetite, alcohol and tobacco smoking behaviours*

Appetite and alcohol consumption: Compared to non-bereaved, bereaved participants at the initial acute assessment were more likely to report feeling less hungry and eating less than usual in the week prior to the assessment (Table 6). There was no difference in the number of standard drinks consumed daily between bereaved and non-bereaved participants acutely. There was no difference in the number of drinks consumed by bereaved participants from the acute to six-month assessment. However, compared to non-bereaved participants, fewer bereaved reported drinking alcohol at the initial assessment (68% vs 88%). Those who did drink were more likely to report a change in alcohol consumption in the week prior to the initial acute assessment. For those who reported a change, there was no consistent direction, in that 60% reported an

increase in consumption and 40% a decrease (Table 6). Four bereaved participants reported binge drinking at the acute assessment and two at the six-month assessment.

Only five bereaved participants reported tobacco smoking at the acute assessment, which was similar to the control group (Table 6). There was no difference in the number smoked acutely compared to the non-bereaved group or over time within the bereaved group. Of the five who reported smoking, two reported an increase in smoking and one a decrease at the acute assessment.

Table 6 Assessment of appetite, alcohol and smoking behaviours

Variable	Response	Bereaved (B)		Non-bereaved (NB)		
		Acute N (%)	6-months N (%)	N (%)	p B vs NB acute	P B acute to 6 mts
In the past week: have you been hungry?	Yes	12 (19%)	30 (52%)	29 (58%)	<0.001	<0.001
In the past week: Have you been eating less?	Yes	39 (63%)	14 (24%)	2 (4%)	<0.001	<0.001
In the past week: Have you been eating more?	Yes	5 (8%)	8 (14%)	4 (8%)	0.635	0.14
Do you currently drink alcohol?	Yes	42 (68%)	37 (64%)	44 (88%)	0.01	0.14
If you currently drink, in the past week: has your alcohol consumption changed?	Yes	20 (48%)	9 (21%)	2 (5%)	<0.001	0.006
	Increased	12 (60%)	3 (33%)	1 (50%)		
	Decreased	8 (40%)	6 (77%)	1 (50%)	0.003	0.03
Mean number of standard drinks per week	Mean (SE)	8.1 (1.8)	8.2 (1.8)	8.9 (1.2)	0.72	0.18
Episodes of binge drinking in the past week	Yes	4 (6%)	2 (3%)	1 (2%)	0.24	0.48
Do you currently smoke?	Yes	5 (8%)	5 (12%)	4 (8%)	0.63	0.42
If you currently smoke, in the past week: has your smoking changed?	Yes	3 (60%)	1 (20%)	0	N/A	N/A
	Increased	2 (67%)	0 (0%)	0 (0%)		
	Decreased	1 (33%)	0 (0%)	0 (0%)	N/A	N/A
Mean number of tobaccos smoked daily	Mean (SE)	16.8 (3.8)	16.4 (3.4)	10.75 (5.2)	0.38	0.25

N/A: Numbers insufficient for valid analysis. SE: Standard error of mean

4.6 *Assessment of sleep duration*

The results of reported sleep behaviours are presented in Table 7. Acutely, bereaved participants reported sleeping fewer hours than non-bereaved participants. Acutely, 56% of bereaved participants reported that sleep time was less than their usual and 10% reported sleeping more than usual. Sleep duration increased over time in the bereaved and at the six-month assessment, 14% of bereaved participants reported sleeping less than usual, which was significantly less than at the acute assessment.

Despite the differences in duration of sleep acutely, there were no significant differences between the mean time spent in bed at night as recorded in their diaries by bereaved and non-bereaved participants (7.5 ±1.7 vs 8.0 ±1.1 hours, p=0.31).

Table 7 Assessment of sleep behaviours

Variable	Bereaved (B)		Non-bereaved (NB)		
	Acute	6-months		p B vs NB acute	p B acute to 6 months
Mean sleep hours per night in the past week mean (SE)	5.88 (0.21)	6.77 (0.16)	7.22 (0.16)	<0.001	<0.001
Less than usual sleep n (%)	35 (56%)	8 (14%)	3 (5%)	<0.001	<0.001
Awakening or insomnia n (%)	46 (74%)	33 (57%)	32 (64%)	0.17	0.004
More then usual sleep n (%)	6 (10%)	5 (9%)	3 (6%)	0.36	0.73

SE: Standard error of mean

4.7 *Physical assessment*

There were no differences between bereaved and non-bereaved participants in BMI and waist circumference at the initial acute assessment (Table 8). In addition, BMI or waist circumference did not change in the bereaved group from the acute assessment to six months (Table 8). From the acute assessment to six months, 60% of bereaved reduced their BMI (mean weight loss 2.62kg), 28% increased their BMI (mean weight gain 3.70 kg) and 12% had no change in weight.

Table 8 Assessment of waist circumference and BMI

Variable	Bereaved (B)		Non-bereaved (NB)		
	Acute Mean (SE)	6-months Mean (SE)	Mean (SE)	p B vs NB acute	p B acute to 6 months
Waist circumference (cm)	92.7 (1.7)	93.9 (1.8)	92.8 (2.5)	0.98	0.52
BMI (kg/m^2)	26.2 (0.7)	26.6 (0.7)	26.7 (0.7)	0.60	0.33

SE: Standard error of mean

4.8 *Cortisol and lipids*

Cortisol: The results of blood cortisol and lipids are presented in Table 9. Morning cortisol levels were higher in bereaved participants compared to non-bereaved acutely and did not change over time from the acute assessment to six months.

Table 9 Assessment of Cortisol and Lipids

Variable	Bereaved (B)		Non-bereaved (NB)		
	Acute	6-months		p B vs NB acute	P B acute to 6 months
Cortisol mmol/L median (IQR)	306 (247-414)	326 (236-390)	266 (220-338)	0.003	0.64
Total Cholesterol mmol/L median (IQR)	4.92 (4.36-5.45)	5.16 (4.40-5.79)	5.44 (4.68-6.09)	0.006	0.01
LDL mmol/L Median (IQR)	2.41 (1.8-3.89)	2.74 (2.05-3.21)	2.94 (2.52-3.77)	<0.001	0.003
HDL mmol/L mean (SE)	1.82 (0.06)	1.75 (0.06)	1.69 (0.06)	0.15	0.04
Triglycerides mmol/L median (IQR)	1.18 (0.90-2.81)	1.18 (0.95-1.84)	1.20 (0.86-1.68)	0.75	0.65

Median scores presented with interquartile range (IQR) SE: Standard error of mean

The relationship between cortisol levels and symptoms of depression, anxiety and anger are summarised in Table 10. There were no significant correlations between cortisol and depression, anxiety or anger at the initial acute assessment.

Table 10 The relationship between cortisol and depression, anxiety and anger at the acute assessment in bereaved participants

	Depression r (P)	Anxiety r (P)	Anger r_S (P)
Cortisol	-0.02 (0.88)	0.01 (0.92)	0.02 (0.96)

There were no significant correlations between cortisol and social support availability (r=0.04, p=0.74) or social support satisfaction (r_S =0.11, p=0.38).

Lipids: Acutely, bereaved participants had lower levels of total cholesterol than non-bereaved that was increased at the six-month assessment (Table 9). This lower total cholesterol level appears to be the result of lower levels of low density lipoproteins (LDL) compared to non-bereaved that was increased at the six-month assessment. There were no differences in HDL or triglyceride levels between groups acutely, although HDL levels decreased significantly from the acute to six-month assessment in the bereaved participants.

The relationship between lipid levels and symptoms of depression and anxiety at the initial acute assessment are summarised in Table 11.

Table 11 The relationship between lipid levels and depression, anxiety and anger in bereaved participants

	Depression r (P)	Anxiety r (P)	Anger r_S (P)
Total Cholesterol	0.24 (0.06)	0.29 (0.02)	0.25 (0.056)
LDL	0.17 (0.19)	0.29 (0.03)	0.35 (0.008)

Lower total cholesterol was associated with lower anxiety and anger accounting for 8.4% (r^2) of shared variance. Lower LDL was associated with less anxiety and anger symptoms accounting for 8.4% (r^2) of shared variance between LDL and anxiety and 12.2% (r^2) of shared variance between LDL and anger. There were no associations between social support availability and total cholesterol (r=0.03, p=0.84) and LDL (r= -0.11 , p=0.93). Likewise there were no associations between social support satisfaction and total cholesterol (r_S =-0.11, p=0.39) and LDL (r_S =0.04, p=0.75).

4.9 *Assessment of inflammatory and thrombotic factors*

The results of analysis of inflammatory and thrombotic analysis are presented in Table 12. There was a trend towards higher total leucocyte count in bereaved participants compared to non-bereaved acutely. Analysis of leucocyte sub-populations revealed that increased neutrophil count was the main contributor to this increased total leucocyte count. Both total leucocyte and neutrophils were significantly lower in the bereaved group at six-months compared to acutely. There were no significant differences in monocyte or lymphocyte levels acutely or changes over time. There was a trend towards higher vWF-ag in the bereaved group acutely compared to the non-bereaved participants. As prior reports indicate lower vWF-ag levels in blood group O individuals (O'Donnell, Boulton, Manning, & Laffan, 2002), blood groups were analysed for all participants. Thirty-nine percent of bereaved participants were group O versus 50% of non-bereaved (p=0.16). While vWF-ag levels had significantly lowered in the bereaved group from acute to six-month assessment, the greatest change was in the non-O bereaved participants (Table 12).

There were no significant differences between groups for CRP, fibrinogen or Factor VIII acutely and no change from acute to six-month assessment in the bereaved group (Table 12).

Table 12 Inflammatory and thrombotic risk factors

Variable	Bereaved		Non-bereaved		
	Acute Median (IQR)	6-months Median (IQR)	Median (IQR)	p B vs NB acute	p B acute to 6 months
Leucocytes $x10^9$/L	6.70 (5.80-7.79)	5.85 (5.07-7.02)	6.20 (5.40-6.95)	0.06	0.001
Neutrophils $x10^9$/L	4.00 (3.35-5.00)	3.60 (2.70-4.25)	3.30 (3.00-3.92)	0.002	0.001
Monocytes $x10^9$/L Mean (SE)	0.53 (0.02)	0.49 (0.02)	0.51 (0.02)	0.64	0.07
Lymphocytes $x10^9$/L	1.70 (1.40-2.15)	1.70 (1.40-2.02)	1.84 (1.40-2.30)	0.60	0.13
CRP mg/L	1.20 (0.75-3.34)	1.50 (0.70-2.40)	1.71 (0.75-2.81)	0.99	0.18
Fibrinogen g/L	3.62 (3.03-4.04)	3.61 (3.17-4.04)	3.57 (3.07-4.13)	0.83	0.94
vWF-ag %	127 (112-143)	121 (103-137)	114 (104-134)	0.055	0.008
Blood group O	117 (98-130)	114 (90-132)	107 (96-120)	0.43	0.23
Blood group non O	139 (118-149)	124 (105-143)	130 (113-139)	0.41	0.02
Factor VIII U/ml	1.25 (1.02-1.52)	1.24 (1.05-1.47)	1.18 (0.90-1.34)	0.08	0.21

Median scores presented with inter quartile range (IQR) with exception of monocytes where data were normally distributed.

The relationship between neutrophils and symptoms of depression, anxiety and anger are summarised in Table 13. There were no associations between neutrophil count and depression, anxiety and anger.

Table 13 The relationship between neutrophil count and depression, anxiety and anger in bereaved participants

	Depression r (P)	Anxiety r (P)	Anger r_s (P)
Neutrophil count	-0.10 (0.43)	-0.19 (0.16)	-0.26 (0.84)

There were no significant associations between social support availability and neutrophils (r=0.05, p=0.70) and or between social support satisfaction and neutrophils (r_s = -0.23, p=0.07).

