The Association of Type-D Personality and Prognosis Following Diagnosis of Cardiovascular Disease: A Review and Meta-Analysis

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A Capstone Project Submitted in Partial Fulfillment of the Requirements of the Renée Crown University Honors Program at Syracuse University

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and Renée Crown University Honors

April 2010

Honors Capstone Project in _____Psychology_____

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Date:_____April 28, 2010_____

Abstract

Type-D personality is characterized by the stable traits of negative affectivity and social inhibition. In recent years, a body of studies has examined the relationship between the presence of Type-D personality and prognosis in cardiovascular patient populations. The present meta-analysis, investigated relationships between Type-D personality and three different outcome measures: major adverse cardiac events, quality of life, and biochemical markers of disease. A random effects meta-analytic model was utilized to calculate omnibus effect sizes for each set of related studies. Tests of homogeneity were conducted, and all studies were coded for the presence of potential moderators. A total of 14 studies were included in the meta-analysis, and one effect size was calculated in the major adverse cardiac event analysis, two were calculated in the quality of life analysis and seven effect sizes were calculated for the biochemical marker analysis. An association was found between Type-D personality and major adverse cardiac events, one measure of quality of life, interleukin-6 levels and tumor necrosis factor-alpha soluble receptor levels. No association was found with respect to cortisol or tumor necrosis factor-alpha levels. All other effect sizes trended towards significance. It is suggested that a broader body of research be conducted in this area in order to generalize these associations. Research is also warranted to investigate the effects of treatment with a focus on alleviating emotional distress on Type-D individuals in order to identify options to improve prognosis in this high-risk patient group.

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Introduction

Since the relatively recent proposal of the Type-D (distressed) personality construct, there has been an abundance of research investigating the relations between Type-D personality and various psychological and somatic symptoms. Type-D personality is the combination of two stable personality constructs: negative affectivity and social inhibition. Negative affectivity is the tendency to consistently experience negative emotions regardless of the time or situation whereas social inhibition is the stable tendency to inhibit the expression of these emotions, experience high levels of insecurity in social situations and act closed-off or reserved for fear of disapproval by others (Denollet, 1998; Denollet, Vaes, & Brutsaert, 2000). Whereas negative affectivity and social inhibition independently have been demonstrated to have detrimental effects on cardiac prognosis, it is their interaction as manifest in the Type-D personality that has been shown in individual studies to be predictive of major adverse cardiac events (MACE) which include death, myocardial infarction, percutaneous coronary intervention and coronary artery bypass grafting surgery (Denollet et al., 2006).

Type-D personality has also been demonstrated to be a stable taxonomy in acute myocardial infarction patients who were assessed for Type-D personality, depression and anxiety at multiple time points over an 18-month period. Variability in mood status and disease severity did not have an association with Type-D personality diagnosis (Martens, Kupper, Pederson, Aquarius, & Denollet,

2007). Issues concerning the similarities and differences between Type-D and depression have also been addressed. However, in further examination by Denollet and colleagues of whether Type-D personality and depression are different forms of emotional distress, it was found that Type-D personality is not due to co-morbid depression as only 25% of their total sample of 340 cardiac patients exhibited both depression and Type-D personality whereas the other 75% were diagnosed with either Type-D personality or depression. This study also concluded that Type-D personality cannot be assumed from a diagnosis of depression and that the findings support the validity of the two forms of distress as separate constructs; depression being a disorder that lacks the trait of social inhibition and Type-D being a stable personality construct including both the personality traits of negative affectivity and social inhibition (Denollet et al, 2009).

The individual constructs which constitute Type-D personality have also been assessed individually to determine their relationship with cardiac prognosis. In a 2006 study, Denollet and colleagues assessed the role which social inhibition plays with respect to the role of negative emotions' effect on cardiac prognosis (Denollet et al., 2006). A total of 875 subjects were assessed on separate scales of negative affectivity and social inhibition six months post percutaneous coronary intervention. It was found that patients with high levels of negative affectivity and social inhibition were more likely to experience MACE than patients who were only classified as having high levels of negative affectivity.

This suggests that it is the interaction between negative affectivity and social inhibition, which together constitute Type-D personality, and not merely the presence of one trait or the other, which may account for poor cardiac prognosis.

Previous research found links between Type-D personality and multiple predictors of poor prognosis in cardiac patients. Type-D is a predictor of clinically significant and chronic anxiety in chronic heart failure and percutaneous coronary intervention patients at one year follow up (Schiffer, Pederson, Broers, Widdershoven, & Denollet, 2008; van Gestel et al., 2007; Spindler, Pederson, Serruys, Erdman, & van Domburg, 2007) and elevated anxiety levels in implantable cardioverter defibrillator patients (Pederson, van Domburg, Theuns, Jordaens, & Wedman 2004). Another risk factor for increased morbidity that has been linked to Type-D personality is vital exhaustion (Kop, 1997; Kop, 1999). In a sample of 171 patients with ischemic heart disease, patients who were identified as having Type-D personality scored higher on assessments of vital exhaustion independent of other variables (Pederson & Middel, 2001). Type-D personality has also been shown to have a relationship with vital exhaustion in percutaneous coronary intervention patients over the course of one year with Type-D patients consistently scoring higher on vital exhaustion assessments than non Type-D patients (Pederson, Daemen, & van de Sande, 2007). Both vital exhaustion and Type-D personality are independently associated with inadequate heart rate recovery, another predictor of morbidity and mortality, in chronic heart failure

patients (von Kanel et al, 2009). Epithelial progenitor cells, necessary for the repair of damage to the body including vascular damage, are reduced by 54% in Type-D chronic heart failure patients as compared to non Type-D patients (Craenenbroeck, Denollet, Paelinck, & Conraads, 2009). Type-D personality has also been linked with low levels of health related behaviors and reduced levels of social support which are associated with a negative impact on cardiac outcomes (Williams et al, 2008). Social support sublevels of structural support (social networking and frequency of contact) and functional support (received and perceived social support) have reliably been connected to cardiac death as well as mortality from other causes (Rozanski, Blumenthal, Davidson, Saab, & Kubzansky, 2005). In research pertaining to potential disease pathways, it has been found that cardiac patients with Type-D personality may experience prolonged disruption of the hypothalamic-pituitary-adrenal axis after acute coronary events resulting in increased cortisol output during the day (Molloy, Perkins-Porras, Strike, & Steptoe, 2008).

Type-D personality has also been found to have predictive power for non-cardiac populations as well. A recent review from the Center of Research on Psychology in Somatic Diseases in Tilburg, Netherlands detailed the associations between Type-D personality and disease in non-cardiac populations. Correlations were found between the presence of Type-D personality and poor performance as well as increased cognitive complaints following traumatic brain injury**,** increased side effects of and poor adherence to treatment of sleep apnea,

poor health related quality of life and increased disease related distress in tinnitus patients, poor mental quality of life in diabetic foot syndrome patients, increased depression and anxiety in chronic pain patients, greater emotional and physical disability in peripheral vestibular patients and among melanoma survivors it was associated with subpar health status as well as a more prominent negative impact of cancer on the patients' lives. In the primary care setting, patients with Type-D personality have been documented as experiencing elevated rates of comorbidity, poor personal evaluations of perceived health status and poor physical as well as inadequate psychosocial functioning. In studies assessing the prevalence of Type-D personality among patient groups, higher prevalence was found in vulvovaginal candidiasis and tinnitus patient groups (Mols & Denollet, 2010).

Quality of Life

Health-related quality of life encompasses the assessment of three different domains: biological functioning, psychological functioning and social functioning. Health status, functional status and quality of life are all terms used to describe the same essential construct. The broad dimensions that are included in assessment of health-related quality of life allow for assessment of the degree of impairment of cherished aspects of life that are not considered traditional health measurements but may be associated with adverse health such as autonomy, ability to work, income and environmental quality. This measurement takes into account not only the physiologic measures most often

relied upon by physicians but other aspects of life which are impacted by chronic disease as well. It is only recently that quality of life has gained attention as a means to provide clinicians with a more complete picture of patient health beyond purely physiological measures such as cholesterol levels or outcome measures such as mortality. Its relevance also extends to examine the effects of disease treatments, such as percutaneous coronary intervention and coronary artery bypass grafting surgery, for which the primary goals are to improve health status as well as quality of life. Health-related quality of life is also a possible source of variance that can often be observed between two patients with the same degree of illness who experience different disease outcomes (Guyatt, Feeny, & Patrick, 1993). Following are examples of studies highlighting quality of life outcomes in cardiovascular patients.

Chronic heart failure is a disease that is increasing in prevalence and promotes poor quality of life due to difficulty breathing, chronic fatigue, multiple re-hospitalizations and peripheral edema which impair daily activities. An additional source of importance for quality of life measures is the expressed desire by the majority of a sample of chronic heart failure patients for an improvement in quality of life over survival (Staneck, Oates, McGhan, Denofrio, & Loh, 2000).

The general consensus of chronic heart failure patients is well stated by Archana (2002):

It is not sufficient, therefore, to offer a patient improved survival and add

years to life unless at the same time treatment also adds life to years…from a patients' perspective, the limitations imposed which adversely affect quality of life and impact upon day-to-day activities at home, leisure time interests and performance at work are of at least equal importance to the constellation of symptoms and signs that form the basis of the medically oriented approach to health assessment. (p. 1806-1807)

Chronic heart failure patients have been observed to experience impairments in all domains of health related quality of life as measured by the SF-36. The physical functioning aspect of quality of life in these patients also has been found to be more severely impaired than in other common chronic illnesses (Hobbs et al., 2002). Poor health-related quality of life has also been associated with adverse outcomes and mortality in chronic heart failure patients (Rodigeuz-Artalejo et al., 2005) and has been predictive of clinical endpoints which indicate that it is a valid measure of health status (Tate et al., 2007).

Peripheral artery disease is classified as a chronic illness for which one of the main goals of treatment is to improve quality of life. Some studies suggest that quality of life in peripheral artery disease patients may generally be poorer than that of chronic heart failure patients (Liles, Kallen, Peterson, & Bush, 2006). Peripheral artery disease limits daily activities and exerts adverse effects on quality of life by impairing walking ability, hindering sleep, decreasing energy, causing leg pain and sometimes requiring amputation or other surgical interventions. Patients report severe limitations in mobility and feelings of

inadequacy, fear, uncertainty and being a burden to family and friends which severely impairs physical as well as mental health related quality of life (Nehler, McDermott, Treat-Jacobson, Chetter, & Regensteiner, 2003). In recent years, the importance of quality of life on the treatment on peripheral artery disease patients has been highlighted, and the need to consider the broader impacts of peripheral artery disease beyond clinical symptoms and mortality has been emphasized. Subjective measures of quality of life have been correlated to functional status and objective measures of disease severity. Low scores on the mental health dimension of quality of life can also cause further impairment of physical health status. Patients who are asymptomatic or experience mild symptoms of disease may not function to the full extent of their capabilities due to their subjective perceptions of their health status (Liles et al., 2006).

Within the population of myocardial infarction patients, main contributors to impaired quality of life, compared to healthy community controls four and five years post myocardial infarction, are reported to be the inability to work, angina, emotional distress, difficulty sleeping and dyspnea (Brown et al., 1999; Wiklund, Herlitz, & Hjalmarson, 1988). The degree of impairment in the quality of life of myocardial infarction patients has also been associated with reduced left ventricular ejection fraction and younger age (Petterson, Kvan, Rollag, Stavem, & Reikvam, 2008; Bengtsson, Hagman, & Wedel, 2001). A reduced quality of life has also been observed in female as opposed to male myocardial infarction patients (Agewall, Berglund, & Henareh, 2003).

