New perspectives on depression and heart disease

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Petra W. Hoen

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Stellingen behorende bij het proefschrift:

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1. Dit proefschrift laat zien dat somatische depressieve symptomen (zoals vermoeidheid en slaapproblemen) sterker voorspellend zijn voor nieuwe hartproblemen en overlijden in patiënten met coronaire hartziekte dan cognitieve depressieve symptomen (zoals schuldgevoelens en concentratieproblemen) (dit proefschrift)

2. Een effectieve behandeling voor somatische depressieve symptomen zou de prognose in hartpatiënten kunnen verbeteren (dit proefschrift)

3. Depressie is geassocieerd met een kortere telomeerlengte in patiënten met coronaire hartziekte (dit proefschrift)

4. Op populatieniveau neemt de telomeerlengte geleidelijk af over de tijd, echter, op individueel niveau kan de telomeerlengte ook toenemen (dit proefschrift)

5. Telomeerlengte lijkt geen verklarend mechanisme voor de associatie tussen depressie en een slechtere hartprognose. Het zou wel een verklarend mechanisme kunnen zijn voor de associatie tussen angst en een slechtere hartprognose (dit proefschrift)

6. Bij het doen van onderzoek naar de relatie tussen lichaam en geest is het in de toekomst belangrijk om ons niet alleen op negatieve, maar ook op positieve emoties te richten (dit proefschrift)

7. Het gunstige effect van positieve emoties op overleving zou bewerkstelligd kunnen worden door gedragsinterventies die ook fysieke training bevorderen (dit proefschrift)

8. Myocardinfarct: het blijft niet alleen bij een ST depressie

9. Ik hou niet van losse eindjes (Elisabeth Blackburn)

10. A cheerful heart is good medicine (Proverbs 17.22)

11. Je moet voor jezelf de lat zo hoog mogelijk leggen, dan kun je er makkelijker onder door

12. It is human nature to seek simple solutions in the face of hard problems (O'Malley, Arch Intern Med 2012)

Petra Hoen

Groningen, 12 september 2012

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New perspectives on depression and heart disease

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Chapter 1

General introduction

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GENERAL INTRODUCTION

Background

Depression and coronary heart disease (CHD) are the two strongest contributors to the global burden of disease.[1] Both disorders are common, and while cardiovascular disease is an important factor directly contributing to mortality, depression is primarily associated with decreased health-related quality of life,[2] and imposes a significant economic burden on society.[3] However, there are also signs that depression may contribute to higher mortality rates, perhaps due to its association with somatic disease, and in particular coronary heart disease.

The term depression can refer both to the presence of depressive symptoms, including low mood and fatigue, and to the presence of depressive disorder, referring to a psychiatric diagnosis. Among the mood disorders defined in the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV), major depressive disorder (MDD) is the most important single disorder in terms of prevalence and severity. MDD is characterized by one or more episodes of depressed mood and loss of interest and is defined in DSM-IV as follows (Box 1).

Category 1
• Depressed mood
• Lack of interest
Category 2
• Change in appetite or weight
• Insomnia or hypersomnia
• Psychomotor agitation or retardation
• Fatigue or loss of energy
• Feelings of worthlessness and guilt
• Concentration problems
• Suicidal ideation

***Box 1**. Diagnostic criteria DSM-IV.*

To be diagnosed with MDD, individuals have to experience at least one of the symptoms from Category 1 and at least three or more symptoms from Category 2, for a total of at least 5 out of 9 symptoms. These symptoms must be present for most of the day, nearly every day, for at least two weeks. MDD is thus operationalized as a syndrome, of which the appearance may vary among individuals.

Depression and cardiovascular disease

Patients with cardiovascular disease have a high risk of developing depression.[4] Approximately one out of five patients is affected by depression following CHD,[5-7] which contrasts with the prevalence of MDD of approximately 7% in the US general population over the last 12 months.[8] Since Carney et al.[9] identified MDD as a risk factor for cardiac events in patients with stable coronary heart disease and Frasure-Smith et al.[10] showed an increased risk of mortality in post-myocardial infarction (MI) depressive patients, the association between clinical depression and CHD raised much attention. Currently, a large body of literature has confirmed that healthy patients with MDD are at risk of developing incident CHD[11, 12] and that depressive patients with established heart disease have an increased risk of suffering adverse cardiovascular outcomes.[13, 14] Specifically, this second line of research has developed exponentially and its results have by now been summarized in several systematic reviews and meta-analyses (Table 1).[6, 13-16]

Table 1. Depression and coronary heart disease: meta-analyses

	Publication year	Number of studies	Patients	Outcomes	Result
Van Melle et al.[14]	2004	22 prospective studies of 16 different cohorts	6,367 MI patients	All-cause mortality, cardiovascular mortality, cardiovascular events	All-cause mortality: OR 2.38 cardiovascular mortality: OR 2.59 cardiovascular events: OR 1.95
Barth et al.[13]	2004	29 prospective studies of 20 different cohorts	11,018 CHD patients	All-cause mortality, cardiovascular mortality	Mortality: OR 2.24 (short term, unadjusted) and OR 1.76 (long term, adjusted)
Nicholson et al.[15]	2006	21 aetiological studies and 34 prognostic studies	146,538 CHD patients	Aetiological: Fatal CHD and incident MI. Prognostic: Fatal CHD and all-cause mortality	Aetiological: future CHD OR 1.81. Prognostic: OR 1.80. Adjusting for LVEF: OR from 2.18 to 1.53
Rutledge et al.[6]	2006	36 studies	149,847 CHD patients	Mortality, hospitalization, clinical events, health care costs, health care use	Mortality and secondary events: RR 2.1
Meijer et al.[16]	2011	31 prospective studies of 29 cohorts	16,889 MI patients	All-cause mortality, cardiovascular mortality, cardiovascular events	All-cause mortality: OR 2.25 cardiovascular mortality: OR 2.71 cardiovascular events: OR 1.59

CHD = coronary heart disease; LVEF = left ventricular ejection fraction; MI = myocardial infarction.

From these meta-analyses, a consistent picture emerges in which depression is a risk factor for cardiac disease progression. The association between post-MI depression and prognosis was not influenced by the way depression was assessed (i.e. depressive symptoms vs. depressive disorder).[14] Although the first studies on the association between post-MI depression and cardiac prognosis may have been too optimistic, suggesting increased odds of 6-11.[10, 17] More recent studies tend to report lower odds ratios for mortality attributed to depression,[18] while a minority of studies even failed to confirm an impact of post-MI depression on cardiac prognosis.[19, 20]

Confounding by cardiac disease severity and overlap between psychosocial factors

Despite the growth and relative consistency of results in this area of research, debates on the interpretation of findings have continued,[21-23] focusing on the extent to which the association can be interpreted as causal.[14, 15, 24, 25] Two issues are central in this discussion: confounding by disease severity and overlap between psychosocial factors.

There is substantial disagreement on the possible confounding of the apparent cardiotoxic effects of depression by MI severity and its consequences.[21, 22, 26] As a first sign of potential confounding, the previous observation that MDD is present in 20-25% of post-MI patients, while the prevalence of depression over the past 12 months in the general population is only 7%, should be kept in mind. However, this could also be due to the fact that MI, for many individuals, can be a significant psychological stressor and trigger depression in persons already at increased risk.[27]

Evidence for the possibility of confounding can be seen in the association between left ventricular ejection fraction (LVEF) and post-MI depression. LVEF is an important determinant of cardiac disease severity in the post-MI setting, and reflects the adequacy of pump function of the heart. In a sample of about 2,000 MI patients, Van Melle et al. observed a dose-response like association between LVEF at the time of MI and subsequent risk of depression during the post-MI year.[26] The authors also summarized the existing studies on this association, and found significantly higher proportions of depression in MI patients with more LVEF dysfunction, although some heterogeneity in findings was observed (Table 2).[21, 22] Confounding may also occur by complaints attributable to the MI, such as pain or physical limitations, or by somatic co-morbidities such as heart failure, diabetes or arthritis.[28] For instance, Watkins et al. showed that in post-MI patients the Beck Depression Inventory (BDI) score was correlated with the Charlson co-morbidity index, in which the number of somatic diseases is counted. Also, the underlying process that has led to the occurrence of the MI, atherosclerosis, may be related directly to the occurrence of depression.

An association between disease severity factors and depression does not automatically imply that the association between depression and cardiac prognosis is confounded. Confounding implies that, when cardiac disease severity is added to a prediction model for cardiac prognosis, the association between depression and prognosis is attenuated.[21] Several of the prognostic studies included have therefore added such an analysis. In their meta-analysis, Van Melle et al. found that, of the five studies that adjusted for LVEF, the association between depression and prognosis was substantially attenuated in one study while in two of the studies, the odds ratios were not even significant anymore. Nicholson and colleagues even concluded that almost half of the variance in the association was explained away when LVEF was added to the prediction models.[15] Thus, LVEF appears to be an important source of possible confounding.[33]

Table 2. Studies presenting the prevalence of depression in post-MI patients according to LVEF (Van Melle et al., Eur Heart J 2005, 26 (24(2650-6))

First author	Sample size (*n*)	LVEF cut-off value (%)	Prevalence of depression (%)		
			Below cut-off	Above cut-off	*P*-value
Frasure-Smith[17]	222	35	35	29	0.43
Frasure-Smith[29]	896	35	39	30	0.03
Bush[30]	285[a]	35	34	19	0.07
Strik[31]	318[b]	50	48	47	0.90
Strik[32]	206[c]	50	39	26	0.06[d]
Carney[21]	766[e]	40	49	46	0.58[d]
Total	2,693	35-50	42	35	<0.01

LVEF = left ventricular ejection fraction.
[a]MI patients ≥65 years
[b]Male patients with first MI
[c]Patients with first MI
[d]Computed from data as presented in article (χ^2 test)
[e]Controls free of depression and social isolation

A second factor that needs to be discussed is the presence of competing psychosocial factors, since observed associations between depression and cardiac prognosis may be related to other psychosocial factor(s) also related to, or underlying, depression.[34] Researchers have tended to evaluate the effects of putative psychological risk factors for physical disease by analyzing or measuring only a single psychological construct at a time.[34] However, the increased risk of cardiac events may extend to patients with symptoms of negative affect other than depression. In the field of psychological and cardiological research, several candidates of such psychosocial risk factors have been investigated, although rarely simultaneously.[35]

Mechanisms underlying the association

Several physiological as well as behavioral mechanisms have been proposed to explain how depression may lead to cardiac events (Table 3).[36-39] Plausible biological candidates include dysregulation of the autonomic nervous system, the hypothalamic-pituitary-adrenocortical axis, increased platelet activity, and alterations in immune functioning and inflammation. Besides biological mechanisms, several behavioral mechanisms have been proposed as well, though remarkably fewer studies evaluated these pathways than the physiological ones.[40] Poor adherence to medication regimens is a common problem and can cause substantial worsening of the disease and its prognosis.[41] Roughly, 50% of patients with chronic conditions are not compliant with their treatment regimen. Adherence rates to medication are higher in short-term treatment regimens in comparison with the longer medication usage in chronic conditions,[42] and post-MI patients are usually put on long-term medication regimens. Thereby, it has been found that depressed patients are less adherent to medication treatment than non-depressed patients.[43] Given that poor adherence is a risk factor for poor cardiac outcome,[44] and the association between depression and poor adherence, poor adherence may be a possible behavioral mediator. Lifestyle modification is an important means of secondary prevention in patients with established CHD, and the two most important examples include smoking cessation and promoting physical exercise. Smoking is an independent major risk factor for CHD,[45] and patients who continue to smoke have an increased mortality risk and poorer cardiovascular prognosis.[46] Patients with mental health problems smoke more, are more often nicotine-dependent and suffer from greater morbidity and mortality from smoking-related illnesses than the general population.[47]

Table 3. Mechanisms through which depression may lead to cardiac events

Biological mechanisms	Behavioral mechanisms
Lower heart rate variability reflecting altered cardiac autonomic tone[50]	Cigarette smoking and hypertension[51, 52]
Inflammatory processes[53]	Nonadherence to cardiac prevention and treatment regimens[54]
Increased platelet aggregation[55]	Dietary factors[54]
Enhanced activity of the hypothalamic pituitary axis[56]	Lack of exercise[57]
Increased whole blood serotonin[58]	Poor social support[59]
Lower omega-3 fatty acid levels[60]	
Antidepressant cardiotoxicity[61]	
Increased catecholamine levels[62]	

Thus, smoking or failure to quit smoking can be a possible explanation for the poorer cardiovascular prognosis in depressed post-MI patients.[48] Lifestyle modification may also involve increasing one's amount of exercise. In a study focused on the association between

health behavior, depressive symptoms, and new cardiovascular events, it was concluded that the association between depressive symptoms and adverse cardiovascular events was largely explained by lack of physical activity.[49] Overall, the extent to which these proposed biological and behavioral mechanisms explain the increased risk of cardiovascular events in depressed patients is unknown.

Treatment

The treatment of depression in CHD patients has drawn a lot of attention, especially because it has the potential to evaluate the extent to which the association between depression and cardiovascular prognosis is causal. In the general population, the most popular forms of treatment are psychotherapy, antidepressant drugs and combinations of the two. A large body of evidence has demonstrated that both forms of treatment are moderately effective in terms of reducing depressive symptomatology, although recently it has been argued that the efficacy of antidepressive drugs has been over-estimated due to publication bias.[63, 64]

Despite the prevalence of depression and its association with negative cardiac prognosis, only a limited number of pharmacological and behavioral randomized controlled trials has been performed in CHD patients with co-morbid depressive disorder. Overall, treating depressive patients has served three goals: studying the safety of antidepressive treatments, evaluating the effects on depression per se (as well as quality of life), and studying the effects of depression treatment on cardiovascular outcomes.

First of all, it is important to know whether treatment is safe. The Sertraline Heart Attack Randomized Trial (SADHART) was designed as a safety trial, and is, to date, the largest RCT evaluating antidepressant medication use for depressed patients with unstable ischemic heart disease (N=369).[65] The primary safety outcome measure was change from baseline in left ventricular ejection fraction. The authors reported that sertraline is a "safe" treatment for depression in patients with recent MI or unstable angina and without other life-threatening medical conditions. Second, the Canadian Cardiac Randomized Evaluation of Antidepressant and Psychotherapy Efficacy Trial (CREATE) evaluated whether depression treatment improved depression scores in CHD patients. CREATE compared citalopram to placebo, and compared short-term interpersonal psychotherapy combined with clinical management to clinical management alone in patients with coronary artery disease (N=284).[66] The authors reported a statistically significant effect of citalopram in comparison with placebo in depressed CHD patients. There was no demonstrable benefit of psychotherapeutic intervention over clinical management alone.

The MIND-IT study was designed to evaluate whether antidepressive treatment for post MI depression improves long term depression status and cardiovascular prognosis.[67, 68]

The MIND-IT study was an effectiveness study rather than an efficacy study, and compared the effects of an active treatment strategy with usual care. In this multicenter randomized clinical trial, patients with a post-MI depressive episode were randomized to intervention (i.e. antidepressive treatment; N=209) or care as usual (CAU; N=122). First-choice treatment consisted of placebo-controlled treatment with mirtazapine. In case of refusal or nonresponse, alternative open treatment with citolapram was offered. In the CAU arm the patient was not informed about the research diagnosis. Psychiatric treatment outside the study was recorded, but no treatment was offered. Both arms were followed for endpoints. Cardiac events included cardiac death or hospital admission for documented non-fatal myocardial infarction, myocardial infarction, coronary revascularisation, heart failure or ventricular tachycardia. Forty-two cardiac events occurred in the time between randomisation and 18 months post myocardial infarction. Antidepressive treatment was significantly more effective than placebo after 8 weeks of treatment,[67] but no differences in depression status or cardiac event rates were found between patients in the intervention arm of the study and the care-as-usual arm at 18 months post-infarction.[68] However, the study was not well powered to evaluate treatment effects on coronary events.

The Enhancing Recovery in Coronary Heart Disease (ENRICHD) determined whether treating depression would alter CHD outcomes. ENRICHD was a randomized trial comparing cognitive behavioral therapy (CBT), plus sertraline in case of insufficient response, with usual care following MI (N= 2481).[69] Overall, this study found that CBT improved depression, although only modestly. However, this study was unable to demonstrate that CBT, in comparison to usual care, reduced the composite endpoint of all-cause mortality and non-fatal-MI over two years.

Some researchers have suggested cardiac benefits for patients receiving antidepressive treatment in secondary analyses. In the ENRICHD trial it was found that the prescription of serotonin reuptake inhibitors was associated with 40% reductions in both recurrent MI and death.[70] In addition, several studies suggest that unsuccessful treatment of depression identifies a subgroup of patients with high cardiac risk, and that response to antidepressive treatment is associated with less subsequent cardiac events.[71, 72] However, both of these findings must be interpreted with caution as they do not represent randomized comparisons.

A recent systematic review evaluated the effect of depression treatment on depressive symptoms and cardiac outcome. Overall, the authors found that depression treatment in CHD patients had only minor effects in terms of reducing depressive symptoms (effect size: 0.20-0.38; r^2: 1%-4%), and that these effects did not lead to enhanced survival.[73]

Unresolved issues

Despite a growing body of literature, many questions about the association between depression and CHD remain unanswered. Because randomized comparisons have found that depression treatment does not affect cardiac prognosis (albeit with reservations about statistical inadequacies), it may be reasonable to assume that depression does not have a causal effect on cardiac events. However, depression is a heterogeneous condition, and it is possible that some types are 'cardiotoxic' while others are not, and some types may respond to treatment while others do not, which relates to the first unresolved issue.

(1) Research still needs to identify cardiac patients who are at the highest risk for adverse cardiac outcome due to the existence of several subtypes of depression. Recently, several studies have reported interesting subgroup analyses and re-analyses of existing epidemiologic studies and clinical trials. The first observation concerns reports that there are prognostic differences between various depressive symptoms and/or symptom clusters. There seems to be a relevant distinction between somatic and cognitive depressive symptoms. Evidence indicates that self-reported somatic/affective, but not cognitive/affective symptoms of depression are highly prevalent in cardiac patients.[74] Furthermore, these symptoms are predictive of cardiovascular mortality and cardiac events, even after somatic health status has been controlled for.[75] The second observation concerns reports that the increased cardiac risk in post–MI depression appears to be restricted to first-ever (incident) depressions in individuals who have not had depression before, however, this evidence is inconsistent.[76-81] Third, the role of depression severity has been considered.[48, 81] Fourth and most recently, the importance of depression persistence and treatment resistance has been evaluated with regard to prediction of cardiac events.[81-83] So far, there is no consensus on which of these distinctions is clinically relevant, but additional research is needed. The identification of certain cardiotoxic aspects of depression could be an important step in the development of interventions. In this context, the distinction between somatic and cognitive depressive symptoms seems to be important as this distinction may contribute to finding an intervention to alleviate the depression-associated risk of cardiovascular events.

(2) The second unresolved issue concerns the fact that the mechanisms underlying the depression-CHD relationship are still poorly understood. More research is necessary to further explore the biological and behavioral pathways. In addition, it is important to broaden our scope and to identify other pathways by which depression may influence adverse outcomes in CHD patients. Recently, cellular aging (measured by telomere length) has been proposed as a new possible mechanism that may underlie the association between depression and cardiovascular prognosis. Telomeres are simple repetitive sequences (TTAGGG) at the ends of eukaryotic chromosomes. They protect somatic cells from genomic instability during

mitotic cell proliferation.[84] Telomeres progressively shorten with each mitotic division due to the limiting nature of linear DNA replication mechanisms. After a critical degree of telomere shortening, cells lose the ability to replicate and may cease dividing (senescence) or undergo programmed cell death.[85] Telomere shortening has therefore been proposed as a marker of biologic aging.[86] Previous cross-sectional studies have found that depression is associated with shorter telomere length.[87-90] In addition, short telomere length is associated with all cause mortality and heart failure in CHD patients.[91] Because telomere length seems to be associated with both depression as well as with morbidity and mortality, this raises the question of whether accelerated cellular aging is a mechanism that contributes to the excess morbidity and mortality associated with depression.[89, 92]

(3) Finally, within the conceptual framework of depression as a potential cardiovascular risk factor, there is a need to expand the traditional scope on negative emotions and to focus on other psychological factors, including positive affect. Positive affect refers to mood states such as joy, activity, and cheerfulness.[93] Research on positive affect has been relatively sparse, but accumulating evidence suggests that positive psychological factors are associated with longevity,[93, 94] and decreased cardiovascular mortality and morbidity.[95-97] However, mixed findings have been reported[98-100] and additional research is needed to elucidate the potential role of positive affect within the depression-heart disease relationship.

Aims and organization of the present thesis

Depression and CHD are the two strongest contributors to the global burden of disease. Despite some efforts, several issues remain unresolved. Three diverse but important issues need further clarification, with regard to the heterogeneity of depression, the mechanistic pathways, and the potential role of positive affect in the complex relationship between depression and CHD. This resulted in the following aims of this thesis.

Part I: Somatic versus cognitive depressive symptoms and prognosis

The first aim of this thesis is to examine the link between somatic and cognitive symptoms of depression and prognosis. Symptom dimensions of post MI depression may be differentially associated with cardiac prognosis, in which somatic symptoms appear to be associated with a worse cardiovascular prognosis than cognitive symptoms. These findings hold important implications for treatment but need to be replicated before conclusions regarding treatment can be drawn. Therefore, *chapter 2* examines the relationship between depressive symptom dimensions following MI and both disease severity and prospective cardiac prognosis. Data from a prospective study following patients hospitalized for acute MI in the Netherlands are used.

Chapter 3 reports on the relationship between cognitive and somatic depressive symptoms and cardiovascular prognosis in patients with stable CHD, based on the Heart and Soul study. The Heart and Soul study is a prospective cohort study focused on psychosocial factors and health outcomes in patients with coronary heart disease. The aim of this chapter is to evaluate whether certain individual symptoms of depression are more cardiotoxic than others. This research question is evaluated in a population with stable CHD because in this sample the depressive symptoms may be less confounded by complaints that are frequently expressed in the direct aftermath of an acute coronary event, like for example fatigue.

All analyses conducted so far on somatic and cognitive symptoms of depression and the relationship with cardiovascular prognosis relied on self-report instruments, including the Beck Depression Inventory and the Patient Health questionnaire. A drawback of self-report instruments is that no weighing of symptoms is performed, as is carried out when establishing a psychiatric diagnosis with a structured interview. Therefore, the independent associations between cardiovascular prognosis and ratings of the individual depressive symptoms based on a structured diagnostic interview are evaluated in *chapter 4*. Analyses are based on the Depression after Myocardial Infarction study (DepreMI), a naturalistic follow-up study which took place in 4 hospitals in the northern part of the Netherlands.

Part II: Telomere length as a possible mechanism

The second aim of this thesis is to examine whether telomere length is a possible mechanism underlying the association between depression and prognosis. Since the discovery of telomeres, there is a growing body of literature linking shortened telomeres with increased age-related morbidity and mortality. Previous studies have found that psychological distress is associated with short telomere length. However, the association between depression and telomere length has not been evaluated in patients with coronary heart disease. Furthermore, the effect of depression on subsequent change in telomere length has not been examined in any patient population. *Chapter 5* examines these issues based on the Heart and Soul study.

Chapter 6 evaluates whether depressive disorders predict telomere length over time in a large population based sample. Lately the role of anxiety in relation with prognosis received more attention, and anxiety appears to be an independent risk factor for CHD and mortality. Therefore, the association between anxiety and telomere length over time is also assessed. Data from the PREVEND study are used, which is a longitudinal study with three measurement waves in a general population cohort.

Part III: Positive affect and prognosis

The third aim of this thesis is to examine whether positive affect is associated with prognosis. Although the impact of negative emotions has been studied extensively, the role that positive emotions have on the prognosis has been less well studied. The aim of *chapter 7* is to examine whether positive affect is associated with improved survival and decreased cardiovascular morbidity in patients with stable CHD. In addition, potential biological and behavioral mechanisms underlying this association are explored. This chapter also uses data from the Heart and Soul study.

General discussion

Finally, in *chapter 8* the main findings of this dissertation are discussed and implications for future research and clinical practice are outlined.