4.10 *Haemodynamic assessment*

Heart rate analysis: The results of 24-hour heart rate analysis are presented in Table 14. Acutely the bereaved participants had higher 24-hour average heart rate compared to non-bereaved. At six months, average heart rate was lower in the bereaved participants compared to their initial acute assessment.

Table 14 24-hour heart rate analysis

Variable	Bereaved		Non-bereaved		
	Acute mean (SE)	6-months mean (SE)	mean (SE)	P B vs NB acute	P B acute to 6 months
24 hour heart rate	75.5 (1.9)	72.1 (1.1)	70.6 (1.2)	0.008	0.03

Median scores presented with inter quartile range (IQR)

The relationship between 24-hour average heart rate and symptoms of depression, anxiety and anger are summarised in Table 15.

Table 15 The relationship between heart rate and depression, anxiety and anger in bereaved participants

	Depression r (P)	Anxiety r (P)	Anger r_s (P)
24-hour heart rate	0.25 (p=0.54)	0.27 (p=0.04)	0.27 (p=0.04)

Increased heart rate was associated with greater anxiety and anger at the acute assessment accounting for 7.3% (r^2) of shared variance between heart rate and anxiety and 7.3% (r^2) of shared variance between heart rate and anger. There were no associations between heart rate and depression symptoms. Additionally, there were no associations between social support availability and heart rate (r=0.01, p=0.94) or between social support satisfaction and heart rate (r_s =0.02, p=0.86).

Heart rate variability: Analysis of heart rate variability revealed lower standard deviation of all R-R intervals (SDNN) in the bereaved participants acutely

compared to non-bereaved. At the six-month assessment, SDNN had not changed significantly in bereaved participants (Table 16).

Table 16 Heart rate variability analysis in bereaved and non-bereaved participants

Variable	Bereaved (B)		Non-bereaved (NB)		
	Acute median (IQR)	6-months median (IQR)	median (IQR)	P B vs NB acute	p B acute to 6 mts
SDNN	116.0 (99-137)	129.2 (99-139)	129.7 (114-155)	0.04	0.23

The relationships between SDNN and symptoms of depression, anxiety and anger in bereaved participants are summarised in Table 17. There were no associations between SDNN and depression, anxiety or anger.

Table 17 The relationship between SDNN and depression, anxiety and anger in bereaved participants

	Depression r (P)	Anxiety r (P)	Anger r_s (P)
SDNN	0.04 (p=0.76)	0.05 (p=0.79)	0.01 (p=0.96)

There were no associations between social support availability and SDNN (r=0.34, p=0.79) or between social support satisfaction and SDNN (r_s =0.04, p=0.71).

Blood pressure: Physical activity, as recorded in participants' diaries while undergoing 24-hour blood pressure recordings, did not differ between bereaved and non-bereaved participants at the acute initial assessment (4.98 vs 5.0, p=0.98; possible

range 1-10). Additionally, in bereaved participants who completed the six-month assessment, there was no difference in activity levels from the initial acute assessment to six months (5.0 vs 5.2, p=0.33).

Manually recorded clinic blood pressure measurements, recorded prior to commencement of 24-hour ambulatory measurements, revealed higher systolic and diastolic pressures in bereaved compared to non-bereaved participants (p=0.01 and 0.03 respectively), (Table 18). There were no changes in systolic or diastolic clinic pressures in the bereaved participants from the acute to six-month assessments.

Analysis of 24-hour blood pressure revealed that systolic blood pressure was higher in bereaved compared to non-bereaved participants (mean mmHg (SE) 131.5 (1.8) vs 125.7 (1.7), p=0.03). There was no significant difference in 24-hour diastolic blood pressure (mean mmHg (SE) 76.4 (0.9) vs 74.9 (0.9), p=0.26). At the six-month assessment, in the bereaved group, 24-hour systolic and diastolic pressures remained unchanged (p=0.28 and 0.58 respectively).

Analysis of daytime blood pressure load revealed that both systolic and diastolic loads were higher in bereaved compared to non-bereaved participants (Table 18). At the six-month assessment, in the bereaved group, systolic load remained unchanged but diastolic load lessened. While participants were sleeping at night-time, there were no significant differences between groups in either systolic or diastolic blood pressure loads at the acute assessment. Additionally while sleeping, there were no changes in

systolic or diastolic loads from the acute to six-month assessment in bereaved participants.

Table 18 24-hour blood pressure analysis in bereaved and non-bereaved participants

Variable	Bereaved (B)		Non-bereaved (NB)		
	Acute mean (SE)	6-months mean (SE)	mean (SE)	P B vs NB acute	P B acute to 6 months
Manually recorded systolic mmHg	139.0 (2.3)	137.0 (2.8)	130.2 (2.7)	0.01	0.24
Manually recorded diastolic mmHg	79.4 (1.1)	78.1 (1.2)	75.5 (1.4)	0.03	0.19
Daytime systolic load (% readings > 140 mmHg)	39.7 (0.03)	28.9 (0.04)	25.8 (0.03)	0.005	0.36
Daytime diastolic load (% readings > 90 mmHg)	20.1 (0.02)	16.1 (0.02)	13.5 (0.02)	0.008	0.03
Night-time systolic load (% readings > 120 mmHg)	37.5 (0.04)	40.0 (0.05)	30.5 (0.04)	0.93	0.29
Night-time diastolic load (% readings > 80 mmHg)	13.4 (0.03)	14.7 (0.04)	10.8 (0.03)	0.63	0.51

SE: Standard error of mean

Further analysis revealed that increased manual blood pressure measurements were predictive of increased daytime systolic and diastolic load with 55% (r^2) of shared

variance between manual systolic and day systolic load and 40% (r^2) of shared variance between manual diastolic and day diastolic load (Table 19). Increased clinic blood pressure measurements were also predictive of increased sleep time systolic and diastolic blood with 35% (r^2) of shared variance between manual systolic and night systolic load and 17.5% (r^2) of shared variance between manual diastolic and night-time systolic load.

Table 19 The relationship between manually recorded blood pressure and blood pressure load in bereaved participants

	Manual Systolic BP r (P)	Manual Diastolic BP r (P)
Daytime systolic load	0.74 (<0.001)	
Daytime diastolic load		0.63 (<0.001)
Night-time systolic load	0.57 (<0.001)	
Night-time diastolic load		0.42 (0.002)

The relationship between daytime and night-time systolic and diastolic load and symptoms of depression and anxiety and anger are summarised in Table 20.

Table 20 The relationship between blood pressure and depression, anxiety and anger in bereaved participants

	Depression r (P)	Anxiety r (P)	Anger r_s (P)
Daytime systolic load (% readings > 140 mmHg)	0.16 (0.22)	0.18 (0.20)	0.28 (0.04)
Daytime diastolic load (% readings > 90 mmHg)	0.18 (0.18)	0.13 (0.36)	0.05 (0.75)

Increased day systolic blood pressure load was associated with greater anger symptoms accounting for 7.8% (r^2) of shared variance. There were no associations between systolic load and symptoms of depression and anxiety. Additionally there were no associations between diastolic load and symptoms of depression, anxiety and anger.

The relationship between blood pressure load and social support scores are summarised in Table 21. There were no associations between social support and either systolic or diastolic blood pressure load.

Table 21 The relationship between blood pressure load and social support scores in bereaved participants

	Social support (SSQ-6) availability r (P)	Social support (SSQ-6) satisfaction r_s (P)
Daytime systolic load (% readings > 140 mmHg)	0.08 (0.56)	0.09 (0.47)
Daytime diastolic load (% readings > 90 mmHg)	0.01 (0.96)	0.03 (0.83)

4.11 *Summary of results*

The bereaved and non-bereaved groups in this study were similar on all characteristics with the exception of more bereaved participants reporting living alone following the death of their spouse/ child. Analysis of psychological state revealed that bereaved participants reported higher symptoms of depression, anxiety and anger at the acute assessment compared to the non-bereaved. At six months, symptoms of

depression, anxiety and anger lessened but depression and anxiety levels remained higher than the recognised cut off levels for the instruments used.

At the acute assessment bereaved participants reported low appetite, reduced food intake and changes in alcohol consumption, with 60% of alcohol drinkers increasing consumption and 40% reducing consumption. Only five bereaved reported being a current smoker with two reporting that this increased in the week prior to the initial acute assessment.

Assessment of sleep behaviours revealed that while bereaved spent the same duration in bed to non-bereaved, at the acute assessment bereaved participants reported sleeping fewer hours than non-bereaved. Fifty-six percent of bereaved reported that this was less than usual for them. Sleep duration improved over time in the bereaved from the initial acute assessment to six months.

No significant changes were seen in waist circumference or BMI in the first six months in the bereaved participants.

Assessment of blood cortisol levels revealed higher levels at the acute assessment in bereaved compared to non-bereaved participants. Cortisol levels did not change in the bereaved participants over time from the initial acute assessment to six months. Additionally, there were no significant correlations between symptoms of depression, anxiety or anger and cortisol levels.

Total cholesterol and LDL levels were lower acutely in the bereaved compared to non-bereaved participants. Both total cholesterol and LDL levels increased over time from the acute assessment to six months. Additionally, lower lipid levels were associated with lower anxiety and anger symptoms in bereaved participants acutely.

Assessment of inflammatory and thrombotic factors revealed that bereaved participants had higher circulating neutrophils and a trend towards higher vWF-ag acutely. Both neutrophil count and vWF-ag were significantly reduced in the bereaved participants at six months compared to the acute assessment. There were no significant correlations between symptoms of depression, anxiety or anger and neutrophil levels. Additionally, no differences were found between bereaved and non-bereaved participants in CRP, fibrinogen or Factor VIII at the acute assessment and no changes were seen in the bereaved group from the initial acute assessment to six months.

Assessment of haemodynamic status revealed that bereaved participants had higher average heart rate at the initial acute assessment compared to non-bereaved. In the bereaved group, heart rate reduced over time from the acute assessment to six months. Increased heart rate was associated with higher levels of anxiety and anger in the bereaved participants at the acute assessment.

Analysis of 24-hour heart rate variability revealed lower SDNN in bereaved participants at the initial acute assessment compared to non-bereaved. At the six-month

assessment, SDNN remained unchanged in the bereaved group. There were no significant correlations between symptoms of depression, anxiety or anger and SDNN.

Assessment of 24-hour blood pressure revealed that, compared to non-bereaved, bereaved participants had higher daytime systolic and diastolic blood pressure loads. However in the bereaved participants, diastolic load reduced over time but systolic load did not change from the acute assessment to six months. Increased symptoms of anger were associated with higher daytime systolic load. No relationships between symptoms of depression and anxiety and blood pressure load were observed. Additionally, manually recorded blood pressures were highly predictive of both daytime and night-time blood pressure loads.