Additionally, interviews of 2,320 male myocardial infarction patients suggest that impairments in mental quality of life, more precisely high levels of stress, social isolation, depression, anxiety, hostility and anger, may be associated with mortality including sudden cardiac death (Ruberman, Weinblatt, Goldberg, & Chaudhary, 1984; Peters, 2001). Percutaneous coronary intervention and coronary artery bypass grafting surgery are two revascularization procedures which aim to improve quality of life. Both of these procedures have been demonstrated to equally improve health related quality of life scores six months post-revascularization (Rumsfeld et al., 2003). Additionally, poor physical health related quality of life has been demonstrated to be an independent predictor of mortality following coronary artery bypass grafting surgery (Rumsfeld et al., 1999).

Biochemical Markers

Additional indicators of prognosis in cardiovascular disease are pro-inflammatory cytokines which are substances released by immune cells in response to tissue injury or infection. Cytokines provoke an immune response drawing white blood cells to the damaged area in order to stimulate tissue repair. Two members of the pro-inflammatory cytokine family are tumor necrosis factor-alpha (TNF-α), and interleukin-6 (IL-6). These substances are activated in a chemical cascade and necessary for immune activation. All produce effects of hyperalgesia via release of prostaglandins, nerve growth factor, sympathetic activation and direct activation of peripheral nocioceptors

(Watkins & Maier, 2000). Pro-inflammatory cytokines often are up-regulated in heart failure patients as they are released by myocardial cells, most notably TNF-α and its soluble receptors (sTNFR-1 and sTNFR-2), in response to cardiac stress. High levels of TNF-α, sTNFR-1, sTNFR-2, and IL-6 have consistently been linked to severity of heart failure and cardiac mortality with sTNFR-2 levels being the most accurate predictor of cardiac mortality (Murray & Freeman, 2003; Valgimigli et al, 2005; Ueland et al, 2005; Deswal et al., 2001). Increased levels of pro-inflammatory cytokines are also associated with the pathogenesis of both atherosclerosis and chronic heart disease (Yudkin, Kumari, Humphries, & Mohamed-Ali, 2000).

Anti-inflammatory cytokines aid in regulation of the inflammatory immune response via cytokine inhibitors and soluble cytokine receptors. Two varieties of anti-inflammatory cytokines are interleukin-10 (IL-10) and interleukin-1 receptor antagonist (IL-1ra). A very delicate balance of pro- and anti-inflammatory cytokines is vital in order to ensure a fully functional and healthy immune system. Disruptions to this balance are extremely detrimental and often result in excessive inflammation and disease. The mechanism of action of IL-1ra is to act as a competitive inhibitor at pro-inflammatory interleukin-1 receptor sites. IL-10 is considered the most essential anti-inflammatory cytokine and works as an inhibitor of activity and production of a wide range of pro-inflammatory cytokines as well as an inhibitor of specific surface expression

molecules which signal an inflammatory response (i.e MHC II complex

molecules) (Opal & DePalo, 2000).

Cortisol is a glucocorticoid often referred to as a stress hormone released

in response to sympathetic stimulation via the hypothalamic-pituitary-adrenal

axis. It has been demonstrated that the hypothalamic-pituitary-adrenal axis is

stimulated by increases in negative affect resulting in increased cortisol levels

(Buchanan, al'Absi, & Lovallo, 1999; Sher, 2005). Chronically elevated cortisol has

a disease promoting effect via its influence on the deposition of abdominal

adipose tissue which is a predictor of cardiovascular disease (Rimm et al., 1995)

via its hyperlipidemia and insulin resistant effects (Sher, 2005). In addition,

cortisol has an inhibitory effect on growth hormone causing growth hormone

deficiencies which are associated with a greater risk of premature cardiovascular

disease (Erfuth, Bulow, Asklisson, & Hagmar, 1999; Hew, O'Neal, Kamarudin,

Alford, & Best, 1998). An important aspect of human circadian rhythm is the

cortisol awakening response. The general secretory pattern of cortisol is a large

increase in secretion resulting in peak cortisol levels after awakening followed by

a decrease in cortisol levels throughout the day ending with the lowest levels at

night and in the early hours of the morning. This is a pattern of increased levels

of cortisol by 50-75% release within thirty minutes of awakening (Clow, Thorn,

Evans, & Hucklebridge, 2004) and has been suggested to be a reliable biological

marker of adrenocortical activity (Pruessner et al, 1997). Increased levels of the

cortisol awakening response have been observed in chronically stressed

individuals in comparison to unstressed controls (Schulz, Kirschbaum, Prubner, & Hellhammer, 1998) whereas increased net output of cortisol throughout the day has been correlated with abdominal obesity (Rosmond, Dallman, & Bjorntorp, 1998).

Summary and Purpose of Current Study

In addition to the numerous investigations linking Type-D personality to various known risk factors for cardiac morbidity and mortality, there is a significant amount of research examining this personality type's value as a prognostic predictor following the diagnosis of heart disease using MACE, quality of life, and biochemical marker endpoints. Though much work has been conducted in examination of the topic as well as a handful of narrative reviews, no meta-analysis has been conducted in this area. The completion of a meta-analysis demonstrates the size of the relationship of Type-D personality with cardiac prognosis following the diagnosis of heart disease using the combined quantitative data from multiple studies. The use of data from multiple studies results in greater statistical power than in the individual studies and thus provides a better overview of the state of the research. Therefore, the objective of the current study is to conduct a meta-analytic review of the associations between Type-D personality and 1) Major adverse cardiac events 2) Quality of Life and 3) Levels of Biochemical Markers.

Methods

Study Search Procedure

Two search procedures were utilized in order to obtain studies used in

the present meta-analysis. First, a keyword search was conducted on the

PsycINFO and PubMed databases. The searches were limited to publications in

the English language and primary studies. All publications up to the time of the

search were eligible. The keyword combinations were *Type-D personality +*

heart, Type-D personality + mortality, Type-D personality + cardiac mortality and

Type-D personality + left ventricular ejection fraction. All titles and abstracts

were examined and potential candidates for the meta-analysis were collected.

Second, an ancestral search was conducted using the Schiffer et al. (2009)

article as a starting point due to its status as the most recent publication at the

time the ancestral search was conducted. References of all articles obtained

during the keyword search were also analyzed for potential studies. Any titles

pertaining to the current topic of study were identified and their abstracts were

checked for inclusion into the pool of candidate studies for the meta-analysis.

Studies were added as they were located by both the principal investigator and

two Ph.D. level collaborators.

Inclusion and Exclusion Criteria

Candidate studies had to meet specific criteria for inclusion into the

meta-analysis. Studies must (a) have a sample patient population with a

diagnosis of chronic heart failure, coronary heart disease, myocardial infarction,

acute coronary syndrome, peripheral artery disease or have undergone

percutaneous coronary intervention, implantable cardioverter defibrillator

implantation, coronary artery bypass grafting surgery, heart transplantation

surgery or be participating in a cardiac rehabilitation program; (b) compare

subsamples of patients diagnosed as Type-D vs. non Type-D; (c) Type-D must be

assessed using the DS-14, DS-16, DS-24 or a reliable and valid measure of both

negative affectivity and social inhibition separately in which high levels of both

negative affectivity and social inhibition are used to classify Type-D patients; (d)

the study endpoint must be either major adverse cardiac events (MACE), quality

of life measures or levels of disease promoting biochemical markers.

At the conclusion of the search, there were fifty potential studies relating

Type-D personality to heart disease. Of those studies, five were excluded

because they either lacked a non Type-D subsample for comparison or assessed

only negative affectivity or social inhibition individually. An additional three

studies were excluded because they used healthy patient samples. Of the

remaining 42 studies, 18 did not include the selected inclusion outcome

measures. An additional five studies were excluded due to the use of the same

patients in multiple studies, and one study was excluded due to a lack of cardiac

events in either patient group. A final four studies were unable to be used in

calculations of effect sizes because not enough statistical data were provided to

calculate an effect size (e.g standard deviations missing). The authors of these

studies were contacted in an attempt to gather additional data but no reply was

received. This left 14 studies in the analysis which were then split into three categories based on their endpoints: five studies were analyzed with an endpoint of MACE, five studies were analyzed for quality of life and four were analyzed with respect to biochemical markers (Figure 1).

Type-D Measurement in Primary Studies

The studies included in the analysis most often utilized the Type-D Scale-14 (DS-14) and the Type-D Scale-16 (DS-16) for the assessment of Type-D personality. On these diagnostic tools, patients indicate the extent to which they agree with statements concerning negative affectivity and social inhibition levels using five point Likert-type scales. A rating of 0 indicates disagreement with the statement whereas a rating of 4 indicates agreement. There are eight items to assess negative affectivity and eight items to assess social inhibition on the DS-16 (Denollet et al., 1996) whereas there are seven of each on the DS-14, the successor of the DS-16 (Emons, Meijer, & Denollet, 2007). The DS-16 and DS-14 both demonstrate evidence of internal consistency as measures of Type-D personality with $\alpha=.89$ and .88 for measures of negative affectivity and $\alpha=.82$ and .86 for social inhibition respectively (Denollet, 2005; Denollet et al., 1996). The cutoff for a classification of Type-D personality is a score of 10 or greater on both subscales. A median split using a cardiac population was used to establish the cutoff point (Denollet, 2005). The Negative Affectivity subscale highly correlates with the Trait Anxiety Scale ($r=.81$) whereas the Social Inhibition subscale highly correlates with the Erdman Inhibition Scale ($r=.73$) (Denollet,

1998). The DS-14 has been assessed using item response theory in both general and clinical populations. Item response theory is a method used to assess the measurement of variables that cannot be directly observed, referred to as latent variables, as well as to assess the precision of cutoff scores used in diagnostic tools. The item response theory assessment of the DS-14 supports the use of the established cut off points in differentiating between Type-D and non Type-D personality in both clinical and non clinical populations (Emons et al., 2007).

Quality of Life Measurement in Primary Studies

The SF-36 (Appendix A) is a 36 item self-evaluation of health status containing scaled measurements for eight different aspects of health: physical functioning, social functioning, role limitation due to physical functioning, role limitations due to emotional functioning, mental health, vitality, pain and the perception of general health (Kaplan, n.d). This evaluation is not disease-specific and assesses a wide range of the dimensions contributing to overall health. The scores for each individual dimension are coded and combined to produce an overall score of health ranging from 0 (poor health) to 100 (excellent health). Cronbach's α exceeds the standard value of 0.85 in all dimensions except social functioning (α=.73). The SF-36 also has adequate levels of test-retest reliability at two weeks among each of the eight dimensions, with r-values ranging from .60 to .80, as well as shows strong evidence of construct validity as the SF-36 is able to discriminate between patient groups with anticipated differences in their health status (Brazier et al., 1992).

The Minnesota Living with Heart Failure Questionairre (MLWHFQ) is a disease-specific assessment of the impact of disease on the quality of life of chronic heart failure patients (Appendix B). The evaluation consists of 21 items rated on a 6-point Likert-type scale rating the impact of heart failure on social, physical, mental and emotional aspects of life. It assesses, overall, the extent to which heart failure limits individuals from living their optimal lifestyle. High scores indicate poor health status. This measurement has high internal consistency with a Cronbach's α ranging from .92 to .95 among numerous studies (Rector, 2005). The Cantril Ladder of Life (Appendix C) is an additional quality of life measure in which subjects are presented with a vertical ladder on which the numbers 1-10 are presented (Jaarsma, Lesman-Leegte, Cleuren, & Lucas, 2005). They subjectively evaluate their lives from 1 (worst possible life) to 10 (best possible life) (Newman, 2005). This is a very general instrument that can be used in all populations and is often used among heart failure patients. The Cantril Ladder of life has a two year test-retest coefficient of .7 (Horley & Lavery, 1991). The Cantril Ladder of Life and the MLWHFQ have an overall correlation coefficient of .36 (Jaarsma et al., 2005).