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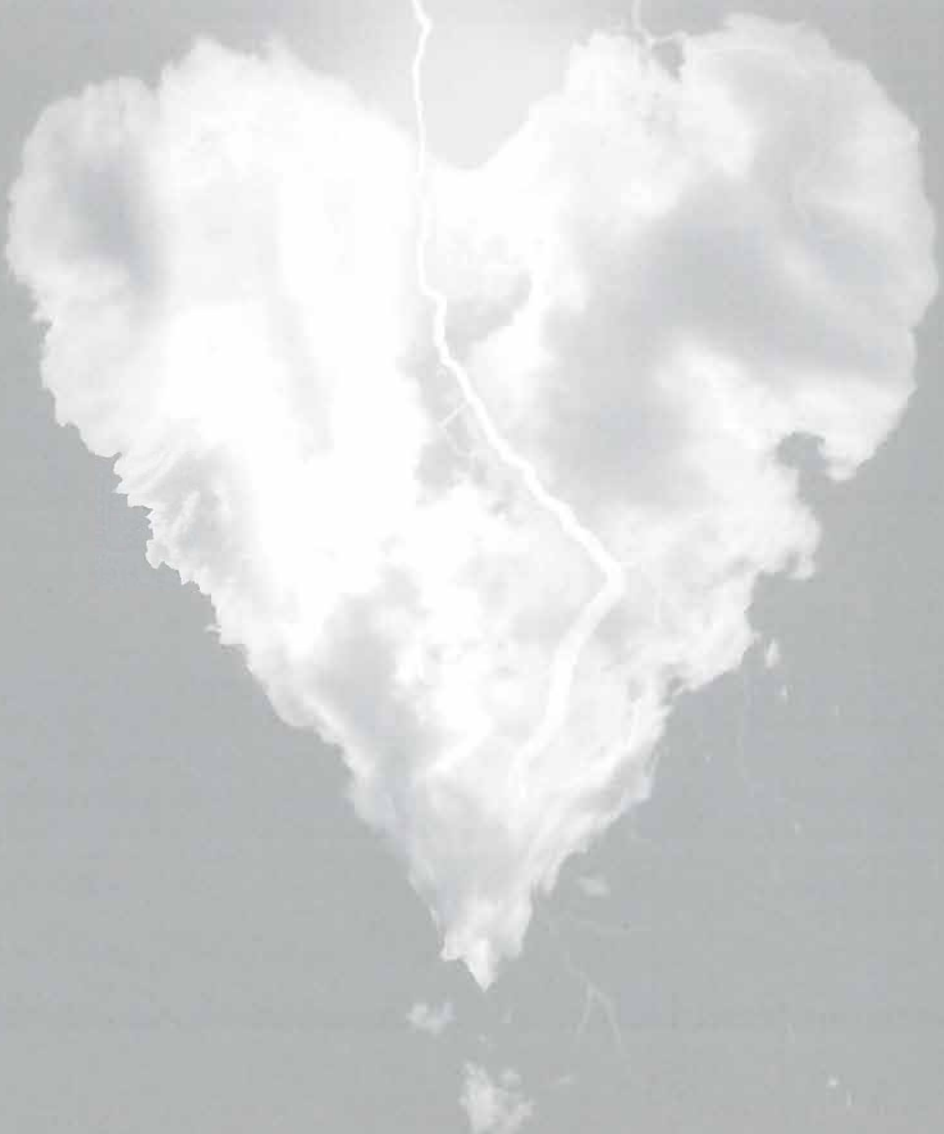
Part I

Somatic versus cognitive depressive symptoms and prognosis



Chapter 2

Symptom dimensions of post-myocardial infarction depression, disease severity and cardiac prognosis

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ABSTRACT

Background | Individual symptoms of post-myocardial infarction (MI) depression may be differentially associated with cardiac prognosis, in which somatic/affective symptoms appear to be associated with a worse cardiovascular prognosis than cognitive/affective symptoms. These findings hold important implications for treatment but need to be replicated before conclusions regarding treatment can be drawn. We therefore examined the relationship between depressive symptom dimensions following MI and both disease severity and prospective cardiac prognosis.

Methods | Patients (n=473) were assessed on demographic and clinical variables and completed the Beck Depression Inventory (BDI) within the first week of hospital admission for acute MI. Depressive symptom dimensions were associated with baseline left ventricular ejection fraction (LVEF) and prospective cardiac death and/or recurrent MI. The average follow-up period was 2.8 years.

Results | Factor analysis revealed two symptom dimensions - somatic/affective and cognitive/affective - in the underlying structure of the BDI, identical to previous results. There were 49 events attributable to cardiac death (n=23) or recurrent MI (n=26). Somatic/affective (p=0.010) but not cognitive/affective (p=0.153) symptoms were associated with LVEF and cardiac death/recurrent MI. When controlling for the effects of previous MI and LVEF, somatic/affective symptoms remained significantly predictive of cardiac death/recurrent MI (HR:1.31; 95% CI:1.02-1.69; p=0.038). Previous MI was also an independent predictor of cardiac death/recurrent MI.

Conclusions | We confirmed that somatic/affective, rather than cognitive/affective symptoms of depression are associated with MI severity and cardiovascular prognosis. Interventions to improve cardiovascular prognosis by treating depression should be targeted at somatic aspects of depression.

INTRODUCTION

The association of depression following myocardial infarction (MI) with progression of heart disease has been studied intensively over last decades.[1-4] The overall consensus is that, although some exceptions have been published, a twofold increased risk of new fatal or nonfatal cardiovascular events is observed for patients with post-MI depression.[4] The extent to which this association is to be attributed to heart disease severity has been the object of debate.[5-9] Some studies have found that almost half of the variance in the association is explained away when left ventricular ejection fraction (LVEF) is added to the prediction models.[8] Others have observed a dose-response like association between LVEF at the time of MI and subsequent risk of depression,[9] although quite some heterogeneity in findings is seen here as well.[7, 10] If the association between post-MI depression and cardiac prognosis is confounded by MI severity, this might explain the limited effects of antidepressant treatment on depression outcomes[11-14] and no effects at all on cardiac outcomes.[11, 14]

Recently, it has been observed that individual symptoms of post-MI depression may be differentially associated with cardiovascular prognosis.[15] In that study somatic/affective symptoms, including sleeping difficulties and fatigue, appeared to be associated with a worse cardiovascular prognosis than cognitive/affective symptoms including shame, guilt and negative self-image. Even though somatic/affective depressive symptoms were confounded by somatic health status, the association between somatic/affective symptoms and cardiac prognosis remained after controlling for MI severity and somatic co-morbidity. This suggests that these somatic/affective symptoms may be an important target for intervention, although this intervention may be different from interventions derived from general psychiatry. However, these findings have not yet been confirmed by other researchers. We therefore set out to replicate the findings by De Jonge et al. [2006], hypothesizing that only somatic/affective symptoms of depression are associated with increased cardiovascular risk in post-MI patients. In addition, we hypothesized that somatic/affective symptoms of depression are associated with baseline LVEF, but that this association does not fully explain the association with poor cardiac prognosis.

METHODS

Study design and patient population

Patients hospitalized for acute MI (n=473) were recruited between May 2003 and June 2006 from four teaching hospitals (Catharina Hospital, Eindhoven; St. Elisabeth Hospital, Tilburg; TweeSteden Hospital, Tilburg; and St. Anna Hospital, Geldrop) in the Netherlands. Inclusion criteria were age >30 and hospitalization due to acute MI. Criteria for diagnosis of

MI were troponin I levels more than twice the upper limit, with typical ischemic symptoms (e.g. chest pain) lasting for more than 10 minutes or ECG evidence of ST segment elevation or new pathological Q-waves. For patients without typical angina, the day of MI onset was identified as the day during hospitalization with peak troponin I levels >1.0 and ECG evidence of ST segment elevation or new pathological Q-waves. Exclusion criteria were significant cognitive impairments (e.g. dementia) and severe medical co-morbidities that increased the likelihood of early death, such as malignant cancer, as verified by medical records and consulting the treating physician. Patients with chronic medical co-morbidities such as diabetes, renal disease, COPD and arthritis were included in the study. Depression was assessed at the time of MI and demographic and medical characteristics were obtained from the medical records. The study protocol was approved by the institutional review boards of the participating hospitals, and after complete description of the study to the subjects, written consent was obtained from all study participants.

Assessment of depressive symptoms

Within the first week of hospital admission for acute MI, patients completed the 21-item Beck Depression Inventory (BDI).[16] Patients were asked to respond with information about depressive symptoms for the period relating to the past week. Each item is rated on a 0-3 scale. A total score is obtained by summing together all the items. The BDI is a reliable and valid measure of depressive symptomatology.[17] A BDI total score ≥ 10 is indicative of at least mild to moderate symptoms of depression and has been associated with poor prognosis in MI patients.[18, 19]

Clinical characteristics

Clinical variables associated with post-MI prognosis were obtained from the patients' medical records. These included prior MI, LVEF, multi-vessel disease, anterior location of index MI, invasive versus conservative treatment of index MI, participation in rehabilitation after index MI, smoking status (self-report), body mass index (BMI), hypertension (systolic blood pressure>140, diastolic blood pressure>90), hypercholesterolaemia (total cholesterol >6.50 mmol/l), systolic/diastolic blood pressure at the time of admission for index MI, history of diabetes mellitus, renal insufficiency, chronic obstructive pulmonary disease, and arthritis. The following medications prescribed to the patient at discharge were also noted: beta-blockers, angiotensin-converting enzyme (ACE) inhibitors, anti-coagulants, statins, diuretics, aspirin, and selective serotonin reuptake inhibitors (SSRIs). Demographic variables included age, gender, marital status, and classified educational level.

Endpoint

The endpoint was a composite of cardiac death and/or recurrent MI, as verified by medical records. Criteria for diagnosis of MI were those used for inclusion in the study. The mean follow-up period was 2.8 years (SD=1.2, range 6-1650 days), and follow-up data was complete for all patients (100%). There is variability in length of follow-up because the last follow-up on all patients was done at set points in time ("waves" of follow-up) while patients were enrolled continuously as a function of acute MI admission to hospital.

Statistical analysis

Principal component analysis (PCA) with oblimin rotation was used to determine the underlying structure of the BDI. A scree plot was adopted to identify the number of components, and subsequent Kaiser-Meyer-Olkin (KMO) and Bartlett's test of sphericity were applied as fit indices. Discrete variables were compared with the Chi-square test and are presented as numbers and percentages. Continuous variables were compared with the Student's t-test and are presented as means ± standard deviations. Linear regression analyses were used to evaluate the relationship between depression and LVEF. Cox proportional hazard regression analyses were performed to investigate the impact of depression on cardiovascular events at follow-up. A p-value < 0.05 was used for all tests to indicate statistical significance. Hazard ratios (HR) with 95% confidence intervals (CI) are reported. All statistical analyses were performed using SPPS version 14.0 for Windows (SPSS Inc.,USA).

RESULTS

Factor structure

PCA revealed a 2-component solution in the underlying structure of the BDI (Table 1). The KMO test (0.87) and Bartlett's test of sphericity ($p<0.001$) indicated that PCA was adequate for these data. The total variance explained was 35%. The 2 factors that were constructed from the PCA reflect somatic/affective and cognitive/affective symptoms of depression. The labelling of the components was based on de Jonge et al.[15]

Table 1. Factor loadings of depressive symptom dimensions and relation to BDI items

	Dimensional structure in de Jonge et al[1]		Dimensional structure in the present study	
Depressive symptoms from BDI	**Somatic/ Affective factor**	**Cognitive/ Affective factor**	**Somatic/ Affective Factor**	**Cognitive/ Affective factor**
Sadness	0.64	0.45	0.48	0.57
Pessimism	0.56	0.58	0.48	0.36
Sense of failure		0.66		0.67
Dissatisfaction	0.69	0.49	0.72	0.38
Guilt		0.70		0.71
Punishment		0.59		0.67
Self-dislike		0.72		0.69
Self-accusations		0.71		0.65
Suicidal ideas		0.49	0.35	0.52
Crying	0.52		0.39	0.32
Irritability	0.45		0.39	0.32
Social withdrawal	0.42	0.51	0.34	
Indecisiveness	0.68	0.40	0.54	0.35
Body-image change		0.57	0.42	0.32
Work difficulty	0.69		0.76	
Insomnia	0.55		0.59	
Fatigability	0.58		0.65	
Loss of appetite	0.42		0.50	
Weight loss				
Somatic preoccupation	0.67		0.51	0.42
Loss of libido	0.50		0.60	

BDI= Beck Depression Inventory.

Demographic and clinical characteristics

Of the original 473 patients, 54 had no echocardiography, leaving 419 (89%) patients to be included in further analyses. Table 2 shows demographic and clinical characteristics of the current sample. Of the 419 MI patients, 22% was female, 16% had a previous MI, 14% was known with diabetes mellitus, 61% was invasively treated for index MI and 62% received cardiac rehabilitation. Mean age was 59 years and mean BMI was 27 kg/m^2. Patients used the following medication: Beta-blockers (87%), ACE-inhibitors (38%), anti-coagulants (8%3), statins (91%), aspirin (82%) and SSRIs (13%). Only 19% were on diuretics. Of patients 39% smoked, 28% had hypertension and 12% hypercholesterolemia. The mean LVEF was 51%.

Table 2. Demographic and clinical baseline predictors of death or recurrent MI (univariate analyses)[1]

	All patients (n=419)	Death/MI (n=49)	Event-free (n=370)	HR	95% CI	p
Demographic characteristics						
Age, mean (SD)	59 (11)	64 (13)	59 (11)	1.04	1.01-1.07	0.003
Female gender	91 (22)	7 (14)	84 (23)	0.60	0.27-1.34	0.216
Partner	344 (82)	38 (78)	306 (83)	0.78	0.39-1.56	0.476
Educational level: high	237 (57)	22 (45)	215 (58)	0.67	0.38-1.18	0.169
Clinical characteristics						
Disease severity						
Previous MI	65 (16)	19 (39)	46 (12)	3.86	2.12-7.01	<.001
LVEF %, mean (SD)	51 (12)	47 (14)	52 (12)	0.97	0.94-0.99	0.007
Multi-vessel disease	136 (32)	17 (35)	119 (32)	1.28	0.68-2.42	0.440
Anterior MI location	159 (38)	19 (39)	140 (38)	1.16	0.63-2.13	0.636
Comorbidity						
Diabetes mellitus	59 (14)	9 (18)	50 (14)	1.36	0.66-2.81	0.400
Renal insufficiency	19 (5)	4 (8)	15 (4)	2.00	0.72-5.56	0.184
COPD	31 (7)	5 (10)	26 (7)	1.40	0.56-3.54	0.473
Arthritis	32 (8)	6 (12)	26 (7)	1.80	0.77-4.23	0.178
Invasive treatment[2]	255 (61)	20 (41)	235 (64)	0.43	0.24-0.75	0.003
Cardiac rehabilitation	260 (62)	26 (53)	234 (63)	0.62	0.35-1.11	0.107
Medication use						
Beta-blockers	363 (87)	40 (82)	323 (87)	0.65	0.32-1.35	0.250
ACE-inhibitors	160 (38)	20 (41)	140 (38)	1.08	0.61-1.92	0.782
Anti-coagulants	347 (83)	44 (90)	303 (82)	1.92	0.76-4.84	0.167
Statins	381 (91)	40 (82)	341 (92)	0.40	0.20-0.83	0.014
Aspirin	344 (82)	34 (69)	310 (84)	0.45	0.25-0.83	0.010
Diuretics	80 (19)	21 (43)	59 (16)	3.55	2.01-6.25	<.001
SSRIs	53 (13)	10 (20)	43 (12)	1.79	0.89-3.58	0.101
Smoking	164 (39)	22 (45)	142 (38)	1.25	0.71-2.20	0.435
BMI, kg/m^2, mean (SD)	27 (4)	26 (5)	27 (4)	0.91	0.84-0.99	0.032
Hypertension	116 (28)	12 (24)	104 (28)	0.75	0.39-1.45	0.394
Hypercholesterolaemia	50 (12)	3 (6)	47 (13)	0.48	0.15-1.54	0.214
Cardiac function						
Systolic BP, mean (SD)	140 (29)	136 (24)	141 (29)	0.99	0.98-1.00	0.207
Diastolic BP, mean (SD)	82 (17)	80 (17)	82 (17)	0.99	0.97-1.01	0.204

HR= hazard ratio; CI= confidence interval; SD= standard deviation; MI= myocardial infarction; LVEF= left ventricular ejection fraction; COPD= chronic obstructive pulmonary disease; ACE= angiotensin-converting enzyme; SSRI= selective serotonin reuptake inhibitor; BMI= body mass Index; BP= blood pressure.

[1] Values are expressed as n (%) of patients unless otherwise indicated

[2] Invasive treatment: percutaneous coronary intervention or coronary artery bypass graft surgery

Association with LVEF

In univariate regression analyses, somatic/affective (ß=-0.099, t=-2.03, p=0.043) but not cognitive/affective symptoms (ß=-0.017, t=-0.34, p=0.733) were related to LVEF. Entering both symptoms dimensions simultaneously into the model confirmed that increased somatic/affective (ß=-0.110, t=-2.07, p=0.039) but not cognitive/affective symptoms (ß=0.028, t=5.30, p=0.596) were related to decreased LVEF.

Table 3. Predictors of death or recurrent MI[1]

	Death/MI (n=49)		
Predictor variables	**HR**	**95% CI**	**p**
Model 1[2]			
Somatic/affective symptoms	1.39	1.08-1.79	0.010
Cognitive/affective symptoms	1.17	0.94-1.44	0.153
Model 2[3]			
Somatic/affective symptoms	1.37	1.03-1.82	0.030
Cognitive/affective symptoms	1.03	0.81-1.32	0.797
Model 3[3]			
Somatic/affective symptoms	1.31	1.02-1.69	0.038
Previous MI	3.25	1.75-6.03	<0.001
LVEF	1.50	0.81-2.79	0.201

HR= hazard ratio; CI= confidence interval; MI= myocardial infarction; LVEF= left ventricular ejection fraction (<40%).
[1]Enter procedure
[2]Univariate analyses
[3]Multivariate analyses

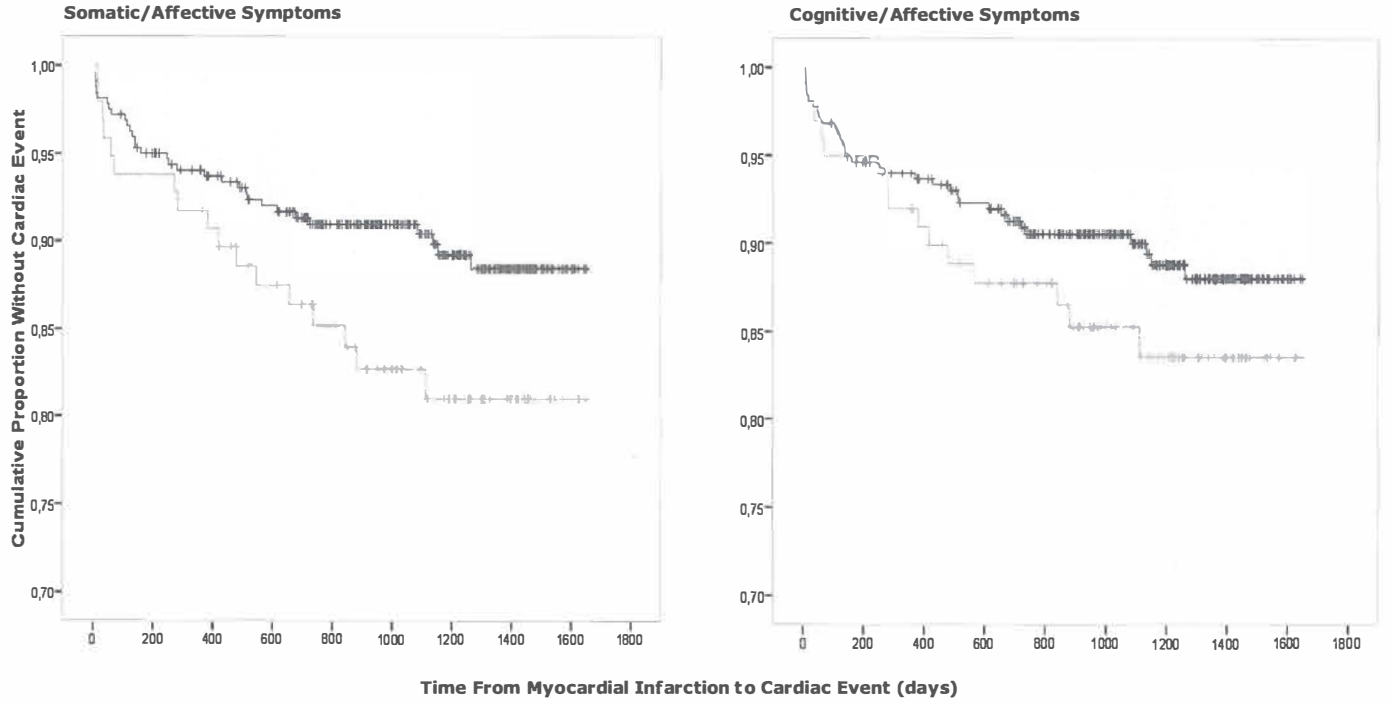
Clinical predictors of death or recurrent MI

There were 49 events attributable to cardiac death (n=23) or recurrent MI (n=26). In univariate analyses, patients experiencing a clinical event were older (p=0.003), more likely to have had a previous MI (p<0.001), to be treated with diuretics (p<0.001) and to have lower mean LVEF (p=0.007) and BMI (p=0.032) than event-free patients (Table 2). These patients were also less likely to have had invasive treatment during hospitalization for the index MI (p=0.003), and to be treated with statins (p=0.014) and aspirin (p=0.010), than event-free patients. When entering all these potential confounders into a multivariate analysis, only previous MI remained as independent predictor. Hence, we adjusted for previous MI – in addition to LVEF - in subsequent multivariate analyses.

Depressive symptoms and prognosis

Relating depressive symptoms with time-related cardiac death or recurrent MI resulted in significant associations for somatic/affective (p=0.010) but not cognitive/affective symptoms (p=0.153) (Table 3, model 1). The association of the somatic/affective factor with cardiac death or recurrent MI remained statistically significant when the two depression factors entered the Cox regression model simultaneously (p=0.030) (Table 3, model 2). When controlling for the effects of previous MI and LVEF, somatic/affective symptoms remained significantly predictive of cardiac death or recurrent MI (p=0.038). In this analysis, previous MI was also an independent predictor of death or recurrent MI (p<0.001) (Table 3, model 3). Survival curves for the two groups (somatic/affective, cognitive/affective) based on the 20% highest scoring individuals are presented in Figure 1. The corresponding log-rank tests to assess the significance of the relationships were 3.69 for the somatic/affective (p=0.055) and 1.49 for the cognitive-affective symptoms (p=0.221).

Figure 1. Event-free survival time following myocardial infarction and relationship with depressive symptoms (N=419)



DISCUSSION

In a sample of 473 MI patients we replicated findings presented earlier by De Jonge et al[15]: 1- the dimensional structure of depressive symptoms following MI was strikingly comparable, 2- only somatic/affective depressive symptoms were associated with baseline LVEF, 3- somatic/affective depressive symptoms were associated with adverse cardiac prognosis, 4- the associations remained after controlling for confounders including LVEF. The need to replicate new findings cannot be overstated given the risk of chance capitalization. The fact that the present findings were consistent with those of De Jonge et al.[15] certainly strengthens the position that depressive symptoms following MI are differentially related to cardiovascular prognosis.

There is considerable evidence that depression is a risk factor for adverse cardiovascular events in cardiac patients. However, a frequent criticism of this literature is that the association between depression and adverse prognosis may be confounded by worse baseline cardiac disease severity in depressed patients. A recent study[20] in patients with stable coronary heart disease found little evidence that depression is associated with worse cardiac disease severity, while the present findings clearly indicate that in acute MI patients somatic/affective depressive symptoms are associated with MI severity. Even though somatic/affective depressive symptoms were confounded by disease severity, they were still prospectively associated with medical outcome. These findings confirm previous studies indicating that somatic depressive symptoms are associated with disease severity,[15, 21] but also that somatic/affective symptoms have an independent effect on adverse cardiac outcome while cognitive/affective symptoms have not.

In the Heart and Soul study it was concluded that somatic depressive symptoms were associated with lower heart rate variability, while cognitive depressive symptoms were not.[22] This can be a potential mechanism underlying the relation between depression and cardiovascular prognosis. Moreover, several of the potential mechanisms that may account for the cardiac effects of depression may be reversed, e.g. increased cytokine levels resulting from left ventricular dysfunction and social and physical limitations that arise from disease itself may play a role in the genesis of post-MI depression.[23] Possibly, in some patients worse MI severity may trigger somatic depressive symptoms and, subsequently, the confluence of MI severity and somatic depressive symptoms leads to adverse medical outcome. This would imply that interventions to improve cardiovascular prognosis by treating depression should be specifically aimed at somatic aspects of depression. Exercise could be an important avenue in that matter.[24]

In response to previous findings by De Jonge et al.[15] on the differential association between depressive symptom dimensions and cardiovascular prognosis, Thombs and colleagues suggested that results could be explained by multicollinearity as the two dimensions were highly correlated.[25] Although we feel this possibility was effectively ruled out, the current results further suggest that those previous findings were quite stable. In the present study, the HR of the somatic/affective symptom dimension regarding cardiovascular events was 1.39 in the univariate model, which persisted when the cognitive/affective dimension was added (HR:1.37). We therefore conclude that multicollinearity does not explain the current findings.

In this study the BDI was used to assess depressive symptoms. It would be of interest to replicate this work using other instruments, particularly those with proportionately more somatic items such as the Hamilton Rating Scale for Depression.[26] With reference to this issue, a recent study that used the nine-item Patient Health Questionnaire[27] to assess depression severity in post-MI patients indicated that somatic symptoms of depression are often overlooked in these patients,[28] while these symptoms may have substantial prognostic power in the prediction of adverse clinical events post-MI. Further, this distinction between somatic and cognitive symptoms of depression may equally be of importance in other cardiac conditions such as chronic heart failure.[29]

Some limitations of the current study should be noted. First, the low number of women (22%) limits the generalizability of the results. Furthermore, patients were relatively healthy with a mean LVEF of 51%. Third, somatic depressive symptoms in MI patients can be confounded by complaints originating from cardiovascular disease itself. We tried to resolve this issue by evaluating a broad spectrum of possible confounding factors, including disease severity, medical co-morbidity, risk factors, and medication use. Finally, we had no information on the overall response rate of the study. However, we were able to look into a subsample of patients (n=63). Of the 63 patients who met the inclusion criteria, 46 gave informed consent, leaving a response rate of 73%. The retention rate of this study has been reported. Despite these limitations, this study was a multi-centre study, making generalization of our results to MI patients more justified.

In summary, we confirmed previous findings[15] that somatic/affective, rather than cognitive/affective symptoms of depression are associated with MI severity and cardiovascular prognosis. The results from this study indicate the need for future research directed to the identification of specific depressive symptoms that are most toxic in terms of predicting adverse cardiovascular prognosis, and to the testing of interventions to alleviate the associated risk.