Chapter Five - Discussion

5.1 *Introduction*

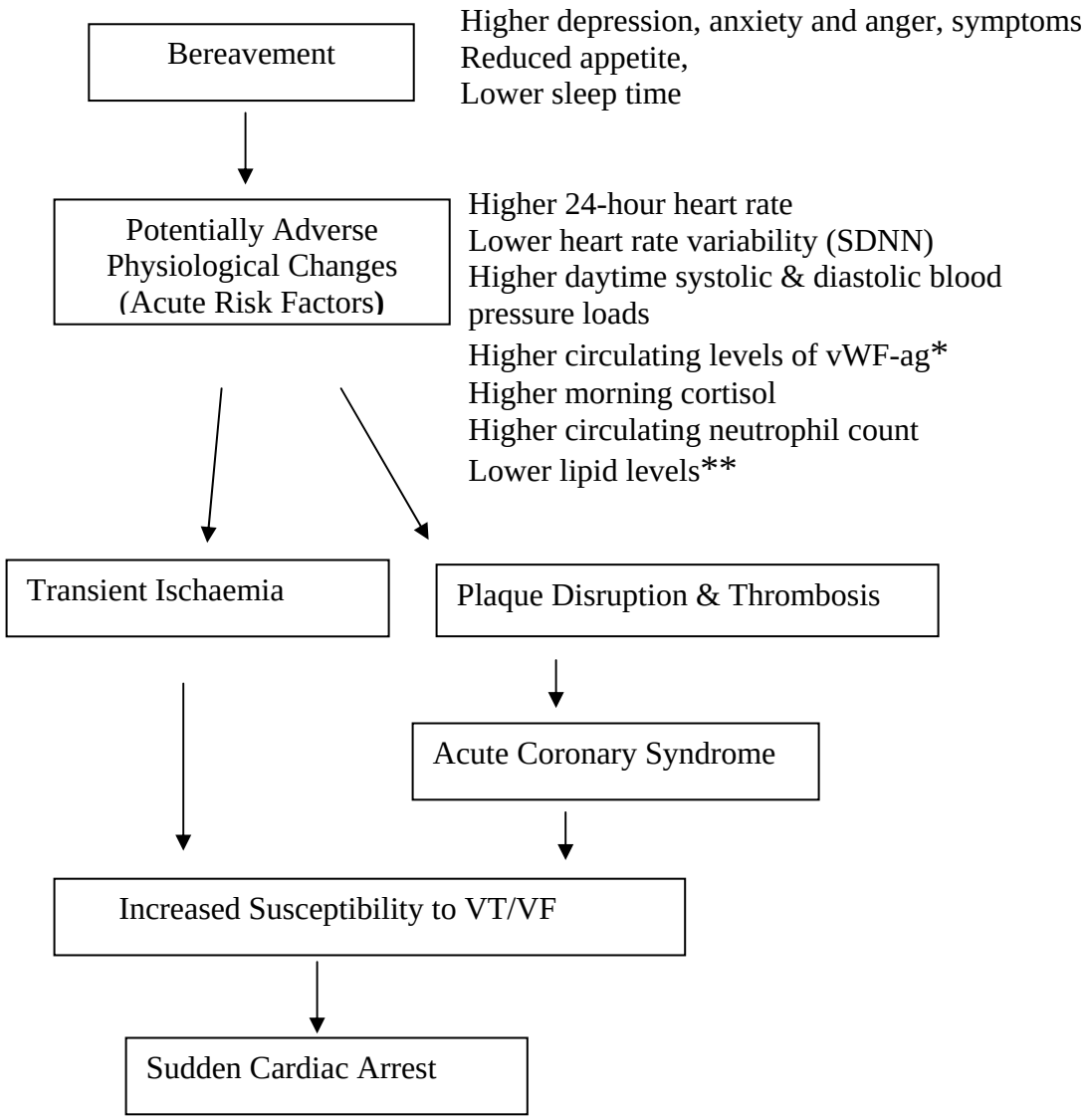
This study prospectively evaluated psychological, behavioural, physical and physiological cardiac risk factors acutely within two weeks of bereavement and again at six months. This is the first prospective study to evaluate the impact of bereavement on acute cardiovascular risk factors in the early weeks of bereavement with follow-up at six months. This period, particularly the early weeks of bereavement, is associated with a higher risk of cardiovascular events. This study provides insight into psychological, behavioural and acute physiological risk factor changes during early bereavement that have been associated with greater risk of AMI and sudden cardiac death. In this chapter the major findings of the study are summarised and then each finding discussed in relation to previous research reports. The strengths and limitations of the study are acknowledged and the implications for future research and practice discussed.

5.2 *Summary of major findings*

The bereaved participants were compared to a non-bereaved group acutely within two weeks of bereavement. The bereaved and non-bereaved groups in this study were similar on all characteristics with the exception of more bereaved participants living alone following the death of their family member.

To address the primary research hypothesis that bereaved participants would

have increased risk factors for myocardial infarction or sudden cardiac death, a comparison of bereaved to non-bereaved participants at the initial acute assessment was conducted. The major differences between the bereaved to non-bereaved participants at the initial acute assessment are summarised in Figure 4.



* between group analysis trend towards higher levels (p=0.055), significantly reduced at six months (p=0.008).
**Note: lower lipid levels potentially protective

Figure 4 Summary of differences between bereaved and non-bereaved participants at the initial acute assessment.

To address the secondary hypothesis (1) that compared to the acute bereavement period, at six months following bereavement there would be a lowering of the cardiovascular risk, a longitudinal evaluation was conducted in which the initial acute assessment was compared to the six-month assessment in the bereaved participants. At six months, depression, anxiety and anger had reduced significantly. Appetite had returned to normal and sleep time had increased. Heart rate, diastolic blood pressure load, VWF-ag and neutrophil levels were lower and blood lipid levels had increased. Cortisol, SDNN and systolic blood pressure remained unchanged.

To address the secondary hypothesis (2) that physiological changes associated with bereavement would be associated with higher grief reactions (depression, anxiety and anger), the relationship between the physiological variables and symptoms of depression, anxiety and anger were described. No significant associations between symptoms of depression and physiological changes acutely were observed. Increased symptoms of anxiety were associated with higher heart rate and cholesterol levels. Increased anger symptoms were associated with higher heart rate, day systolic blood pressure and higher cholesterol levels.

To determine if levels of social support were associated with lower cardiovascular risk, the relationships between levels of social support and physiological changes observed were described. No significant relationships between social support (availability or satisfaction) and physiological changes acutely were observed.

5.3 *Psychological assessment*

Depression, anxiety and anger: In this study, symptoms of depression, anxiety and anger were all significantly elevated in the first two weeks of bereavement. Although symptoms improved over time, depression and anxiety levels remained incompletely resolved at six months. These findings are consistent with previous reports of declining but unresolved psychological symptoms six months after bereavement (Gerra et al., 2003; Maciejewski, Zhang, Block, & Prigerson, 2007; Prigerson et al., 1997). While bereaved participants had higher anger scores acutely compared to non-bereaved, levels were only mildly elevated and were resolved at six months. One study suggests a peak in anger at five months after loss (Maciejewski et al., 2007), however the current study would suggest that following death in a critical care unit, anger is not a persistent psychological response to bereavement for the surviving spouse or parent.

5.4 *Behavioural assessment*

Appetite, alcohol and smoking behaviours: At the acute assessment, bereaved participants reported low appetite and reduced food intake. Eating may be determined to a large extent by cultural, social and psychological pressures (Elsner, 2002) and loss of appetite has been previously reported during bereavement in elderly populations (Clayton, Halikes, & Maurice, 1971; Shahar, Schultz, Shahar, & Wing, 2001). The results in the current study confirm previous reports of reduced appetite in bereavement and that for most, appetite returns to normal by six months. The results also suggest that increased food intake is not a contributor to increased cardiac risk in the acute early period of bereavement.

Acutely, bereaved participants reported changes in alcohol consumption, with 60% of alcohol drinkers increasing and 40% reducing consumption, reflecting individual differences in response to the loss. This is consistent with previous reports in bereavement (Stroebe, 2001) and has been suggested to be a potential mediator of increased cardiac risk during bereavement, particularly in men (Stroebe, Schut, & Stroebe, 2007). Further investigation into the effects of alcohol consumption in bereavement is warranted in light of the complex relationship between alcohol consumption and cardiovascular risk (Baer et al., 2002).

Only five bereaved participants reported being a current smoker, with two reporting that this increased in the week prior to the initial acute assessment. While the low numbers reporting changes in smoking behaviours make it difficult to form definitive conclusions, increased tobacco smoking has been previously reported by surviving family members of killed soldiers (Santic, Lukic, Sesar, Milicevic, & Ilakovac, 2006), and associated with increased health risk in bereaved spouses (Hart et al., 2007).

Sleep disturbance: Assessment of sleep behaviours revealed that while bereaved participants spent the same duration in bed as non-bereaved, at the acute assessment bereaved participants reported sleeping fewer hours than non-bereaved. Fifty-six percent of bereaved participants reported that this sleep time was less than usual for them. Sleep duration improved in the bereaved participants from the acute assessment to six months. While sleep disturbance in bereavement can become persistent and

debilitating for some individuals, for most in uncomplicated bereavement it returns to pre-bereavement levels (Clayton, 1980; Richardson, Lund, Caserta, Dudley, & Obray, 2003).

Disturbed sleep patterns are a prominent feature of depressive symptomatology, affecting more than 80% of people experiencing depression (Armitage & Hoffmann, 2001; Reynolds & Kupfer, 1987). Preservation of normal sleep after spousal bereavement has been previously associated with less depressive symptoms in the first two years after loss, with bereaved who reported no depressive symptoms recording normal sleep electroencephalographic (EEG) patterns (Armitage & Hoffmann, 2001). Reduced sleep time as a result of an increased hypothalamic-pituitary-adrenal axis stress reaction may exacerbate depressive symptoms since a strong bidirectional relationship between sleep and depression has been previously suggested (Riemann, Berger, & Voderholzer, 2001). In view of reports of an association between sleep loss and inflammatory activation (Irwin, Wang, Ribeiro, Cho, Olmstead, Breen et al., 2008) and increased cardiac risk (Gangwisch, Heymsfield, Boden-Albala, Buijs, Kreier, Pickering, et al., 2006; Taylor, Lichstein, & Durrence, 2003), future research is needed to determine if reduced sleep early in bereavement contributes to the increased cardiac risk.

5.5 *Physical assessment*

Waist circumference and BMI: Waist circumference and BMI did not differ to non-bereaved participants acutely and no significant changes were seen from the acute

assessment to six months in the bereaved participants. Previous studies have reported weight loss following spousal loss (Rosenbloom & Whittington, 1993; Shahar et al., 2001), although these studies relied on retrospective self reports and were conducted in elderly individuals presenting with complicated bereavement. The results in the current study suggest that in the early acute bereavement period reduced appetite does not appear to result in significant weight loss. Potential explanations for this may include: 1) bereaved participants had reduced activity in the acute time period, 2) bereaved participants perceived that they were eating less than the actually were or 3) bereaved participants ate different food types to their normal dietary intake during the acute bereavement time period.

5.6 *Physiological assessment*

Cortisol: Assessment of blood cortisol levels revealed higher levels at the acute assessment in bereaved participants compared to non-bereaved participants. Cortisol did not change in the bereaved over time from the initial acute assessment to six months. These findings are consistent with some, but not all, previous reports of cortisol during bereavement.

One study reported higher cortisol levels in a small sample of nine bereaved women assessed within six months of loss where the death was unexpected (Irwin, Daniels, Risch, Bloom, & Weiner, 1988). Another reported elevated morning cortisol levels several years following loss compared to non-bereaved in a sample of bereaved participants following parental loss (Nicolson, 2004). Breier, (1989) reported increased

afternoon blood cortisol in adults who experienced early parental loss, with higher levels inversely associated with quality of life. However, not all studies of bereavement have reported elevated cortisol. A study of bereaved parents reported no changes in cortisol at two, four, six or eight months following loss (Spratt & Denney, 1991). Another study of 14 bereaved adults reported no difference in plasma cortisol at 10, 40 and 180 days following bereavement compared to a non-bereaved sample, but did report blunted cortisol suppression to dexamethasone administration at 10 days compared to follow-up assessment at 40 days (Gerra et al., 2003).