The Health Complaints Scale (Appendix D) assesses 12 somatic and 12 cognitive common health complaints (Denollet, 1994). This instrument has been found to exhibit high internal consistency with a Cronbach's α of approximately .89 as well as sufficient test-retest reliability at three months with a Pearson's correlation coefficient of approximately .69. The Health Complaints Scale has

shown good construct validity as correlated with the disability and well-being

dimensions of the Heart Patients Psychological Questionnaire (Denollet, 1994).

The World Health Organization Quality of Life assessment instrument

(WHOQOL) (Appendix E) is a 100 item quality of life measure providing a

culturally sensitive subjective self report measurement of a broad range of

dimensions of quality of life with respect to their various levels of importance

(Trompenaars, Masthoff, Van Heck, Hodiamont, & De Vries, 2005; World Health

Organization, 1997). It has high levels of internal consistency with Cronbach's α

ranging from .73 to .91 among the five sub-domains of physical health,

psychological health, level of independence, social relationships and

environment as well as α=.91 for overall quality of life and general health. The

WHOQOL has also been shown to exhibit an adequate level of construct validity

when correlated with multiple related questionnaires such as the Sickness

Impact Profile, Fatigue Impact Scale, Self-Esteem Scale, Life Orientation Test,

Social Support Questionnaire, Profile of Moods Scale and the Standard Bipolar

Five-Factor Markers (De Vries & Van Heckk, 1997).

Coding of Study Characteristics

Each study was coded independently for both study level characteristics

and effect size level characteristics (Lipsey & Wilson, 2001; Appendix F). The

clinical variables which were coded were those most consistently reported in the

primary studies. Common authors and sample sources were included in the

coding due to the concentrated group of investigators as well as limited

geographical area in which Type-D research has been conducted. The recorded

study level characteristics were: publication year, inclusion of Denollet or

Pederson as authors, sample source (by hospital or cardiac rehabilitation

program), specific cardiac diagnosis/treatment/procedure, gender proportion

(percentage male), mean age, method of patient selection, study design, sample

size and diagnostic tool used to assess Type-D personality. Also recorded for

study level characteristics were the proportions of the sample engaging in

tobacco use, with impaired left ventricular ejection fraction (LVEF),

hyperlipidemia, hypertension, diabetes, renal impairment, NYHA Class III/IV and

with Type-D personality. It was also noted whether the baseline characteristics

significantly differed between the Type-D and non Type-D groups. The study-

level characteristics were examined as a source of possible extrinsic and

substantive variables in moderator analysis.

The recorded effect size level characteristics (Appendix F) were: length of

time of study, specific outcome construct measured, type of data effect size is

based on (dichotomous frequencies and proportions indicating the occurrence of

an event or means and standard deviations), page number on which the effect

size data was found, better or worse outcome for Type-D group, either all

dichotomous frequencies and proportions or means and standard deviation

data, whether Type-D personality was found to be a significant predictor of

worse outcome using 1) univariate significance testing and 2) multivariate

significance testing and the confidence rating in effect size computation based

on whether any estimation was necessary for data presented graphically without presentation of exact numbers. The confidence in the data was rated on a scale of 1-5. A rating of 1 indicated a high level of estimation with minimal statistical data. A rating of 2 indicated moderate estimation. For example, this would be necessary for studies reporting only multifactor ANOVA statistics as a basis for estimation. A confidence rating of 3 required some estimation such as that due to unconventional statistics needing to be converted to conventional statistics or incomplete conventional statistics. A rating of 4 required only slight estimation whereas a confidence rating of 5 required no estimation and effect sizes could be calculated directly from the data (Lipsey & Wilson, 2001). The effect size level coding provided the data necessary to compute effect sizes and provided a source of possible method variables in moderator analysis.

All coding was completed independently by two individual coders: the primary investigator of this study and an individual with a master's degree in cardiac rehabilitation/exercise physiology. A coding book (Appendix F) and coding sheets (Appendix G) were developed by the primary investigator and the second coder was provided with extensive training with the well-defined coding book (Appendix F). There was agreement on 100% of the study level characteristics and 98.6% of the effect size level characteristics for studies included in the MACE analysis. For the studies included in the quality of life analysis there was 100% agreement on the study level characteristics and 99.4% agreement on the effect size level characteristics. There was 100% agreement on

both study level and effect size level characteristics for studies included in the biochemical markers analysis. In cases of disagreement a decision was made following the conference of the raters.

Effect Size Computation

Effect sizes were computed and presented as either odds ratios or Hedge's *d*. Effect sizes were reported as odds ratios when individual effect sizes were gathered from dichotomous frequencies and proportions and were reported in the terms of Hedge's *d* when the individual effect size data was derived from means and standard deviations. In analyses that combined effects from multiple studies, effect sizes were weighted by their inverse variance. All effect sizes were computed using Comprehensive Meta-Analysis Software (Biostat, 2002).

For the MACE analysis, only one overall effect size was calculated. There were two effect sizes calculated in the quality of life analysis: one using the combined effects from studies with continuous data as well as one computed from studies with dichotomous data. In the biochemical markers analysis multiple effect sizes were calculated. First, effect sizes were calculated individually for each of the inflammatory cytokines IL-6 and TNF-α, as well as TNF-α soluble receptors sTNFR-1 and sTNFR-2. An effect size was then calculated for TNF-α combined with sTNFR-1 and sTNFR-2. These were then combined along with IL-6 to obtain an overall inflammatory cytokine effect size. An effect

size was then computed for combined anti-inflammatory chemicals IL-10 and IL-1ra. Lastly, the effect size for cortisol levels was computed.

Test of Homogeneity

A test of homogeneity is an indicator of the extent to which each individual effect size is an estimate of the same population effect. This test is represented by the variable Q. In a sample yielding a homogenous effect size, Q is non-significant ($p>.05$) signifying that the individual effect sizes within the overall mean effect size only differ with respect to sampling error. For samples in which Q is significant ($p<.05$) the individual effect sizes are said to be heterogeneous implying that individual effect size differences do not result from only sampling error. In this case, other moderators must be considered in further analysis as potential sources which could account for the heterogeneity of the individual effect sizes (Hedges, 1982; Lipsey & Wilson 2001)

In samples in which the number of individual effect sizes is small, the statistical power of Q is reduced resulting in the possibility that the test of homogeneity may fail to indicate a heterogeneous sample when a heterogeneous sample is present. For this reason, we have also included values for the I^2 index to complement the Q statistic results. The I^2 statistic not only indicates whether or not heterogeneity is present but also provides information about the extent to which individual effect sizes are heterogeneous. By convention, the values of $I^2=0$ (0%), $I^2=25$ (25%), $I^2=50$ (50%), and $I^2=75$ (75%) indicate homogeneity, low heterogeneity, medium heterogeneity, and high

heterogeneity respectively (Huedo-Medina, Sanchez-Meca, & Marin-Martinez, 2006). If heterogeneity was indicated based on a significant Q-value, each individual study included in the effect size calculation was examined for potential moderators. The identified potential moderators were then discussed as variables to be considered for future research in this area

Meta-Analytic Model

Multiple meta-analytic models can be utilized in the completion of a meta-analysis: fixed-effects, random-effects or mixed-effects. The fixed-effects model is used when the source of heterogeneity between studies included in the analysis is believed to have come from the study level and effect level coding characteristics. A random-effects model is appropriate when variance between studies is ascribed to sources of variability that are assumed to be randomly distributed beyond random sampling error. Lastly, when the variance between studies beyond that which can be attributed to sampling error is thought to be primarily systematic but an additional random component of effect size distribution is still present, a mixed-effects model should be employed (Lipsey & Wilson, 2001). Due to the presence of heterogeneity in the present analysis that was not systematic, the random-effects model was utilized.

Results

A summary of all numerical values for individual statistics is provided in Table 2.

Major Adverse Cardiac Events Analysis

There were five studies included in the analysis with MACE as endpoints. This yielded five individual effect sizes from a total of 2,066 cardiac patients (Type-D=584, non Type-D= 1,482). All studies utilized a longitudinal design, included either Denollet or Pederson as researchers and had a patient sample that was more than 50% male in composition. Three studies took place in Belgium with patients from the Antewerp Cardiac Rehabilitation Program whereas the remaining two studies were conducted in the Netherlands. Four of the five studies reported 20-29% prevalence of Type-D personality whereas one study reported Type-D prevalence between 30-39%. One study reported the Type-D sample as being more likely to smoke than the non Type-D sample whereas no other significant differences in baseline characteristics between the two groups were reported. All studies were rated at 100% confidence as all necessary data for effect size calculation was provided, and no estimation was needed.

The test of homogeneity produced a non-significant Q=3.27 indicating homogenous individual effect sizes. This was further verified by an I^2 value of 0%. Type-D personality was associated with a higher occurrence of MACE (OR=3.42, 95% CI=2.48-4.73, p<.001). These results demonstrate that individuals with Type-D personality have more than three times greater odds of suffering a myocardial infarction, percutaneous coronary intervention, coronary artery bypass grafting surgery or cardiac death following the diagnosis of heart disease than those without Type-D personality.

Quality of Life Analysis

A total of five studies were included in the quality of life analysis. Two of these studies were included in the computation of a single effect size as data were presented dichotomously with a total sample size of 521 patients (Type-D=188, non Type-D=333). The remaining three studies were included in an additional computation of effect size as continuous data were provided with a total sample size of 368 patients (Type-D=98, non Type-D=270). Three studies were completed in the Netherlands, two in Sweden and one in the UK. Three of the five studies included either Denollet or Pederson as researchers. Two studies were longitudinal whereas the remaining three were cross sectional. One study reported that, at baseline, Type-D patients were more likely to have diabetes and have a lower level of education than non-Type-D patients. No other differences in baseline characteristics were reported. In all studies, greater than 50% of the sample was male and mean ages were within the range of 50-69 years. Two studies reported the prevalence of Type-D personality to be 20-29%, two reported the prevalence to be 30-39%, whereas one study had an abnormally high prevalence of Type-D personality within the range of 40-49%. The data from four of the studies was rated at 100% confidence. One study required slight estimation of means and standard deviations from a figure presented graphically and, therefore, confidence was rated as 3.5 out of 5.

Analysis of the quality of life studies presenting data dichotomously produced a significant effect size (OR=3.48, CI= 2.37-5.11, p<.001) as well as

homogeneity between studies (Q=.21, p=.65, I^2=0) indicating that individuals with Type-D personality have more than three times greater odds of experiencing a poor quality of life when diagnosed with heart disease than non-Type-D individuals. In the analyses which included the three studies with continuous data, the test of homogeneity resulted in a significant Q value of 51.88 (p<.001) and an I^2 value of 96.15% indicating the presence of heterogeneity beyond sampling error alone. The effect size for the relationship between the presence of Type-D personality and poor quality of life was found to be significant (d=-1.23, p=.01).

Potential sources of moderators between individual studies as sources of heterogeneity in the data were identified. Aquarius (2007) had an increased proportion of smokers and small sample size. Karlsson (2007) differed with respect to investigators and a very general and simplistic measure of quality of life versus the detailed MLWHFQ and WHOQOL-BREF utilized in the other studies. Specific cardiac diagnosis and quality of life measurement differed among all three studies.

Before these results are discussed further, a narrative review of the results of the four excluded quality of life studies is warranted. The first of the four excluded studies was conducted at Tweesteden Teaching Hospital in Tilburg, Netherlands on 166 patients being treated for chronic heart failure. The patients' disease-specific quality of life was assessed using the MLWHFQ and general health status was assessed with the SF-36 at baseline and a one year follow-up.