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Chapter 3

Differential associations between specific depressive symptoms and cardiovascular prognosis in patients with stable coronary heart disease

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ABSTRACT

Objectives | The purpose of this research was to evaluate the relationship between cognitive and somatic depressive symptoms and cardiovascular prognosis.

Background | Depression in patients with stable coronary heart disease (CHD) is associated with poor cardiac prognosis. Whether certain depressive symptoms are more cardiotoxic than others is unknown.

Methods | In the Heart and Soul study, 1019 patients with stable CHD were assessed using the Patient Health Questionnaire to determine the presence of the 9 depressive symptoms included in the Diagnostic and Statistical Manual of Mental Disorders-Fourth Edition. The mean age of the patients was 67 years, and 82% were men. A comparison was made on a new cardiovascular event (myocardial infarction, stroke, transient ischemic attack, or congestive heart failure) or death (mean follow-up duration 6.1±2.0 years) on the basis of cognitive and somatic sum scores and for patients with or without each of those specific depressive symptoms. Demographic characteristics, cardiac risk factors, and cardiac medication were controlled for.

Results | After adjustment for demographic data and cardiac risk factors, each somatic symptom was associated with 14% greater risk of events (HR:1.14; 95% CI:1.05-1.24; p=0.002). Fatigue (HR:1.34; 95% CI:1.07-1.67; p=0.01), appetite problems (HR:1.46; 95% CI:1.12-1.91; p=0.005), and sleeping difficulties (HR:1.26; 95% CI:1.00-1.58; p=0.05) were most strongly predictive of cardiovascular events. In contrast, cognitive symptoms (HR:1.08; 95% CI:0.99-1.17; p=0.09) were not significantly associated with cardiovascular events.

Conclusions | In patients with stable CHD, somatic symptoms of depression were more strongly predictive of cardiovascular events than cognitive symptoms, although the confidence intervals surrounding these estimates had substantial overlap. These findings are highly consistent with those of previous studies. Further research is needed to understand the pathophysiological processes by which somatic depressive symptoms contribute to prognosis in patients with CHD.

INTRODUCTION

By 2020, the most important causes of disability-adjusted life-years are predicted to be coronary heart disease (CHD) and major depression.[1] Patients with CHD are at increased risk for developing depression.[2] Likewise, patients with depression are at increased risk for developing cardiovascular (CV) disease, including congestive heart failure (CHF), myocardial infarction (MI), stroke and CV death.[3-5] In recent decades, the effects of depression in patients with CHD have been extensively studied.[3, 6, 7] Several randomized controlled trials have been undertaken to evaluate the efficacy of antidepressant therapy in patients with CHD. However, in most of these studies, treatment had only minor effects on reducing depressive symptoms.[8]

A reason for these findings may be the heterogeneity of depression as a syndrome.[9] Depression is a syndrome consisting of 9 depressive symptoms, according to the criteria of the Diagnostic and Statistical Manual of Mental Disorders-Fourth Edition (DSM-IV).[10] Several researchers over time have distinguished somatic symptoms from cognitive symptoms of depression.[11-13] In recent years, this distinction has been applied to patients with CHD.[14] It has been found that somatic symptoms of depression had a relatively high prevalence[15] and were more strongly associated with CV prognosis,[14, 16-18] medical comorbidity,[13] and heart rate variability.[19] At this time, it remains to be determined which of these symptoms has the most cardiotoxic contribution in terms of CV prognosis in patients with stable CHD.

We hypothesized the existence of differential associations of specific depressive symptoms with CV prognosis. We chose to investigate this research question in a population with stable CHD because in this sample, depressive symptoms may be less confounded by complaints that are frequently expressed in the direct aftermath of an acute coronary event, like for example fatigue. The identification of certain cardiotoxic symptoms within the diagnosis of depression would be an important step in the development of antidepressive interventions that aim to alleviate the depression-associated risk of CV events.

METHODS

Design and patients

This study was based on data from the Heart and Soul Study, a prospective cohort study focused on psychosocial factors and health outcomes in patients with stable CHD. Details regarding methods of the Heart and Soul Study have been described previously.[20] Patients had to meet the following inclusion criteria: 1) history of MI or coronary revascularization; 2) angiographic evidence of at least 50% stenosis in at least one coronary vessel; and 3) a

diagnosis of CHD by an internist or cardiologist. Exclusion criteria were: 1) a history of MI in the past 6 months; 2) poor exercise tolerance (inability to walk one block); and 3) planning to move from the local area within 3 years.

We initially mailed letters to 15,438 patients who had International Classification of Diseases-9th Revision codes for CHD based on administrative databases at 2 U.S. Department of Veterans Affairs medical centers, 1 university medical center, and 9 public health clinics in northern California. Because administrative data are not necessarily correct or current, many of these letters were mailed to bad addresses or to persons who did not meet eligibility criteria. Of the 2,495 patients who returned the form indicating that they would be interested in participating, 370 were excluded on the basis of the pre-defined exclusion criteria, and 505 could not be reached by telephone. Of the 1,620 patients who were confirmed to meet the eligibility criteria, 596 declined to participate, and 1,024 (63%) enrolled. Between September 2000 and December 2002, all participants completed a baseline assessment, including a medical history interview, a fasting blood draw, a physical examination, an exercise treadmill test with stress echocardiography, a comprehensive health status questionnaire, and 24-hours urine collection. All participating patients signed informed consent forms. The study protocol was approved by the institutional review boards of the participating hospitals.

Baseline characteristics

Baseline characteristics of the study sample included sociodemographic data, history of CV disease, and cardiac disease severity. The sociodemographic characteristics were age, sex, and marital status and were determined by questionnaire. History of CV disease was determined by self-report and included MI, congestive heart failure and stroke. All participants underwent resting echocardiography using an Acuson Sequoia ultrasound system (Siemens Medical Solutions USA, Inc., Mountain View, California) with a 3.5 MHz transducer. Standard 2-dimensional views and performed planimetry with a computerized digitization system were obtained to determine left ventricular ejection fraction (LVEF). Smoking was determined by self-report, and body mass index was assessed. Participants were instructed to bring their medication bottles to their appointment, and study personnel recorded all current medications, including dose and frequency use.

Assessment of depressive symptoms

The 9-item Patient Health Questionnaire (PHQ)[10] was used to determine the presence and severity of the 9 depressive symptoms listed in the DSM-IV. The PHQ is a self-report checklist derived from the interview used in the Primary Care Evaluation of Mental Disorders.[21] This instrument measures the presence of depressive symptoms during the previous two weeks, each scored as follows: 0 = not at all, 1 = several days, 2 = more than half the days, or 3 = nearly every day.

This study evaluated the effect of each depressive symptom both as a dichotomous variable using the standard cut point of ≥2 for the presence of the first 8 depressive symptoms and ≥1 for the presence of the symptom suicidal ideation (in concordance with the manual)[10] and as a log-transformed continuous variable. The nine symptoms of depression in the PHQ, based on the DSM-IV classification of depression in the DSM-IV, are: 1) depressed mood; 2) loss of interest; 3) appetite problems; 4) sleeping difficulties; 5) psychomotor agitation/ retardation; 6) fatigue; 7) feelings of worthlessness; 8) concentration problems; and 9) suicidal ideation.

Somatic and cognitive depressive symptoms

Following earlier work, depressive symptoms were categorized as follows: depressed mood, lack of interest, worthlessness, concentration problems and suicidal ideation were considered to be cognitive symptoms, and appetite problems, sleeping difficulties, psychomotor agitation or retardation, and fatigue were considered to be somatic symptoms.[18, 19]

Endpoints and follow-up

After the baseline examination, we conducted annual telephone follow-up interviews with participants (or their proxies), asking specifically about hospitalization for "heart trouble." For any reported event, medical records, electrocardiograms, death certificates, and coroners' reports were retrieved and reviewed by two independent blinded adjudicators. In the event of disagreement, the adjudicators conferred, reconsidered their classification, and requested consultation from a third blinded adjudicator as necessary. The primary study endpoints were CV events, including heart failure, MI, stroke, transient ischemic attack, or death.

For patients to be diagnosed with heart failure, they had to be hospitalized for a clinical syndrome meeting at least two of the following criteria: paroxysmal nocturnal dyspnea, orthopnea, elevated jugular venous pressure, pulmonary rales, third heart sound, cardiomegaly or pulmonary edema on chest radiography. A clear change in these symptoms from the patients' usual clinical status and either peripheral hypoperfusion (in the absence of other causes) or peripheral or pulmonary edema requiring intravenous diuretic, inotropic, or vasodilator therapy was a necessary condition [22]. Standard criteria were used for defining nonfatal MI.[23] Stroke was defined as new neurological deficit, which must not have been the result of brain trauma, tumor, infection or other cause. Transient ischemic attack was defined as a focal neurological deficit (in the absence of head trauma) lasting between 30 seconds and 24 hours, with rapid evolution of the symptoms to the maximal level of deficit < 5 minutes and with subsequent complete resolution. Death was determined by death certificates and coroners' reports.

Statistical analysis

We used Cox proportional hazards regression (i.e. survival analysis) to estimate the differential effects of the 9 depressive symptoms on cardiac events. Hazard ratios (HRs) with 95% confidence intervals (CIs) are reported. The Cox regression procedure is a method of estimating time-to-event models in the presence of censored cases. Cases are censored either at the occurrence of the first CV event or at the end of follow-up, whichever comes first. Cox regression analyses were conducted for evaluating the effects of each specific depressive symptom, controlling for age and gender. Second, multivariate effects were evaluated after controlling for variables previously found to predict CV events in this cohort (age, sex, diabetes mellitus, history of MI, history of stroke, history of heart failure, LVEF, BMI, and smoking)[22] and for use of cardioprotective medications (aspirin, beta-blockers, statins, and renin-angiotensin system inhibitors). Each depressive symptom was entered both as a log-transformed continuous variable and as a dichotomous variable. Interactions were checked between the specific depressive symptoms and sex and age. All statistical analyses were performed using SPSS version 14.0 (SPSS, Inc., Chicago, Illinois).

RESULTS

Of the 1,024 enrolled CHD patients, 1,019 (>99%) were available for follow-up. Patient characteristics are presented in Table 1. The prevalence of each specific depressive symptom is presented in Table 2. A total of 399 events occurred (MI, heart failure, stroke, TIA or death) during an average of 6.1 ± 2.0 years of follow-up.

In age-adjusted analyses, both somatic and cognitive symptoms were associated with an increased risk for CV events. The annual rate of events ranged from 5.9% among those with no somatic symptoms to 12.6% among those with 4 somatic symptoms, and from 6.4% among those with no cognitive symptoms to 11.4% among those with 5 cognitive symptoms (Figure 1). Each somatic symptom was associated with a 21% increased rate of CV events (HR:1.21;95%CI:1.11-1.31; p<.0001), and this association remained strong after adjustment for potential confounding variables (HR:1.14;95%CI:1.05-1.24) (Table 2). Each cognitive symptom was associated with a 12% increased rate of CV events in age-adjusted analyses (HR:1.12;95%CI:1.03-1.21;p=0.006). After further adjustment for potential confounding variables, the cognitive sum score did not significantly predict CV events (HR:1.08;95%CI:0.99-1.17;p=0.09).

Table 1. Baseline characteristics of the study sample (n = 1019)

	N (%) or mean ± SD
Age	67 ±11
Gender (male)	836 (82)
Married	436 (43)
History of MI	545 (54)
History of CHF	179 (18)
History of stroke	148 (15)
Diabetes Mellitus	265 (26)
Left ventricular ejection fraction	0.62 ± 0.10
Current smoking	199 (20)
Body Mass Index (kg/ m^2)	28 ±5
Aspirin	790 (78)
Beta blocker	591 (58)
Statin	655 (64)
Renin-angiotensin system inhibitor	524 (51)
Antidepressant use	187 (18)

CHF = congestive heart failure; MI = myocardial infarction; SD= standard deviation.

Table 2. Age-adjusted annual rate of CV events (MI, CHF, stroke, TIA or death) among participants with and without specific depressive symptoms

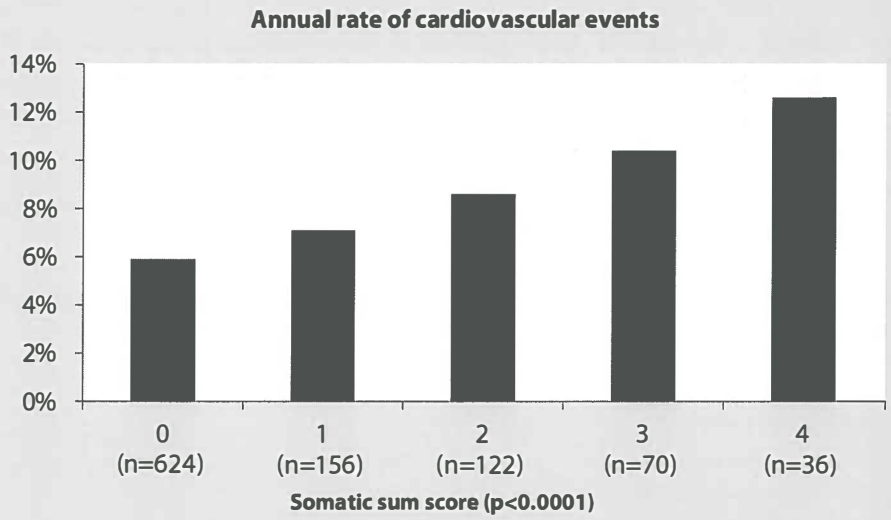
	With symptom		Without symptom		Age-adjusted HR (95% CI)	p	Fully adjusted HR (95% CI)[1]	p
	n	Age-adjusted event rate	n	Age-adjusted event rate				
Somatic symptoms								
Fatigue	267	9.1%	746	6.1%	1.49 (1.20-1.84)	0.0003	1.34 (1.07-1.67)	0.01
Appetite problems	160	11.1%	858	6.2%	1.76 (1.37-2.28)	<.0001	1.46 (1.12-1.91)	0.005
Psychomotor agitation/retardation	85	9.3%	934	6.7%	1.39 (0.99-1.95)	0.06	1.31 (0.93-1.85)	0.13
Sleeping difficulties	249	8.7%	766	6.3%	1.38 (1.11-1.72)	0.004	1.26 (1.00-1.58)	0.05
Somatic sum score[2]					1.21 (1.11-1.31)	<.0001	1.14 (1.05-1.24)	0.002
Cognitive symptoms								
Depressed mood	114	9.7%	900	6.6%	1.48 (1.10-1.99)	0.01	1.32 (0.97-1.80)	0.08
Lack of interest	129	9.8%	889	6.5%	1.50 (1.14-1.97)	0.004	1.21 (0.91-1.61)	0.19
Worthlessness	114	9.1%	904	6.6%	1.36 (0.99-1.86)	0.06	1.22 (0.88-1.69)	0.23
Concentration problems	129	8.2%	890	6.7%	1.22 (0.90-1.64)	0.19	1.10 (0.81-1.49)	0.55
Suicidal ideation	111	8.4%	908	6.7%	1.26 (0.92-1.71)	0.15	1.25 (0.91-1.72)	0.18
Cognitive sum score[2]					1.12 (1.03-1.21)	0.006	1.08 (0.99-1.17)	0.09

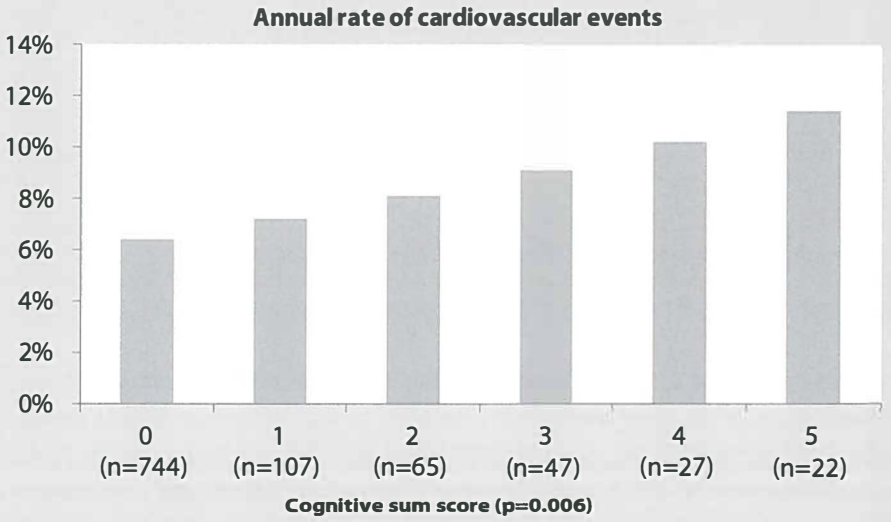
CI= confidence interval; CV= cardiovascular; HR= hazard ratio; MI= myocardial infarction; CHF= congestive heart failure; TIA= transient ischemic attack.

[1]Adjusted for age, sex, diabetes mellitus, history of MI, history of stroke, history of heart failure, left ventricular ejection fraction, body mass index, smoking, aspirin, beta blocker use, statin use, and renin-angiotensin system inhibitor use

[2]Entered as a continuous variable

Figure 1. Age-adjusted annual rate of cardiovascular events (myocardial infarction, heart failure, stroke, transient ischemic attack or death) during an average of 6.1 years follow-up by number of somatic or cognitive depressive symptoms[1,2]

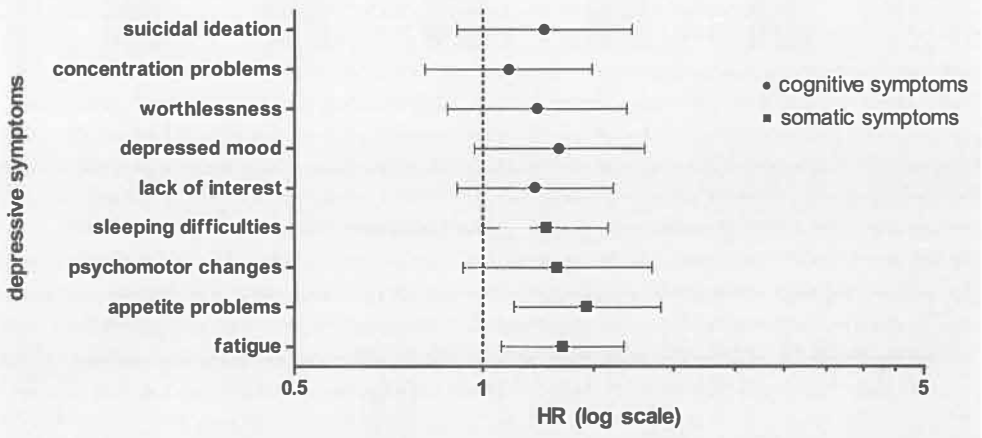




[1]Somatic sum score = number of somatic symptoms with score of ≥2;
[2]Cognitive sum score = number of cognitive symptoms with score of ≥2 (or ≥1 for suicidal ideation)

When entered as dichotomous variables, several symptoms were associated with CV events in age-adjusted models. After further adjustment for age, sex, diabetes mellitus, history of MI, history of stroke, history of heart failure, left ventricular ejection fraction, body mass index, smoking, and use of cardioprotective medications, 3 of the somatic symptoms (fatigue, appetite problems and sleeping difficulties) were independently predictive of CV events (Table 2). These were also the 3 most common symptoms. None of the cognitive symptoms were independently predictive of CV events. We observed no evidence for an interaction of specific depressive symptoms with age or sex in predicting CV events (all p values for interaction = NS). In Figure 2, the HRs and 95% CIs of specific depressive symptoms with CV events are visualized in a forest plot.

Figure 2. Association between specific depressive symptoms (entered as a dichotomous variable) and cardiovascular events[1]



[1]Hazard ratios (HRs) with 95% confidence intervals, adjusted for age, sex, diabetes mellitus, history of myocardial infarction, history of stroke, history of heart failure, left ventricular ejection fraction, body mass index, smoking, aspirin, beta blocker use, statin use, and renin-angiotensin system inhibitor use

When each depressive symptom was entered as a log-transformed continuous variable, the following symptoms were associated with poor cardiac prognosis: fatigue (p=0.0001), appetite problems (p<0.0001), sleeping difficulties (p=0.03), depressed mood (p=0.005), and suicidal ideation (p=0.02) (Table 3). After multivariate adjustment, only fatigue and appetite problems remained significantly associated with CV events. Thus, when entered as continuous variables, 2 of 4 somatic symptoms and none of the cognitive symptoms were independently predictive of cardiovascular events (Table 3).

Table 3. Bivariate and multivariate associations of specific depressive symptoms (entered as continuous variables) with CV events

	HR[1] (95% CI)	p[1]	HR[2] (95% CI)	p[2]
Somatic symptoms				
Fatigue	1.21 (1.10-1.33)	0.0001	1.15 (1.04-1.27)	0.007
Appetite problems	1.27 (1.15-1.41)	<0.0001	1.17 (1.06-1.30)	0.003
Psychomotor agitation/retardation	1.14 (1.00-1.29)	0.05	1.12 (0.98-1.28)	0.10
Sleeping difficulties	1.11 (1.01-1.21)	0.03	1.07 (0.98-1.18)	0.14
Cognitive symptoms				
Lack of interest	1.11 (0.99-1.25)	0.07	1.04 (0.93-1.17)	0.48
Depressed mood	1.19 (1.05-1.33)	0.005	1.13 (1.00-1.28)	0.05
Worthlessness	1.11 (0.98-1.26)	0.09	1.10 (0.97-1.25)	0.15
Concentration problems	1.02 (0.90-1.15)	0.75	1.00 (0.88-1.13)	0.94
Suicidal ideation	1.25 (1.03-1.53)	0.02	1.14 (0.94-1.39)	0.19

HR= hazard ratio; CI= confidence interval.
[1] Adjusted for age and gender
[2] Adjusted for age, gender, diabetes mellitus, history of MI, history of stroke, history of heart failure, left ventricular ejection fraction, body mass index, smoking, aspirin, beta blocker use, statin use, and renin-angiotensin system inhibitor use

DISCUSSION

In a sample of 1,019 patients with stable CHD, we evaluated the association between specific symptoms of depression and CV events. Both somatic and cognitive symptoms were associated with an increased risk for CV events. However, after adjustment for CV risk factors and disease severity, somatic symptoms appeared to be more strongly predictive of CV events than cognitive symptoms of depression. Fatigue, appetite problems, and sleeping difficulties were the symptoms most strongly predictive of CV events. These results may be of importance for identifying depressed patients who are at highest risk of developing CV events and for identifying potential therapies to improve CV outcomes in patients with CHD.

Earlier studies have found that somatic symptoms of depression are more strongly predictive of CV events than cognitive symptoms of depression.[14, 16-18] However, given the high prevalence of somatic symptoms such as fatigue, loss of appetite and sleeping difficulties in patients after MI, it was unclear whether these findings were restricted to this patient population. Our study extends these findings to outpatients with stable CHD by demonstrating that somatic symptoms are more strongly predictive of CV events in this patient population.

It is difficult to ascertain whether somatic depressive symptoms are due to depression or to worse underlying heart disease. Indeed, on the basis of our findings, one might conclude that general somatic malaise or fatigue (and not depression) is the predictor of poor outcomes. However, we tried to overcome this difficulty by carefully measuring and adjusting for history of MI, diabetes, left ventricular ejection fraction, smoking, body mass index, and use of cardioprotective medications. The extent to which differences in these variables explained the effect of somatic symptoms on CV events appeared to be limited, as bivariate and adjusted effects on CV prognosis were highly comparable. In addition, we purposefully enrolled a uniform sample of patients with stable CHD so that the association between depressive symptoms and cardiac prognosis would not be confounded by the severity of a recent acute coronary event. Finally, although fatigue, appetite problems, and sleeping difficulties were the strongest predictors of CV events, these were also the most common depressive symptoms in this population. For example, depressed mood was associated with a 32% increased rate of CV events (HR 1.32, 0.97-1.80; p=0.08), but only 114 participants had depressed mood. In contrast, fatigue was associated with a 34% increased rate of CV events, but the 267 participants with fatigue yielded a tighter CI (HR 1.34, 95% CI, 1.07-1.67; p=0.01). Thus, the lack of an association between cognitive symptoms and CV events may be due in part to smaller number of patients with cognitive symptoms.

In this study, specific depressive symptoms on the basis of the PHQ were used. Major depressive disorder as measured by the computerized Diagnostic Interview Schedule did not predict CV events in the Heart and Soul Study,[22] whereas self-reported depressive symptoms as measured by the PHQ strongly predicted CV events. It is unclear why this discrepancy occurred. It is possible that participants felt more comfortable reporting depressive symptoms on an anonymous questionnaire than in a face-to-face interview, making the interview a less accurate measure of depression.

Only one randomized trial has been adequately powered to evaluate the effect of depression treatment on CV prognosis in CAD patients. The Enhancing Recovery in Coronary Heart Disease Patients (ENRICHD) trial showed that cognitive behavioral therapy decreased depression and improved social support, but did not affect CV prognosis. One possible explanation for the lack of benefit is that patients with CHD may have depressive symptoms below the threshold levels required for antidepressant treatment to be of benefit. Two recent studies[24, 25] have suggested that patients with lower grade depression may not benefit from antidepressant treatment as much as those with more severe symptoms. If most patients with CHD have low levels of depressive symptoms, then antidepressant treatment might not be effective. Although some nonrandomized studies of post-MI patients have shown that use of antidepressants or a reduction in depressive symptoms was associated with a

decreased risk for CV events,[26-28] the observational design of these studies prevents a firm conclusion regarding causality.