Cortisol, an essential component of the hypothalamic-pituitary-adrenal (HPA) axis, was not associated with depression, anxiety or anger acutely in the bereaved. Dysregulation of the HPA-axis with associated high cortisol has been typically associated with chronic stress states such as depression (Deuschle, Weber, Colla, Depner, & Heuser, 1998), but not consistently with episodic stress states. One laboratory experimental study that explored the relationship between state anxiety and cortisol, suggests that the biological aspects of the stress response can be highly individual (Boudarene, Legros, & Timsit-Berthier, 2002). In this study, subjects with identical anxiety scores were observed with or without elevated cortisol levels. However, in view of the reported association of cortisol with increased cardiac risk (Fraser et al., 1999; Koertge et al., 2002) and reduced quality of life (Breier, 1989), future research is needed to establish if cortisol mediates or modulates health risk in early bereavement and identify those most at risk.

Lipids: Total cholesterol and LDL levels were lower acutely in the bereaved compared to non-bereaved participants. Both total cholesterol and LDL levels increased over time from the acute assessment to six months. Additionally, lower lipid levels were associated with lower psychological stress (anxiety and anger symptoms) in bereaved participants acutely. Cholesterol levels have not been reported previously during bereavement and reports of the associations between life stress and cholesterol have been inconsistent. Yearly tax time has been associated with increased cholesterol levels in accountants (McCann et al., 1999), possibly due to increased dietary intake. Conversely, work stress in nurses, accompanied by depression symptoms, has been associated with lower LDL levels (Fraser et al., 1999).

The results in the current study suggest that reduced appetite and food intake may contribute to lower lipid levels that return to normal as the bereaved regain their appetite. Another potential explanation for decreased lipids may relate to hypercortisolemia, as an inverse correlation between cortisol and cholesterol has been reported previously, particularly in subjects with higher BMI (Kopf et al., 2004). The results suggest that increased cholesterol is not a contributor to the increased cardiac risk in early bereavement.

Inflammatory and thrombotic factors: Leucocytes, specifically neutrophils, were higher in the bereaved participants acutely compared to the non-bereaved group and were reduced in bereaved participants at the six-month assessment. There were no differences in monocyte and lymphocyte counts between bereaved and non-bereaved

groups at the acute assessment or over time from the acute assessment to six months in the bereaved participants. Neutrophils are inflammatory phagocytitic cells involved in the removal and/or destruction of foreign antigens. However, it is monocytes and lymphocytes that appear to play a more significant role in inflammation of atherosclerotic plaques. Inflammation plays a significant role in the pathogenesis and progression of atherosclerosis and subclinical concentration of inflammatory markers, including leucocytes, have been reported to correlate to cardiovascular mortality and morbidity in both healthy individuals and individuals with known coronary artery disease (Phillips, Neaton, Cook, Grimm, & Shaper, 1992; Ridker, Cushman, Stampfer, Tracy, & Hennekens, 1997).

Studies have demonstrated increased mobilisation of leucocytes, including neutrophils, during times of stress such as public speaking (Bosch, Berntson, Cacioppo, Dhabhar, & Marucha, 2003) and in individuals suffering PTSD after Hurricane Andrew (Ironson et al., 1997). While increased circulating neutrophil count has not been reported previously in early bereavement, extensive evidence of immune cell imbalance in bereavement exists. The first study to report immune changes in bereavement identified reduced lymphocyte responses to mitogenic stimulation at two and six weeks of bereavement (Bartrop, Luckhurst, Lazarus, Kiloh, & Penny, 1977). Since then, consistently altered T-cell subpopulations and natural killer (NK) cell activity have been reported during bereavement (Goodkin et al., 1996; Irwin et al., 1988; Linn, Linn, & Jensen, 1984).

The results in the current study suggest that neutrophils become mobilized during bereavement. Similar to previous bereavement studies, lymphocyte or monocyte counts were not increased (Goodkin et al., 1996; Irwin et al., 1988; Linn et al., 1984). There are several possible explanations for the increased neutrophil levels. Increased circulation of leucocytes may be secondary to increased cortisol, as cortisol has been associated with immune cell alteration in bereavement (Irwin, Daniels, Smith, Bloom, & Weiner, 1987; M. Stroebe, 2001). Increased haemodynamic load may also have contributed to increased mobilisation of inflammatory cells from the endothelium. Higher leucocyte count has been associated with increased heart rate and lower heart rate variability (SDNN), suggesting the possibility of activation of the inflammatory system by autonomic imbalance in favour of sympathetic system activation (Sajadieh et al., 2004). Additionally increased behavioural risk factors, such as smoking may have partially contributed to the increased neutrophil levels, although the numbers of bereaved participants reporting increased smoking acutely was small, making this a less likely explanation.

Assessment of thrombotic factors revealed a trend towards higher vWF-ag in bereaved compared to non-bereaved participants, with levels reducing significantly in the bereaved participants from the acute assessment to six months. von Willebrand factor, a major haemostatic regulatory molecule synthesised by endothelium and involved in platelet aggregation, has been identified as an independent risk factor for the incidence of fatal or nonfatal myocardial infarction (Morange et al., 2004). While not previously reported in bereavement, evaluations of prothrombotic factors during mental

stress have revealed inconsistent findings. Higher circulating vWF-ag levels have been associated with post traumatic stress symptoms (von Kanel et al., 2008), but negatively associated with depression and anxiety symptoms in healthy subjects (von Kanel et al., 2005) and in individuals with chronic depression (Walsh, Dinan, Condren, Ryan, & Kenny, 2002).

No differences were found between bereaved and non-bereaved participants in fibrinogen, CRP or Factor VIII at the acute assessment. Additionally no changes were observed in these variables in the bereaved participants from the initial acute assessment to six months. Fibrinogen has not been previously reported in bereavement. Reports of the association of fibrinogen and mental stress have been inconsistent, with work stress associated with higher fibrinogen is some studies (Brunner et al., 1996; Fenga, Micali, Cacciola, Trimarchi, & Germano, 2004; Theorell, 2002), but not in others (Alfredsson et al., 2002; Vrijkotte, van Doornen, & de Geus, 1999). Additionally a recent study of over six thousand individuals reported no relationship between psychological distress symptoms and fibrinogen, although psychological distress symptoms did predict incident CHD (Nabi et al., 2008). Interestingly though, loneliness was associated with higher fibrinogen in one study of 240 working men and women aged 47-59 years (Steptoe, Owen, Kunz-Ebrecht, & Brydon, 2004). Reports of fibrinogen levels in individuals with depression have focused mainly on chronically depressed samples with inconsistent findings. While higher fibrinogen was associated with greater depression in one study (Kop et al., 2002), more recent studies have reported no significant relationships (Empana et al., 2005; Schroeder et al., 2007; Whooley et al., 2007)

Despite reports of elevated CRP in chronically depressed individuals (Ford & Erlinger, 2004; Tiemeier et al., 2003) the findings in the study reported here are consistent with recent findings that CRP does not appear to mediate the relationship between episodes of depressive symptoms and cardiovascular risk (Arbelaez, Ariyo, Crum, Fried, & Ford, 2007; Bremmer et al., 2008). The increased circulating leucocytes and VWF-ag, but not Fibrinogen, Factor VIII or CRP would suggest that in early bereavement there is increased mobilisation of inflammatory and thrombotic cells from the endothelium, possibly due to increased haemodynamic stress, but not evidence of liver involvement in producing inflammatory acute phase reactants.

Heart rate: Assessment of haemodynamic status revealed that bereaved participants had higher 24-hour average heart rate at the initial acute assessment compared to the non-bereaved group. In the bereaved participants, heart rate reduced over time from the acute assessment to six months. Additionally, increased heart rate was associated with higher anxiety and anger, but not depression scores in the bereaved participants acutely.

To date, 24-hour heart rate has not been reported in bereavement. However, one study of ten bereaved individuals, assessed between two and 24 months following loss, reported higher heart rate, measured over a five minute interval, compared to both a depressed group and a non-depressed control group (O'Connor, Allen, & Kaszniak, 2002). Similar to the results in the study reported here, heart rate was higher in the

bereaved group and more depression symptoms were not associated with higher heart rate.

Also, similar to the results reported here, symptoms of anxiety have been previously associated with raised heart rate during laboratory induced stress (Cumming, Olphin, & Law, 2007) and during time of mental stress in Air Force cadets (Falaschi et al., 2003). Likewise, symptoms of anger, which characteristically arise from a perceived demeaning offence or personal injustice (Lazarus, 1991), have been consistently associated with increases in heart rate (Fredrickson et al., 2000; Siegman, 1993; Sinha, Lovallo, & Parsons, 1992). No association was found between social support and heart rate, as has been reported in both depressed and non-depressed subjects in a recent study exploring associations of psychosocial factors with heart rate (Ohira et al., 2008).

The results in the study reported here confirm that in early bereavement, 24-hour average heart rate is elevated, possibly due to sympathetic overactivity. Higher heart rates have been increasingly linked to greater cardiovascular risk and mortality (Dyer et al., 1980; Gillum, Makuc, & Feldman, 1991; Greenland et al., 1999; Kannel, Kannel, Paffenbarger, & Cupples, 1987; Kizilbash et al., 2008; Koh et al., 1999; Palatini & Julius, 2004) and reported to be an independent predictor of coronary artery plaque rupture (Heidland & Strauer, 2001). In one study of patients with existing heart disease, an increase of five beats per minute in 24-hour assessment, as seen in the bereaved participants acutely in this study, increased the risk of new coronary events by 14%,

after controlling for the confounding effect of other risk factors (Aronow, Ahn, Mercando, & Epstein, 1996).

Heart rate variability: Analysis of 24-hour heart rate variability, revealed lower SDNN (the standard deviation of all normal R-R intervals in a full 24-hour recording) in bereaved participants at the initial acute assessment compared to the non-bereaved group, indicating decreased parasympathetic activity. At the six-month assessment, SDNN had not significantly changed in the bereaved group. To date, autonomic function in bereavement has only been reported in one small study of ten bereaved individuals, who were recruited between two and 24 months following bereavement. The study reported no difference in heart rate variability between bereaved, depressed and non-depressed groups (O'Connor et al., 2002). Heart rate variability in this sample of ten bereaved was assessed by monitoring the respiratory sinus arrhythmia (RSA) band, considered to be an indicator of parasympathetic activity, determined from a five minute ECG analysis. However the prognostic value of this heart rate variable (RSA) is unclear as it is SDNN, a more global heart rate variability variable, which has been associated with increased cardiac risk (Bigger et al., 1995).

In the study by Bigger et al. (1995), patients following acute myocardial infarction had significantly lower SDNN compared to a matched sample of middle-aged healthy men. In the study reported here, the values for SDNN for the bereaved at the acute assessment were similar to the values of the patients one year following AMI and the non-bereaved values were similar to the healthy subjects in the study by Bigger at

al. (1995). The prognostic value of lower SDNN following AMI was also demonstrated in another study where reduced 24-hour SDNN was associated with increased mortality one year following AMI. Similarly, a two year follow up of 6,693 patient who underwent 24-hour ambulatory ECG monitoring reported increased risk of sudden death in patients with lower short-term heart rate variability (equivalent of SDNN measure) after controlling for cardiac dysfunction and history of AMI (Ohira et al., 2008).

There were no relationships found between symptoms of depression, anxiety or anger and SDNN. The lack of a significant relationship between depression and SDNN was unexpected as depression has been associated with reduced heart rate variability. In patients following AMI, higher depression symptoms have been associated with reduced heart rate variability (Carney et al., 2001) and likewise in samples of patients diagnosed with depression (Rechlin, Weis, Spitzer, & Kaschka, 1994; Roose, Glassman, & Dalack, 1989). Additionally, in the ten bereaved individuals studied by O'Connor et al. (2002), higher depression scores were associated with lower heart rate variability. However, the participants in the O'Connor study were studied several months later than in the bereaved sample reported here.