Though there was an overall improvement in general health status over time,

Type-D's reported poorer disease-specific as well as general physical and mental

health status at both time points. Type-D was an independent predictor of poor

disease-specific mental health status, social functioning, role emotional

functioning, general health and increased bodily pain following multivariate

analysis (Schiffer et al., 2008). The second excluded study, also in Tilburg,

Netherlands at St. Elisabeth Hospital, examined the relationship of Type-D

personality with quality of life and stress in 150 peripheral artery disease

patients. Quality of life was measured with the WHOQOL-100 and the Perceived

Stress Scale-10. Type-D personality was equally present in patients with mild,

moderate and severe levels of disease though Type-D patients reported poorer

quality of life and more perceived stress than non Type-D patients. After

adjustments for disease status, age and gender, Type-D personality remained

significantly associated with an impaired quality of life (Aquarius, Denollet,

Hamming, & De Vries, 2005). The third excluded study was conducted with 186

surviving heart transplant recipients transplanted at the Erasmus Medical Center

in Rotterdam, Netherlands between 1985 and early 2003. Perceived health

related quality of life was assessed with the SF-36. Type-D transplant recipients

reported poorer quality of life than non Type-D patients on all aspects of the SF-

36, excluding bodily pain. Type-D personality was an independent predictor of

poor outcome on all dimensions of the SF-36 except bodily pain and general

health. Of interest, the 18% prevalence of Type-D personality in this study was

abnormally low in comparison to other samples. It is hypothesized that this could

be due to the greater mortality rates of Type-D patients as evidenced in other

studies as well as this meta-analysis, or the socially inhibited manner in which

Type-D patients tend to present themselves resulting in a possible decreased

patient advocacy and reduced placement of Type-D patients on the heart

transplant list (Pederson et al., 2006). The final excluded study assessed the

relation between Type-D personality and health related quality of life at baseline

and three months in 154 implantable cardioverter defibrillator implantation

patients. Quality of life was measured by the SF-36. Though general

improvement was observed with time, Type-D patients consistently reported

poorer quality of life than non Type-D patients (Pederson, Thomas, Muskens-

Heemskerk, Erdman, & Jordaens, 2007).

Biochemical Markers Analysis

There were a total of four studies with endpoints of biochemical markers

of disease. All analysis conducted with pro-inflammatory cytokines was

conducted from the data of 305 patients (Type-D=105, non Type-D=200)

whereas anti-inflammatory cytokine analysis encompassed 84 patients (Type-

D=32, non Type-D=52) and cortisol analysis included 66 patients (Type-D=23, non

Type-D=43). Two studies were conducted in Belgium, one in England and one in

the Netherlands. Three of the four studies included either Denollet or Pederson

as researchers. Three studies were cross-sectional in design whereas one was

longitudinal. Two studies found Type-D patients more likely to be NYHA Class

III/IV at baseline, one study reported that Type-D patients were more likely to be older, and one study reported Type-D patients as more likely to be taking diuretics. No other significant differences at baseline were reported. All studies consisted of samples with more than 50% males and a 30-39% prevalence of Type-D personality. All studies were rated at 100% confidence as all data necessary for calculating effect sizes was provided and no estimation was needed.

The levels of inflammatory cytokine IL-6 were found to be elevated in patients with Type-D personality (d=-.26, p=.03) and the test of homogeneity indicated homogenous individual effect sizes (Q=.04, p=.98, I^2=0%). The analysis of elevated inflammatory cytokine TNF-α and its soluble receptor levels (d=-1.58, p=.07) and combination analysis of elevated IL-6, TNF-α, sTNFR-1, and sTNFR-2 levels (d=-1.10, p=.07) in Type-D versus non Type-D individuals both trended towards significance. Both TNF-α, sTNFR-1, and sTNFR-2 combined analysis (Q=76.30, p<.001, I^2=97.39%) and the combined IL-6, TNF-α, sTNFR-1, and sTNFR-2 (Q=48.37, p<.001, I^2=95.87%) analysis were also found to be heterogeneous indicating that the variance among individual effect sizes cannot be explained by mere sampling error. The effect size for TNF-α excluding the effects of sTNFR-1 and sTNFR-2 was found to be insignificant (d=-1.07, p=.17) as well as heterogeneous (Q=67.07, p<.001, I^2=97.02%). Significance was found for the effects of sTNFR-1 and sTNFR-2 alone (d=-1.82, p=.05), however, heterogeneity was present (Q=81.97, p<.001, I^2=97.56%). In analysis of anti-

inflammatory chemicals IL-10 and IL-1ra (d=-.42, p=.06) the results also trended towards significance with Type-D individuals having lower levels of anti-inflammatory cytokines. The last biochemical analysis of the association between Type-D and cortisol levels did not produce significant results (d=-.24, p=.35).

All heterogeneous studies were examined for the presence of potential moderators. Denollet (2009) was identified as a possible source of variance due to a greater proportion of the sample being classified as NYHA Class III/IV, a greater mean sample age, the presence of kidney dysfunction in fourteen of the Type-D patients and a longitudinal study design whereas the other studies were cross-sectional.

Discussion

Results from the MACE analysis demonstrate a large effect size indicating the association of Type-D personality with odds of experiencing a myocardial infarction, cardiac mortality, coronary artery bypass grafting surgery and percutaneous coronary intervention that are more than three times greater than in non Type-D individuals. When quality of life data were presented dichotomously, indicating only whether quality of life was impaired or not, the results indicated that Type-D patients had more than three times greater odds of being classified as having a poor quality of life than those without Type-D personality. When data were presented continuously, indicating the severity with which quality of life was impaired, in the form of numerical scores on the

various quality of life assessments, the effect size was also found to be significant. The consistent results of the four previously summarized excluded studies which assess quality of life in heart disease patient groups using similar and psychometrically accepted instruments also support the presence of a relationship between Type-D personality and poor health-related quality of life. The increased sample size would also have increased the statistical precision and perhaps have provided a more homogenous outcome.

The test of homogeneity with respect to the continuous data quality of life analysis implies the presence of moderators in the studies contributing to heterogeneity beyond that solely from sampling error. One of these possible moderators is the variety of quality of life measures used in the studies. Three different quality of life measures were used in the analysis, and though they all have a common objective of measuring quality of life, each differed with respect to the others. The SF-36 and Cantril Ladder of Life both measure general quality of life whereas the MLWHFQ is disease specific. The Cantril Ladder of Life is a very general single measure of the discrepancy between the patients' real versus ideal life whereas the SF-36 and MLWHFQ results are based on a combination of scores on multiple detailed dimensions of quality of life. Though all studies used cardiovascular disease patient populations, each of three studies included patients with differing diagnoses. The three patient populations were either diagnosed with acute myocardial infarction or peripheral artery disease, underwent coronary artery bypass grafting surgery, or were generally referred to

cardiac rehabilitation with no specific diagnosis provided. This raises the possibility that differing diagnoses, though all falling under the umbrella of cardiovascular disease, may be associated with the variation between effect sizes. Additionally, one study took place over a twelve week period with quality of life measurements taken at both baseline and twelve weeks. However, the patient sample underwent cardiac rehabilitation between quality of life measures so only baseline data were utilized in the effect size calculation in order to reduce variability between studies. One study was prospective in nature but only provided quality of life scores using the Cantril Ladder of Life at baseline whereas the other study was also prospective in nature but only provided raw, unadjusted data usable in the present meta-analysis for baseline WHOQOL scores. If all of these studies had had usable test-retest data, it is possible that the quality of life scores may have presented a more precise picture of the patients' quality of life as well as less heterogeneity between the effect sizes. These are important variables consider for future research in this area as well as any future meta-analysis conducted when a larger sample size is available.

Of the biochemical markers, the inflammatory cytokines IL-6, sTNFR-1 and sTNFR-2 were most prominently associated with Type-D personality. Type-D patients displayed significantly higher levels of these cytokines compared to non Type-D patients. Though the elevated levels of TNF-α in Type-D patients did not reach significance, when the TNF-α and its soluble receptor levels were combined the results trended towards significance. This pattern may be due to

the fact that the majority of TNF-α is found on cell surfaces and has a stimulatory effect triggering the release of sTNFR-1 and sTNFR-2 into plasma. Therefore, sTNFR-1 and sTNFR-2 are strong indicators of sustained elevated levels of TNF-α and are regarded as more accurate predictors of adverse outcome in heart disease, primarily chronic heart failure (von Haehling, Jankowska, & Anker, 2004). Additionally, it has been indicated that the plasma complex formed by circulating TNF-α and its soluble receptors stabilizes TNF-α and enhances as well as prolongs its pro-inflammatory effects in the body (Aderka, Engelmann, Maor, Brakebush, & Wallach, 1992). The combined effect of elevated TNF-α, sTNFR-1, sTNFR-2, and IL-6 levels in Type-D versus non Type-D patients also trended towards significance. There was, however, a relatively small sample size for each analysis resulting in the possibility that an increased sample size may have caused the effect sizes that strongly trended towards significance to become significant.

The individual effect sizes from which the overall effect size was determined for these non significant analyses as well as the sTNFR-1 and sTNFR-2 analysis were found to be heterogeneous indicating the presence of possible moderators causing variance to be greater than that which can be explained by sampling error alone. The studies varied slightly with respect to mean patient ages of 57, 59.1 and 65.7 years. The study in which the mean patient age was highest also had the highest levels of pro-inflammatory cytokines. TNF-α levels have been positively correlated with advancing age (Deswal et al., 2001). The

same study also included 14 Type-D patients with kidney dysfunction which is

also associated with increased pro-inflammatory cytokine levels (Knight et al.,

2004; Pecoits-Filho et al., 2003). This may explain a portion of the between study

variability and in future research clinical variables that have independent

associations with biochemical marker levels should be considered. It should also

be noted that all data used in the present meta-analysis were raw data

unadjusted for clinical variables such as age, gender, and disease severity.

Anti-inflammatory cytokine analysis presented a trend towards

significantly lower levels in Type-D versus non Type-D patients. Cortisol levels did

not differ between Type-D and non Type-D individuals. This may have been

affected by the measurement of awakening cortisol levels as well as cortisol

awakening response in a hospital setting where sleep patterns are interrupted by

ambient light and noises throughout the night. A study by Molloy and colleagues

(2008) measured cortisol awakening response as well as cortisol levels

throughout the day in a non-hospital setting using a patient sample overlapping

with that of our analysis. They also found no statistically significant difference

between Type-D and non Type-D patients with respect to the cortisol awakening

response. They did, however, find elevated levels of cortisol output throughout

the day in Type-D versus non Type-D individuals. A study using monozygotic and

dizygotic twin pairs found that chronic stress as well as genetics have a

substantial influence on cortisol levels after awakening but do not influence the

cortisol profile over the course of the day (Wust, Wolf, Federenko, Hellhammer,

& Kirschbaum,2000). This is an area that may warrant further study, as there has been much focus on the magnitude of the cortisol awakening response in connection to disease.

Cardiac rehabilitation, particularly rehabilitation with a focus on relieving emotional distress through group and individual interventions, has been shown to reduce mortality in coronary heart disease patients (Denollet & Brutsaert, 2001). It also may decrease the level of impairment associated with Type-D personality and may facilitate improvement in DS-14 scores to a more favorable level (Binder, Kohls, Schmid, & Saner, 2007). In contrast, other studies have observed improvements in the quality of life of Type-D patients following cardiac rehabilitation without improvements in DS-14 scores (Karlsson et al., 2007). There are a broad range of options available to alleviate the distress caused by Type-D personality such as pharmacological intervention with anti-depressants to increase social confidence and reduce the intensity of negative emotions, psychotherapy to teach social skills and provide emotional support, cognitive behavioral therapy or exercise (Sher, 2005). However, further research is needed to determine whether any of these options to alleviate chronic stress as well as emotional distress have any effect in Type-D individuals.