Our present findings provide further support for the conceptualization of depression as a heterogeneous syndrome in which some aspects may be more strongly related to CV prognosis than others. This raises the possibility that to improve CV outcomes, interventions for depression should be specifically directed at somatic symptoms. Cognitive depressive symptoms, such as feelings of worthlessness and suicidal ideation, have been specific targets for intervention in psychotherapy,[29] while exercise interventions, for example, may specifically improve somatic symptoms, perhaps even irrespective of depression.[22, 30] However, interventions for depression such as cognitive behavioral therapy or antidepressant medication therapy probably affect both cognitive and somatic symptoms, so the specificity with which somatic symptoms can be targeted with standard interventions for depression is unclear. Perhaps efforts should be made to improve rates of exercise uptake in patients with CHD, regardless of depression status, particularly given the known CHD benefits of exercise and the very low rate of adherence to this basic recommendation in both depressed and nondepressed patients.

To achieve a better understanding of the syndrome of depression and to develop effective treatments, it is important to identify potential mechanisms that may underlie the association between depression and coronary disease.[31] Earlier studies examined how depression may lead to adverse clinical outcome.[32-35] In a previous report from the Heart and Soul Study it was concluded that somatic depressive symptoms were associated with lower heart rate variability, whereas cognitive depressive symptoms were not.[19] There are also studies that point to inflammation as an important mechanism underlying the relation between depression and CV prognosis.[36] Inflammation also may be more strongly associated with somatic than with cognitive depressive symptoms.[33] Taken together, these results suggest that individual symptoms of depression may have differential associations with several mechanisms, leading to a worse cardiac prognosis. Understanding the mechanisms that may lead to the worse cardiac prognosis observed in depressed patients with CHD will be crucial for the design of future trials. [31] Future studies are therefore needed to evaluate the mechanisms that may be involved in the deleterious effects of sleeping difficulties, fatigue, appetite problems and psychomotor changes on CV prognosis.

The strengths of this study include the cohort size, the prospective ascertainment of CV morbidity and mortality with a large number of events, and the detailed baseline assessment that allowed adjustment for important confounding variables. However, some limitations of this study should be noted. First, this study included only outpatients with stable CHD, so

we cannot comment on the differential effects of depressive symptoms in healthy people or in patients after acute coronary syndromes. Second, the participants in this study were mainly older men. Therefore, the results may not be generalizable to women or to other patient populations. However, we adjusted for age and sex and found no indication for any interaction with age or sex. Third, although depressive symptoms are independently associated with poor CV prognosis in patients with CHD, we cannot completely rule out the possibility that this association is confounded by worse underlying CV disease[37] or other comorbidities.[38] Finally, although the HRs and p values suggest that somatic symptoms were more strongly associated with CV prognosis than cognitive symptoms, the CIs surrounding these estimates had substantial overlap, so further research is necessary before any definitive conclusions can be drawn.

In conclusion, we found that somatic symptoms of depression were responsible for the increased risk of CV events in patients with stable CHD. Hopefully, this finding will lead to the development of new treatments for depression in patients with CHD. The results of this study indicate the need for future research directed at the identification of the underlying pathophysiological processes by which somatic depressive symptoms contribute to prognosis in patients with CHD and to the testing of interventions to alleviate the associated risk.

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Chapter 4

Interview-based ratings of somatic and cognitive symptoms of depression and their impact on cardiovascular prognosis

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LETTER TO THE EDITOR

Evidence indicates that self-reported somatic/affective but not cognitive/affective symptoms of depression are highly prevalent in cardiac patients,[1] and are predictive of cardiovascular mortality and cardiac events, even after somatic health status has been controlled for.[2, 3] Recently, these findings were replicated in two independent samples of post-MI (myocardial infarction) patients[4, 5] and in patients with chronic heart failure.[6] These findings may help to develop symptom-targeted interventions to reduce both depression and cardiac disease progression. However, one major disadvantage of the analyses conducted so far is that they relied on self-report instruments such as the Beck Depression Inventory (BDI). A drawback of self-reported depressive symptoms is that no weighing of symptoms is performed, as is carried out when establishing a psychiatric diagnosis with a structured interview. In the latter, symptoms only count when they are present most of the time, for at least two weeks, affect daily functioning and are not a consequence of a physical condition. As a result, it remains unclear to what extent findings using self-reported symptoms reflect clinically meaningful information.

We therefore evaluated the independent association between cardiovascular prognosis and ratings of the individual depressive symptoms based on a structured diagnostic interview. We used data from the Depression after Myocardial Infarction study (DepreMI), a naturalistic follow-up study which took place in four hospitals in the northern part of the Netherlands.[7] The study included 468 MI patients, of whom 118 met DSM-IV criteria for post-MI depressive disorder, and 115 had a cardiac event during a mean follow up of 2.5±0.8 years. We used an adapted version of the Composite International Diagnostic Interview (CIDI) version 1.1, a fully standardized psychiatric diagnostic interview that can be used to assess mental disorders according to the definitions and criteria of DSM-IV.[8] The CIDI is recommended for epidemiologic research that requires diagnostic measures of depression and for which the time and resources to diagnose depression are available.[9] A specific advantage of the version used in the DepreMI study is that each individual symptom of depression was assessed in all participants, in contrast with most of the psychiatric interviews, which terminate the depression section when no core symptoms of depression are present.

Based on our previous work, we computed sum scores for the presence of cognitive symptoms (lack of interest, depressed mood, worthlessness, concentration problems, suicidal ideation; score range 0-5) and somatic symptoms (sleeping difficulties, fatigue, appetite problems, psychomotor changes; score range 0-4). Cox regression analyses were conducted to evaluate the associations of the somatic and cognitive sum scores with the risk of subsequent cardiovascular events. To further pinpoint the potential effects, the

association of each individual depressive symptom with prognosis was evaluated on an explorative basis. In univariate analyses, interview ratings of somatic symptoms were found to be associated with poor cardiovascular prognosis (HR=1.28; p=0.002), while ratings of cognitive symptoms were not (HR=1.11; p=0.102). After adjustment for confounders (age, gender, left ventricular ejection fraction, history of MI, Killip class, history of diabetes, anterior site of MI, smoking, hypertension, dyslipidemia and BMI), both somatic and cognitive symptom ratings were found to be associated with adverse cardiac outcome (HR=1.38, p=<0.001 and HR=1.19, p=0.014, respectively) (Table 1). Multivariate analyses revealed the following somatic depressive symptoms to be significantly associated with cardiovascular events (ranked by HR): psychomotor agitation/retardation, fatigue, and appetite problems. Importantly, two cognitive depressive symptoms were also significantly associated with cardiovascular events: lack of interest and suicidal ideation (Table 1).

Table 1. Association of specific depressive symptoms with cardiac death or events

	Univariate model 1		Multivariate model 2[1]	
	HR (95% CI)	p	HR (95% CI)	p
Somatic symptoms				
Psychomotor agitation/retardation	1.91 (1.29-2.83)	0.001	2.14 (1.44-3.20)	<0.001
Fatigue	1.47 (1.00-2.16)	0.049	1.89 (1.26-2.83)	0.002
Appetite problems	1.51 (1.04-2.19)	0.031	1.49 (1.01-2.21)	0.047
Sleeping difficulties	1.12 (0.77-1.64)	0.560	1.21 (0.81-1.80)	0.356
Sum score	1.28 (1.10-1.50)	0.002	1.38 (1.18-1.62)	<0.001
Cognitive symptoms				
Lack of interest	1.63 (1,11-2.39)	0.014	1.66 (1.11-2.48)	0.015
Suicidal ideation	1.35 (0.91-2.01)	0.135	1.54 (1.00-2.37)	0.048
Worthlessness	1.36 (0.90-2.07)	0.159	1.33 (0.86-2.07)	0.198
Concentration problems	1.13 (0.77-1.65)	0.539	1.36 (0.89-2.08)	0.158
Depressed mood	0.94 (0.64-1.39)	0.769	1.06 (0.69-1.63)	0.778
Sum score	1.11 (0.98-1.25)	0.102	1.19 (1.04-1.36)	0.014

HR= hazard ratio; CI= confidence interval.

[1] Included confounders: age, gender, left ventricular ejection fraction, history of myocardial infarction, Killip class, history of diabetes, anterior site of myocardial infarction, smoking, hypertension, dyslipidemia, and BMI as covariates

Thus, using symptom-specific data from a structured diagnostic interview the following findings were obtained. First, we confirmed that, after adjusting for potential confounders, the presence of somatic symptoms of depression was associated with an increased risk of cardiovascular events. Second, in contrast with previous studies using self-report

data, interview ratings of cognitive symptoms of depression were also associated with a significantly increased risk in multivariate analysis, although less strongly than somatic symptoms (HR 1.20 vs. 1.39, respectively). Third, contrary to previous studies, adjustment for potential confounders resulted in higher effect estimates, while generally in studies using self-report data adjustment leads to lower estimates.

These discrepancies may be explained by the fact that interview-based symptoms are based on strict criteria derived from the DSM, based on their presence, severity, consequences and etiology. This may result in less attenuation of the estimates by potential confounders compared to self-report data. The use of interview-based measurement may be more sensitive in detecting clinically relevant cognitive symptoms and it is possible that these clinically relevant cognitive symptoms result in a higher level of cardiotoxicity.

The recent distinction between somatic and cognitive symptoms supports the conceptualization of depression as a heterogeneous syndrome, in which some symptoms are more related to cardiovascular prognosis than others. It is possible that, in order to improve cardiovascular outcome, interventions for depression should be directed at specific depressive symptoms. Cognitive symptoms have been specific targets for intervention in psychotherapy, while exercise interventions (for example) may improve somatic symptoms in particular. However, cognitive-behavioral therapy potentially affects both cognitive and somatic symptoms, with some variation due to different foci of attention (e.g. behavioral activation vs. cognitive therapy). The specificity with which specific depressive symptoms could be targeted with standard interventions is unclear, but might have important implications for improving cardiovascular prognosis.

In conclusion, when using a structured diagnostic interview, both somatic and cognitive symptoms of depression were associated with adverse cardiac outcome after adjusting for potential confounders. In contrast to previous studies, the findings were actually strengthened in the multivariate model. As yet, cognitive symptoms of depression cannot be simply discarded as risk factors for heart disease progression. Rather, we argue that for a better understanding of the association between depression and cardiovascular disease progression, a more thorough assessment of depressive symptoms is needed by using interview-based ratings in addition to self-report data.

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Part II

Telomere length as a possible mechanism

Chapter 5

Depression and leukocyte telomere length in patients with coronary heart disease: data from the Heart and Soul study

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ABSTRACT

Objective | Shortened telomere length has been associated with mortality in patients with coronary heart disease (CHD) and is considered as an emerging marker of biological age. Whether depression is associated with telomere length or trajectory has not been evaluated in patients with CHD.

Methods | In a prospective cohort study, we measured leukocyte telomere length in 952 participants with stable CHD at baseline and in 608 of these participants after 5 years of follow-up. The presence of major depressive disorder in the past month was assessed using the computerized Diagnostic Interview Schedule at baseline. We used linear and logistic regression models to evaluate the association of depression with baseline and 5-year change in leukocyte telomere length.

Results | Of the 952 participants, 206 (22%) had major depression at baseline. After the adjustment for age and sex, the patients with current major depressive disorder had shorter baseline telomere length than those without depression (mean ± SE: 0.86±0.02 versus 0.90±0.01, P=0.02). This association was similar (but no longer statistically significant) after adjustment for body mass index, smoking, diabetes, left ventricular ejection fraction, statin use, antidepressant use, physical inactivity, and anxiety (0.85±0.02 versus 0.89±0.01, P=0.06). Depression was not predictive of 5-year change in telomere length after adjustment for the mentioned covariates and baseline telomere length.

Conclusions | Depression is associated with reduced leukocyte telomere length in patients with CHD but does not predict 5-year change in telomere length. Future research is necessary to elucidate the potential mechanisms underlying the association between depression and telomere length.

INTRODUCTION

Telomeres are specialized tandem deoxyribonucleic acid (DNA) repeat sequences (TTAGGG) n located at the ends of eukaryotic chromosomes, which protect somatic cells from genomic instability during mitotic cell proliferation.[1] During mitosis the telomere is not fully replicated because of the inherent properties of DNA polymerase, resulting in obligate telomere shortening with each cell division. Eventually, telomere shortening can result in cessation of mitosis (senescence) or programmed cell death (apoptosis).[2] Thus, telomere attrition has been proposed as the basis for a 'biological clock' that integrates the cumulative effect of environmental stressors independently of chronological age.[3]

Since the discovery of telomeres, there is a growing body of literature linking shortened telomeres with increased age-related morbidity and mortality. Previous studies have found that psychological distress is associated with short telomere length in otherwise healthy adults[4-6] and in older patients with heart failure.[7] However, the association between depression and telomere length has not been evaluated in patients with coronary heart disease (CHD). Furthermore, the effect of depression on subsequent change in telomere length over time has not been examined in any patient population. Evaluating this effect is of importance for our understanding of human telomere biology over time in depressed patients.

Both depression and short telomere length predict mortality in patients with CHD.[8-11] Whether depression is associated with leukocyte telomere length or telomere trajectory among patients with stable CHD is unknown. We sought to investigate the association among depression, telomere length, and telomere trajectory in a prospective cohort study of patients with stable CHD. In addition, we evaluated whether differences in leukocyte telomere length might contribute to the adverse cardiovascular outcomes associated with depressive symptoms.

METHODS

Design and participants

The Heart and Soul Study is a prospective cohort study focused on psychosocial factors and health outcomes in patients with stable CHD. Details regarding the study design have been described previously.[12] Between September 2000 and December 2002, 1024 patients were recruited from 12 outpatient clinics in San Francisco Bay Area. Inclusion criteria were history of myocardial infarction (MI) or coronary revascularization, angiographic evidence of at least 50% stenosis in at least one coronary vessel, or a diagnosis of CHD by an internist or

cardiologist. Patients were excluded if they had a history of MI in the past 6 months, were unable to walk one block, or were planning to move out of the local area within 3 years. Patients underwent a baseline study examination that included a comprehensive health interview, blood samples, medical history, questionnaire, psychosocial questionnaire, and exercise treadmill test with stress echocardiography. Of the 1024 enrolled patients, 954 provided DNA samples for analysis at baseline, and 608 of these participants provided DNA samples again after 5 years of follow-up.[13] The study protocol was approved by the appropriate institutional review boards, and all participants signed an informed consent.

Assessment of depression

We ascertained the presence of major depressive disorder (MDD) in the past month according to Diagnostic and Statistical Manual, Fourth Edition, criteria. We used the modified Computerized National Institute of Mental Health Diagnostic Interview Schedule (CDIS-IV), a highly structured interview designed to yield psychiatric diagnosis.[14] The CDIS-IV is a validated computerized version of the health care professional-administered, structured clinical interview for the diagnosis of psychiatric illness. Trained research assistants administered the interview during the daylong study appointment. We also assessed the presence and severity of depressive symptoms using the nine-item Patient Health Questionnaire (PHQ-9).[15] The PHQ-9 is a self-report checklist derived from the Primary Care Evaluation of Mental Disorders interview.[16] The PHQ-9 measures the presence of depressive symptoms during the previous two week (0 = not at all, 1 = several days, 2 = more than half the days, 3 = nearly every day). We evaluated PHQ as a continuous variable (range = 0-27).

Telomere length assay

Details regarding telomere length assay in the Heart and Soul Study have been described previously.[13] Telomere length measurements were performed in a blinded fashion without knowledge of depression status. According to standard procedures, genomic DNA was isolated from the peripheral blood leukocytes that were stored at -70 degrees Celsius. Purified DNA samples were diluted in 96-well microtiter source plates to a fixed concentration of 3 ng/ul. A quantitative polymerase chain reaction-based assay was used to measure relative mean telomere length. This assay compares the mean telomere repeat sequence copy number (T) to a reference single copy gene copy number (S) in each sample. Standard curves were derived from serially diluted reference DNA. The T/S ratio was calculated from the average quantity of the reference DNA found to match with each experimental sample for the copy number of the targeted template (for T: the number of telomere repeats, and for S: the number of β-globin gene copies). The equation for conversion from T/S ratio to base pairs for this study was base pairs = 3274+2413*(T/S).[13] The inter-assay coefficient of variability for telomere length measurement was 3.7%, and the intra-assay coefficient of variability was 2.5%.

Other baseline characteristics

Age, sex, ethnicity, education, smoking status, and alcohol use were determined by questionnaire. Weight and height were measured, and body mass index (BMI, kg/m²) was calculated. Comorbid conditions were determined by self-report and included hypertension, MI, congestive heart failure, and diabetes mellitus. Anxiety was assessed with the Hospital Anxiety and Depression Scale (HADS). We assessed left ventricular ejection fraction (LVEF) using a resting echocardiography. Resting systolic and diastolic blood pressure was measured manually using a standard sphygmomanometer. To assess physical activity, we asked, "Which of the following statements best describes how physically active you have been during the last month, that is, done activities such as 15 to 20 minutes of brisk walking, swimming, general conditioning, or recreational sports?" The participants chose from one of the following six categories: not at all active, a little active (1-2 times per month), fairly active (3-4 times per month), quite active (1-2 times per week), very active (3-4 times per week), or extremely active (≥5 times per week). Self-report has been shown to be a reliable, valid, and accurate method of assessing physical activity.[17, 18] The participants who reported that they were not at all or a little active were considered physically inactive. Low- and high-density lipoprotein cholesterol levels were determined from fasting venous blood samples. The participants were instructed to bring their medication bottles to their appointment, and study personnel recorded all current medications, including dose and frequency use.

Hearth failure and death

To determine whether differences in leukocyte telomere length might contribute to the adverse cardiovascular outcomes associated with depressive symptoms, we evaluated the association of depressive symptoms with mortality before and after adjustment for baseline telomere length. Annual telephone interviews were conducted with participants or their proxies asking about emergency department visits, hospitalizations, or death. For any reported event, medical records, death certificates, and coroner's reports were reviewed by two independent blinded adjudicators. In the event of disagreement, a third blinded adjudicator reviewed the event and determined the outcome variable. To be diagnosed with heart failure, patients had to be hospitalized for a clinical syndrome involving an acute change in at least two of the following: paroxysmal nocturnal dyspnea, orthopnea, elevated jugular venous pressure, pulmonary rales, third heart sound, cardiomegaly, or pulmonary edema on chest radiography. Death was confirmed by review of death certificates.

Statistical analyses

For descriptive purposes, the participants were grouped based on the presence or absence of current major depression (by CDIS-IV) and compared on clinical and demographic variables, using T tests and X^2 tests. Telomere length was normally distributed. For primary

analyses, the association between depression and mean telomere length at baseline was examined using generalized linear models (for telomere length as a continuous variable) and logistic regression for short telomere length, defined a priori as having leukocyte telomere length in Quartile I versus IV.

Percent change in telomere length was calculated as [(follow-up T/S - baseline T/S) x 100] divided by baseline T/S. The association between depression and 5-year change in telomere length was assessed using generalized linear models (for percent change in telomere length as a continuous variable) and logistic regression models for predicting telomere shortening (defined a priori as a > 10% decrease in telomere length) versus maintained (± 10% change in telomere length) or lengthened (>10% increase in telomere length).[13] For multivariable models, the following covariates were chosen based on cross-sectional associations with telomere length and depression: age, sex, diabetes, BMI, smoking, LVEF, statin use, antidepressant use, physical inactivity, and anxiety.[9] To determine whether the effect of depression on telomere trajectory differed in patients with shorter or longer baseline telomere length, we tested an interaction term (depression x baseline telomere length) as a predictor of shortening.

We have previously reported that depressive symptoms, but not MDD, predict subsequent heart failure and death in the Heart and Soul Study.[18] To evaluate whether telomere length may be a mediator in this association, we estimated the association of depressive symptoms with heart failure or death using Cox proportional hazards models, with and without adjustment for baseline telomere length. Statistical analyses were performed using SAS software version 9.1 (SAS Institute inc, Cary, North Carolina).

RESULTS

Of the 954 patients who provided DNA samples for analysis at baseline, two had no CDIS measurement, leaving 952 patients to be included in further analyses. The baseline characteristics of the study population categorized by current depression are presented in Table 1. Of the 952 patients, 206 (22%) participants had current (past month) depression. Compared with participants who did not have depression, those with depression were younger and less likely to be male. They were more likely to have higher LVEF, to smoke, to have diabetes mellitus, to have a higher anxiety score, to use antidepressants, and to be physically inactive, but less likely to use statins.

Table 1. Baseline characteristics of 952 participants with baseline measurement of telomere length

Variable	Current depression (n=206)	No current depression (n=746)	p
Demographic characteristics			
Age (years)	61.7±10.8	68.1±10.6	<0.001
Male	143(69%)	632(85%)	<0.001
White	124(60%)	449(60%)	0.98
High school graduate	182(88%)	646(87%)	0.56
Body mass index (kg/m^2)	29.01±5.66	28.31±5.31	0.10
Regular alcohol use	60(29%)	216(29%)	0.98
Current smoking	58(28%)	131(18%)	<0.001
Comorbid conditions			
Hypertension	146(71%)	526(71%)	0.96
Myocardial infarction	100(49%)	408(55%)	0.13
Congestive heart failure	37(18%)	126(17%)	0.72
Diabetes mellitus	66(32%)	186(25%)	0.04
Anxiety score	8.90±4.09	4.45±3.30	<0.001
PHQ score	10.73±5.58	3.53±4.12	<0.001
Cardiac disease severity and risk factors			
Resting left ventricular ejection fraction	0.63±0.07	0.61±0.10	0.005
Low-density lipoprotein cholesterol (mg/dl)	107.54±36.74	103.31±32.84	0.12
High-density lipoprotein cholesterol (mg/dl)	45.35±14.84	45.63±13.93	0.80
Systolic blood pressure	132.84±21.90	133.06±20.93	0.90
Diastolic blood pressure	75.26±11.96	74.43±11.23	0.36
Physical inactivity	95(45%)	250(34%)	0.002
Medication use			
Aspirin	158(77%)	574(77%)	0.94
Beta blocker	114(55%)	433(58%)	0.49
Renin-angiotensin system inhibitor	102(50%)	386(52%)	0.57
Statin	119(58%)	492(66%)	0.03
Antidepressant use	99(48%)	78(10%)	<0.001

SD= standard deviation; PHQ= Patient Health Questionnaire.
Data are presented as N (%) or mean ± SD

Depression and baseline telomere length

After adjustment for age and sex, patients with current MDD had shorter telomere length than patients without current depression (mean ± SE: 0.86±0.02 versus 0.90±0.01, P=0.02). This association was similar (but no longer statistically significant) after further adjustment

for BMI, smoking, diabetes, LVEF, statin use, antidepressant use, physical inactivity, and anxiety (0.85±0.02 versus 0.89±0.01, P=0.06) (Table 2). The difference of 0.04 T/S units is comparable with 97 base pairs. Compared with nondepressed participants, those with major depression had a 71% greater odds of having short telomere length (adjusted OR:1.71; 95% CI: 0.98-2.98; p=0.06) (Table 3). When entered as a continuous variable, higher depressive symptom scores were also associated with shorter telomere length, adjusted for age, sex, diabetes, BMD, smoking, LVEF, and statin use (beta coefficient = -0.00297; p=0.03). Again, this association was no longer statistically significant after further adjustment for antidepressant use, physical inactivity and anxiety (beta coefficient = -0.00231; p=0.17).

Table 2. Telomere length (analyzed as a continuous variable, mean +/- standard error) by the presence of major depressive disorder among 952 participants at baseline

Adjusted for	Current depression (n=206)	No current depression (n=746)	p
Age, sex	0.86±0.02	0.90±0.01	.02
Age, sex, diabetes, BMI, smoking	0.86±0.02	0.89±0.01	.04
Age, sex, diabetes, BMI, smoking, LVEF, statin use, physical inactivity, and antidepressant use	0.85±0.02	0.89±0.01	.04
Age, sex, diabetes, BMI, smoking, LVEF, statin use, physical inactivity, antidepressant use, and anxiety	0.85±0.02	0.89±0.01	0.06

BMI= body mass index; LVEF= left ventricular ejection fraction.

Table 3. Association between major depressive disorder and short telomere length (analyzed as a dichotomous variable, Quartile I versus IV)

Adjusted for	Odds Ratio (95% CI)	p
Age, sex	1.73 (1.08-2.79)	0.02
Age, sex, diabetes, BMI, smoking	1.65 (1.03-2.67)	0.04
Age, sex, diabetes, BMI, smoking, LVEF, statin use, physical inactivity, and antidepressant use	1.72 (1.02-2.89)	0.04
Age, sex, diabetes, BMI, smoking, LVEF, statin use, physical inactivity, antidepressant use, and anxiety	1.71 (0.98-2.98)	0.06

CI= confidence interval; BMI= body mass index; LVEF= left ventricular ejection fraction.

Depression and 5-year change in telomere length

Of the 1024 original enrolees, 195 had died before the 5-year examination, and 667 (80%) of the eligible 829 participants completed the 5-year follow-up examination. Of the 667 participants who completed the 5-year examination, 59 were missing telomere length measurements at baseline and/or follow-up, leaving 608 participants for the analysis of 5-year change. Compared with the 221 participants who were alive at 5 years but not included in the analyses, these 608 participants had similar age and baseline telomere length.