Similar to the results in the study reported here, in one study anxiety was not associated with reduced heart rate variability in a population based sample of 150 subjects (Virtanen et al., 2003). However, in a study of 300 healthy women, not discussing anger (anger in) and lower levels of social support were associated with lower heart rate variability but depression symptoms were not (Horsten et al., 1999). In

Horsten's study, after adjusting for lifestyle factors such as activity, smoking and BMI, the association between anger and heart rate variability was no longer significant. The relationship between social support and heart rate variability in bereavement remains undocumented and results of the study reported here suggest availability and satisfaction with social support are not associated with changes in heart rate variability.

Reduced SDNN in the bereaved participants confirm sympathetic dominance in the modulation of heart rate early in bereavement (Lombardi, 2002). In view of the lack of association between symptoms of depression, anxiety or anger and heart rate variability early in bereavement, further research is required to determine if behavioural factors contributed to the lower SDNN, as smoking and alcohol consumption have been previously associated with lower heart rate variability (Felber Dietrich et al., 2006). Additionally, as poorer sleep has been previously associated with reduced heart rate variability, the association of sleep with heart rate variability requires further exploration, as reduced sleep was reported by so many bereaved individuals at the initial acute assessment (Hall et al., 2004).

Blood pressure: Assessment of 24-hour blood pressure revealed that acutely bereaved participants had higher daytime systolic and diastolic blood pressure loads compared to the non-bereaved group. In the bereaved participants, diastolic load reduced over time, but systolic load did not change from the acute assessment to six months. Ambulatory blood pressure has been reported to be predictive of cardiovascular events in several population-based studies, even after adjustment for established risk

factors (Clement et al., 2003; Fagard et al., 2008; Kario et al., 2001; Sander, Kukla, Klingelhofer, Winbeck, & Conrad, 2000). Studies in hypertensive patients suggest that blood pressure load, defined as 140/90 while awake and 120/80 when asleep, is a better determinant in indices of hypertension than either clinic or mean ambulatory pressure (Fagard, Brguljan, Thijs, & Staessen, 1996; Verdecchia et al., 2002).

While no studies of 24-hour blood pressure monitoring in early bereavement have been reported, elevated blood pressure has been associated with bereavement. A prospective survey of 150 future widows and widowers interviewed at the time of their spouse's hospital admission and at 6-, 13-, and 25-month follow-up indicated that the presence of traumatic grief symptoms approximately six months after the death of the spouse predicted self reported high blood pressure at 13- or 25-month follow-up (Prigerson et al., 1997). Another longitudinal study of surviving spouses from deceased Alzheimer patients, studied at six month intervals for 18 months, reported higher systolic BP compared to a control group of non-caregivers (Grant et al., 2002). In Grant's study, despite improvement seen in mood, raised systolic blood pressure persisted at the final assessment (on average 12 months after bereavement), similar to the findings in the study reported here.

A recent study confirmed the finding of increased prevalence of hypertension, regardless of the presence of other cardiovascular risk factors in family members of killed soldiers (Santic et al., 2006). Comparing family members of killed soldiers to neighbouring families who did not experience bereavement, only the stress of mourning

was associated with higher prevalence of hypertension after controlling for other cardiac risk factors. Over time, on average four years, the proportion of hypertensive participants decreased in the group with a killed family member, further suggesting that at least a part of their hypertension might have been of psychological origin, and that blood pressure takes considerable time to resolve after bereavement (Santic et al., 2006).

Anger appears to result in emotion-specific autonomic nervous system activity (Sinha, Lovallo, & Parsons, 1992) and in the study reported here was associated with elevated systolic blood pressure load in the bereaved acutely. Elevated blood pressure has been reported in response to emotions, with several studies reporting increased vascular resistance and subsequent raised blood pressure in response to anger and fear (Roberts & Weerts, 1982; Schwartz, Weinberger, & Singer, 1981; Sinha et al., 1992). With the known association between individuals with high trait hostility (Dembroski, MacDougall, Costa, & Grandits, 1989) and greater anger-induced cardiovascular changes, causing increased cardiovascular risk, further research is required to identify those most likely to suffer anger during early bereavement.

In the current study, no difference was found in night-time blood pressures, either between bereaved and non-bereaved participants or in the bereaved participants over time. This may be in part due to the fact that approximately 20% of bereaved participants chose to not wear the BP monitor over night, thus reducing the power to detect differences in BP at night-time. It is possible that the participants who chose not

to wear the monitor overnight had elevated BP and as a result may have found the cuff uncomfortable due to the increased cuff pressures required, resulting in their decision to cease the monitoring at night. As such, the author cannot be confident that the finding that night blood pressure is not elevated is reflective of the participants' true night pressures.

5.7 *Strengths and limitations of the study*

This is the first study to prospectively evaluate the impact of bereavement on cardiovascular risk factors in the early weeks of bereavement and again at six months. Physiological changes in early bereavement are relatively unexplored prior to this study, possibly due to the difficulties in recruiting bereaved participants and conducting cardiac evaluation in the midst of such a major life stress event. A major strength of this study is the recruitment of bereaved individuals in the early weeks of bereavement, the time of highest cardiovascular risk, and again at six months when risk is substantially lower. Another strength is the recruitment of a non-bereaved sample for comparison to help identify acute physiological changes.

This study had several limitations that should be considered in the interpretation of the findings. First, since the bereaved participants were recruited from critical care areas of acute hospitals, a limitation relates to generalisibility of the findings to the broader community. This sample of bereaved participants were chosen because of the social worker presence which facilitated their recruitment.

It is possible that the hospital admission itself, in the absence of bereavement, may have caused a stress reaction in relatives as a recent study suggests that hospitalization accounts for between 16% and 22% of the mortality risk associated with death of a spouse (Christakis & Allison, 2006). As such, some of the findings in the bereaved participants may be a result of the stress associated with the stress of hospitalisation prior to the death, and not just the bereavement itself. Likewise, it is possible that some of the non-bereaved group would have been experiencing stress or altered behaviours following the admission of their family member, although assessments were conducted on average one month following discharge and the psychological assessment did not reveal significant symptoms of depression, anxiety or anger. Participating in the study may have modified the responses of bereaved participants. However, since participants responded positively to participation in the study, it is likely this would not have increased stress levels or favoured the research hypothesis. The bereaved were predominantly spouses with only four parents. Although no differences were observed in mean values of psychological levels between the bereaved parents and spouses, the number of parents was too small to confidently exclude differences. Another limitation of this study is the lack of pre-bereavement data, although inclusion of the non-bereaved sample allows comparison to a similar sample recruited from the same hospitals as the bereaved.

The results presented need to be considered in light of the limitations of the sample size and number of statistical assessments conducted. The risk of both type I and type II error need to be considered as the sample size recruited was lower than required

to achieve 90% power to detect differences for the primary study variables and a number of statistical assessments were conducted. Adjustment of the significance level was not applied as findings reported here are biologically plausible and adjustment of the p-value may have resulted in rejection of clinically significant changes (Perneger, 1998), not previously reported. Despite these limitations, the results presented make a unique contribution to bereavement research, and will provide impetus for larger studies to determine if the changes seen in this sample of bereaved individuals are representative of larger populations.

5.8 *Implications for research and clinical practice*

This study demonstrates that it is possible to recruit and monitor bereaved individuals during the early acute period. The author is confident that participation in the study did not create additional stress for bereaved individuals. In fact many bereaved expressed gratitude at being offered the opportunity to participate in the study. Several welcomed the recognition of bereavement as a stressful life event and vocalised appreciation of the researchers concern for their well being. Additionally, many bereaved participants expressed their hope that the study results may benefit future bereaved individuals.

The success in recruiting bereaved participants when approached directly, but not when other family members were approached, is also noteworthy and may guide future bereavement researchers when establishing recruitment processes. Additionally, for many the first available time to conduct the initial assessment was the day after the

funeral when other family members had returned to work or their own families. It may be possible to monitor bereaved individuals earlier than achieved in this study, if the assessment was more focused and therefore required less time and utilised less invasive techniques that have become available since commencement of this study.

While inflammatory, prothrombotic and heart rate changes were resolved by six months, longer term assessment of blood pressure may be required for individuals during bereavement. The association between clinic measured blood pressure and day and night systolic and diastolic loads would suggest that clinic measures may serve as a reliable assessment of BP in early bereavement.

Even though higher levels of social support have been associated with lower cardiovascular risk among the general population, the results of this study suggest clinicians should not assume that well supported individuals are less at risk of physiological changes in early bereavement. In light of evidence that support from health professionals at the time of death reduces mortality risk in bereavement, thought should be given to strategies that support family members at the time of death (Christakis & Iwashyna, 2003). For example, in one study, use of family conferences and communication brochures resulted in lower psychological stress following bereavement in relatives of patients dying in intensive care (Lautrette et al., 2007). Such strategies should be evaluated for their effectiveness in not only reducing psychological distress, but also their potential impact on cardiovascular risk in early bereavement.

While large epidemiological studies identify that the relative risk of cardiac mortality and morbidity is increased significantly in early bereavement, the absolute risk is extremely small and even a substantial increase in that risk may not appear clinically meaningful. However, this study confirms that acute bereavement is associated with increased psychological, behavioural and physiological cardiac risk factors. Recognition that these risk factors in bereavement may trigger cardiovascular events supports the need for health care providers to monitor such individuals more closely, especially individuals with established risk. While some of the physiological changes reported in this study may not appear clinically significant for the healthy younger individual in the short term, for older individuals, and those with a history of cardiac disease, even small changes would increase cardiac risk considerably. Additionally, recognition of the association between bereavement and increased cardiac risk should provide impetus for individuals to act on cardiac symptoms during this time by seeking medical advice and not ignoring symptoms.

5.9 *Future recommendations*

This study represented a sample of bereaved spouses and parents from the critical care environment and therefore cannot be considered representative of all bereaved individuals. Response to bereavement may be highly individual and therefore confirmation of the findings reported here is required in other bereaved populations. As discussed earlier, this sample was chosen due to the feasibility of recruitment but there was generally a degree of anticipation and preparation for the death. While challenging, recruitment of bereaved individuals from areas such as emergency departments, where

unanticipated death would be more likely, is warranted to determine if unanticipated bereavement results in greater increase of cardiac risk factors.

Additional research is required to identify the determinants of increased risk factors to help identify those most at risk. Identification of those most at risk would help health care providers and concerned friends and family members to provide greater surveillance in early bereavement.

Consideration should be given to potential interventions to reduce cardiac risk such as interventions that reduce haemodynamic burden, although large samples may be required to evaluate their effectiveness. Additionally, interventions that promote sleep preservation during bereavement should be considered and evaluated as loss of sleep was such a prominent feature in the bereaved participants.

This study was concerned with the increased cardiovascular risk early in bereavement and the results presented in this thesis relate to the primary and secondary research aims. However, many questions remain unanswered in relation to adjustment and recovery to this major life stress. Further analysis is required to identify those who were not psychologically or physiologically recovered at six months and identify the factors that contribute to prolonged stress in these individuals.

5.10 *Summary of research findings discussed*

The following is a summary of the research findings discussed. Consistent with prior reports, symptoms of depression, anxiety and anger were all significantly elevated in the first two weeks of bereavement. Although symptoms improved over time, depression and anxiety levels remained incompletely resolved at six months. Of note, bereaved participants did not score highly on the anger inventory and symptoms were resolved at six months.

At the acute assessment bereaved participants reported low appetite and reduced food intake. Acutely bereaved participants reported changes in alcohol consumption, with 60% of alcohol drinkers increasing and 40% reducing consumption that is consistent with prior bereavement research. Only five bereaved reported being a current smoker with two reporting that this increased in the week prior to the initial acute assessment. Consistent with previous bereavement research, reduced sleep time was a prominent feature during bereavement. While bereaved participants spent the same duration in bed as non-bereaved, at the acute assessment bereaved participants reported sleeping fewer hours than non-bereaved. Sleep improved in the bereaved participants at six months.