There are limitations to the present meta-analysis that should be noted. These studies were conducted by a moderately concentrated group of investigators and were restricted demographically to encompass patients from a small number of countries in Europe. There is a need for additional research that

encompasses a broader demographic to replicate the previous findings concerning Type-D personality and adverse cardiac prognosis. Effect sizes, particularly those concerning quality of life and biochemical markers, were computed from small sample sizes, many of which were heterogeneous, which enforces the need for a broader body of research on the topic. The abundance of trends towards significance despite small effect sizes still strongly suggests an association between Type-D personality and poor cardiac prognosis.

These findings converge to strongly suggest that Type-D personality is a predictor of poor prognosis following a diagnosis of cardiovascular disease which may possibly be explained by disease pathways involving pro- and anti-inflammatory cytokines. This supports the need for a brief and simple screening of cardiovascular patients for Type-D personality in order to provide supplemental treatment to this high risk patient population.

Appendix A

SF-36(tm) Health Survey

Instructions for completing the questionnaire: Please answer every question. Some questions may look like others, but each one is different. Please take the time to read and answer each question carefully by filling in the bubble that best represents your response.

Patient Name: _____
SSN#: _____ Date:_____
Person helping to complete this form:

_____
_____

1. In general, would you say your health is:
❑   Excellent
❑   Very good
❑   Good
❑   Fair
❑   Poor

2. Compared to one year ago, how would you rate your health in general now?
❑   Much better now than a year ago
❑   Somewhat better now than a year ago
❑   About the same as one year ago
❑   Somewhat worse now than one year ago
❑   Much worse now than one year ago

3. The following items are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?
a. Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports.
❑   Yes, limited a lot.
❑   Yes, limited a little.
❑   No, not limited at all.
b. Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf?
❑   Yes, limited a lot.
❑   Yes, limited a little.
❑   No, not limited at all.
c. Lifting or carrying groceries.
❑   Yes, limited a lot.
❑   Yes, limited a little.
❑   No, not limited at all.

d. Climbing several flights of stairs.
- ❑ Yes, limited a lot.
- ❑ Yes, limited a little.
- ❑ No, not limited at all.

e. Climbing one flight of stairs.
- ❑ Yes, limited a lot.
- ❑ Yes, limited a little.
- ❑ No, not limited at all.

f. Bending, kneeling or stooping.
- ❑ Yes, limited a lot.
- ❑ Yes, limited a little.
- ❑ No, not limited at all.

g. Walking more than one mile.
- ❑ Yes, limited a lot.
- ❑ Yes, limited a little.
- ❑ No, not limited at all.

h. Walking several blocks.
- ❑ Yes, limited a lot.
- ❑ Yes, limited a little.
- ❑ No, not limited at all.

i. Walking one block.
- ❑ Yes, limited a lot.
- ❑ Yes, limited a little.
- ❑ No, not limited at all.

j. Bathing or dressing yourself.
- ❑ Yes, limited a lot.
- ❑ Yes, limited a little.
- ❑ No, not limited at all.

4. During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of your physical health?
a. Cut down the amount of time you spent on work or other activities?
☐ Yes ☐ No
b. Accomplished less than you would like?
☐ Yes ☐ No
c. Were limited in the kind of work or other activities
☐ Yes ☐ No
d. Had difficulty performing the work or other activities (for example, it took extra time)
☐ Yes ☐ No

5. During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?
a. Cut down the amount of time you spent on work or other activities?

☐ Yes ☐ No
b. Accomplished less than you would like
☐ Yes ☐ No
c. Didn't do work or other activities as carefully as usual
☐ Yes ☐ No

6. During the past 4 weeks, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?
❑ Not at all
❑ Slightly
❑ Moderately
❑ Quite a bit
❑ Extremely

7. How much bodily pain have you had during the past 4 weeks?
❑ Not at all
❑ Slightly
❑ Moderately
❑ Quite a bit
❑ Extremely

8. During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?
❑ Not at all
❑ Slightly
❑ Moderately
❑ Quite a bit
❑ Extremely

9. These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the past 4 weeks.
a. did you feel full of pep?
❑ All of the time
❑ Most of the time
❑ A good bit of the time
❑ Some of the time
❑ A little of the time
❑ None of the time
b. have you been a very nervous person?
❑ All of the time
❑ Most of the time
❑ A good bit of the time

❑ Some of the time
❑ A little of the time
❑ None of the time

c. have you felt so down in the dumps nothing could cheer you up?
❑ All of the time
❑ Most of the time
❑ A good bit of the time
❑ Some of the time
❑ A little of the time
❑ None of the time

d. have you felt calm and peaceful?
❑ All of the time
❑ Most of the time
❑ A good bit of the time
❑ Some of the time
❑ A little of the time
❑ None of the time

e. did you have a lot of energy?
❑ All of the time
❑ Most of the time
❑ A good bit of the time
❑ Some of the time
❑ A little of the time
❑ None of the time

f. have you felt downhearted and blue?
❑ All of the time
❑ Most of the time
❑ A good bit of the time
❑ Some of the time
❑ A little of the time
❑ None of the time

g. did you feel worn out?
❑ All of the time
❑ Most of the time
❑ A good bit of the time
❑ Some of the time
❑ A little of the time
❑ None of the time

h. have you been a happy person?
❑ All of the time
❑ Most of the time
❑ A good bit of the time
❑ Some of the time
❑ A little of the time
❑ None of the time

i. did you feel tired?

❑ All of the time
❑ Most of the time
❑ A good bit of the time
❑ Some of the time
❑ A little of the time
❑ None of the time

10. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting friends, relatives, etc.)?
❑ All of the time
❑ Most of the time
❑ Some of the time
❑ A little of the time
❑ None of the time

11. How TRUE or FALSE is each of the following statements for you?
a. I seem to get sick a little easier than other people
❑ Definitely true
❑ Mostly true
❑ Don't know
❑ Mostly false
❑ Definitely false
b. I am as healthy as anybody I know
❑ Definitely true
❑ Mostly true
❑ Don't know
❑ Mostly false
❑ Definitely false
c. I expect my health to get worse
❑ Definitely true
❑ Mostly true
❑ Don't know
❑ Mostly false
❑ Definitely false
d. My health is excellent
❑ Definitely true
❑ Mostly true
❑ Don't know
❑ Mostly false
❑ Definitely false

Appendix B

MINNESOTA LIVING WITH HEART FAILURE® QUESTIONNAIRE

The following questions ask how much your heart failure (heart condition) affected your life during the past month (4 weeks). After each question, circle the 0, 1, 2, 3, 4 or 5 to show how much your life was affected. If a question does not apply to you, circle the 0 after that question.

Did your heart failure prevent you from living as you wanted during the past month (4 weeks) by -

	No		Little	Very		
1. causing swelling in your ankles or legs?	0	1	2	3	4	5
2. making you sit or lie down to rest during the day?	0	1	2	3	4	5
3. making your walking about or climbing stairs difficult?	0	1	2	3	4	5
4. making your working around the house or yard difficult?	0	1	2	3	4	5
5. making your going places away from home difficult?	0	1	2	3	4	5
6. making your sleeping well at night difficult?	0	1	2	3	4	5
7. making your relating to or doing things with your friends or family difficult?	0	1	2	3	4	5
8. making your working to earn a living difficult?	0	1	2	3	4	5
9. making your recreational pastimes, sports or hobbies difficult?	0	1	2	3	4	5
10. making your sexual activities difficult?	0	1	2	3	4	5
11. making you eat less of the foods you like?	0	1	2	3	4	5
12. making you short of breath?	0	1	2	3	4	5
13. making you tired, fatigued, or low on energy?	0	1	2	3	4	5
14. making you stay in a hospital?	0	1	2	3	4	5
15. costing you money for medical care?	0	1	2	3	4	5
16. giving you side effects from treatments?	0	1	2	3	4	5

17. making you feel you are a burden to your
    family or friends?   0   1   2   3   4   5
18. making you feel a loss of self-control
    in your life?   0   1   2   3   4   5

19. making you worry?   0   1   2   3   4   5
20. making it difficult for you to concentrate
    or remember things?   0   1   2   3   4   5

21. making you feel depressed?   0   1   2   3   4   5

_____

_____

11/10/04

Appendix C

Cantril Ladder of Life

All of us want certain things out of life. When you think about what really matters in your own life, what are your wishes and hopes for the future? In other words, if you image you own future in the best possible light, what would you life look like then, if you are to be happy? Take your time thinking about
this.

Now taking the other side to the picture, what are your fears and worries about the future? In other words, if you image your future in the worst possible light, what would your life look like then? Here is a picture of a ladder. The top of the ladder represents the best possible life and the bottom the worst for you. Where on the ladder do you feel you personally stand at the present time?

10 BEST POSSIBLE LIFE
9_____
8_____
7_____
6_____
5_____
4_____
3_____
2_____
1_____
0 WORST POSSIBLE LIFE

Appendix D

Health Complaints Scale

Name:_____ Sex:_____ Age:_____
Date:_____

Below are a number of problems and complaints that ill people often have. Please read each item carefully and then **circle the appropriate number** next to that problem. Indicate how much each problem has **bothered you lately**. Please use the following scale to record your answers.

0 NOT AL ALL   1 A LITTLE BIT   2 MODERATELY   3 QUITE A BIT 4 EXTREMELY

Lately, how much were you bothered by the following specific problems:

[A1]Sleep that is restless or disturbed
→ 0 1 2 3 4

[A2]Tightness of the chest
→ 0 1 2 3 4

[A3]Feeling that you are not rested
→ 0 1 2 3 4

[A4]Fatigue
→ 0 1 2 3 4

[A5]Trouble falling asleep
→ 0 1 2 3 4

[A6]Inability to take a deep breath
→ 0 1 2 3 4

[A7]Stabbing pain in heart or chest
→ 0 1 2 3 4

[A8]Feeling exhausted without any reason
→ 0 1 2 3 4

[A9]Shortness of breath
→ 0 1 2 3 4

A10Pain in heart or chest
→ 0 1 2 3 4

A11Feeling weak
→ 0 1 2 3 4

A12Feeling you can't sleep
→ 0 1 2 3 4

Lately, how much have you been bothered by the following problems:

B1The idea that your bad health is the biggest problem in your life
→ 0 1 2 3 4

B2Not being able to work fluently, also with hobbies
→ 0 1 2 3 4

B3Being afraid of illness
→ 0 1 2 3 4

B4The idea that you were able to take on much more work formerly
→ 0 1 2 3 4

B5Feeling blocked in getting things done
→ 0 1 2 3 4

B6The idea that you have a serious illness
→ 0 1 2 3 4

B7Feeling you are not able to do much
→ 0 1 2 3 4

B8The idea that something serious is wrong with your body
→ 0 1 2 3 4

B9Feeling you are no longer worth as much as you used to be
→ 0 1 2 3 4

B10Feeling despondent
→ 0 1 2 3 4

[B11]worrying about your health
➔ 0 1 2 3 4

[B12]Thinking that all your worries would be over in you were physically healthy
➔ 0 1 2 3 4

Appendix E

54

55

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57

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59

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Appendix F

STUDY-LEVEL CODING MANUAL

Source Descriptors:

1. Study ID Number (In bold at beginning of reference)

2. Publication Year (Last two digits)

3. Does the study include either Denollet, J or Pederson SS in its list of authors?
    1. Yes   2. No

Sample Descriptors:

4. What is the source of the sample? Specify by the hospital or program from which they were selected.
    1. Antewerp Cardiac Rehabilitation Program/University Hospital of Antewerp
    2. Rotterdam Cardiology Hospital/Organization for Cardiac Rehabilitation
    3. Harefield Hospital
    4. TweeSteden Teaching Hospital
    5. St. Elisabeth Hospital
    6. London Hospitals
    7. Danderyd Hospital
    8. Erasmus Medical Center
    9. General Practice

5. What is the specific cardiac diagnosis or necessary treatment/procedure of the patients which qualified them for the study? Select multiple diagnoses if the sample included more than one cardiac pathology or procedure.
    1. Myocardial Infarction
    2. Coronary Artery Bypass Grafting Surgery (CABG)
    3. Angioplasty/Percutaneous Coronary Intervention (PCI)
    4. Referred to/Participating in Cardiac Rehabilitation Program
    5. Chronic/Congestive Heart Failure (CHF), specify if systolic/diastolic noted
    6. Peripheral Artery Disease (PAD)
    7. Coronary Heart Disease (CHD)
    8. Acute Coronary Syndrome (ACS)
    9. Heart Transplant
    10. Implantable Cardioverter Defibrillator (ICD) Implantation

6. Predominant gender of sample. Select the code for the correct proportion of men in the sample.
    1. <5% male   2. 5-50% male

3. 50% male   4. 50-95% male
5. >95% male   6. Information not reported

7. Mean age of sample. Select correct age bracket or indicate that it is stratified by percent greater than a specific age.
1. 20-49 years old   2. 50-59 years old
3. 60-69 years old   4. 70-79 years old
5. 80 years or older   6. Information reported as % of
7. Information not reported   sample greater than a specified age
     (please specify the age)

8. Proportion of sample that engages in tobacco use. Select the correct percentage bracket.
1. 0-24% smokers   2. 25-49% smokers
3. 50-74% smokers   4. 75-89% smokers
5. 90-100% smokers   6. Information not reported

9. Proportion of sample with impaired Left Ventricular Ejection Fraction (LVEF). This has no absolute definition and is defined slightly different from study to study. Select based on the proportion that is less than the cut-off percentage specified in the study. For example, one study may specify the proportion of patients with an LVEF <50% while another specified the proportion with an LVEF <40%, code for the proportion defined as impaired according to the specific study. Only a mean LVEF is provided specify and provide the mean.
1. 0-24% impaired LVEF   2. 25-49% impaired LVEF
3. 50-74% impaired LVEF   4. 75-89% impaired LVEF
5. 90-100% impaired LVEF   6. Information not reported
7. Only mean LVEF reported (specify)

10. Proportion of sample with hyperlipidemia/hypercholesterolemia/dyslipidemia. Select the correct percentage bracket.
1. 0-24% high cholesterol   2. 25-49% high cholesterol
3. 50-74% high cholesterol   4. 75-89% high cholesterol
5. 90-100% high cholesterol   6. Information not reported

11. Proportion of sample with hypertension. Select the correct percentage bracket.
1. 0-24% hypertension   2. 25-49% hypertension
3. 50-74% hypertension   4. 75-89% hypertension
5. 90-100% hypertension   6. Information not reported

12. Proportion of sample with diabetes. Select the correct percentage bracket.

1. 0-24% diabetes	2. 25-49% diabetes
3. 50-74% diabetes	4. 75-89% diabetes
5. 90-100% diabetes	6. Information not reported

13. Proportion of sample with renal impairment. Select the correct percentage bracket.

1. 0-24% renal impairment	2. 25-49% renal impairment
3. 50-74% renal impairment	4. 75-89% renal impairment
5. 90-100% renal impairment	6. Information not reported

14. Proportion of sample classified as NYHA Class III and IV. Select the correct percentage bracket.

1. 0-24% severe disease	2. 25-49% severe disease
3. 50-74% severe disease	4. 75-89% severe disease
5. 90-100% severe disease	6. No information reported

15. Proportion of the sample classified as Type-D Personality. Select the correct percentage bracket.

1. 0-9% Type-D	2. 10-19% Type-D
3. 20-29% Type-D	4. 30-39% Type-D
5. 40-49% Type-D	6. 50-59% Type-D
7. 60-69% Type-D	8. 70-79% Type-D
9. 80-89% Type-D	10. 90-100% Type-D
11. Information not provided	

16. Are the baseline characteristics of the Type-D's vs. non Type-D's significantly different?
> 1. Yes (specify which aspects are significantly different)
> 2. No
> 3. Information not provided

Research Design Descriptors:

17. How were the patients selected? Choose best possible selection.
> 1. A consecutive series of patients at a particular hospital or rehabilitation program were approached and asked to participate in the study
> 2. Patients being treated at a particular hospital or rehabilitation program were approached and asked to participate in the study, however whether they were consecutively selected is not indicated
> 3. Patients were selected from the registry of another larger study/database
> 4. Patients were selected based on past treatment received (retrospective selection)

18. What was the study design? Choose the best possible selection.
> 1. Longitudinal
>> 1a. Prospective

1b. Retrospective
2. Cross Sectional

19. What was the total sample size of the study? Select the correct bracket.
1. <100 patients   2. 100-199 patients
3. 200-299 patients   4. 300-399 patients
5. 400-499 patients   6. >500 patients

20. What was the measure used to assess Type-D personality?
1. DS-14   2. DS-16
3. DS-24   4. Measure NA and SI separately and then
                                       Combined to classify as Type D (please
                                       specify which measures were used for NA
                                       and SI)

EFFECT SIZE LEVEL CODING MANUAL

1. Study ID Number

2. Effect Size Number

Dependent Measure Descriptors:

3. Effect size type. Not sure how this applies because there isn't really any interventions, they all seem to be post-tests but some have multiple post tests and some have only one so do we need to code for this and if so what options would we use?

4. What was the length of time of the study. For studies in which follow up varies, code for the mean time of follow-up.
1. 0 weeks   2. 1-4 weeks
3. 5-12 weeks   4. 13-24 weeks
5. 25-52 weeks   6. 53-156 weeks
7. 157-260 weeks   8. >260 weeks

5. What was the outcome construct that was measured? Select all sub-categories that apply.
1. Major Adverse Cardiac Event
         1a. Cardiac Death   1b. Myocardial Infarction
         1c. PCI   1d. CABG

2. Quality of Life Measurement
         2a. Health Complaints Scale
         2b. Global Mood Scale

2c. Short Form Health Survey SF-36
2d. Minnesota Living with Heart Failure Questionnaire
(MLWHFQ)
2e. World Health Organization Quality of Life Assessment
Instrument-100 (WHOQOL)
2f. Perceived Stress Scale-10
2g. Cantril Ladder of Life

3. Body Chemical Levels
3a. TNF-alpha   3b. sTNFR-1 and 2
3c. IL-6   3d. IL-10
3e. IL-1ra   3f. Cortisol

6. What was the type of data the effect size was based on?
1. Dichotomous frequencies and proportions
2. Means and standard deviations
3. Other (specify)

7. Specify the page number on which the effect size data was found

8. Was the outcome better or worse for the Type-D group? This should be only based on the numbers and not on the significance reported in the study
1. Better   2. Worse   3. No Difference

9. When dichotomous frequencies and proportions are reported:
9a. What is the Type-D sample size?
9b. What is the non Type-D sample size?
9c. How many total events, or what proportion of the group experienced an event occurred in the Type-D group? (when death is reported the event should only be counted if it is a cardiac death)
9d. How many total events, or what proportion the group experienced an event in the non Type-D group? (when death is reported the event should only be counted if it is a cardiac death)

10. When means and standard deviations are reported:
10a. What is the Type-D sample size?
10b. What is the non Type-D sample size?
10c. What was the mean for the Type-D group?
10d. What was the mean for the non Type-D group?
10e. What was the standard deviation for the Type-D group?
10f. What was the standard deviation for the non Type-D group?

11. If a test of significance was completed, was having Type-D personality found to be a significant predictor of a worse outcome? (If there is a case where there was significance for some measurements but not others select "1" and verify which outcomes were significant)

| 1. Yes | 2. No | 3. Significance testing not done |

12. In studies when significance testing was done a second time using multivariate logistic regression controlling for other variables/step-wise/logistic regression/MANCOVA, was having Type-D personality found to be a significant predictor of a worse outcome? (If there is a case where there was significance for some measurements but not others select "1" and verify which outcomes were significant)

| 1. Yes | 2. No | 3. Multivariate testing not done |

13. Report the effect size to two significant figures using a plus sign when there is a better outcome for the Type-D's and a minus sign when there is a worse outcome for the Type-D's.

14. What is the confidence rating in effect size computation?
1. Highly estimated (have N and crude p-value only, such as p<.1, and must reconstruct via rough t-test equivalence)
2. Moderate estimation (have complex but relatively complete statistics, such as multi factor ANOVA, as a basis for estimation)
3. Some estimation (have unconventional statistics and must convert to equivalent t-values or have conventional statistics but incomplete, such as exact p-level)
4. Slight estimation (must use significance testing statistics rather than descriptive statistics, but have complete statistics of conventional sort)
5. No estimation (have descriptive data such as means, standard deviations, frequencies, proportions, etc. and can calculate the effect size directly)

Appendix G.

Study-Level Coding Form for Type-D Meta-Analysis

Bibliographic Reference:
Source Descriptors

1. Study ID Number:
2. Publication Year:
3. Denollet, J or Pederson SS an author?

Sample Descriptors

4. Source of the sample:
5. Specific cardiac diagnosis or treatment:
6. Predominant Gender:
7. Mean age:
8. Proportion engaging in tobacco use:
9. Proportion with impaired LVEF:
10. Proportion with hyperlipidemia/hypercholesterolemia/dyslipidemia:
11. Proportion with hypertension:
12. Proportion with diabetes:
13. Proportion with renal impairment:
14. Proportion NYHA Class III or IV:
15. Proportion with Type-D personality:
16. Baseline characteristics for Type-D's and non Type-D's significantly
       different?

Research Design Descriptors:

17. How patients were selected:
18. Study design:
19. Total sample size:
20. Measure used to assess Type-D Personality:

Effect Size Level Coding Form for Type-D Meta-Analysis

1. Study ID number:
2. Effect size number:

Dependent Measure Descriptors

3. Effect size type:
4. Length of time of study:
5. Outcome construct measured:
6. Type of data the effect size was based on:

7. Page number on which effect size data was found:

8. Outcome better or worse for Type-D group:

9a. Type-D sample size:

9b. Non Type-D sample size:

9c. n(total events in Type-D group):

9d. n(total events in non Type-D group):

10a. Type-D sample size:

10b: Non Type-D sample size:

10c. Type-D group mean:

10d. Non Type-D group mean:

10e. Type-D group standard deviation:

10f. Non Type-D group standard deviation:

11. With significance testing was Type-D a significant predictor of worse outcome?

12. In controlled significance testing was Type-D a significant predictor of worse outcome?

13. Effect size to two significant figures with +/- signs:

14. Confidence rating in effect size computation:

Figure 1.
Exclusion of Studies
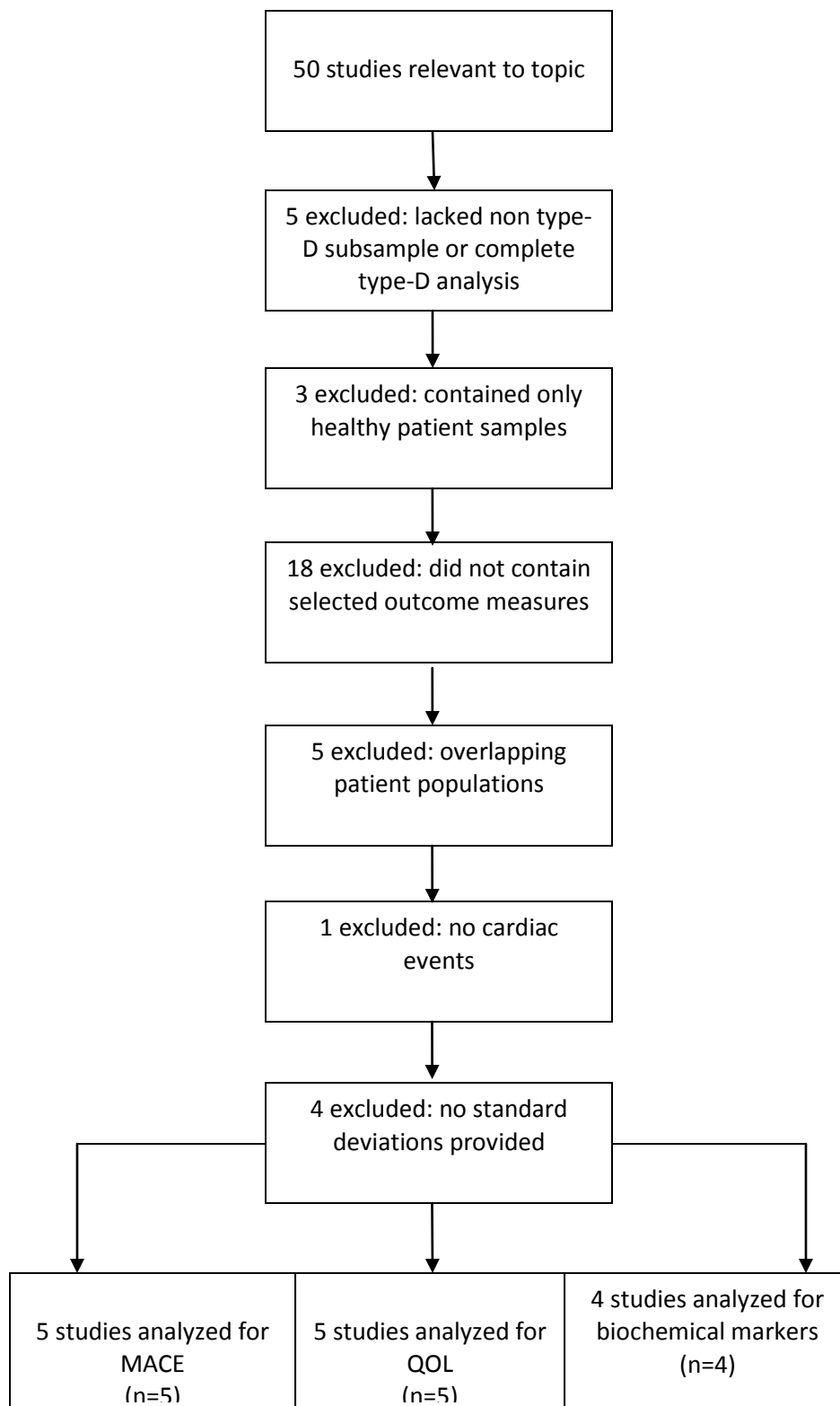
Capstone Project Summary

A meta-analysis is a research method which takes all of the studies done on a particular research topic and allows researchers to combine the results and to better examine the nature of the area of investigation. Results are reported in terms of a quantitative measure referred to as an effect size. This allows for an increased sample size which means a meta-analysis has greater statistical power than individual studies. A large quantity of primary research has been completed to examine whether there is a relationship between Type-D personality and negative outcomes for heart disease patients, but no meta-analysis has been completed in the area. The cardiovascular patient populations that have been studied are those diagnosed with chronic heart failure, coronary heart disease, peripheral artery disease or acute coronary syndrome, were attending cardiovascular rehabilitation, underwent coronary artery bypass grafting surgery or percutaneous coronary intervention (angioplasty), or experienced a myocardial infarction (heart attack). It is for that reason I chose to complete a meta-analysis on this topic for my Capstone Project.

A person who exhibits Type-D personality experiences a high level of negative emotions such as anger, sadness, and anxiety. In addition, they do not express their emotions and are extremely socially reserved for fear of rejection by others. Screening for Type-D personality is accomplished by a brief fourteen item psychometrically sound self-survey questionnaire called the DS-14. The DS-14 presents statements such as "I am often happy", "I am often in a bad mood", and "I often find myself worrying about something". Individuals completing the survey rank statements such as these on a scale of 0-5 indicating the truth of the statement as it pertains to them. This method of identification of Type-D personality has been shown to produce consistent results over

time which is important because Type-D is a stable construct that remains constant in individuals unlike depression, for example, which changes in severity and can disappear as time progresses.

The first step of this research was to conduct a literature search using PsycInfo and Pubmed as well as a backwards search through references of recent articles on the topic, called an ancestral search, in order to obtain all the research that had been completed to date on the topic. The most common theme among the articles was the examination of whether Type-D personality in cardiovascular patients was associated with: 1) higher incidences of major adverse cardiac events (MACE) which were described as cardiac death, myocardial infarctions, coronary artery bypass grafting surgery, or percutaneous coronary intervention (formerly referred to as an angioplasty), 2) poor quality of life, or 3) higher levels of disease promoting pro-inflammatory and lower levels of disease preventing anti-inflammatory cytokine levels. Separate analysis was conducted for each outcome.

A list of criteria was established for the inclusion or exclusion of each study to ensure that only studies done in a similar manner and with adequate data would be included in the analysis. This reduced the total number of studies to five for the MACE analysis, five for the quality of life analysis, and four for the biochemical markers analysis. All of the studies were then coded. This involved the development of a coding book detailing all of the variables within the study and options to classify each study with respect to each of their characteristics. This allows for direct comparison of the similarities and differences between the studies and helps identify sources of variation between the studies which could affect the results. In order to ensure this was done

correctly, each study was coded by both myself and another masters level individual trained using the coding manual.

Once all of the data were coded, they were passed to Dr. Glen Spielmans who is a meta-analytic expert at Metropolitan State University in Minnesota. He calculated effect sizes for each individual study and overall effect sizes for all related studies. He also conducted significance testing and tests to determine the degree of variability between studies. If studies are found to be heterogeneous, meaning there is more variability between the individual studies than is due to sampling error alone, moderators within the studies need to be identified as possible sources of that variation.

The results indicated that cardiovascular patients with Type-D personality had more than three times greater odds of experiencing a major adverse cardiac event following diagnosis then non Type-D patients. The quality of life analysis was divided into two separate effect sizes depending on whether the individual studies reported quality of life with dichotomous data (does the patient have a poor quality of life or not) or continuous data (to what degree is the patients' quality of life impaired). The effect size using dichotomous data was significant indicating that Type-D patients had more than three times greater odds of experiencing an impaired quality of life than non Type-D patients. The effect size calculated using continuous data came extremely close to being significant. The sample size for the calculation was small because four studies had to be excluded due to omissions in their reported data. It is hypothesized that had these studies been included and the sample size been larger, the relationship between Type-D personality and quality of life may have reached significance for the continuous data as well.

There were multiple effect sizes calculated in the biochemical markers analysis in order to observe the relationship between Type-D personality and levels of individual chemicals as well as combinations of chemicals. IL-6 and TNF-α are pro-inflammatory cytokines. When pro-inflammatory cytokines are elevated for sustained periods of time they have a disease promoting effect. High sustained levels of TNF-α cause the release of its soluble receptors, sTNFR-1 and sTNFR-2, into blood plasma. Consequently, these are more accurate indicators of sustained elevated TNF-α levels than the presence of TNF-α plasma levels alone. Elevated levels of these pro-inflammatory cytokines have been demonstrated to predict mortality among cardiovascular patients. The results show that Type-D patients are more likely than non Type-D patients to have elevated levels of IL-6, sTNFR-1, and sTNFR-2. There were no differences found between the patient groups with respect to TNF-α levels. However, when analysis was completed using combined levels of TNF-α, sTNFR-1, and sTNFR-2 the elevation of these levels in Type-D patients compared to non Type-D patients was nearly found to be significant. Combination of the levels of all the pro-inflammatory chemicals was also nearly found to be significantly higher in Type-D individuals.

IL-10 and IL-1ra are anti-inflammatory cytokines which have inhibitory effects on the pro-inflammatory cytokines in order to regulate the inflammatory process and prevent the excess inflammation that leads to disease. Significance was not reached, but there was a trend towards lower levels of these chemicals in Type-D versus non Type-D patients. Cortisol is a chemical with both inflammatory and anti-inflammatory properties. Chronically elevated cortisol levels promote disease progression as well as abdominal obesity which has been linked to high cholesterol and atherosclerosis. No

differences were found among cortisol levels between the Type-D and non Type-D

patient groups.

All of the biochemical marker analyses had small sample sizes as this is a

relatively new direction of research. Many of the obtained effect sizes bordered on, but

did not reach, significance. With such small sample sizes this suggests that there may

still be a relationship between levels of these chemicals and Type-D personality. Further

research in this area is needed to establish a definite relationship.

Variability between studies which was greater than that due to sampling error

alone was also found in the quality of life analysis using continuous data as well as many

of the biochemical analysis data. Because of this, differences between the studies that

could possibly affect the data needed to be considered. Quality of life was assessed with

a different measurement instrument in each of the quality of life studies that presented

their data in a continuous form. Though the aim of each of these tools was to assess

quality of life, they all did so in a different way. One was specific to the effect of chronic

heart failure on quality of life while the other two could be generalized to all patient

groups. One was very simple, basically a rating of how your current life compares to you

ideal life, while the other two assessed extremely detailed dimensions of quality of life

with specific questions. If the same quality of life measure had been used in all three

studies it is possible that there would be less variability between the studies. Also,

though each study used a patient population falling under the umbrella of

cardiovascular disease, each patient population differed in their specific diagnosis. One

study used patients generally in cardiac rehabilitation, one used myocardial infarction or

coronary artery bypass grafting surgery patients and the last used peripheral artery

disease patients. This could also account for variability between studies. Possible

sources for variation between studies in the biochemical marker analysis were differences in average patient age and the inclusion of fourteen kidney dysfunction patients within the Type-D group in one study. Both advancing age and kidney dysfunction have been found to be sources of elevated levels of pro-inflammatory cytokines.

The findings of this meta-analysis have some important implications. Not only was Type-D personality found to be a powerful predictor of major adverse cardiac events and poor quality of life in cardiovascular patients, but it is also strongly suggested that it has links to disease promoting biochemicals that have been found to predict mortality in this patient population. All of the primary research was conducted in a small number of countries in Europe, primarily the Netherlands, by a concentrated group of researchers. This study urges for a broader body of research to be completed in order to draw more definite conclusions and allow for the results to be generalized to a more expansive demographic.

The study also calls attention to the need for Type-D screening to be completed on cardiovascular patients as this is a very high risk patient group, and the prevalence of Type-D personality has been found to be about 20-39% in patient samples. It also suggests that research be conducted to examine possible treatments to improve the prognosis for Type-D individuals. Some suggested treatments are pharmacological with anti-depressants to decrease the intensity of negative emotions, exercise, cognitive behavioral therapy, social skills training and coping mechanisms. All of these treatments aim to decrease emotional distress and increase social support. A definite association has been established between Type-D personality and poor prognosis in this meta-analysis. This research should further call attention to the need for additional and

specialized treatment to improve the survival of Type-D patients and, hopefully, in the

future will result in changes in the clinical environment to facilitate this high-risk patient

groups' survival rates.