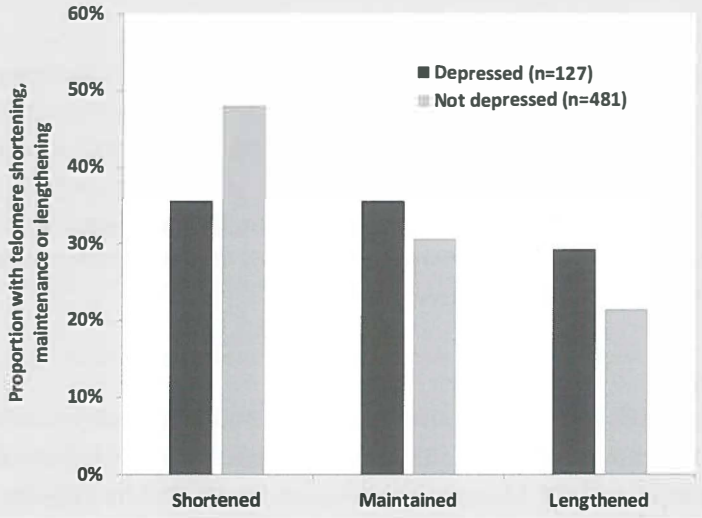
Overall, 276 participants (45%) experienced telomere shortening, 192 (32%) maintained their telomere length (±10%), and 140 experienced telomere lengthening (23%). Compared with the 481 nondepressed participants, the 127 participants with MDD at baseline were less likely to experience telomere shortening (35% vs. 48%) and more likely to experience telomere lengthening (26% vs. 21%) (Figure 1). After adjustment for age, sex, diabetes, BMI, smoking, LVEF, statin use, antidepressant use, physical inactivity, and anxiety, MDD was associated with a 32% decreased odds of shortening. However, this association was not significant after further adjustment for shorter baseline telomere length in the depressed participants (OR: 0.76; 95% CI: 0.40-1.44; p=0.40) (Table 4).

Table 4. Association between major depressive disorder and subsequent shortening in leukocyte telomere length (>10% decrease)

Adjusted for	Odds ratio (95% CI)	p
Age, sex	0.66 (0.43-1.00)	0.05
Age, sex, diabetes, BMI, smoking	0.67 (0.44-1.01)	0.06
Age, sex, diabetes, BMI, smoking, LVEF, statin use, physical inactivity, and antidepressant use	0.63 (0.40-0.99)	0.04
Age, sex, diabetes, BMI, smoking, LVEF, statin use, physical inactivity, antidepressant use, and anxiety	0.68 (0.42-1.12)	0.13
Age, sex, diabetes, BMI, smoking, LVEF, statin use, physical inactivity, antidepressant use, anxiety, and baseline telomere length	0.76 (0.40-1.44)	0.40

CI= confidence interval; BMI= body mass index; LVEF= left ventricular ejection fraction

Figure 1. Proportion of participants who experienced telomere shortening, maintenance or lengthening during 5 years of follow-up (p=0.03 from overall chi square), unadjusted for age or baseline telomere length



When the 5-year percent change in telomere length was analyzed as a continuous variable, participants with MDD were also less likely to experience telomere shortening than those without depression (percent change: -0.9±2.4% versus -6.6±1.9%; p=0.03), adjusted for age, sex, diabetes, BMI, smoking, LVEF, statin use, antidepressant use, physical inactivity, and anxiety. Again, this association was no longer significant after adjustment for shorter baseline telomere length in the depressed participants (percent change = -3.0±1.7% versus -5.6±1.3%; p=0.13) (Table 5). We found no evidence that the effect of depression on change in telomere length differed in patients with shorter or longer baseline telomere length (p for interaction = 0.78).

Table 5. Five-year change in telomere length (analyzed as a continuous variable) by the presence of major depressive disorder among 608 participants who provided follow-up DNA samples

Adjusted for	Current depression (n =127)	No current depression (n=481)	p
Age, sex	- 0.6% ± 2.0%	-5.2% ± 1.3%	0.03
Age, sex, diabetes, BMI, smoking	-1.9% ± 2.2%	-6.1% ± 1.6%	0.05
Age, sex, diabetes, BMI, smoking, LVEF, statin use, physical inactivity, and antidepressant use	-1.1% ± 2.2%	-6.5% ± 1.9%	0.02
Age, sex, diabetes, BMI, smoking, LVEF, statin use, physical inactivity, antidepressant use, and anxiety	-0.9% ± 2.4%	-6.6% ± 1.9%	0.03
Age, sex, diabetes, BMI, smoking, LVEF, statin use, physical inactivity, antidepressant use, anxiety, and baseline telomere length	-3.0% ± 1.7%	-5.6% ± 1.3%	0.13

Data are presented as mean (standard error of the mean)
DNA= deoxyribonucleic acid; BMI= body mass index; LVEF= left ventricular ejection fraction.

Depressive symptoms and cardiovascular outcomes

As of December 18 2009, vital status was known for 949 (>99%) of the 954 study participants, and there were 277 deaths. Each standard deviation (5.5-point) increase in PHQ depressive symptom score was associated with a 16% increased rate of death (age-adjusted HR: 1.16; 95% CI: 1.04-1.31; p=0.01) and a 24% increased rate of heart failure (HR:1.24; 95% CI: 1.07-1.45; p=0.006). The adjustment for shorter baseline telomere length in the depressed patients did not affect these associations (HR:1.14; 95% CI: 1.01 – 1.28; p=0.03 for death; HR:1.23; 95% CI: 1.05-1.44; p=0.009 for heart failure).

DISCUSSION

In a sample of 952 patients with stable CHD, we found that major depression was associated with a 71% greater odds of having short telomere length. The participants with major

depression had an average telomere length that was 97 base pairs shorter than those without depression. Assuming an average rate of loss of around 42 base pairs per year,[13] this indicates that their leukocytes had aged the equivalent of 2.3 additional years, compared with patients without depression.

Depression and baseline telomere length

Previous cross-sectional studies have found that psychosocial factors are associated with shorter telomere length, but the relation between depression and telomere length has not previously been evaluated in patients with CHD. Epel et al. demonstrated that the chronicity and perceived severity of psychosocial stress was directly associated with accelerated telomere shortening in middle-aged healthy women (n = 65).[4] Simon et al. measured leukocyte telomere length in 44 individuals with chronic mood disorders and 44 nonpsychiatric ill age-matched control subjects and found that telomere length was significantly shorter in those with mood disorders.[6] Lung et al found an association between depression and short telomere length among 253 depressed patients compared with 411 community controls.[5] Another study found that poor perceived mental health, but not depressive symptoms, was associated with shorter telomere length in 890 patients with congestive heart failure.[7] Our study adds to this growing literature by demonstrating that depression is associated with short telomere length in patients with CHD. In addition, our findings demonstrate that, although associated with shorter baseline telomere length, current depression does not predict subsequent shortening.

Underlying mechanisms

Further research is necessary to examine the mechanisms underlying the association between depression and reduced telomere length in CHD patients. Potential links between depression and shortened telomere length could be oxidative stress and inflammation.[19] Previous studies have demonstrated an association between depression and oxidative stress. Depressed patients have increased levels of circulating oxidative stress markers and decreased levels of anti-oxidant enzymes.[20-22] In addition, some, but not all studies, have found that depression is associated with increased levels of pro-inflammatory cytokines.[23, 24] Both oxidative stress and pro-inflammatory cytokines have been found to influence telomere length. Oxidative stress has a negative effect on telomere length, through inhibition of telomerase activity[25] and direct erosion of GGG triplets in telomeric DNA.[26] Pro-inflammatory cytokines may either decrease or increase telomerase activity[27-29] and are thought to lead to immune cell turnover, and thus decreased telomere length through greater replicative history.

Depression and 5-year change in telomere length

Little is known concerning the dynamic regulation of telomere length over time. Recently, it has become apparent that telomeres may lengthen as well as shorten.[13, 30] In our sample, less than half of the participants experienced telomere shortening, and almost a quarter actually lengthened their telomeres during the 5-year follow-up period. In this longitudinal study we observed that MDD was associated with a 32% decreased odds of shortening (i.e., greater odds of lengthening). However, short baseline telomere length is by far the strongest predictor of subsequent lengthening, and this association was not significant after further adjustment for shorter baseline telomere length in depressed participants. Therefore, depression does not seem to predict 5-year subsequent change in telomere length independently. These findings are in concordance with the previous studies that found that telomere trajectory is powerfully influenced by baseline telomere length and that both healthy individuals and CHD patients with the longest telomeres experienced the greatest amount of shortening, whereas those with shorter telomeres either maintained or increased in their length.[13, 13, 30, 30, 31]

An important regulator of this negative feedback is the enzyme telomerase, which is a reverse transcriptase enzyme that restores telomere length. Telomerase has been shown to act preferentially on short telomeres in mice models and cell culture systems.[32-35] Moreover, chronically stressed caregivers who are also high in depressive symptoms have increased levels of telomerase.[36] Thus, it is possible that depression may have contributed to shorter baseline telomeres, but over a follow-up time of 5 years, the subsequent negative feedback from those short telomeres may overwhelm any independent effect on trajectory. Alternatively, the current findings are consistent with a model in which depression is a consequence of short telomeres or in which a shared (genetic) risk factor is responsible for both depression and short telomere length at baseline.

Depression and mortality

Currently, a large body of literature has confirmed that depressive symptoms are associated with greater mortality among patients with established CHD.[8, 11] A recent study showed that shorter telomere length was associated with all-cause mortality and heart failure in patients with stable CHD.[9] Because depression is associated with shorter telomere length, this raises the question of whether accelerated cellular aging is a mechanism that contributes to the excess morbidity and mortality associated with depression.[6, 37] To our knowledge, we are the first study that evaluates whether shortened telomere length may potentially underlie the relationship between depression and heart failure and mortality. Adjustment for baseline telomere length in the depressed patients did not affect the association between depression and prognosis.

Strengths and limitations

Our study has several strengths, including repeated measurements of telomere length; measurement of multiple potential confounding variables including BMI, LVEF, smoking, and physical inactivity; and detailed assessments of depression. However, some limitations of this study should be noted. First, this study included stable CHD patients, and mainly older men. Thus, the results may not generalize to women or to healthy or acute coronary syndrome populations. Second, we did not measure the impact of telomerase activity on the prognostic value of leukocyte telomere length. Third, telomere length measurements were restricted to circulating leukocytes, do not necessarily reflect telomere length in other cell compartments, and do not inform about accelerated aging of any particular immune cell subpopulation. Fourth, the association between depression and shortened telomere length may have been the result of greater cardiac disease severity in depressed patients, although we attempted to address this possibility by carefully measuring and adjusting for cardiovascular disease severity. Fifth, the severity of depressive symptoms was relatively low with an average PHQ score of 10.7 among depressed participants. Finally, we did not assess the chronicity or duration of depression at the baseline examination nor did we account for continued depression or other psychiatric diagnoses at follow-up.

CONCLUSIONS

To our knowledge, this is the first study to examine and report an association between depression and telomere length in patients with stable CHD. In summary, we found that patients with current depression had a shorter telomere length at baseline. However, current depression did not predict subsequent change in telomere length. Future research is necessary to elucidate the mechanism underlying the association between depression and telomere length.

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Chapter 6

Association between anxiety but not depressive disorders and leukocyte telomere length after two years follow-up in a population based sample

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ABSTRACT

Background | Telomere length is considered an emerging marker of biological aging. Depression and anxiety are associated with excess mortality risk, but the mechanisms remain obscure. Telomere length might be involved, since it is associated with psychological distress as well as with mortality. The aim of this study was to test whether anxiety and depressive disorders predict telomere length over time in a large population based sample.

Methods | All analyses were performed in a longitudinal study in a general population cohort of 974 participants. The Composite International Diagnostic Interview was used to measure the presence of anxiety and depressive disorders. Telomere length was measured using monochrome multiplex polymerase chain reaction at approximately 2 years follow-up. We used linear multivariable regression models to evaluate the association between anxiety and depressive disorders and telomere length, adjusting for adverse life events, lifestyle factors, educational level and antidepressant use.

Results | The presence of anxiety disorders predicted shorter telomeres at follow-up (β=-0.073, t=-2.302, p=0.022). This association was similar after controlling for adverse life events, lifestyle factors, educational level and antidepressant use (β=-0.077, t=-2.144, p=0.032). No association was found between depressive disorders and telomere shortening at follow-up (β=0.010, t=0.315, p=0.753).

Conclusion | This study found that anxiety disorders predicted shorter telomere length at follow-up in a general population cohort. The association was not explained by adverse life events, lifestyle factors, educational level and antidepressant use. How anxiety disorders might lead to accelerated telomere shortening and whether this might be a mediator explaining the excess mortality risk associated with anxiety deserves further investigation.

INTRODUCTION

Telomeres are simple repetitive sequences (TTAGGG) at the ends of eukaryotic chromosomes. They protect somatic cells from genomic instability during mitotic cell proliferation.[1] Telomeres progressively shorten with each mitotic division due to the limiting nature of linear DNA replication mechanisms. After a critical degree of telomere shortening, cells lose the ability to replicate and may cease dividing (senescence) or undergo programmed cell death.[2] Telomere shortening has therefore been proposed as a marker of biologic aging.[3] In support of this notion, shorter leukocyte telomere length has been shown to be associated with age-related morbidity and mortality.[4]

The question arises which factors influence the shortening of telomeres. Several studies have indicated that psychosocial stress is associated with shorter telomeres, and thereby increased biological age, in apparently healthy persons.[5, 6] The presence of depressive and anxiety disorders has been examined in relation to telomere length in only a few cross-sectional, non population based studies. Mood disorders seem to be associated with shorter telomere length,[7-10] although mixed findings have been reported.[11] Recently, one study focused on anxiety and telomere shortening but did not observe differences between cases and controls in the entire cohort.[12] Depression and anxiety are of particular interest in relation with telomere length, not only because these disorders are treatable to a certain degree, but also because they are associated with excess morbidity and mortality in the general population.[13-16]

To adequately address whether depression or anxiety are related to accelerated telomere shortening we study a large population based sample, with valid assessment of psychopathology and with telomere length measure after 2 years follow-up. In addition, we aim to gain more insight into the mediators involved in the process of telomere shortening by evaluating this prospective effect. Both depression and anxiety are associated with an unhealthy lifestyle,[17, 18] and telomere length might be affected by several lifestyle factors such as BMI, smoking, alcohol consumption, and exercise frequency.[19-22] Furthermore, factors related to anxiety and depression, such as medication use, might have an influence on telomere length. A better understanding could help explaining the excess mortality associated with depression and anxiety.

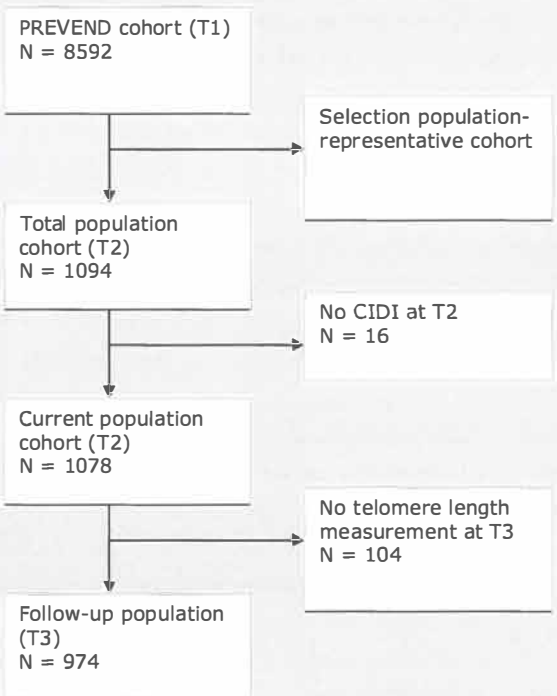
Therefore, we sought to investigate the prospective association between anxiety and depressive disorders and telomere length after 2 years follow-up in a population based sample. In addition, we evaluated whether the association was explained by adverse life events, lifestyle factors, educational level and medication use.

METHODS

Patients

The current study has been performed in a cohort derived from PREVEND (Prevention of Renal and Vascular End stage Disease). The PREVEND study is an ongoing prospective study investigating risk factors for renal and cardiovascular disease. The recruitment of participants for PREVEND has been extensively described elsewhere.[23] Three waves were available for this study: The baseline screening was completed in 1998 (T1), followed by two follow-up visits at 4.2 (T2) and 6.4 (T3) years from baseline (Figure 1, Figure 2).

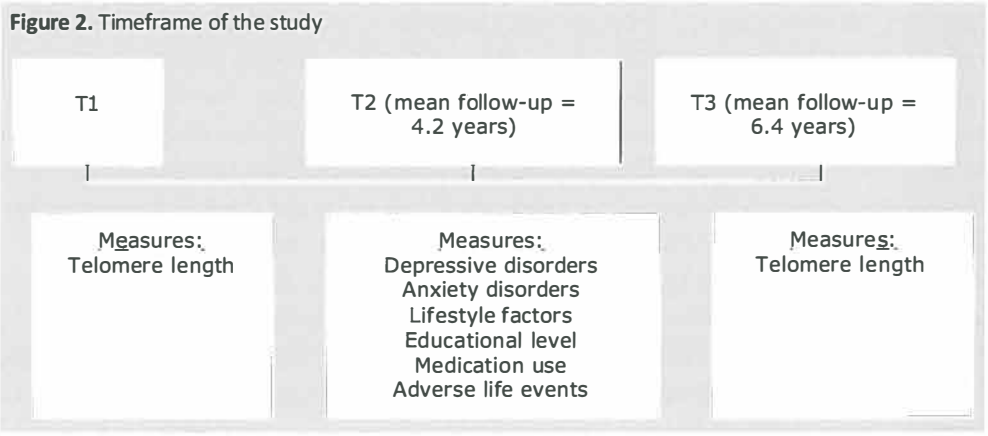
Figure 1. Flow chart representing the number of participants included in the analyses



The PREVEND sample consisted of 8592 subjects randomly selected from the population of the city of Groningen with oversampling for albuminuria (T1). Selection of subjects for the present study was aimed at recruiting a representative sample of the general population of Groningen, while simultaneously rectifying PREVEND's oversampling for albuminuria. Albuminuria-negative participants were combined with a random sample of albuminuria-positive participants until a population-representative ratio was achieved. Research assistants approached participants (n=2554) in the PREVEND study during their visit to the out-patient clinic during follow-up.

Questionnaires were completed by a total of 1094 participants (43%), forming the population cohort of the present study (T2). There was no significant difference in gender and age between PREVEND participants who were invited to participate in the present study but declined and PREVEND participants who agreed to participate.
Follow-up measurements were completed by a total of 974 participants (89%) at T3 (Figure 1). The study was approved by the medical ethics committee and written consent was obtained from all participants. We used data from T2 and T3 in our primary analyses. Data from T1 are used for a post-hoc analysis.

Figure 2. Timeframe of the study



Anxiety and depressive disorder

We ascertained the presence of depressive and anxiety disorders in the past 12 months, using the Composite International Diagnostic Interview (CIDI). The CIDI is a comprehensive, fully standardised psychiatric diagnostic interview that is used to assess mental disorders according to the definitions and criteria of the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV). A fully computerized version of the CIDI 2.1 was applied, suitable for self-administration. Trained interviewers were present for questions and for participants that needed computer help. The CIDI is used worldwide and WHO field research has found high interrater reliability,[24] high test–retest reliability,[25] and high validity for depressive and anxiety disorders.[26, 27] The CIDI, version 2.1, was administered at T2 (figure 2). Depressive disorders that were diagnosed included major depressive disorder and dysthymia. The anxiety disorders that were diagnosed with the CIDI used in this study included panic disorder, generalized anxiety disorder, social phobia, and agoraphobia. Of the 1094 enrolled participants, 1078 participants completed the CIDI (99%).

Telomere length

Telomere length measurements were performed in a blinded fashion. To avoid any impact of variation in DNA extraction method on telomere length measurement, all samples analyzed in the current study were extracted uniformly using the same DNA extraction kit (Qlamp, Qiagen, Venlo, The Netherlands) from frozen full-blood samples anticoagulated with EDTA according to the instructions of the manufacturer. DNA samples from different collection time points were mixed and randomly extracted to neutralize potential batch-effects. Mean telomere length was measured with the recently modified QPCR protocol using a single well strategy to measure both the telomere (T) and single reference (S) signal.[28] All experimental DNA samples were assayed in triplicate which were measured on different plates but in the same well position. Samples of the three different time points were equally divided over our PCR schedule to prevent potential time or seasonal influences. The ratio of telomere and single copy (reference) gene content (T/S ratio) is a relative measure of telomere length. Samples were run in triplicate and the intra-assay coefficient of variation was 2% (T), 1.9% (S) and 4.5% (T/S ratio). Reproducibility data was obtained for 216 subjects from PREVEND and good agreement between T/S ratios was observed (R^2=0.99, P<0.0001, inter-run CV 3.9%). The calibrator sample used was made up of a mixture of DNAs from young adult individuals (around 25 years). There was a highly significant decline in T/S ratio with age in PREVEND (-0.0047 (SE 0.0004) decrease in T/S ratio per year increase in age (P = 1.073x 10-28) confirming the internal validity of the assay. Of the 1078 participants, 974 participants provided DNA samples at T3.

Additional variables

Weight and height were measured and body mass index (BMI kg/m^2) was calculated. Smoking, alcohol consumption and exercise frequency were assessed by written self-report at T2. Smoking was categorised as non-smoker, 1-5, 6-10, 11-15, 16-20, or more than 20 cigarettes/day. Alcohol consumption was categorised in the following categories: never or almost never, 1-4 units/month, 2-7 units/week, 1-3 units/day and ≥4 units/day. Exercise frequency was categorised as never, once/week, twice or more/week. Educational level was retrieved from questionnaires. Low educational level was defined as lower secondary education or less, middle educational level was defined as higher secondary education, and high educational level was defined as tertiary education. Antidepressant medication use (nonselective monoamine-reuptake inhibitors, selective serotonin reuptake inhibitors, and monoaminde oxidase inhibitors) was derived from the InterAction database containing pharmacy-dispensing data.[29]

Adverse life events were assessed using the List of Threatening Experiences (LTE); a sum score of the LTE for each participant was calculated by adding the scores of all different life events of all the age-categories (with 5 age categories and 12 life events the maximum score 60).[30, 31]

Statistical analyses

Telomere length was not normally distributed and therefore natural log transformed. For descriptive purposes, participants were grouped based on the presence or absence of past year depressive or anxiety disorders (by CIDI) and compared on demographic variables and lifestyle factors, using T tests and X^2 tests. The association between depressive disorders, anxiety disorders and telomere length after 2 years follow-up was examined using multivariable regression analyses. Covariates that were known to be associated with telomere length, anxiety and/or depression in previous studies were chosen a priori. First, we adjusted for comorbid depressive or anxiety disorders, because the presence of these disorders showed substantial overlap, and for adverse life events.[12] Second, we adjusted for level of education[32] and for lifestyle factors, including BMI, smoking, alcohol consumption, and exercise frequency.[18-22, 33] Third, we adjusted for antidepressant use. All multivariable analyses were adjusted for the potential confounders gender and age.[34] We performed two post hoc analyses to further examine the association between anxiety disorder and telomere shortening. First, we were interested in the influence of telomere length before the assessment of anxiety disorders. Because we do not have telomere length at T2, we adjusted for telomere length at T1 (4 years before the CIDI assessment). Second, anxiety disorders were divided in generalized anxiety disorders (GAD) vs. other anxiety disorders (including panic disorder, social phobia, and agoraphobia) and the association with telomere length at follow-up was evaluated. We were particularly interested in this distinction, because GAD is characterized by anxious-misery and might therefore be more closely related to depression than to the other anxiety disorders that are mainly characterized by fear and physiological hyperarousal.[35] Both post-hoc analyses were adjusted for the potential confounders gender and age. Statistical analyses were performed using PASW version 18.0.

RESULTS

Demographic characteristics

At T2, the mean age of the study population was 53 years (standard deviation (SD) 11.4 years, minimum 33 years, maximum 80 years), with 46% males. Of the 1094 participants, 16 had no CIDI measurement at T2. Table 1 summarises the characteristics of the 1078 participants. At T2, 108 participants (10%) had an anxiety disorder in the past 12 months, and 97 (9%) had a depressive disorder in the past 12 months. 36 participants had both an anxiety and depressive disorder in the past 12 months. Compared with participants who did not have an anxiety disorder, those with an anxiety disorder were more often female, were more likely to smoke higher numbers of cigarettes, used more often antidepressants, and experienced more adverse life events. Compared with participants who did not have a depressive disorder, those with a depressive disorder were younger, more often female, were

more likely to smoke higher numbers of cigarettes, were more likely to use antidepressants, and experienced more adverse life events (Table 1). Follow-up data at T3 were available for 974 participants. There were no significant differences in age, gender, and telomere length between the 104 participants who were not included in the follow-up and these 974 participants. Mean follow-up duration from T2 to T3 was 2.2 years.