In contrast to prior retrospective reports in elderly bereaved persons, bereavement was not associated with changes to waist circumference and BMI with no differences observed between bereaved and non-bereaved participants at the acute

assessment and no significant changes from the acute assessment to six months in the bereaved participants.

Assessment of blood cortisol levels revealed higher levels at the acute assessment in bereaved compared to non-bereaved participants. Cortisol did not change in the bereaved over time from the initial acute assessment to six months. No significant relationships were observed between higher level of psychological stress (depression, anxiety and anger symptoms) and cortisol at the acute assessment.

Assessment of cholesterol levels in bereavement have not been reported previously and reported of cholesterol during periods of life stress have revealed conflicting findings. Total cholesterol and LDL levels were lower acutely in the bereaved participants compared to non-bereaved. Both total cholesterol and LDL levels increased over time from the acute assessment to six months. Additionally, lower lipid levels were associated with lower psychological stress (anxiety and anger symptoms) in bereaved participants acutely.

Consistent with prior research reports, leucocytes, specifically neutrophils, were higher in the bereaved participants acutely compared to the non-bereaved group and were reduced in bereaved participants at the six-month assessment. Higher circulating neutrophil levels were not associated with higher psychological stress (depression, anxiety and anger).

Not previously reported in bereavement, assessment of thrombotic factors revealed a trend towards higher vWF-ag in bereaved compared to non-bereaved participants, with levels reducing significantly in the bereaved participants from the acute assessment to six months. No differences were found between bereaved and non-bereaved participants in fibrinogen, CRP or Factor VIII at the acute assessment or in bereaved participants from acute to six-month assessment.

To date, 24-hour heart rate, heart rate variability and blood pressure have not been reported in the early acute bereavement period. Assessment of haemodynamic status revealed that bereaved participants had higher 24-hour average heart rate at the initial acute assessment compared to the non-bereaved group. In the bereaved participants, heart rate reduced over time from the acute assessment to six months. Additionally, higher anxiety and anger symptoms were associated with higher heart rate.

Analysis of 24-hour heart rate variability, revealed lower SDNN in bereaved participants at the initial acute assessment compared to the non-bereaved group. At the six-month assessment, SDNN had not significantly changed in the bereaved group. There were no associations between SDNN and depression, anxiety or anger at the acute assessment.

Assessment of 24-hour blood pressure revealed that acutely bereaved participants had higher daytime systolic and diastolic blood pressure loads compared to

the non-bereaved group. In the bereaved participants, diastolic load reduced over time but systolic load did not change from the acute assessment to six months. Anger was associated with elevated systolic blood pressure load in the bereaved at the acute assessment.

Social support was not associated with acute physiological changes seen in the bereaved participants at the acute assessment.

Chapter Six - Conclusion

6.1 *Introduction*

This thesis reports the results of on a prospective evaluation of cardiac risk factors in early bereavement in a sample recruited from the acute care setting. The study focused on the physiological changes in the early acute bereavement period. This study also explored the relationships between physiological risk factor changes and psychological state and social support in the early acute bereavement period.

As identified in Chapter One, coronary heart disease is the leading cause of death in Australia. Recent scientific advances have lead to greater understanding of both traditional risk factors for heart disease, as well as the physiological mechanism of acute coronary events and activities that promote acute changes. Considerable evidence exists that many acute coronary events do not occur in a random fashion but may be "triggered" by external stressors. An association between acute psychological states, such as depression, anxiety and anger, and risk of acute cardiac events has been discussed and potential mechanisms proposed. Bereavement, a unique psychological stress where acute symptoms of depression, anxiety and anger may last for several weeks and months, has been associated with increased morbidity and mortality, most notably in surviving spouses. Coronary heart events appear to account for up to approximately half of the increased deaths during early bereavement, although the exact physiological changes contributing to increased risk remain relatively unexplored during this vulnerable time.

In the second chapter the epidemiological evidence reporting increased cardiovascular risk and mortality in bereavement was reviewed. Risk appears greatest in the immediate weeks after bereavement and remains significantly elevated for the first six months. Both males and females are at risk and risk appears to be across all age groups. A representation of the manner in which bereavement potentially triggers acute myocardial infarction and sudden cardiac death was proposed based on existing scientific evidence of physiological pathways associated with stress states.

In chapter three the study design was described, that utilised a descriptive comparative design in which a longitudinal evaluation of psychosocial, behavioural and physiological factors in bereaved individuals are compared to a reference group of non-bereaved individuals. Bereaved participants were spouses, partners or parents of deceased patients who died in critical care units and non-bereaved participants were family members of discharged hospital patients.

6.2 *Summary of findings*

As described in chapter four, symptoms of depression, anxiety and anger were significantly elevated in the first two weeks of bereavement and depression and anxiety levels remained incompletely resolved at six months. At the acute assessment, bereaved participants reported low appetite and reduced food intake. Acutely, 60% of bereaved participants who regularly drank alcohol, reported increased alcohol consumption with 40% reducing consumption. Of the five bereaved participants who reported being a

current smoker, two reported that this increased in the week prior to the initial acute assessment.

While bereaved participants spent the same duration in bed as non-bereaved, at the acute assessment they reported sleeping fewer hours than non-bereaved, which was improved at six months. Waist circumference and BMI did not differ to non-bereaved participants acutely and no significant changes were seen from the acute assessment to six months in the bereaved participants.

Assessment of blood cortisol levels revealed higher levels at the acute assessment in bereaved compared to non-bereaved participants that did not change in the bereaved over time from the initial acute assessment to six months. Total cholesterol and LDL levels were lower acutely in the bereaved compared to non-bereaved and both increased over time from the acute assessment to six months. Additionally, lower lipid levels were associated with lower psychological stress (anxiety and anger symptoms) in bereaved participants acutely.

In the bereaved participants acutely, leucocytes were higher compared to the non-bereaved group and were reduced in bereaved participants at the six-month assessment. Assessment of thrombotic factors revealed a trend towards higher vWF-ag in bereaved compared to non-bereaved participants with levels reducing significantly in the bereaved participants from the acute assessment to six months. No differences were found between bereaved and non-bereaved participants in fibrinogen, CRP or Factor

VIII at the acute assessment or in bereaved participants from acute to six-month assessment.

Haemodynamic assessment revealed that bereaved participants had higher 24-hour average heart rate at the initial acute assessment compared to the non-bereaved that reduced in the bereaved over time from the acute assessment to six months. Analysis of 24-hour heart rate variability, revealed lower SDNN in bereaved participants at the initial acute assessment compared to the non-bereaved group. At the six-month assessment, SDNN had not significantly changed in the bereaved group.

Assessment of 24-hour blood pressure revealed that acutely bereaved participants had higher daytime systolic and diastolic blood pressure loads compared to the non-bereaved group. In the bereaved participants, diastolic load reduced over time but systolic load did not change from the acute assessment to six months. Anger was associated with elevated systolic blood pressure load in the bereaved acutely.

In conclusion, the material presented in this thesis make a unique contribution to bereavement research. While focus at the time of bereavement is naturally directed on the deceased person, the health and welfare of bereaved survivors is of great concern to medical, nursing and social work professionals, as well as family and friends. The results from this evaluation provide insight into the impact of early bereavement and the recognition that bereavement is associated with increased cardiac risk, should provide

an impetus for individuals to act on cardiac symptoms by seeking medical advice and for health care providers to monitor such individuals more closely.

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Appendix A

Participant Information Sheet

Currently, a group of clinicians at Royal North Shore Hospital (RNSH) are examining the bodily and emotional consequences of fatal illness and injury on families. Approval to conduct this research has been given by the Human Research Ethics Committee (HREC) of Northern Sydney Health. The project is funded by North Shore Heart Research Foundation.

While death is a natural part of the life process and is a universal experience, the effect of the loss of a child, partner or spouse can be traumatic for the surviving loved one and can increase the risk of heart problems. Some call this "the broken heart". Research has shown that temporary changes in immune function, clotting and stress hormones occur after bereavement but the reason for this is not well understood. This study will provide insight into the reasons for the known increased risk of heart attack in the recently bereaved, and may provide clues for improved management of bereaved people in the future. It is possible that some medication as well as lifestyle changes could reduce or prevent heart risk in the distant future.

A member of the project team will ask your permission to participate in the study. If you are agreeable we will conduct a confidential health assessment, which will include height and weight, waist circumference, blood pressure, pulse and electrocardiogram. This initial assessment will be conducted within 2 weeks of your partners/child's death. We will also ask you to complete questionnaires about your medical history, personal circumstances, any treatments you may be having and how you have been feeling. The questionnaires will take about 45 minutes to complete. Blood will also be drawn from your arm to assess immune function, blood clotting and stress hormones. We would also like to monitor your heart rhythm and blood pressure recordings for 24 hours with small portable monitors. The two cardiac monitors are small box like devices that may be worn unnoticeably under your clothing and are personally fitted to ensure you are comfortable. You will be free to carry on with your day as normal during the assessment period. We would appreciate repeating these same tests in six months time.

Another group of volunteers in the community who include people involved with the hospital will be volunteering to have the same tests performed as you as "volunteers" in the study.

There are some possible adverse effects or risks related to this project. The procedure of taking blood from your arm may cause discomfort and carries the minimal risk of bruising. The blood pressure monitor may disturb your sleep but this has been reported rarely by people who have such monitoring. You will be shown how to turn the monitors off should you choose at any time during the assessment period. It is also possible that completing questionnaires may cause some degree of anxiety. In such an event, you are encouraged to inform the project investigator about your feelings.

While there will be no direct benefit to you from participating, an indirect benefit may occur, in that any concerning results identified during your health assessment, such as a

disturbance in heart rhythm, will be forwarded to you and your physician for follow-up. In addition, a broader indirect benefit to the community may occur through knowledge resulting from the project being used to assist in the care of bereaved people in the future.

Should any medical issues of concern be identified related to this study, the project investigators directly involved in the study may need to contact your doctor to obtain relevant medical information, or may need to examine your medical records as they relate to this project.

You can obtain further information by contact the Project Investigators:
Tom Buckley RN, on 9926 8305 or [redacted].
Professor Geoffrey Tofler on 99266359
Dr Roger Bartrop on 99267746.

Appendix B

Advertisement for recruitment of Volunteers

A group of clinicians and scientists at Royal North Shore Hospital (RNSH) are conducting a study examining the physical and emotional consequences of fatal illnesses and injuries on families. We are requesting assistance from community-minded non-bereaved individuals who are willing to assist in this important project by agreeing to be volunteers (as controls for comparison to bereaved participants). Approval to conduct this research has been given by the Human Research Ethics Committee (HREC) of Northern Sydney Health and the project is funded by North Shore Heart Research Foundation.

What is involved in being a volunteer?

The assessment may be conducted at your own home or at the hospital if more convenient and would include the following; a confidential health assessment, which will include height and weight, waist circumference, blood pressure, pulse and an electrocardiogram. We will also ask you to complete some questionnaires on your medical history, personal circumstances, any treatments you may be having and how you have been feeling. Blood will also be collected for laboratory analysis of your immune function, blood clotting and stress hormones. We would also monitor your blood pressure and cardiac rhythm for 24 hours with two small, portable monitors. The two cardiac monitors are small box like devices that may be worn unnoticeably under your clothing and are personally fitted to ensure you are comfortable. You will be free to carry on with your day as normal during the assessment period. We would appreciate repeating these same tests in six months time.

How long would this take?