Table 1

Study Information Chart

Study	Sample	Type-D Measurement	Construct Measured	Effect Size
Denollet et al., 2000	319 patients at Antewerp Cardiac Rehabilitation Center eligible if had myocardial infarction, coronary artery bypass grafting surgery, or percutaneous coronary intervention within 2 months of entering program (Jan. 1989-Dec 1992)	DS-16	MACE: Cardiac Death, Myocardial Infarction, Coronary Artery Bypass Grafting Surgery, Percutaneous Coronary Intervention	*OR* = 4.14
Pederson et al., 2004	875 patients treated with percutaneous coronary intervention as part of	DS-14	MACE: Cardiac Death, Myocardial Infarction	*OR* = 4.47
Schiffer et al., 2009	232 chronic heart failure outpatients From cardiology unit of Tweesteden teaching hospital	DS-14	MACE: Cardiac Death	*OR* = 2.16
Denollet et al., 2006	337 chronic heart disease patients participating in Antewerp Cardiac Rehabilitation Center (Jan. 1993-Dec. 1997)	DS-16	MACE: Cardiac Death, Myocardial Infarction, Coronary Artery Bypass Grafting Surgery, Percutaneous Coronary Intervention	*OR* = 2.88
Denollet et al., 1996	303 chronic heart disease patients participatingin Antewerp Cardiac Rehabilitation Center (Jan 1985-Dec 1988)	State Trait Anxiety Inventory (negative affectivity measure) Social Inhibition Scale of the Heart Patients Psychological Questionnaire (social inhibition measure)	MACE: Cardiac Death	*OR* = 4.98

Al-Ruzzeh et al., 2005	437 coronary artery bypass grafting surgery patients who came in for annual follow-up at Harefield Hospital	DS-14	QOL: SF-36	*OR* =3.63
Pelle et al., 2008	368 patients referred to Rotterdam Organization for Cardiac Rehabilitation	DS-14	QOL: SF-36	*d* = -.62
Schiffer et al., 2005	84 systolic heart failure patients visiting heart failure outpatient clinic at Tweesteden teaching hospital	DS-14	QOL: Health Complaints Scale, MLWHFQ	*OR* = 2.86
Karlsson et al., 2007	224 acute myocardial infarction or coronary artery bypass grafting surgery patients from Danderyd Hospital	DS-14	QOL: Cantril Ladder of Life	*d* = -2.2
Aquarius et al., 2007	150 peripheral artery disease patients from outpatient clinic at St. Elisabeth Hospital	DS-14	QOL: WHOQOL	*d* = -.88
Denollet et al., 2008	130 chronic heart failure patients from outpatient heart failure clinic at University Hospital of Antewerp	DS-14	Biochemical Markers: TNF-α, sTNFR-1, sTNFR-2, IL-6	*d* = -2.70
Denollet et al., 2009	165 chronic heart failure outpatients from Tweesteden teaching hospital	DS-14	Biochemical Markers: TNF-α, sTNRF-1, sTNFR-2, IL-6, IL-10, IL-1ra	*d* = -.51
Conraads et al., 2006	91 chronic heart failure patients from outpatient clinic of University Department of Cardiology	DS-14	Biochemical Markers: TNF-α, sTNRF-1, sTNRF-2, IL-6	*d* = -.57

Whitehead et al., 2007	72 acute coronary syndrome patients recruited from four London hospitals	DS-16	Biochemical Markers: Cortisol	d=-.24

*MACE: Major Adverse Cardiac Event

Table 2

Summary of Statistical Data for Individual Analyses

Construct	k	n(Type-D)	n(non Type-D	OR	CI	d	Z	p(ES)	Q	p(Q)	I^2
MACE[a]	5	584	1482	3.42	2.48-4.73			<.001	3.27	.51	0%
QOL (Dichotomous Data)	2	188	333	3.48	2.37-5.11			<.001	.21	.65	0%
QOL (Continuous Data)	3	98	270			-1.23	2.61	.01	51.88	<.001	96.15%
IL-6	3	105	200			-.26	2.17	.03	.04	.98	0%
TNF-α	3	105	200			-1.07	1.38	.17	67.07	<.001	97.02%
sTNFR-1 + sTNFR-2	3	105	200			-1.84	1.97	.05	81.97	<.001	97.56%
TNF-α, sTNFR-1 + sTNFR-2	3	105	200			-1.58	1.80	.07	76.30	<.001	97.39%
IL-6 , TNF-α, sTNFR-1 + sTNFR-2	3	105	200			-1.10	1.84	.07	48.37	<.001	95.87%
IL-10 + IL-1ra	1	32	52			-.42	1.86	.06			
Cortisol	1	23	43			-.24	.93	.35			

[a]MACE- Major Adverse Cardiac Event (Cardiac Death, MI, CABG, or PCI)

Table 3

Summary of Moderator Analysis Data

Included Studies	Excluded Study	Moderators Tested For	d	Z	P(ES)	Q	P(Q)	I²
QOL: Aquarius et al., 2007 + Karlsson et al., 2007	Pelle et al., 2008	Longitudinal design Patients underwent cardiac rehabilitation	-1.54	2.34	.019	26.01	<.001	96.16%
QOL: Aquarius et al., 2007 + Pelle et al., 2008	Karlsson et al., 2007	Different group of researchers Simplistic and generalized QOL measurement	-.50	1.33	.18	12.24	<.001	91.83%
QOL: Karlsson et al., 2007 + Pelle et al., 2008	Aquarius et al., 2007	Larger proportion of smokers Smaller sample size	-1.16	1.13	.26	87.69	<.001	98.86%
Pro-inflammatory Cytokines: Conraads et al., 2006 + Denollet et al., 2008	Denollet et al., 2009	Higher proportion of patients NYHA III/IV Longitudinal design Greater mean age Fourteen Type-D patients with kidney dysfunction	-1.63	1.53	.13	37.28	<.001	97.32%

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Appendix E

WHOQOL-BREF

About You

Before you begin we would like to ask you to answer a few general questions about yourself by circling the correct answer or by filling in the space provided.

1. What is your gender   Male   Female

2. What is your date of birth?   _____ / _____ / _____
                                      Day   Month   Year

3. What is the highest education you received?

    None at all

    Elementary School
    High School
    College

4. What is your marital status?

Single	Separated
Married	Divorced
Living as Married	Widowed

5. Are you currently ill?   Yes   No

6. If something is wrong with your health, what do you think it is?   illness/problem

    _____

Instructions

This questionnaire asks how you feel about your quality of life, health, or other areas of your life. Please answer all the questions. If you are unsure about which response to give to a question, please choose the one that appears most appropriate. This can often be your first response.

Please keep in mind your standards, hopes, pleasures and concerns. We ask that you think about your life in the last two weeks. For example, thinking about the last two weeks, a question might ask:

	(Please circle the number)				
For office use	Not at all	A little	Moderately	Mostly	Completely
Do you get the kind of support from others that you need?	1	2	3	4	5

You should circle the number that best fits how much support you got from others over the last two weeks. So you would circle the number 4 if you got a great deal of support from others. o

	(Please circle the number)				
For office use	Not at all	A little	Moderately	Mostly	Completely
Do you get the kind of support from others that you need?	1	2	3	④	5

You would circle number 1 if you did not get any of the support that you needed from others in the last two weeks. o

	(Please circle the number)				
For office use	Not at all	A little	Moderately	Mostly	Completely
Do you get the kind of support from others that you need?	①	2	3	4	5

Please read each question, assess your feelings, and circle the number on the scale that gives the best answer for you for each question.

For office use		(Please circle the number)				
		Very poor	Poor	Neither poor nor good	Good	Very Good
G1 / G1.1	1. How would you rate your quality of life?	1	2	3	4	5

For office use		(Please circle the number)				
		Very dissatisfied	Dissatisfied	Neither satisfied nor dissatisfied	Satisfied	Very satisfied
G4 / G2.3	2. How satisfied are you with your health?	1	2	3	4	5

The following questions ask about **how much** you have experienced certain things in the last two weeks.

For office use		(Please circle the number)				
		Not at all	A little	A moderate amount	Very much	An extreme amount
F1.4 / F1.2.5	3. To what extent do you feel that physical pain prevents you from doing what you need to do?	1	2	3	4	5
F11.3 / F13.1.4	4. How much do you need any medical treatment to function in your daily life?	1	2	3	4	5
F4.1 / F6.1.2	5. How much do you enjoy life?	1	2	3	4	5

	(Please circle the number)				
For office use	Not at all	A little	A moderate amount	Very much	An extreme amount
F24.2 / F29.1.3 6. To what extent do you feel your life to be meaningful?	1	2	3	4	5

	(Please circle the number)				
For office use	Not at all	Slightly	A Moderate amount	Very much	Extremely
F5.2 / F7.1.6 7. How well are you able to concentrate?	1	2	3	4	5
F16.1 / F20.1.2 8. How safe do you feel in your daily life?	1	2	3	4	5
F22.1 / F27.1.2 9. How healthy is your physical environment?	1	2	3	4	5

The following questions ask about **how completely** you experience or were able to do certain things in the last two weeks.

	(Please circle the number)				
For office use	Not at all	A little	Moderately	Mostly	Completely
F2.1 / F2.1.1 10. Do you have enough energy for everyday life?	1	2	3	4	5
F7.1 / F9.1.2 11. Are you able to accept your bodily appearance?	1	2	3	4	5
F18.1 / F23.1.1 12. Have you enough money to meet your needs?	1	2	3	4	5

	(Please circle the number)				
For office use	Not at all	A little	Moderately	Mostly	Completely
F20.1 / F25.1.1 13. How available to you is the information that you need in your day-to-day life?	1	2	3	4	5
F21.1 / F26.1.2 14. To what extent do you have the opportunity for leisure activities?	1	2	3	4	5

	(Please circle the number)				
For office use	Very poor	Poor	Neither poor nor well	Well	Very well
F9.1 / F11.1.1 15. How well are you able to get around?	1	2	3	4	5

The following questions ask you to say how **good** or **satisfied** you have felt about various aspects of your life over the last two weeks.

	(Please circle the number)				
For office use	Very dissatisfied	Dissatisfied	Neither satisfied nor dissatisfied	Satisfied	Very satisfied
F3.3 / F4.2.2 16. How satisfied are you with your sleep?	1	2	3	4	5
F10.3 / F12.2.3 17. How satisfied are you with your ability to perform your daily living activities?	1	2	3	4	5
F12.4 / F16.2.1 18. How satisfied are you with your capacity for work?	1	2	3	4	5

			(Please circle the number)			
For office use			Very dissatisfied	Dissatisfied	Neither satisfied nor dissatisfied	Satisfied	Very satisfied
F6.4 / F8.2.2	19.	How satisfied are you with your abilities?	1	2	3	4	5
F13.3 / F17.2.3	20.	How satisfied are you with your personal relationships?	1	2	3	4	5
F15.3 / F3.2.1	21.	How satisfied are you with your sex life?	1	2	3	4	5
F14.4 / F18.2.5	22.	How satisfied are you with the support you get from your friends?	1	2	3	4	5
F17.3 / F21.2.2	23.	How satisfied are you with the conditions of your living place?	1	2	3	4	5
F19.3 / F24.2.1	24.	How satisfied are you with your access to health services?	1	2	3	4	5
F.23.3 / F28.2.2	25.	How satisfied are you with your mode of transportation?	1	2	3	4	5

The follow question refers to **how often** you have felt or experienced certain things in the last two weeks.

			(Please circle the number)		
	Never	Seldom	Quite often	Very often	Always

For office use

F8.1 / F10.1.2

26. How often do you have negative feelings, such as blue mood, despair, anxiety, depression?

	Never	Seldom	Quite often	Very often	Always
	1	**2**	**3**	**4**	**5**

Did someone help you to fill out this form? *(Please circle Yes or No)*　　　　Yes　　　　　　　No

How long did it take to fill out this form?　　　　　　　　　　_____

THANK YOU FOR YOUR HELP