Table 1. Characteristics of 1078 participants

	Anxiety disorder (108)	No anxiety disorder (970)		Depressive disorder (97)	No depressive disorder (980)	
	N (%) or mean ± SD		p	N (%) or mean ± SD		p
Age	52.2 (9.5)	53.6 (11.5)	0.19	51.3 (10.7)	53.7 (11.3)	0.046
Male gender	40 (37)	460 (47)	0.04	35 (36)	465 (47)	0.03
Lifestyle factors						
BMI	25.9 (4.0)	26.6 (4.1)	0.13	26.5 (4.5)	26.5 (4.0)	0.93
Smoking						
0 cigarettes/day	70 (66)	749 (77)		63 (65)	755 (77)	
1-5 cigarettes/day	9 (9)	37 (4)		7 (7)	39 (4)	
6-10 cigarettes/day	2 (2)	41 (4)		3 (3)	40 (4)	
11-15 cigarettes/day	7 (7)	60 (6)	0.001	8 (8)	59 (6)	0.001
16-20 cigarettes/day	7 (7)	51 (5)		5 (5)	53 (5)	
>20 cigarettes/day	11 (10)	30 (3)		11 (11)	30 (3)	
Alcohol consumption						
No, almost never	23 (22)	189 (20)		19 (20)	192 (20)	
1-4/month	23 (22)	165 (17)		23 (24)	165 (17)	
2-7/week	32 (30)	335 (35)	0.58	32 (33)	335 (34)	0.51
1-3/day	22 (21)	231 (24)		19 (20)	234 (24)	
4 or more/day	7 (7)	47 (5)		4 (4)	50 (5)	
Exercise frequency						
No exercise	57 (53)	499 (52)		50 (52)	505 (52)	
Once/week	26 (24)	270 (28)	0.70	32 (33)	264 (27)	0.29
Twice or more/week	24 (22)	196 (20)		15 (16)	205 (21)	
Other						
Education						
None	5 (5)	43 (5)		5 (6)	43 (5)	
Low	28 (28)	238 (27)		28 (31)	237 (26)	
Middle	34 (33)	236 (26)	0.42	25 (28)	245 (27)	0.61
High	36 (35)	381 (42)		32 (36)	385 (42)	
Antidepressant use	12 (11)	16 (2)	<0.001	14 (15)	14 (1)	<0.001
Adverse life events	7 (4)	5 (3)	<0.001	7 (4)	5 (3)	<0.001

Association between depression, anxiety disorder and telomere length

In the regression model adjusted for age and gender, the presence of anxiety disorder predicted shorter telomere length at follow-up (β=-0.073, t=-2.302, p=0.022). Besides

anxiety, age was also predictive of shorter telomere length (β=-0.148, t=-4.658, p=<0.001). No association was found between depressive disorders and telomere length at follow-up (β=0.010, t=0.315, p=0.753) (table 2).

After adjustment for comorbid depression/anxiety, adverse life events, lifestyle factors, educational level and antidepressant use, the association between any anxiety disorder last year and telomere length at follow-up remained (β=-0.077, t=-2.144, p=0.032). In addition to the predictive effect of anxiety on telomere length, BMI (β=-0.075, t=-2.136, p=0.033) and exercise frequency (β=0.087, t=2.552, p=0.011) were also predictive of telomere length at follow-up.

Table 2. Multivariable associations between depression, anxiety and telomere length at follow-up (N = 974)

	B	Std error	β	t	p
Depressive disorder[1]	0.012	0.039	0.010	0.315	0.753
Depressive disorder[2]	0.045	0.041	0.037	1.090	0.276
Depressive disorder[3]	0.038	0.043	0.031	0.897	0.370
Depressive disorder[4]	0.032	0.044	0.026	0.727	0.468
Anxiety disorder [1]	-0.084	0.036	-0.073	-2.302	0.022
Anxiety disorder[2]	-0.092	0.039	-0.080	-2.372	0.018
Anxiety disorder[3]	-0.092	0.040	-0.080	-2.289	0.022
Anxiety disorder[4]	-0.087	0.041	-0.077	-2.144	0.032

[1] Adjusted for age, gender
[2] Adjusted for age, gender, comorbid depressive/anxiety disorders, adverse life events
[3] Adjusted for age, gender, comorbid depressive/anxiety disorders, adverse life events, BMI, smoking, alcohol consumption, exercise frequency, education level
[4] Adjusted for age, gender, comorbid depressive/anxiety disorders, adverse life events, BMI, smoking, alcohol consumption, exercise frequency, education level, antidepressant use

Post hoc analyses

To further explore the association between anxiety disorder and telomere length, we performed two additional post hoc analyses. First, we adjusted for age, gender, and telomere length at T1 (four years before the CIDI assessment). The association between anxiety and telomere at follow-up was similar, but no longer significant (β=-0.063, t=-1.947, p=0.052).

Second, we evaluated whether the presence of GAD or any other anxiety disorder was predictive of telomere shortening at follow-up, while adjusting for age and gender. 67 (7%) had any other anxiety disorder and 46 (5%) had GAD. The presence of any other anxiety

disorders (including panic disorder, agoraphobia and social phobia) predicted telomere shortening (β=-0.088, t=-2.776, p=0.006), while generalized anxiety disorder did not (β=-0.008, t=-0.242, p=0.809).

DISCUSSION

Our study suggests that anxiety disorders predict shorter telomere length over time. In contrast, no prospective association was found between depressive disorders and telomere length. The association of anxiety disorder with telomere length was not explained by adverse life events, lifestyle factors, educational level and antidepressant use.

We are the first to study the direct relation between anxiety disorder, depressive disorder and telomere length in a population based sample in a longitudinal setting. Only one previous study focused on the association between anxiety disorders and telomere length. This cross-sectional study found that the older half of the anxiety disorder patients exhibited significantly shorter telomeres than healthy controls.[12] Our study shows that the presence of anxiety in the past year predicts telomere length after 2 years follow-up in the total sample. It should be noted that that this association does not generalize to all types of anxiety disorders.

Although anxiety seems to predict telomere length in our study, we were unable to confirm previously reported associations with depressive disorders and reduced telomere length in leukocytes. The finding that anxiety predicts telomere length over time, while depression does not, might be explained by the phenomenological and etiological differences between anxiety and depressive disorders. Most of the insights about mechanisms associated with telomere erosion originate from research on oxidative stress and inflammation, indicating both as important influences on telomere length.[36-39] Earlier research suggests that both anxiety and depression are associated with oxidative stress and inflammation.[40-43] However, the contrasting associations between anxiety and depression with telomere length suggest that a mechanism that is not shared between these disorders is important for telomere shortening. Symptoms of anhedonia and the absence of positive affect are specific to depression, whereas symptoms of physiological hyperarousal and thoughts of future threat are more prominent in anxiety.[35] It is possible that mainly these features related to extreme physiological stress are of importance for telomere damage. In support of this, we found that specifically the presence of panic disorder, agoraphobia and/or social phobia was driving the effects on telomere length at follow-up. These anxiety disorders are mainly characterized by fear, while generalized anxiety disorder and depression are identifiable as anxious-misery disorders.[35, 44] This finding suggests that in patients with anxiety, especially

fear (usually accompanied by extreme physiological hyperarousal) could be an important factor in telomere shortening. Further research is required to yield mechanistic insight underlying the association between anxiety and telomere shortening.

In our analyses, we adjusted for several factors. The association between anxiety disorders and telomere length at follow-up was independent of adverse life events, lifestyle factors, level of education and antidepressant use. Therefore, further research on the association between anxiety and accelerated telomere shortening should look at other potential mediators. The longitudinal setting of our study enabled us to assess anxiety as a predictor of telomere length at 2 years follow-up. Our study therefore suggests that anxiety leads to accelerated telomere shortening. However, it is also possible that participants with anxiety had already shorter telomeres to start with. To further explore this possibility we performed a post-hoc analysis. A limitation of this study is that telomere length was assessed 4 years before psychopathology was measured. The association was only marginally reduced after adjusting for telomere length at T1, but lost statistical significance. It remains possible that telomere length before the measurement of anxiety drives the association between anxiety and telomere length at follow-up. With this study design we cannot further disentangle this possibility. More longitudinal studies with multiple repeated measurements of telomere length and psychopathology are necessary.

Given the importance of anxiety in determining shortened lifespan and more rapid onset of diseases typically associated with aging, such as cardiovascular disease, our findings might have potential clinical relevance.[15, 16] Because anxiety seems to be associated with accelerated telomere shortening, this raises the question whether accelerated cellular aging is a mechanism that contributes to the excess morbidity and mortality associated with anxiety.

The majority of earlier studies observed an association between depression and telomere length,[7-10] which is in contrast with the present study. However, it should be kept in mind that most sample sizes were relatively small. A reason for the conflicting findings may also be the longitudinal setting of our study, while the previous studies were cross-sectional. Wolkowitz et al. found that depressed individuals did not differ from controls in telomere length. However, they did observe that accelerated aging at the level of leukocyte telomeres is proportional to lifetime exposure to major depressive disorder.[45] Therefore it is possible that telomere length is a reflection of cumulative factors over time. In our study we focused at telomere length and depressive disorder in a relatively short period. In addition, our null finding could be due to the differences in study population. Earlier studies included inpatients,[9] chronic severely depressed patients,[7, 46] or patients within psychiatric care.[10]

Because our study is based on a general population representative cohort, our participants might be relatively milder depressed than these patients.

There are several strengths of this study. First, we used data from a large population based cohort, thereby increasing generalizability of our results to the population at large. In addition, our study had a longitudinal design, while previous studies assessing the association between depression, anxiety and telomere length were cross-sectional. The longitudinal setting of our study enabled us to assess anxiety disorder as a predictor of telomere length at follow-up. Still, when interpreting our results, the following limitations should be taken into account. First, although we adjusted for multiple carefully measured potential confounding variables, the possibility of residual confounding cannot be excluded. Second, our measurements were restricted to telomere length in leukocytes and do not necessarily reflect telomere length in other cell compartments or tissues of interest. The third limitation of our study is that we assessed psychopathology only at one moment (T2); no repeated measures of psychopathology were available. Finally, telomere length was only measured at T1 and T3 and we did not assess telomere length and psychopathology at the same point in time.

In summary, anxiety disorders were predictive of short telomere length at follow-up in a population based sample. The association was not explained by adverse life events, lifestyle factors, educational level and antidepressant use. The mechanisms that connect anxiety disorders to accelerated telomere shortening, and their relation with the excess mortality risk associated with anxiety disorders, deserves further study.

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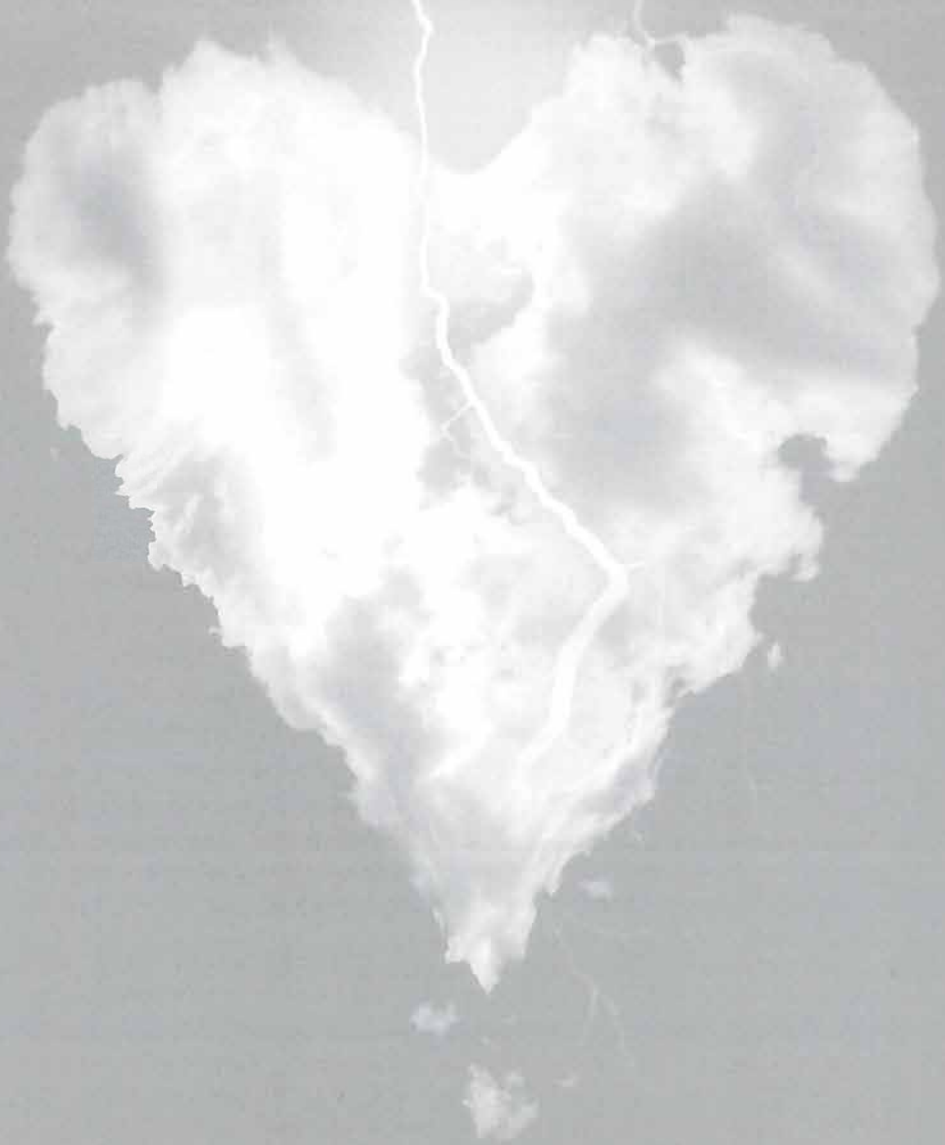
Part III

Positive affect and prognosis



Chapter 7

Why does having a positive attitude make you live longer? Findings from the Heart & Soul Study

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Submitted

ABSTRACT

Background | Positive affect can improve survival, but the mechanisms responsible for this association are unknown. The aim of the present study was to evaluate the association between positive affect and mortality in patients with stable coronary heart disease (CHD), and to determine biological and behavioral factors that might explain this association.

Methods | The Heart and Soul study is a prospective cohort study of 1017 outpatients with stable CHD. Baseline positive affect was assessed using the 10-item positive affect subscale of the Positive and Negative Affect Schedule. Cox proportional hazard regression was used to estimate the risk of mortality and cardiovascular events (heart failure, myocardial infarction, stroke, transient ischemic attack) associated with positive affect, adjusting for baseline cardiac disease severity and depression. We also evaluated the extent to which these associations were explained by potential biological and behavioral mediators.

Results | A total of 369 patients (36%) died during a mean of 7.1 (±2.5) years follow-up. Positive affect was not significantly associated with myocardial infarction, heart failure, stroke or transient ischemic attack. However, each standard deviation (8.8-point) increase in positive affect score was associated with a 16% decreased risk of all-cause mortality (HR: 0.84; 95% CI: 0.76-0.92; p=0.001). After adjustment for cardiac disease severity and depressive symptoms, positive affect remained significantly associated with improved survival (HR: 0.87; 95% CI: 0.78-0.97; p=0.01). Although further adjustment for potential biological mediators only minimally affected this association (HR: 0.89; 95% CI: 0.80-0.99; p=0.04), the association was no longer significant after adjustment for behavioral factors, and particularly physical inactivity (HR: 0.94; 95% CI: 0.84-1.17; p=0.31).

Conclusion | In this sample of outpatients with CHD, positive affect was associated with improved survival. This association was largely explained by physical inactivity.

INTRODUCTION

Cardiovascular disease is the leading cause of death in the world. Psychological factors have been associated with increased morbidity and mortality in patients with coronary heart disease (CHD), but most research has focused on negative emotions, such as anxiety[1] and depression.[2] There is now growing recognition that positive emotions, such as joy and cheerfulness, may also provide important protective effects.[3] Accumulating evidence suggests that positive psychological factors may actually improve longevity[3, 4] and decrease morbidity and mortality from cardiovascular disease.[5-7]

The idea that improving positive attitude might help people live longer has considerable appeal. However, several unresolved questions remain. First, it is important to examine whether positive and negative affect have independent prognostic effects. In one study, adjustment for depressed mood attenuated the observed relationship between positive affect and long-term survival in cardiac catheterization patients.[8] Second, the association between positive affect and cardiac prognosis may be confounded by worse severity of heart disease, with greater disease burden causing impairment in positive affect. Third, it is unclear what mechanisms could explain the association of positive affect with improved health outcomes.

We have previously found that depressive symptoms predicted adverse outcomes in patients with coronary heart disease, independent of baseline cardiac disease severity, and that this association was largely explained by poor health behaviors, especially medication non-adherence and physical inactivity.[9] These findings led us to wonder whether the improved survival associated with positive affect might also be explained by health behaviors. Therefore, the aims of this study were to examine whether positive affect is associated with improved survival and decreased cardiovascular morbidity, independent of cardiac disease severity and depression, and to explore biological and behavioral factors that could explain this association.

METHODS

Design and patients

The Heart and Soul study is a prospective cohort study that focused on psychosocial factors and health outcomes in patients with CHD. Details regarding the study design have been described previously.[10] Between September 2000 and December 2002, 1024 participants were recruited from 12 outpatient clinics in San Francisco Bay Area. Patients had to meet the following inclusion criteria: history of myocardial infarction (MI) or coronary

revascularization, angiographic evidence of at least 50% stenosis in at least one coronary vessel, or a diagnosis of CHD documented by an internist or cardiologist. Exclusion criteria were: a history of MI in the past 6 months, unable to walk one block, or planning to move from the local area within 3 years. All participants completed a baseline examination that included a comprehensive health interview, blood samples, medical history, psychiatric interview, questionnaire, echocardiogram, exercise treadmill test, 24 hour ambulatory electrocardiogram, and 24 hour urine collection. Of the 1024 participants who completed the baseline examination, 1022 completed the positive affect scale and 4 participants were lost to follow-up, leaving 1018 participants for this analysis. The study protocol was approved by the appropriate Institutional Review Boards, and all participants signed an informed consent.

Baseline characteristics

Age, gender, ethnicity, educational achievement, and medial history were determined by self-reported questionnaire. Weight and height were measured and body mass index (BMI kg/m^2) was calculated. Participants were instructed to bring their medication bottles to their appointment, and study personnel recorded all current medications. Medications were categorized using Epocrates Rx (San Mateo, CA).

Positive affect

Positive affect was measured using the Positive and Negative Affect Schedule (PANAS)[11] that includes 10 items on positive affect: alert, inspired, active, interested, excited, strong, enthusiastic, determined, proud, and attentive. Patients rated the extent to which they had felt each of these items during the past week on a 5-point scale (ranging from 1 = 'not at all' to 5 = 'extremely'), with total scores ranging from 10 to 50. Good concurrent and construct validity have been established for the PANAS, and the reliability has been reported to range from 0.86 to 0.90 for positive affect.[11, 12]

Cardiac disease severity and risk factors

All participants underwent resting echocardiography using an Acuson Sequoia ultrasound system (Mountain View, California). Standard 2-dimensional views and performed planimetry with a computerized digitization system were obtained to determine left-ventricular ejection fraction (LVEF). Participants were categorized as having diastolic dysfunction if their mitral inflow ratio of peak early-to-late diastolic filling velocity was more than 0.75 and if the velocity time integral in their pulmonary vein was greater during diastole than during systole.[13] Fasting venous blood samples were drawn to determine low- and high-density lipoprotein cholesterol levels.

Depression

The presence of major depressive disorder (past month) was ascertained using the Computerized Diagnostic Interview Schedule for the DSM-IV (C DIS IV).[14] The validity and reliability of computerized versions of the Diagnostic Interview Schedule have previously demonstrated acceptable.[15] We also assessed depressive symptoms using the 9-item Patient Health Questionnaire (PHQ), a self-report instrument that measures the frequency of experiencing each symptom corresponding to the 9 DSM-IV criteria for depression. Using a standard cut-point of 10 or higher, the PHQ has demonstrated excellent validity compared with a structured diagnostic interview for depression.[16, 17]

Potential biological mediators

Heart rate variability (HRV) was assessed using three-channel 24-hour ambulatory Holter electrocardiography.[18] Measures of HRV included the SD of 5-minute mean NN intervals and the natural log of very low frequency power. Cortisol and norepinephrine excretion were measured in 24-hour urine samples. Cortisol was assessed by radioimmunoassay or high performance liquid chromatography/tandem mass spectrometry. Norepinephrine was analyzed by gas chromatography-mass spectrometry.[19, 20] High-pressure liquid chromatography with electrochemical detection to assay whole blood serotonin levels was used. High-sensitivity C-reactive protein (CRP) levels were measured using the Roche Integra assay or the Beckman Extended Range assay.[21] We measured blood levels of 2 omega-3 fatty acids, docosahexaenoic acid and eicosapentaenoic acid by capillary gas chromatography as the percentage composition of total fatty acid methyl esters in the red blood cell membranes.[22]

Potential behavioral mediators

Smoking and alcohol use were determined by self-report. To assess medication adherence, the following question was asked: 'In the past month, how often did you take your medications as the doctor prescribed?' Possible responses were: 'All of the time' (100%), "Nearly all of the time" (90%), "Most of the time" (75%), "About half the time" (50%), or "Less than half the time" (50%). Medication non-adherence was defined as taking prescribed medications 75% of the time or less.[23] Physical activity was assessed with the following questions: "which of the following statements best describes how physically active you have been during the last month, that is, done activities such as 15 to 20 minutes of brisk walking, swimming, general conditioning, or recreational sports?" Participants chose from 1 of the following 6 categories: not at all active, a little active (1-2 times per month), fairly active (3-4 times per month), quite active (1-2 times per week), very active (3-4 times per week), or extremely active (≥5 times per week). Self-report has been shown to be a reliable, valid, and accurate method of assessing physical activity.[24, 25]

Mortality and cardiovascular events

After the baseline examination, annual telephone follow-up interviews with participants or their proxies were conducted asking about emergency room visits, hospitalizations, or death. For any reported cardiovascular event, medical records, death certificates, and coroner's reports were reviewed by two independent blinded adjudicators. In the event of disagreement a third blinded adjudicator reviewed the event and determined the outcome variable. The primary study endpoint was mortality. Death was determined by death certificates and coroner's report. We also evaluated cardiovascular events, including heart failure, myocardial infarction, stroke and transient ischemic attack. To be diagnosed with heart failure, patients had to be hospitalized for a clinical syndrome involving an acute change in at least two of the following: paroxysmal nocturnal dyspnea, orthopnea, elevated jugular venous pressure, pulmonary rales, third heart sound, cardiomegaly or pulmonary edema on chest radiography. Standard criteria were used for defining myocardial infarction.[26] Stroke was defined as new neurological deficit, which must not have been the result of brain trauma, tumor, infection, or other cause. Transient ischemic attack (TIA) was defined as a focal neurological deficit (in the absence of head trauma) lasting between 30 seconds and 24 hours, with rapid evolution of the symptoms to the maximal level of deficit in less than 5 minutes and with subsequent complete resolution.

Statistical analysis

For descriptive purposes, participants were grouped based on the median split (i.e. ≥ 32) for categorizing low and high levels of positive affect, and were compared on clinical and demographic variables using T tests and X^2 tests. C-reactive protein was log transformed because it did not have a normal distribution. We used Cox proportional hazard regression (i.e. survival analysis) to estimate the risk of all-cause mortality associated with positive affect both as a continuous variable (i.e. per SD increase) and as a dichotomous variable (i.e. based on median split). As a secondary analysis, we also evaluated the association between positive affect and cardiovascular events (myocardial infarction, heart failure, stroke or transient ischemic attack).

To examine whether a covariate changed the strength of association between positive affect and all-cause mortality, the percent change in the effect size (age-adjusted log hazard ratio or beta coefficient) was calculated for positive affect (entered as a dichotomous variable), after adjustment for the potential confounder or explanatory factor. Participants missing the covariate of interest were excluded from nested models to avoid any artifact due to different sample sizes. We sequentially considered demographic characteristics, comorbid conditions, severity of cardiac disease, medication and measures of depression as potential confounders. We then evaluated biological and behavioral mechanisms as potential explanatory factors. All variables that resulted in a more than 5% change in the effect size

(log HR) for positive affect were considered potential confounders or explanatory variables and included in the final multivariable model.[27] To determine whether any effect of positive affect differed by age, sex, race, or depressive symptoms, we checked for interactions with these variables.

The log-linearity assumption for continuous variables was verified by checking for improvement in fit after addition of quadratic and cubic terms. The proportional hazards assumption of these models were verified using log-minus-log survival plots and by checking for secular patterns in Schoenfeld residuals. A forest plot was constructed for visual interpretation of the results. Analyses were performed using SPSS version 18.0.

RESULTS

The baseline characteristics of the study population categorized by low or high positive affect are presented in Table 1. Compared with participants who had low positive affect, those with high positive affect were older, more educated, had lower BMI, had higher HDL, and were less likely to be depressed or to use antidepressants. High positive affect was also associated with lower CRP, less smoking, more medication adherence, and more physical activity.