The initial health assessment, questionnaires and collection of blood would take about two hours. The follow-up monitoring period will be for 24 hours. The repeat assessment at six months will take the same amount of time.

What are the benefits for me?

While there will be no direct benefit to you from participating, an indirect benefit may occur, in that any concerning results identified during your health assessment, such as a disturbance in heart rhythm, will be forwarded to you and your physician for follow-up. addition, a broader indirect benefit to the community may occur through knowledge resulting from the project being used to assist in the care of bereaved people in the future.

How can I get further information?

Contact the Project Investigator, Tom Buckley on 9926 8305 / [redacted] or e-mail tom.buckley@uts.edu.au

Appendix C Consent forms

Consent Form to Participate in a Research Project

I,_____
(name of participant)
of_____
(street) (suburb/town) (state & postcode)

have been invited to participate in a research project entitled The Cardiovascular Health of Bereaved Families Study (CARBER Study). This project has been funded by the North Shore Heart Research Institute.

In relation to this project I have read the Participant Information Sheet and have been informed of the following points:

1. Approval has been given by the Human Research Ethics Committee (HREC) of Northern Sydney Health and the University of Technology, Sydney.

2. The aim of the project is to understand why an increase in heart disease risk has been found in bereaved family members. It is also hoped to gain clues about preventive measures to reduce the risk of heart problems following bereavement.

4. The procedure will involve a confidential health assessment, which will include my height and weight, waist circumference, blood pressure, pulse and an electrocardiogram. I will also be asked to complete some questionnaires about my medical history, personal circumstances, any treatments I may be having and how I have been feeling. Blood will also be drawn from my arm to assess my immune function, blood clotting and stress hormones. My heart rhythm and blood pressure recordings will also be monitored for 24 hours with portable monitors. These same tests will be repeated in six months time.

5. There are some possible adverse effects or risks related to this project. The procedure of taking blood from my arm may cause some discomfort and carries the minimal risk of bruising. It is also possible that completing questionnaires may cause me some degree of anxiety. In such an event I am encouraged to inform the project investigator about my feelings. I may also feel uncomfortable answering certain items on the questionnaire. If so, I can choose to not answer those questions.

6. Should I develop a problem which I suspect may have resulted from my involvement in this project, I am aware that I may contact the Chief Investigator of the project, Professor Geoffrey Tofler, Department of Cardiology, on 9926 6359

7. Should I have any problems or queries about the way in which the study was conducted, and I do not feel comfortable contacting the research staff, I am aware that I may contact the Manager, Research Office, Royal North Shore Hospital on 9926 8106.

8. I can refuse to take part in this project or withdraw from it at any time without having to give a reason and without affecting my medical care.

9. Participation in this project will not result in any extra medical and hospital costs to me.

10. I understand that my research records will be stored in a locked cabinet, in a secured building. Electronic data will be kept in a secure database that is password protected. The research team, authorised personnel, the study sponsor, and regulatory entities may have access to my study records to protect my safety and welfare.

11. I consent to the collection, processing, reporting and transfer within or outside Australia of my personal and/or sensitive information for healthcare and/or medical research purposes. All data to be transferred will be de-identified, therefore not including my name, address or phone number. My information will be identified by my Date of Birth and Initials as well as a numerical random code.

12. I understand that my initials and date of birth and a unique study number will identify my medical information. This information is potentially identifiable but all precautions will be taken by the clinical staff to ensure the information will be kept confidential.

13. If the results of my tests or information regarding my medical history are published, my identity will not be revealed.

14. While participating in this study, I should not take part in any other research project without approval from the investigators. This is to protect myself from possible injury arising from such things as extra blood drawing.

15. I understand that should any medical issues of concern be identified as a consequence of being involved in this study, that I will be informed and referred to my doctor for follow-up. In giving my consent, I acknowledge that the project investigators directly involved in the study, may contact my doctor to obtain relevant medical information or may examine my medical records only as they relate to this project.

16. I understand that this research is being undertaken under the supervision of Professor Geoffrey Tofler (Department of Cardiology, Phone: 9926 6359), Professor Sharon McKinley (Intensive Care Unit) and Associate Professor Roger Bartrop (Department of Psychological Medicine, Phone: 9926 7111)

17. I declare that I am over the age of 18 years. After considering all these points, I accept the invitation to participate in this project.

I also state that I have/have not participated in any other research project in the past 3 months. If I have, the details are as follows:

_____

Dr _____ on: _____
(phone and page numbers)

Date: _____ Witness:_____
(Please print name)

Signature: _____ Signature: _____
(of participant/volunteer) (of witness)

Investigators' confirming statement:

I have given this research participant information on the study, which in my opinion is accurate and sufficient for the participant to understand fully the nature, risks and benefits of the study, and the rights of a research participant. There has been no coercion or undue influence. I have witnessed the signing of this document by the participant.

Investigator's Name: _____

Investigator's Signature:_____

LETTERHEAD – ROYAL NORTH SHORE HOSPITAL
Northern Sydney Health -Royal North Shore Hospital
Consent Form to Participate as a Volunteer in a Research Project

I,_____
(name of participant)
of_____
(street) (suburb/town) (state & postcode)

have been invited to participate as a volunteer in a research project entitled The Cardiovascular Health of Bereaved Families Study (CARBER Study). This project has been funded by the North Shore Heart Research Institute.

In relation to this project I have read the Volunteer Information Sheet and have been informed of the following points:

2. Approval has been given by the Human Research Ethics Committee (HREC) of Northern Sydney Health and the University of Technology, Sydney.

2. The aim of the project is to gain understanding into why an increase in heart disease risk has been found in bereaved family members. It is also hoped to gain clues about preventive measures to reduce the risk of heart problems following bereavement.

4. The procedure will involve a confidential health assessment which will include my height and weight, waist circumference, blood pressure, pulse and an electrocardiogram. I will also be asked to complete some questionnaires about my medical history, personal circumstances, any treatments I may be having and how I have been feeling. Blood will be drawn from my arm to assess my blood clotting, immune function, and stress hormones. My heart rhythm and blood pressure recordings will also be monitored for 24 hours with portable monitors. These same tests will be repeated in six months time.

5. There are some possible adverse effects or risks related to this project. The procedure of taking blood from my arm may cause some discomfort and carries the minimal risk of bruising. It is also possible that completing questionnaires may cause me some degree of anxiety. In such an event I am encouraged to inform the project investigator about my feelings. I may also feel uncomfortable answering certain items on the questionnaire. If so, I can choose to not answer those questions.

6. Should I develop a problem which I suspect may have resulted from my involvement in this project, I am aware that I may contact the Chief Investigator of the project, Professor Geoffrey Tofler, Department of Cardiology, on 9926 6359

7. Should I have any problems or queries about the way in which the study was conducted, and I do not feel comfortable contacting the research staff, I am

aware that I may contact the Manager, Research Office, Royal North Shore Hospital on 9926 8106.

8. I can refuse to take part in this project or withdraw from it at any time without having to give a reason and without affecting my medical care.

9. Participation in this project will not result in any extra medical and hospital `costs to me.

10. I understand that my research records will be stored in a locked cabinet, in a secured building. Electronic data will be kept in a secure database that is password protected. The research team, authorised personnel, the study sponsor, and regulatory entities may have access to my study records to protect my safety and welfare.

11. I consent to the collection, processing, reporting and transfer within or outside Australia of my personal and/or sensitive information for healthcare and/or medical research purposes. All data to be transferred will be de-identified, therefore not including my name, address or phone number. My information will be identified by my Date of Birth and Initials as well as a numerical random code.

12. I understand that my initials and date of birth and a unique study number will identify my medical information. This information is potentially identifiable but all precautions will be taken by the clinical staff to ensure the information will be kept confidential.

13. If the results of my tests or information regarding my medical history are published, my identity will not be revealed.

14. While participating in this study, I should not take part in any other research project without approval from the investigators. This is to protect myself from possible injury arising from such things as extra blood drawing.

15. I understand that should any medical issues of concern be identified as a consequence of being involved in this study, that I will be informed and referred to my doctor for follow-up. In giving my consent, I acknowledge that the project investigators directly involved in the study, may contact my doctor to obtain relevant medical information or may examine my medical records only as they relate to this project.

16. I understand that this research is being undertaken under the supervision of Professor Geoffrey Tofler (Department of Cardiology, Phone: 9926 6359), Associate Professor Roger Bartrop (Department of Psychological Medicine, Phone: 9926 7111) and Tom Buckley, RN.

17. I declare that I am over the age of 18 years.

After considering all these points, I accept the invitation to participate in this project.

I also state that I have/have not participated in any other research project in the past 3 months. If I have, the details are as follows:

Dr _____ on: _____
(phone and page numbers)

Date: _____ Witness:_____
(Please print name)

Signature: _____ Signature: _____
(of participant/volunteer) (of witness)

Investigators' confirming statement:

I have given this research participant information on the study, which in my opinion is accurate and sufficient for the participant to understand fully the nature, risks and benefits of the study, and the rights of a research participant. There has been no coercion or undue influence. I have witnessed the signing of this document by the participant.

Investigator's Name: _____

Investigator's Signature:
_____Date:_____

Appendix D Sociodemographic questionnaire

Participant Study Number_____

Date of assessment_____Date of

Review_____

Participant's details

Name_____

__DOB: _____ Sex M F

Address_____

__

Surburb_____Post

Code_____

Phone

Home_____Work_____Mobile_____

Next of kin

Name

_____

Address_____

__

Surburb_____Post Code_____

Phone Home_____Work_____Mobile_____

Deceased's details

Name_____

__

Sex M F DOB: _____

DOD:_____

Relationship to participant_____

Number of years of marriage/relationship (if

partner):_____

Cause of death_____

Sudden Yes No Expected Yes No

Date of first notification/diagnosis of condition that caused

death_____

Primary carer for the deceased Yes No

Sociodemographic data

In which country were you born?
□ Australia □ Other (please specify)
_____

Do you usually speak a language other than English at home?
□ No □ Yes (please specify)
_____

Are you an Aboriginal or Torres Strait Islander? □ Yes □ No

What is your current marital status?
□ Married □ Living with partner but not married □ Widowed
□ Divorced □ Separated but not divorced □ Never married

Who lives with you currently?
□ Live alone □ Spouse/partner □ Dependent child □ Dependent adult
□ Other relative □ Friend □ Paid employee □ Other

What is your religion?_____ □ I have no religion

What is the highest level of education that you have completed?
□ Year 8 or below of secondary school □ Year 9 or 10 of secondary school
□ Year 11 or 12 of secondary school □ Diploma, TAFE or Trade certificate

□ University degree □ Post graduate studies

What is your employment status?

□ Worked full time for payment or profit □ Worked part time for payment or profit
□ Unpaid work in family business □ Other unpaid work
□ Retired □ Do not have a job

What is/was your occupation?
_____
(If retired, what was your occupation when working)

Do you currently receive a government pension, allowance or benefit?
□ No □ Yes If Yes, please specify_____

Before tax is taken out, which of the following ranges best describes your household's approximate income, from all sources, over the last 12 months?
□ Less than $10,000 □ $10,001 - $20,000 □ $20,001 - $40,000

□ $40,001 - $60,000 □ $60,001 - $80,000 □ More than $80,000

Appendix E Clinical history questionnaire

Medical History

Has a doctor ever told you that you have any of the following conditions?	Yes	No
A heart attack, coronary, angina, or myocardial infarction?	1	2
Congestive heart failure or CHF?	1	2
An irregular heart rhythm, such as atrial fibrillation, ventricular or atrial tachycardia?	1	2
Problems with the valves in your heart?	1	2
Peripheral vascular disease, sometimes called “claudication,” ?	1	2
Hypertension or high blood pressure?	1	2
A stroke, brain haemorrhage or transient ischaemic attack ?	1	2
Diabetes, sugar in urine, or high blood sugar?	1	2
Lung disease, such as chronic bronchitis, asthma, emphysema, or “COPD”?	1	2
Cancer, malignancy, or tumour of any type?	1	2
Cirrhosis or liver disease?	1	2
Kidney disease – such as kidney failure, kidney stones, recurrent urinary tract infections?	1	2
Any fractured bones?	1	2
Osteoporosis?	1	2
Degenerative arthritis or osteoarthritis?	1	2
Rheumatoid arthritis or lupus?	1	2
Epilepsy or fitting?	1	2
Parkinson’s Disease?	1	2
Alzheimer’s disease, memory loss from small strokes, or “dementia”?	1	2

Problems with stomach or bowels such as ulcer disease, hiatal hernia, gastritis, inflammatory bowel disease, diverticulitis, or reflux disease?	1	2
Thyroid problems?	1	2
Problems with the blood such as anaemia?	1	2
Problems with the immune system (such as HIV)?	1	2
Problems with sleep such as chronic snoring or obstructive sleep apnea?	1	2
Any other medical conditions Please specify_____	1	2
Psychiatric conditions		
Schizophrenia or schizoaffective disorder?	1	2
Bipolar disorder?	1	2
Depression?	1	2
Anxiety disorder?	1	2
Treatment for drug or alcohol dependency?	1	2
Other psychiatric conditions Please specify_____	1	2
Other conditions		
Serious accidents or falls?	1	2
Surgical procedures or operations Please specify_____	1	2
Do you have any known allergies? Please specify:_____	1	2
Do/did you have a first degree relative (mother, father or sibling) who has been diagnosed with a heart disease, stroke or blood vessel disease prior to 60 years of age?	1	2

Medications:

Are you taking any medications prescribed by a doctor? □ Yes No □

If yes, name of medication(s)_____

Appendix F 24-hour activity diary

Participant No:

Contact: Phone:

Activity Record

	Posture				**Mood/Emotions**					
Time	Standing	Sitting	Lying	Activity	Calm/ Contented	Depressed	Anxious	Agitated/ Frustrated	Angry	Other #See below

	Posture				Mood/Emotions					
Time	Standing	Sitting	Lying	Activity	Calm/ Contented	Depressed	Anxious	Agitated/ Frustrated	Angry	Other #See below

Other: Chest pain or discomfort, Short of breath, Palpitations, Feeling Dizzy

Time to Sleep: Time out of bed:

Slept Overnight: Yes No

Comments:

Appendix G Social Support Scale

1. Whom can you really count on to help you with practical things when you really need it? (eg. transport, child minding) a) Please indicate **how many** people: _____						
	Very Dissatisfied	Quite a bit Dissatisfied	Somewhat Dissatisfied	Somewhat Satisfied	Quite a bit Satisfied	Very Satisfied
b) Please circle a value to indicate **how satisfied** you are with the support you receive in this situation:	1	2	3	4	5	6
2. Whom can you really count on to distract you from your worries when you feel under stress? a) Please indicate **how many** people: _____						
	Very Dissatisfied	Quite a bit Dissatisfied	Somewhat Dissatisfied	Somewhat Satisfied	Quite a bit Satisfied	Very Satisfied
b) Please circle a value to indicate **how satisfied** you are with the support you receive in this situation	1	2	3	4	5	6
3. Whom can you really count on to help you feel more relaxed when you are under pressure or tense? a) Please indicate **how many** people: _____						
	Very Dissatisfied	Quite a bit Dissatisfied	Somewhat Dissatisfied	Somewhat Satisfied	Quite a bit Satisfied	Very Satisfied
b) Please circle a value to indicate	1	2	3	4	5	6

how satisfied you are with the support you receive in this situation						
4. Who accepts you totally, including both your worst and your best points? a) Please indicate **how many** people: _____						
	Very Dissatisfied	Quite a bit Dissatisfied	Somewhat Dissatisfied	Somewhat Satisfied	Quite a bit Satisfied	Very Satisfied
b) Please circle a value to indicate **how satisfied** you are with the support you receive in this situation	1	2	3	4	5	6
5. Whom can you really count on to care about you, regardless of what is happening to you? a) Please indicate **how many** people: _____						
	Very Dissatisfied	Quite a bit Dissatisfied	Somewhat Dissatisfied	Somewhat Satisfied	Quite a bit Satisfied	Very Satisfied
Please circle a value to indicate **how satisfied** you are with the support you receive in this situation:	1	2	3	4	5	6
6. Whom can you really count on to help you feel better, when you are feeling generally down-in-the-dumps? a) Please indicate **how many** people: _____						
Please circle a value to indicate **how satisfied** you are with the	Very Dissatisfie	Quite a bit Dissatisfie	Somewhat Dissatisfie	Somewhat Satisfied	Quite a bit Satisfied	Very Satisfied

support you receive in this situation:	d	d	d			
	1	2	3	4	5	6
7. Whom can you really count on to console you when you are very upset? a) Please indicate **how many** people: _____						
	Very Dissatisfied	Quite a bit Dissatisfied	Somewhat Dissatisfied	Somewhat Satisfied	Quite a bit Satisfied	Very Satisfied
b) Please circle a value to indicate **how satisfied** you are with the support you receive in this situation:	1	2	3	4	5	6

Appendix H CES-D Questionnaire

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

Appendix I Spielberger state anxiety and anger scales

A number of statements that people use to describe themselves are given below. Read each statement and then circle the number which best describes how you are feeling *right now*. There are no right or wrong answers. Do not spend too much time on any one statement. Circle the appropriate number to the right of the statement that *best* describes you *present feelings*.

	HOW I FEEL RIGHT NOW	Not at all	Somewhat	Moderately so	Very much so
1	I feel calm	1	2	3	4
2	I feel secure	1	2	3	4
3	I am tense	1	2	3	4
4	I am regretful	1	2	3	4
5	I feel at ease	1	2	3	4
6	I feel upset	1	2	3	4
7	I am presently worrying over possible misfortunes	1	2	3	4
8	I feel rested	1	2	3	4
9	I feel anxious	1	2	3	4
10	I feel comfortable	1	2	3	4
11	I feel self-confident	1	2	3	4
12	I feel nervous	1	2	3	4
13	I am jittery	1	2	3	4
14	I feel “high strung”	1	2	3	4
15	I am relaxed	1	2	3	4
16	I feel content	1	2	3	4
17	I am worried	1	2	3	4
18	I feel over-excited and “rattled”	1	2	3	4
19	I feel joyful	1	2	3	4
20	I feel pleasant	1	2	3	4

Spielberger state anger scale

A number of statements that people use to describe themselves are given below. Read each statement and then circle the number which best describes how you are feeling *right now*. There are no right or wrong answers. Do not spend too much time on any one statement. Mark the answer that *best* describes you *present feelings*.

	HOW I FEEL RIGHT NOW	Not at all	Somewhat	Moderately so	Very much so
1	I am furious	1	2	3	4
2	I feel irritated	1	2	3	4
3	I feel angry	1	2	3	4
4	I feel like yelling at somebody	1	2	3	4
5	I feel like breaking things	1	2	3	4
6	I am mad	1	2	3	4
7	I feel like banging on the table	1	2	3	4
8	I feel like hitting someone	1	2	3	4
9	I feel like swearing	1	2	3	4
10	I feel annoyed	1	2	3	4
11	I feel like kicking somebody	1	2	3	4
12	I feel like cursing out loud	1	2	3	4
13	I feel like screaming	1	2	3	4
14	I feel like pounding somebody	1	2	3	4
15	I feel like shouting out loud	1	2	3	4

Appendix J Health behaviours assessment

Smoking: Which of the following best describes your smoking status?

□ Daily smoker □ Weekly smoker □ Irregular smoker □ Ex-smoker □ Never smoked

If you are a smoker, type: □ Tobaccos □ Cigars □ Pipes

Number per day (usual) _____ Age commenced (in years) _____

Has your smoking increased (or decreased) in the past week □ Yes □ No

Describe smoking pattern (ie. number per day in past week)

_____

Alcohol: Do you currently drink alcohol? □Yes □ No If no, did you in the past? □ Yes □ No

If yes, please describe your usual drinking pattern:

number of standard drinks per day _____ Number of standard drinks per week_____

Are there occasions when you drink more than 4 (if female) or 6 (if male) standard drinks in one session?

□ Yes □ No _____If yes, how often does this occur? _____

Has your alcohol consumption changed in the past week? □ Yes □ No

If there has been a change, has it: increased □ or decreased □

Describe your alcohol consumption pattern in past week

Number of days you drank alcohol

_____

Number of standard drinks per day

_____

Any episodes of heavy (binge) drinking

_____

Sleeping patterns

Describe sleeping pattern in the past week:

How many hours per night: _____

Is this more than usual □ Yes No □

Is this less than usual: □ Yes No □

Any wakening or insomnia □ Yes No □

Any other comments:

Appetite/eating pattern:

Describe your appetite and eating pattern in the past week:

Have you been hungry ? □ Yes No □

Have you been eating more ? □ Yes No □

Have you been eating less than usual ? □ Yes No □

Appendix K

Table A-1 Valid numbers for psychological and sleep and behaviours assessment in bereaved and non-bereaved participants

Variable	Bereaved		Non-bereaved
	Acute N	6-months N	N
Depression	62	58	50
Anxiety	62	58	50
Anger	62	58	50
Mean sleep hours per night in the past week	62	58	50
Less than usual sleep	62	58	50
Awakening or insomnia	62	58	50
More then usual sleep	62	58	50
Waist circumference	62	58	50
BMI	62	58	50

Table A-2 Valid numbers for assessment of appetite, alcohol and smoking behaviours in bereaved and non-bereaved participants

Variable	Response	Bereaved		Non-bereaved
		Acute	6-months	
		N	N	N
In the past week: have you been hungry?	Yes	62	58	50
In the past week: Have you been eating less?	Yes	62	58	50
In the past week: Have you been eating more?	Yes	62	58	50
Do you currently drink alcohol	Yes	62	58	50
If you currently drink, in the past week: has	Yes	62	58	50
your alcohol consumption changed	Increased	62	58	50
	Decreased	62	58	50
Mean number of standard drinks per week		62	58	50
Episodes of binge drinking in the past week	Yes	62	58	50
Do you currently smoke	Yes	62	58	50
If you currently smoke, in the past week: has	Yes	62	58	50
your smoking changed	Increased	62	58	50
	Decreased	62	58	50
Mean number of tobaccos smoked daily		62	58	50

Table A-3 Valid numbers for laboratory assessments in bereaved and non-bereaved participants

Variable	Bereaved		Non-bereaved
	Acute	6-months	
	N	N	N
Cortisol	62	58	50
	62	58	50
Total Cholesterol			
LDL	62	58	50
HDL	62	58	50
Triglycerides	62	58	50
Leucocytes	62	58	50
Neutrophils	62	58	50
Monocytes	62	58	50
Lymphocytes	62	58	50
CRP	62	58	50
Fibrinogen	62	58	50
vWF-ag	62	58	50
Factor VIII U/ml	62	58	50

Table A-4 Valid numbers for haemodynamic assessments in bereaved and non-bereaved participants

Variable	Bereaved		Non-bereaved
	Acute	6-months	
	N	N	N
24 hour heart rate	57	54	49
SDNN	53	51	49
Manually recorded systolic pressure	62	58	50
Manually recorded diastolic pressure	62	58	50
24-hour systolic	50	46	50
24-hour diastolic	50	46	50
Daytime systolic load	58	53	50
Daytime diastolic load	58	53	50
Night-time systolic load	50	46	50
Night-time diastolic load	50	46	50