Table 1. Baseline characteristics of 1018 participants with stable CHD, by positive affect

	Low positive affect (n=514)	High positive affect (n=504)	p
Demographic characteristics			
Age, mean (SD) years	66.2 (11.1)	67.6 (10.6)	0.04
Male sex, No. (%)	419 (81.5)	416 (82.5)	0.67
White, No. (%)	309 (60.1)	303 (60.1)	0.99
High school graduate, No. (%)	434 (84.4)	452 (90.0)	0.01
BMI, mean (SD) kg/m^2	28.8 (5.7)	28.0 (4.9)	0.02
Comorbid conditions, No. (%)			
Hypertension	370 (72.4)	349 (69.2)	0.27
Myocardial infarction	268 (52.5)	277 (55.3)	0.38
Stroke	69 (13.5)	78 (15.5)	0.38
Revascularization	289 (56.6)	311 (61.7)	0.09
Congestive heart failure	91 (17.8)	87 (17.4)	0.85
Diabetes Mellitus	140 (27.3)	124 (24.7)	0.33
Medication use, No. (%)			
Aspirin	395 (76.8)	394 (78.2)	0.61
Beta blocker	294 (57.0)	298 (59.1)	0.49
Angiotensin system inhibitor	259 (50.4)	264 (52.4)	0.52
Statin	316 (61.5)	337 (66.9)	0.07
Cardiac disease severity			
LVEF, mean (SD) years	61.7 (9.6)	61.7 (9.7)	0.97
Diastolic dysfunction, No. (%)	56 (12.2)	60 (13.4)	0.60
LDL, mean (SD) mg/dL	104.0 (33.5)	104.4 (33.9)	0.85
HDL, mean (SD) mg/dL	44.9 (13.7)	46.7 (14.4)	0.04
Depression, No. (%)			
Major depressive disorder	165 (32.2)	83 (16.5)	<0.001
Depressive symptoms	163 (31.7)	36 (7.1)	<0.001
Tricyclic antidepressant use	21 (4.1)	23 (4.6)	0.71
SSRI use	69 (13.4)	28 (5.6)	<0.001
Other antidepressant use	51 (9.9)	27 (504)	0.006
Biological factors, mean (SD)			
HRV (SDANN) ms	108.6 (34.4)	109.2 (37.8)	0.80
HRV (lnVLF) ms^2	6.3 (0.81)	6.4 (0.94)	0.45
Serotonin (non SSRI users), ng/mL	118.2 (68.7)	123.7 (86.8)	0.30
Cortisol, ug/day	34.1 (22.0)	35.7 (20.4)	0.28
Norepinephrine, ug/day	51.1 (26.8)	52.4 (26.3)	0.46
Log hsCRP, mg/L	0.82 (1.31)	0.60 (1.31)	0.009
Fatty acids, %DHA+EPA	4.1 (2.0)	4.3 (2.10	0.09
Behavioral factors, No. (%)			
Regular alcohol use	139 (27.3)	153 (30.5)	0.26
Smoking	130 (25.4)	69 (13.7)	<0.001
Medication non-adherence	59 (11.6)	24 (10.4)	<0.001
Physical activity			
Not at all active	136 (26.6)	52 (10.4)	<0.001
A little active	108 (21.1)	74 (14.7)	
Fairly active	83 (16.2)	73 (14.5)	
Quite active	70 (13.7)	84 (16.7)	
Very active	81 (15.8)	136 (27.1)	
Extremely active	34 (6.6)	83 (16.5)	

SD= standard deviation; BMI= body mass index; LVEF= left ventricular ejection fraction; LDL= low-density lipoprotein cholesterol; HDL= high-density lipoprotein cholesterol; SSRI= selective serotonin reuptake inhibitor; HRV= heart rate variability; SDANN= SD of 5-minute mean NN intervals; lnLVF= natural log of very low frequency; CRP= C-reactive protein; DHA= docosahexaenoic acid; EPA= eicosapentaenoic acid.

A total of 369 patients (36%) died during an average of 7.1 ± 2.5 years follow-up.
Each standard deviation (8.8 point) increase in PANAS positive affect score was associated with a 16% decreased risk of death (age-adjusted HR: 0.84; 95% CI: 0.76-0.92; p = 0.001). Positive affect was not significantly associated with subsequent heart failure, myocardial infarction, or stroke/TIA (Table 2).

Table 2. Association between positive affect, cardiovascular events, and mortality per standard deviation (8.8-point) increase in positive affect score

Event	Number of events	Age-adjusted HR (95% CI) per SD increase	p
Heart failure	171	0.87 (0.74-1.01)	0.07
Myocardial infarction	123	0.93 (0.78-1.11)	0.44
Stroke or TIA	46	1.03 (0.76- 1.38)	0.87
All-cause mortality	369	0.84 (0.76- 0.92)	0.001

HR= hazard ratio; CI= confidence interval; SD= standard deviation; TIA= transient ischemic attack.

Several markers of disease severity and depression were considered as potential confounding factors of the link between positive affect and mortality. Adjustment for history of MI, LVEF, depressive symptoms, and use of SSRIs each changed the strength of association between positive affect and mortality by ≥5% and thus met the criterion for potential confounding (Table 3). Adjustment for several biological (CRP, omega-3 fatty acids) and behavioral (smoking, medication non-adherence, physical inactivity) factors also diminished the strength of association between positive affect and mortality. Accounting for physical inactivity resulted in the largest (30%) reduction in the strength of the positive affect-mortality relationship.

After adjustment for potential confounding factors, positive affect remained significantly associated with decreased mortality (HR: 0.87; 95% CI: 0.78-0.97, p = 0.01). Further adjustment for potential biological mediators (CRP and omega-3 fatty acids) only minimally attenuated the association between positive affect and mortality (HR: 0.89; 95% CI: 0.80-0.99; p = 0.04) (Table 4). However, the association between positive affect and mortality was no longer significant after further adjustment for smoking, medication non-adherence, and physical inactivity (HR: 0.94; 95% CI: 0.84-1.17; p = 0.31). We found no evidence that the association between positive affect and mortality varied by age, sex, race, and depressive symptoms (all P values for interaction ≥ 0.10).

Table 3. Change in the strength of the association between positive affect and mortality (expressed as the percent change in the beta coefficient for positive affect) after adjustment for potential confounders and mediators

Variable	Change in effect size after adjustment, %
Demographic characteristics	
Male sex	1.5
White	1.0
High school graduate	-1.5
BMI	3.1
Comorbid conditions	
Hypertension	-0.6
Myocardial infarction	8.1
Stroke	1.7
Revascularization	-0.9
Congestive heart failure	-0.9
Diabetes Mellitus	-2.8
Cardiac disease severity	
LVEF	5.5
Diastolic dysfunction	4.7
LDL	-0.5
HDL	-2.5
Medication use	
Aspirin	-1.1
Beta blocker	-0.1
Angiotensin system inhibitor	0.8
Statin	-0.2
Depression	
Major depressive disorder	-3.2
Depressive symptoms	-19.9
Tricyclic antidepressant use	2.4
SSRI use	-7.9
Other antidepressant use	-4.7
Potential biological mediators	
HRV (SDANN)	2.1
HRV (lnVLF)	-2.0
Serotonin in non SSRI users	-1.5
Cortisol	-2.6
Norepinephrine	-0.1
CRP	-10.3
Omega-3 fatty acid levels	-7.5
Potential behavioral mediators	
Regular alcohol use	-1.1
Smoking	-19.1
Medication non-adherence	-5.4
Self reported physical activity	-30.2

BMI= body mass index; LVEF= left ventricular ejection fraction; LDL= low-density lipoprotein cholesterol; HDL= high-density lipoprotein cholesterol; SSRI= selective serotonin reuptake inhibitor; CRP= C-reactive protein.

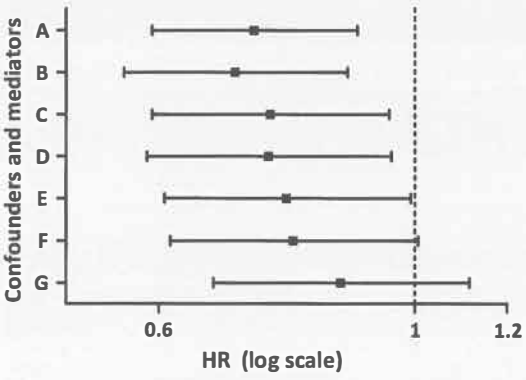
Table 4. Association between positive affect and mortality, with sequential adjustment for potential confounders and mediators

	Positive affect (median split)		Positive affect (per 8.8-point increase)	
	HR (95% CI)	p	HR (95% CI)	p
Potential confounders				
Model A[1]	0.73 (0.59-0.89)	0.002	0.84 (0.76-0.92)	0.001
Model B[2]	0.70 (0.57-0.86)	0.001	0.84 (0.76-0.93)	0.001
Model C[3]	0.74 (0.60-0.93)	0.01	0.87 (0.78-0.97)	0.01
Potential mediators				
Model D[4]	0.77 (0.61-0.96)	0.02	0.89 (0.80-0.99)	0.04
Model E[5]	0.80 (0.64-1.00)	0.05	0.90 (0.81-1.00)	0.06
Model F[6]	0.81 (0.65-1.02)	0.07	0.91 (0.82-1.02)	0.09
Model G[7]	0.87 (0.69-1.10)	0.25	0.94 (0.84-1.17)	0.31

HR= hazard ratio; CI= confidence interval; MI= myocardial infarction; LVEF= left ventricular ejection fraction; SSRI= selective serotonin reuptake inhibitor; CRP= C-reactive protein.
[1]**Model A**: adjusted for age
[2]**Model B**: adjusted for model A, history of MI, LVEF
[3]**Model C**: adjusted for model B, depressive symptoms, SSRI use
[4]**Model D**: adjusted for model C, CRP, omega-3 fatty acid levels
[5]**Model E**: adjusted for model D, smoking
[6]**Model F**: adjusted for model E, medication adherence
[7]**Model G**: adjusted for model F, physical activity

When positive affect was assessed as a dichotomous variable, 33% (167/504) of patients with high positive affect and 39% (202/514) of patients with low positive affect died. High positive affect was associated with a 27% decreased risk of death (HR: 0.73; 95% CI: 0.59-0.89; p = 0.002) (Table 4; Figure 1). This association remained essentially unchanged when adjusted for potential confounding factors (HR: 0.74; 95% CI: 0.60-0.93; p = 0.01), and it was only modestly attenuated after further adjustment for potential biological mediators (HR: 0.77, 95% CI: 0.61-0.96; p = 0.02). However, there was no significant association between positive affect and mortality after adjustment for smoking, medication non-adherence, and physical inactivity (HR: 0.87; 95% CI: 0.69-1.10; p = 0.25).

Figure 1. Association between positive affect (entered as a dichotomous variable) and all-cause mortality. Hazard ratio (HR) and 95% CI, with sequential adjustment for potential confounders and mediators



Adjustment variables

Model A: adjusted for age

Model B: adjusted for model A, history of MI, LVEF

Model C: adjusted for model B, depressive symptoms, SSRI use

Model D: adjusted for model C, CRP, omega-3 fatty acid levels

Model E: adjusted for model D, smoking

Model F: adjusted for model E, medication adherence

Model G: adjusted for model F, physical activity

MI= myocardial infarction; LVEF= left ventricular ejection fraction; SSRI= selective serotonin reuptake inhibitor; CRP= C-reactive protein.

DISCUSSION

In this prospective cohort study of more than 1000 outpatients with stable CHD, we found that positive affect was associated with a 27% reduction in mortality during a mean follow-up of 7 years. After adjustment for cardiac disease severity and depressive symptoms, positive affect remained associated with improved survival. Potential biological mediators did not seem to explain this association. However, the association between positive affect and survival was no longer significant after adjustment for behavioral factors, particularly physical inactivity. These findings suggest that patients with a positive attitude may live longer because they are better in adopting a healthier lifestyle, and especially in getting more exercise.

Positive affect and survival

Increasing evidence indicates that high levels of positive affect are associated with increased survival,[3,4] although mixed findings have been reported.[8,28] Our study extends this literature in several important ways. First, we carefully measured and adjusted for both major depressive disorder and depressive symptoms to verify that the association between positive affect and mortality was independent of depression. Second, we performed a detailed assessment of baseline cardiovascular disease severity and risk factors to rule out the possibility that greater underlying cardiac disease severity was responsible for this association. Third, we simultaneously examined numerous potential biological and behavioral mediators

and evaluated the extent to which each of these potential mechanisms might explain the association between positive affect and mortality.

Not just the absence of depression

There is an ongoing debate in the literature as to whether positive affect and negative affect are independent of each other, or rather bipolar extremes of the same mood dimension.[3, 8, 29] Therefore, it is important to evaluate whether research on positive psychology and health is simply reframing existing knowledge concerning negative emotion, or is adding a distinctive dimension to psychosomatic medicine.[3] In a study of cardiac catheterization patients, Brummett and colleagues observed that adjustment for depressive emotion attenuated the observed relationship between positive affect and long-term survival,[8] whereas positive affect was independently associated with cardiac outcomes in coronary patients after adjustment for depressive symptoms.[5] In another study, the association between emotional vitality and decreased risk of incident CHD also remained significant after controlling for depressive symptoms.[30] In our sample, adjusting for 'depressive symptoms' reduced the effect size for positive affect size by 17%. However, even after controlling for depressive symptoms, positive affect remained significantly associated with improved survival. The robustness of this association after accounting for depressive symptoms suggests important and separate relationships between positive emotions and survival. These findings are consistent with the understanding that optimal functioning transcends the simple absence of negative affect.[31]

Potential biological pathways

It is plausible that multiple biological and behavioral pathways may link positive emotional experience with health outcomes. Potential biological variables include mechanisms that may directly impact physiological functioning by eliciting changes in neuroendocrine processes. In one experimental study, positive affect was related to higher norepinephrine levels and lower cortisol response to awakening in a sample of 328 individuals.[32] In the Whitehall II study, positive affect was associated with reduced levels of the inflammatory marker CRP in healthy women but not in men.[33] Another mechanism through which positive affect may protect against adverse outcome is by increasing heart rate variability.[34] Although little is known about the association of positive affect with omega-3 fatty acids, both CRP and omega-3 fatty acids accounted for a more than 5% change in the effect size of positive affect. However, after adjusting for CRP and omega 3 fatty acids positive affect was still independently predictive of survival.

Behavioral pathways

Happy individuals may also have more favorable health habits and make healthier behavioral choices than less happy people. Higher-state positive affect is related to lower prevalence of

smoking,[35] reduced alcohol consumption,[36] and exercising regularly.[37] Positive affect might also increase adherence to medical regimens among patients, resulting in less severe illness, faster recovery and longer survival.[3] In this study, we found that the association between positive affect and survival was no longer present after adjustment for physical activity. These findings raise the possibility that the increased survival rate associated with positive affect could be explained by physical activity and other positive health behaviors that travel with exercise.

Exercise: cause or consequence

Since we evaluated positive affect and physical activity at the same point in time, we cannot determine whether physical inactivity was the cause or result of positive affect. There is abundant evidence that positive emotions and exercise are closely linked. The association is almost certainly bidirectional, because high positive affect is associated with a greater likelihood of engaging in physical activity,[38] and engaging in physical activity induces positive affect.[39, 40] Therefore, enhancing positive affect can presumably increase physical activity, and physical activity can elevate positive affect. Regardless of whether physical activity was the cause or a result of positive affect, it appeared to explain a large part of the association between positive affect and survival. These findings suggest that exercise may be partly responsible for greater survival in patients with positive affect and underscore the many reasons to encourage exercise in patients with heart disease.

Positive affect and cardiovascular events

In contrast to all-cause mortality, we did not find a significant association between positive affect and heart failure, myocardial infarction, stroke or TIA. These findings are consistent with results from the Whitehall II study, which found no relationship between positive mood and cardiovascular morbidity.[41] However, they are in contrast to the results of other studies demonstrating reduced cardiovascular morbidity with high positive mood.[5-7] It is unclear why we did not find a significant association between positive affect and cardiovascular events. One possibility is that our study was under-powered to evaluate cardiovascular events. Although the 95% confidence intervals overlapped one, the hazard ratios for heart failure and myocardial infarction were in the expected direction, estimating a 13% reduction in heart failure hospitalization and a 7% reduction in myocardial infarction for each 8.8-point increase in positive affect score. Since the number of deaths far exceeded the total number of cardiovascular events (myocardial infarction, heart failure, stroke and transient ischemic attack combined), we had more power to detect a significant association between positive affect and mortality.

Future directions

Future studies are warranted to further examine the impact of positive affect on health outcomes. If the findings of the current study are confirmed, positive affect may provide a new target for intervention trials. Up to now, trials have mainly focused on negative emotions. However, psychological interventions should not only target the reduction of negative emotions but also seek to enhance positive emotions. The findings of the present study suggest the possibility that the improved survival associated with positive affect could be enhanced by behavioral interventions that include exercise training. Evidence suggests that cardiac rehabilitation may be promising in this context. Cardiac rehabilitation aims to return the individual to optimal emotional function, and exercise is considered to be the cornerstone of cardiac rehabilitation.[42] In a clinical trial of cardiac rehabilitation among men with CHD, rehabilitation patients, but not control patients, reported a significant improvement in positive affect over time.[43] Another study confirmed that the positive affect measure of the Global Mood Scale[31] was the most responsive to the beneficial effect of cardiac rehabilitation as compared to 8 other health-related quality of life outcome measures.[44] Hence, it may be hypothesized that individuals with CHD may benefit from the effects of physical activity by incorporating daily lifesytle patterns of behavior that are conducive to higher generation of positive affect and better health outcomes.

Limitations and strengths

This study has several strengths, including the prospective design with a mean follow-up duration of 7 years, the large cohort size, the standard assessment of positive affect and disease severity, and the careful measurement of potential biological and behavioral explanatory factors. However, a number of limitations must be considered. First, we only included outpatients with stable CHD, and thus cannot comment on the effects of positive affect in the general population. Nonetheless, cardiovascular disease remains the leading cause of death in the world, and reducing mortality in patients with cardiovascular disease would have major public health importance. Second, the participants in this study were mainly older men, and the results may not be generalizable to women or to other patient populations. However, we did not observe any interaction between positive affect and gender. Third, we did not assess dietary factors other than blood levels of omega-3 fatty acids. Finally, although we carefully assessed cardiac disease severity, we cannot rule out the possibility of unmeasured or residual confounding due to the observational nature of this study.

Conclusions

In conclusion, the current study showed that, after a mean follow-up of 7 years, positive affect was associated with improved survival in patients with CHD. This association was not

explained by biological markers but largely by physical activity. Enhancing a cardiac patient's ability to experience positive affect, for example by participating in cardiac rehabilitation, may open new avenues to improve survival in patients with CHD.

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Chapter 8

General discussion

GENERAL DISCUSSION

The general aim of this thesis was to study the potential effects of depression on prognosis in patients with coronary heart disease. To further elucidate this intriguing association, we studied three important and more specific issues to provide a deeper understanding of the role of depression in CHD. In the first part of this thesis we focused on the relationship between cognitive and somatic depressive symptoms and prognosis. In the second part of this thesis we examined a relatively new mechanism that could potentially underlie the association between depression and cardiovascular prognosis. In the final part of this thesis, we broadened the depression-CHD link by including positive emotions in the prognostic model.

Interpretation of findings

Somatic versus cognitive depressive symptoms and prognosis

Because randomized comparisons have found that depression treatment does not affect cardiac prognosis, it may be reasonable to assume that depression may not have a causal effect on cardiac events. However, depression is a heterogeneous condition, and an alternative explanation could be that some types of depression are cardiotoxic while others are not, and that some types of depression may respond to treatment while others do not. It is therefore important to identify patients who are at the highest risk for adverse cardiac outcome. The distinction between symptom dimensions of depression may be of importance in this respect. In *chapter 2* we found that somatic depressive symptoms appear to be more important predictors of prognosis in MI patients compared with cognitive depressive symptoms. This finding is in concordance with other studies that found that somatic depressive and not cognitive depressive symptoms were associated with adverse outcomes is patients following MI,[1-4] and in patients with chronic heart failure,[5] although opposite findings in CABG patients were also reported.[6, 7]

Our findings indicate that in acute MI patients somatic depressive symptoms are associated with MI severity. Even though somatic depressive symptoms were confounded by disease severity, they were still prospectively associated with medical outcome. These findings confirm previous studies indicating that somatic depressive symptoms are associated with disease severity[1, 8] but also that somatic symptoms have an independent effect on adverse cardiac outcome while cognitive symptoms have not. To derive further insight in the relationship, we chose to investigate this research question in a population with stable CHD. We carefully measured and adjusted for a range of confounders. In addition, we purposefully enrolled a uniform sample of patients with stable CHD so that the association between depressive symptoms and cardiac prognosis would not be confounded by the severity of

a recent acute coronary event. Again, we demonstrated that somatic symptoms are more strongly predictive of cardiovascular events in this stable CHD population *(chapter 3)*.

It is not clear why somatic depressive symptoms are associated with a particularly high risk of adverse cardiac outcomes. Two possible explanations may be considered. The first explanation could be that the association between depressive symptoms and adverse prognosis may be confounded by worse baseline cardiac disease severity, although we adjusted for a broad spectrum of confounders. A difficulty with somatic symptoms is that somatic symptoms alone do not 'make depression'. As a secondary analysis we analyzed the effects of individual somatic symptoms on cardiovascular prognosis in patients with and without current MDD (on the basis of the computerized Diagnostic Interview Schedule).[9] Overall the somatic symptoms were more strongly predictive of cardiovascular events in patients without MDD (n=795) than in patients with MDD (n=222). This finding supports the hypothesis that the cardiotoxicity of the somatic symptoms was not necessarily related to depression. Notably, the increased risk of cardiovascular events in patients with somatic symptoms was independent of several important confounders, including history of MI, history of heart failure, and LVEF. However, although controlling for confounders serves a useful function, it cannot transform observational studies into natural experiments.[10] Therefore, several important questions remain: Where do these somatic symptoms come from? And what is the true cardiotoxicity of depression? So far, it remains possible that the association we found between specific symptoms and increased risk of cardiac events was due to worse cardiovascular disease severity that was not otherwise accounted for in our multivariable models. For future studies it will be important to focus on the relationship between somatic symptoms and cardiovascular disease, including the issue of confounding.

Another possible explanation may be related to the finding from several clinical trials that depression in CHD patients that does not respond to treatment is associated with a particularly high risk of adverse cardiac outcomes.[11, 12] Since residual symptoms after depression treatment are often somatic, these particular symptoms might reflect persistent or chronic depression and this might explain the differential associations found for somatic and cognitive depressive symptoms with impaired prognosis in patients with CHD.[13, 14] Recently, a model has been proposed integrating the literature of post-MI depression.[15] This model has been built upon the hypothesis that depression in CHD patients consists of mixtures of two types of depression, denoted as somatic and cognitive depression. In the first type of depression, post-MI depression is a reflection of underlying biological processes. These processes include the underlying heart disease, inflammation, the autonomic nervous system, and dysfunction of the hypothalamic pituitary-adrenal axis. This particular type of depression is dominated by somatic depressive symptoms. It has been proposed that mainly this type of depression, when it persists, can become a causal factor in disease progression.

The second type of depression is dominated by cognitive depressive symptoms, usually improves over time and is less cardiotoxic than somatic depression. This type of depression is the result of vulnerability to stressful life events (i.e. the MI).

More insight in the etiological pathways that link somatic depressive symptoms to CHD progression is needed. However, to date research on symptom dimensions of distress in relation to potential mediating mechanisms is scarce. In a previous report from the Heart and Soul Study it was concluded that somatic depressive symptoms were associated with lower heart rate variability, whereas cognitive depressive symptoms were not.[16] There are also studies that point to inflammation as an important mechanism underlying the relation between depression and cardiovascular prognosis.[17] Inflammation also may be more strongly associated with somatic than with cognitive depressive symptoms.[18] Finally, deregulated hypothalamic pituitary-adrenal axis functioning may also be involved in the etiology of somatic symptoms of depression, although its role less clear.[19] Taken together, these results suggest that individual symptoms of depression may have differential associations with several mechanisms, leading to a worse cardiac prognosis. Future studies are therefore needed to evaluate the mechanisms that may be involved in the deleterious effects of somatic depressive symptoms.

All analyses conducted so far on somatic and cognitive symptoms of depression and their relationship with cardiovascular prognosis relied on self-report instruments. Using symptom specific data from a structured diagnostic interview we confirmed that after adjusting for confounders the presence of somatic symptoms was associated with an increased risk of cardiovascular events. However, in contrast with previous studies using self-report data, we found that interview-ratings of cognitive symptoms were also associated with an increased risk of cardiovascular events, although still less strongly than somatic symptoms *(Chapter 4)*. These discrepancies may be explained by the fact that the use of interview-based measurements of depression may be more sensitive in detecting clinically relevant cognitive symptoms and it is possible that these clinically relevant cognitive symptoms result in a higher level of cardiotoxicity. These findings suggest that the association between depressive symptom dimensions and prognosis might depend on the type of depression assessment. More research is needed to evaluate the relationship between depressive symptom dimensions measured with questionnaires and diagnostic interviews and cardiac prognosis in different patient populations.

Telomere length as a possible mechanism

Telomeres are simple repetitive sequences (TTAGGG) at the ends of eukaryotic chromosomes. They protect somatic cells from genomic instability during mitotic cell proliferation.[20] Telomeres progressively shorten with each mitotic division due to the limiting nature of

linear DNA replication mechanisms. After a critical degree of telomere shortening, cells lose the ability to replicate and may cease dividing (senescence) or undergo programmed cell death.[21] Telomere shortening has therefore been proposed as a marker of biologic aging.[22] Consistent with their utility as 'biomarkers of aging', shortened telomeres have been shown to be associated with age-related morbidity and mortality.

The question arises which factors influence the shortening of telomeres. From a conceptual point of view, mental health is a crucial component of successful aging. This prompted researchers to investigate telomere biology in a psychological context as well. Several studies have indicated that psychosocial stress is associated with shorter telomeres, and thereby increased biological age, in apparently healthy persons[23, 24] and in older patients with heart failure.[25] In addition, previous cross-sectional studies have found that depression was associated with shorter telomere length.[26-29] *Chapter 5* adds to this growing literature by demonstrating that depression is associated with short telomere length in patients with stable CHD. Further research is necessary to examine the mechanisms underlying the association between depression and reduced telomere length in CHD patients. Potential links between depression and shortened telomere length could be oxidative stress and inflammation.[30] Previous studies have demonstrated an association between depression and oxidative stress. Depressed patients have increased levels of circulating oxidative stress markers and decreased levels of anti-oxidant enzymes.[31-33] Additionally, some, but not all studies, have found that depression is associated with increased levels of pro-inflammatory cytokines.[34, 35] Both oxidative stress and pro-inflammatory cytokines have been found to influence telomere length. Oxidative stress has a negative effect on telomere length, through inhibition of telomerase activity[36] and direct erosion of GGG triplets in telomeric DNA.[37] Pro-inflammatory cytokines may either decrease or increase telomerase activity[38-40] and are thought to lead to immune cell turnover, and thus decreased telomere length through greater replicative history.

We were the first to study the effect of depression on subsequent change in telomere length. Little is known concerning the dynamic regulation of telomere length over time. Recently, it has become apparent that telomeres may lengthen as well as shorten.[41, 42] For example, in the Heart and Soul study less than half of the participants experienced telomere shortening, and almost a quarter actually lengthened their telomeres during the 5 year follow up period. In this longitudinal study we observed that major depressive disorder was associated with a 32% decreased odds of shortening (i.e., greater odds of lengthening) (*chapter 5*). In *chapter 6* we extended this research question to the general population. In the PREVEND study we found that depression was not associated with telomere shortening over time.

We can only speculate why we did not found an association between depression and telomere shortening over time. A possible explanation may be that there is a compensatory response to cellular damage in depressed patients. In the Heart and Soul study short baseline telomere length (and not depression) was by far the strongest predictor of subsequent lengthening, and the association between depression and lengthening was not significant after further adjustment for shorter baseline telomere length in depressed participants. These findings are in concordance with previous studies which found that telomere trajectory is powerfully influenced by baseline telomere length and that both healthy individuals and CHD patients with the longest telomeres experienced the greatest amount of shortening, while those with shorter telomeres either maintained or increased in their length.[41-43] An important potential regulator of this negative feedback is the enzyme telomerase, which is a reverse transcriptase enzyme that restores telomere length. Telomerase has been shown to act preferentially on short telomeres in preclinical and clinical settings.[44-46] Moreover, chronically stressed caregivers, and depressed individuals have increased levels of telomerase.[23, 47] Thus, it is possible that depression may have contributed to shorter baseline telomeres, but over a follow-up time of 5 years, the subsequent negative feedback from those short telomeres may overwhelm any independent effect on trajectory. Another possible explanation could be related to the treatment of depression. Traditional antidepressants have several functions apart from increasing intrasynaptic monoamine concentrations; they have anti-inflammatory[48, 49] and antioxidant[50, 51] effects. Because oxidative stress and inflammation have been opposed as potential links between psychosocial factors and shortened telomere length, it is possible that antidepressants protect the telomeres by decreasing oxidative stress and inflammation and in this way preventing them from getting shorter.

Because telomere length seems to be associated with both depression as well as with morbidity and mortality, this raises the question of whether accelerated cellular aging is a mechanism that contributes to the excess morbidity and mortality associated with depression.[26, 52] We were the first to examine this association. However, in *chapter 5* we found no evidence for the fact that telomere length is a mediator in the relationship between depression and heart failure and mortality. Because we studied this in a stable CHD population this finding may not be generalizable to other populations. The present thesis provides no definite answer as to the importance of telomere length as a possible mechanism underlying the association between depression and cardiovascular prognosis. Therefore, more information is necessary in the future.

Lately the role of anxiety in relation with the prognosis received more attention, and anxiety appears to be an independent risk factor for CHD and mortality.[53, 54] Therefore, the association between anxiety and telomere length over time could be of importance. Only one cross-

sectional study focused on the association between anxiety and telomere length. They did not observe differences between cases and controls in the entire cohort, but the older half of the anxiety disorder patients exhibited significantly shorter telomeres than healthy controls of the same age.[55]. In *chapter 6* we found that anxiety disorders predicted shorter telomere length at follow-up in a general population. The association was not explained by adverse life events, lifestyle factors, educational level and antidepressant use. Based on our findings anxiety seems to be of more importance than depression regarding telomere attrition. The finding that anxiety predicts telomere length over time, while depression does not, might be explained by the phenomenological and etiological differences among anxiety and depressive disorders. Symptoms of anhedonia and the absence of positive affect are specific to depression, whereas symptoms of physiological hyperarousal and thoughts of future threat are more prominent in anxiety.[56] It is possible that mainly these features related to extreme physiological stress are of importance for telomere damage. In support of this, we found that specifically the presence of panic disorder, agoraphobia and/or social phobia was driving the effects on telomere length at follow-up. These anxiety disorders are mainly characterized by fear, while generalized anxiety disorder and depression are identifiable as anxious-misery disorders.[56, 57] This finding suggests that in patients with anxiety, especially fear (usually accompanied by extreme physiological hyperarousal) could be an important factor in telomere shortening. However, these findings should be interpreted with caution because of the limited number of participants having a specific type of anxiety disorder.

Due to the lack of longitudinal studies, it is not known whether telomere shortening is a cause or consequence of stress and psychiatric disorders. The longitudinal setting of our study enabled us to assess anxiety as a predictor of telomere length at follow-up. Based on *chapter 6* one could hypothesize that anxiety leads to accelerated telomere shortening. However, it is also possible that participants with anxiety had already shorter telomeres to start with. To further explore this possibility we performed a post-hoc analysis. The association was only marginally reduced after adjusting for telomere length at T1 (4 years before CIDI assessment), but lost statistical significance. Therefore, it remains possible that telomere length before the measurement of anxiety drives the association between anxiety and telomere length at follow-up. With our study design we could not further disentangle this possibility.

Positive affect and prognosis

As been described in the first part of this thesis, there has been a shift to dismantling the depression construct in order to uncover its most cardiotoxic components. In addition, there is a need to expand the traditional scope on negative emotions and to focus on other psychological factors, including positive affect. There is now growing recognition that

positive emotions may also provide important protective effects.[58] Accumulating evidence suggests that positive psychological factors may actually improve longevity,[58, 59] and decrease morbidity and mortality from cardiovascular disease,[60-63] although mixed findings have been reported.[64-66] In *chapter 7* we showed that positive affect was associated with a 27% reduction in mortality in stable CHD patients during a mean follow-up of 7 years. We did not found an association between positive affect and cardiovascular morbidity.

The idea that improving positive attitude might help people live longer has considerable appeal. However, there are several unresolved issues regarding positive affect and health outcomes. There is an ongoing debate in the literature whether positive affect and negative affect are independent of each other, or that they are bipolar extremes of the same mood dimension.[58, 65, 67] Therefore, it is important to evaluate whether research on positive psychology and health is simply reframing existing knowledge concerning negative emotion, or is adding a distinctive dimension to psychosomatic medicine.[58] Brummett and colleagues observed that in a study of cardiac catheterization patients, adjustment for depressive emotion attenuated the observed relationship between positive affect and long-term survival.[65, 65] In another study, the association between emotional vitality and decreased risk of coronary heart disease remained after controlling for depressive symptoms.[68] In our sample, adjusting for 'depression' did not reduce the effect size, while adjusting for 'depressive symptoms' reduced the effect size for positive affect size by 17%. However, when we adjusted for depressive symptoms in our final model, positive affect remained associated with improved survival. The consistency of the association between positive affect and survival after accounting for depression suggests important and separate relationships between positive emotions and survival. These findings are consistent with the understanding that optimal functioning transcends the simple absence of negative affect.[69]

It is plausible that multiple biological and behavioral pathways may link positive emotional experiences with health outcomes. Potential biological variables include mechanisms that may directly impact on the physiological functioning, including neuroendocrine processes, inflammation, HRV, or omega-3 fatty acids. People with high positive affect may also have more favourable health habits and make healthier behavioral choices than people with low positive affect. After further adjusting for biological and behavioral variables, we found that the association was not explained by biological markers but largely by physical activity. These findings hint at the possibility that the increased survival rate associated with positive affect could be explained by physical activity and other positive health behaviors that travel with exercise.

Our study evaluated positive affect and physical activity at the same point in time, therefore we cannot determine whether physical inactivity was the cause or result of positive affect. There is abundant evidence that positive emotions and exercise behavior are tied together, but it is difficult to determine the directionality of this association. The association is presumably bidirectional, because high positive affect is associated with a greater likelihood of engaging in physical activity,[70] and engaging in physical activity induces positive affect.[71, 72] Therefore, enhancing positive affect can presumably increase physical activity, and physical activity can elevate positive affect. Regardless of whether physical activity was the cause or a result of positive affect, it appeared to explain a large part of the association between positive affect and survival. Our findings raise the possibility that increasing exercise may contribute to the protective effects of positive affect regarding survival.

Implications for clinical practice and future research

Somatic versus cognitive depressive symptoms and prognosis

Our current findings provide further support for the conceptualisation of depression as a heterogeneous syndrome in which some aspects may be more strongly related to cardiovascular prognosis than others. It is possible that depression treatment trials in CHD patients have primarily targeted the cognitive symptoms of depression and their inability to demonstrate reductions in cardiovascular morbidity and mortality may be partly attributable to under-treatment of the somatic features of depression. Although treating cognitive depressive symptoms is of importance, it may not directly result in improved cardiovascular outcome. The results from studies focusing on somatic and cognitive depressive symptoms indicate the need for future research directed at identifying the underlying pathofysiological processes by which somatic depressive symptoms contribute to prognosis in CHD patients. In addition, various interventions must be tested in order to alleviate the associated risk. Perhaps standard depression treatments are ineffective for somatic depressive symptoms because of their atypical etiology and underlying physiology. In order to prevent the cardiotoxic effects of depression, treatments must lead to improvement in CHD risk factors in order to normalize atherosclerosis and CHD abnormalities, like inflammation and reduced heart rate variation.[15] Both of these factors might be addressed by interventions that are not yet specifically known as antidepressant therapies.

Our findings have important clinical implications. Researchers and clinicians should pay specific attention to somatic depressive symptoms. With reference to this issue, a recent study that used the PHQ-9 to assess depression severity in post-MI patients indicated that somatic symptoms of depression are often overlooked in these patients, while these symptoms may have substantial prognostic power in the prediction of adverse clinical

events post-MI.[2] Close monitoring of somatic depressive symptoms might help to improve clinical care for depressed CHD patients. If patients do not respond to antidepressant or psychotherapy with regard to somatic symptoms, additional treatments (i.e. exercise training) may be considered.

Telomere length as a possible mechanism

The role of factors that might explain the association between depression and CHD outcomes remains largely unknown. As anxiety appears to be an independent risk factor for CHD and mortality, there is a need to derive further insight in the mechanisms underlying this association as well. The present thesis provides no definite answer as to the importance of telomere length as a possible mechanism underlying the association between depression and cardiovascular prognosis, but it indicates that telomere length might be of importance in the anxiety-CHD association. Because the research field that focuses on psychopathology and telomere length is relatively new and inconclusive, a lot of questions surrounding this relationship remain unanswered. The rather inconsistent findings may be due to fluctuation of telomere length over time. To gain more insight in to this possibility, more longitudinal studies with multiple repeated measurements (waves) are necessary in the future. To derive further insight in the association between psychopathology and telomere length durations and sample sizes should increase, hence the most gain can be achieved by increasing the number of waves. Furthermore, it would be interesting to confirm the observations by following telomere length in individual patients.

Although telomere attrition might be a useful marker in a (psychological) successful aging context, practical applicability is limited. Consequently, there is a need to mechanistically unravel epidemiologic associations. Known telomere attrition determinants explaining the epidemiologic associations are inflammation and oxidative stress, directing novel research into deeper exploration of their involvement in psychopathology. Additional mechanistic insight is required by further research in the field, for example, by investigating additional mechanisms of telomerase activity in response to psychological factors.

Finally, future studies would be needed to ascertain the clinical significance of the telomere system in relation to psychopathology and cardiovascular prognosis, and whether direct manipulation of this system might hold promise for novel therapeutics. Hopefully, these efforts will assist us to fully understand mental health as an integral part of successful aging.

Positive affect and prognosis

This thesis also indicates the need for focusing on positive affect. We showed that, in contrast to depression, positive affect was associated with improved survival. Therefore, a

more comprehensive approach to treatment, including individualized treatment of a wide variety of psychological factors, may be more successful in improving prognosis. A more nuanced picture of the mental state of CHD patients may help in the development of more effective interventions to reduce adverse outcomes.

Physical exercise may be a relevant target for intervention in CHD patients. It has been found that the increased risk of adverse cardiovascular events associated with depression was largely explained by behavioral factors, notably lack of physical exercise.[73] Recent evidence suggests that exercise may be effective in treating both depression and CHD risk factors,[74, 75] but no randomized clinical trials have examined the effects of exercise on clinical outcomes in depressed cardiac patients. In *chapter 7* we showed that physical exercise seems to be an important pathway between positive affect and survival as well. Up to now, trials have mainly focused on negative emotions. However, interventions should not only target the reduction of negative emotions but also seek to enhance positive emotions. Cardiac rehabilitation may be promising in this matter. Cardiac rehabilitation aims to return the individual to optimal emotional function, and exercise is considered to be the cornerstone of cardiac rehabilitation.[76] It may be hypothesized that individuals with CHD may benefit from the effects of physical activity by bending their lifestyles to include daily life patterns of behavior that are conducive to higher generation of positive affect and to lower the depression status, thus increasing future health outcomes. Therefore, a randomized controlled trial is needed to evaluate the effects of exercise therapy on depression, positive affect and prognosis in CHD patients.

Limitations of the present thesis

One important limitation of this thesis is that we used data from observational studies. Even with extensive statistical control of reliable measured covariates, it is impossible to rule out the possibility of unmeasured or residual confounding in observational data.[10] It is possible that depression reflects some unknown indicator of more advanced cardiac disease, or that depression and CHD are the products of common causes, for example genetic factors. In addition, the association between positive affect and cardiac prognosis may be confounded by the severity of heart disease, with a greater disease burden causing impairment in positive affect. Because experimental studies with a randomized design minimize confounding by unmeasured as well as measured factors, more research is necessary regarding depression, positive affect and cardiovascular disease based on randomized controlled trials in order to rule out the possibility of confounding. Another limitation is that, although the somatic symptoms were the strongest predictor of cardiovascular events, these were also more prevalent. Thus, the lack of association between cognitive symptoms and cardiovascular events may be due in part to smaller numbers of patients

with cognitive symptoms. Furthermore, the confidence intervals around the hazard ratios overlapped. Performing a meta-analysis on cognitive and somatic depressive symptoms in relationship with the prognosis will be useful to derive further information. Another limitation of the studies included in the second part of this thesis is that associations with telomere length were restricted to telomere length in leukocytes. This measure of telomere length does not necessarily reflect telomere length in other cell compartments or tissues of interest. Furthermore, since they circulate throughout the whole body, they are seen as representatives of systemic processes. Therefore, the effects of psychosocial factors on telomere length of specific tissues should be examined in future studies.

Concluding remarks

Depression and CHD are the two strongest contributors to the global burden of disease, and the co-occurrence of depression and CHD represents a great challenge in psychosomatic medicine. Whether depression is a causal risk factor for CHD has not yet been established. Overall, depression treatment in CHD patients had only minor effects in terms of reducing depressive symptoms, and these effects did not lead to enhanced survival. More research into differential associations between symptom dimensions of depression and prognosis in terms of predicting adverse health outcomes could lead to effective treatment strategies to prevent future cardiac events. In addition, this thesis illustrates that there is a need to expand the traditional scope on negative emotions and to focus on other psychological factors, including positive affect. More information is needed to understand the exact role of depression and other psychological factors in patients with coronary heart disease and their implications. Hopefully, these efforts will lead to the improvement of both psychological status and medical prognosis in patients with CHD.

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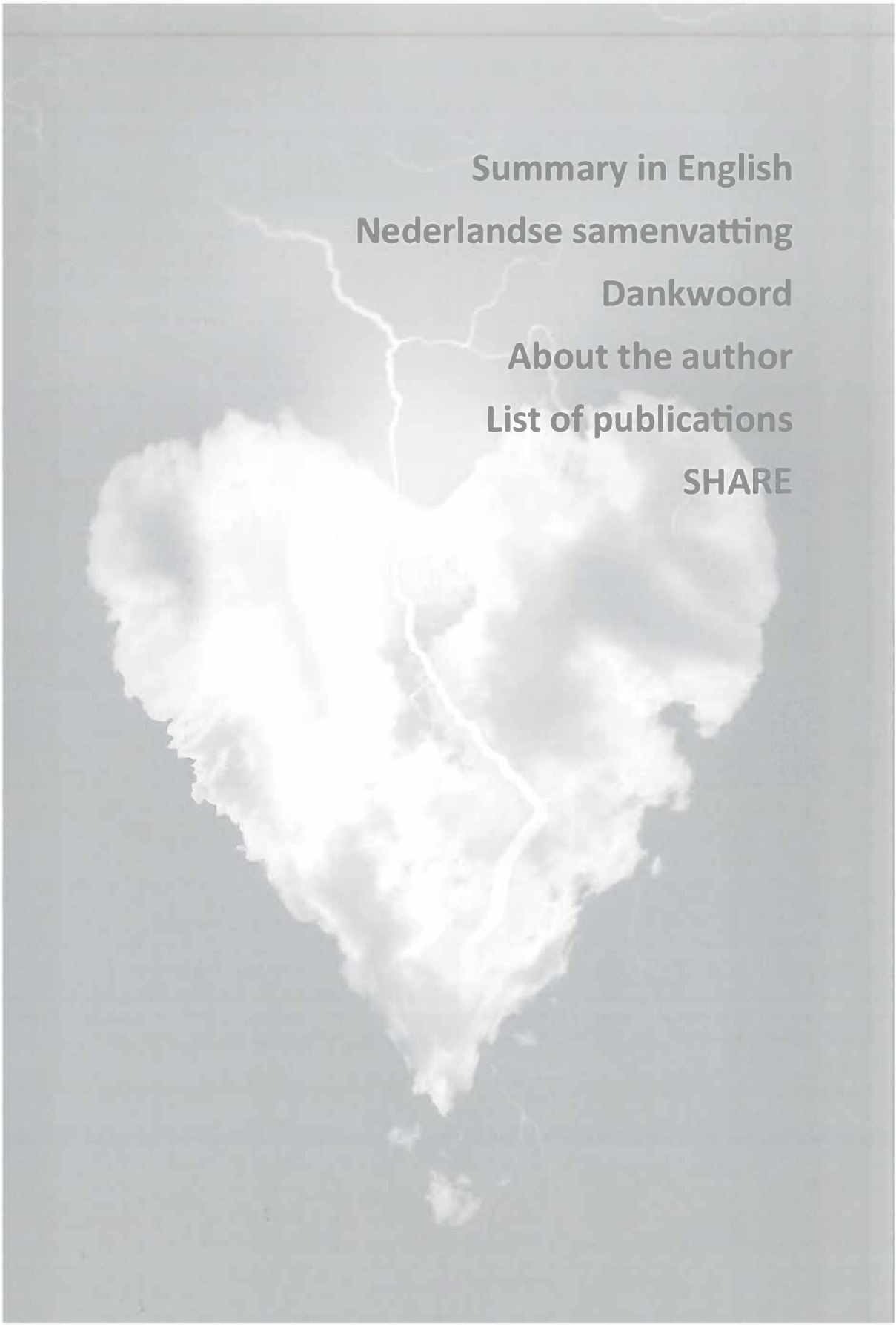

Summary in English

Nederlandse samenvatting

Dankwoord

About the author

List of publications

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Summary in English

Patients with coronary heart disease (CHD) have a high risk of developing depression. Approximately one out of five patients is affected by depression following CHD, which contrasts with the prevalence of major depression of approximately 7% in the general population over the last 12 months. Compared to non-depressed CHD patients, those with a depressive episode have a 2 to 2.5 times greater risk of subsequent cardiac events or mortality. The field of depression and CHD has expanded enormously over the last two decades, but continues to be faced with several unresolved issues. This thesis provides a deeper understanding of the potential effects of depression on prognosis in patients with CHD. The first aim of this thesis was to examine the relationship between cognitive and somatic depressive symptoms and prognosis. The second aim of this thesis was to examine a relatively new mechanism that could potentially underlie the association between depression and cardiovascular prognosis. The final aim of this thesis was to broaden the depression-CHD link by including positive emotions in the prognostic model.

Somatic versus cognitive depressive symptoms and prognosis

The first part of this thesis focused on the association between somatic and cognitive symptoms of depression and prognosis. Because randomized clinical trials have found that depression treatment does not affect cardiac prognosis, it may be reasonable to think that depression does not have a causal effect on cardiac events. However, an alternative explanation lies in the observation that depression is a heterogeneous condition. It is possible that some subtypes of depression are cardiotoxic while others are not, and that some subtypes may respond to treatment while others do not. It is therefore important to identify patients who are at the highest risk for adverse cardiac outcomes. The distinction between different symptom dimensions of depression may be of importance in this respect. In *Chapter 2* we assessed the differential associations of somatic and cognitive depressive symptoms measured with the Beck Depression Inventory with both disease severity and prospective cardiac prognosis in 473 patients with myocardial infarction (MI). The results showed that somatic but not cognitive symptoms were associated with MI severity and cardiovascular prognosis. Even though somatic depressive symptoms were confounded by disease severity, they were still prospectively associated with medical outcome. These findings confirm previous studies indicating that somatic depressive symptoms are associated with disease severity, but also that somatic symptoms have an independent effect on adverse cardiac outcome while cognitive symptoms do not.

In *Chapter 3* we examined the existence of differential associations of specific depressive symptoms on cardiovascular prognosis. We chose to investigate this research question in a population with 1,019 stable CHD patients because in this sample, the depressive symptoms may be less confounded by complaints that are frequently expressed in the direct aftermath

of an acute coronary event. Depressive symptoms were assessed with the Patient Health Questionnaire. After adjustment for demographic data and cardiac risk factors, each somatic symptom was associated with 14% greater risk of events. Fatigue, appetite problems and sleeping difficulties were most strongly predictive of cardiovascular events. In contrast, cognitive symptoms were not significantly associated with cardiovascular events.

All previous analyses conducted on somatic and cognitive symptoms of depression and the relationship with cardiovascular prognosis relied on self-report instruments, including the Beck Depression Inventory and the Patient Health Questionnaire. We therefore evaluated the independent association between cardiovascular prognosis and ratings of the individual depressive symptoms based on a structured diagnostic interview (CIDI) *(Chapter 4)*. Using symptoms-specific data from a structured diagnostic interview the following findings were obtained. First, we confirmed that, after adjusting for potential confounders, the presence of somatic symptoms of depression was associated with an increased risk of cardiovascular events. Second, in contrast with previous studies using self-report data, interview-ratings of cognitive symptoms of depression were also associated with a significantly increased risk in multivariate analysis, although less strongly than somatic symptoms. These findings suggest that the association between depressive symptom dimensions and prognosis might depend on the type of depression assessment. More research is needed to evaluate the relationship between depressive symptom dimensions measured with questionnaires and diagnostic interviews and cardiac prognosis in different patient populations.

Telomere length as a possible mechanism

The mechanisms underlying the depression-CHD relationship are still poorly understood. It is important to broaden our scope and identify other pathways by which depression may influence adverse outcomes in CHD patients. Recently, cellular aging has been proposed as a possible mechanism that may underlie the association between depression and cardiovascular prognosis. *Chapter 5* assessed whether depression is associated with telomere length or trajectory in patients with stable CHD. In a sample of 952 patients with stable CHD, we found that major depression was associated with a 71% greater odds of having short telomere length at baseline. This indicates that their leukocytes had aged the equivalent of 2.3 additional years, compared with patients without depression. However, current depression did not predict subsequent change in telomere length. In addition, we could not confirm that accelerated cellular aging is a mechanism that contributes to the excess morbidity and mortality associated with depression.

In *Chapter 6,* we tested whether depressive disorders predict telomere length over time in a large population-based sample of 911 participants. Recently, the prognostic role of

anxiety has received more attention, and accumulating evidence suggests that anxiety is an independent risk factor for CHD and mortality. Therefore, we were also interested in the association between anxiety and telomere length over time. Both depressive and anxiety disorders were assessed with the CIDI. This study found that anxiety disorders predicted shorter telomere length at follow-up. The association was not explained by adverse life events, lifestyle factors, educational level or antidepressant use. In contrast, no association was found between depressive disorders and telomere length at follow-up. How anxiety disorders might lead to accelerated telomere shortening and whether this might be a mediator explaining the excess mortality risk associated with anxiety deserves further investigation.

Positive affect and prognosis

Although the impact of negative emotions on cardiovascular prognosis has been studied extensively, research on positive affect has been relatively sparse. In *Chapter* 7, we established whether positive affect is associated with improved survival and decreased cardiovascular morbidity in patients with stable CHD. Each standard deviation increase in PANAS positive affect score was associated with 16% decreased risk of death after a median follow-up of 7 years. We did not find an association between positive affect and cardiovascular morbidity. After adjustment for cardiac disease severity and depressive symptoms, positive affect remained associated with improved survival. Biological variables did not seem to explain this association. However, the association between positive affect and survival becomes non-significant after adjustment for physical activity. These findings seem to suggest that the improved survival associated with positive affect could potentially be enhanced with behavioral interventions that include exercise training.

Concluding remarks

The overarching purpose of this thesis was to provide further insight into the association between depression and prognosis in patients with coronary heart disease.

The first part of this thesis further supports the conceptualization of depression as a heterogeneous syndrome, in which some aspects may be more strongly related to cardiovascular prognosis than others. Further research is needed to understand the pathophysiological processes by which somatic depressive symptoms contribute to prognosis in CHD patients. This research into differential associations between symptom dimensions of depression and prognosis in terms of predicting adverse health outcomes could lead to effective treatment strategies to prevent future cardiac events.

The second part of this thesis focused on biological aging as a possible mechanism underlying the association between psychopathology and adverse prognosis. More research

is necessary to assess the exact role of telomere length. Hopefully, these efforts will assist us in fully understanding mental health as an integral part of successful aging.
Finally, this thesis demonstrates the importance of focusing on factors other than depression, including positive affect. We showed that, in contrast to depression, positive affect was associated with improved survival. Therefore, a more comprehensive approach to treatment may be more successful in improving prognosis.

In conclusion, this thesis demonstrates the need for novel perspectives on depression and cardiovascular disease regarding the heterogeneity of depression, the mechanistic pathways that link depression to CHD, and the potential importance of other psychosocial factors. Hopefully, a more nuanced picture of the mental state of CHD patients will help in the development of more effective interventions to reduce adverse outcomes.

Nederlandse samenvatting

Patiënten met coronaire hartziekte (CHZ) hebben een verhoogd risico op depressieve klachten. Na een hartinfarct maakt ongeveer 1 op de 5 patiënten een depressieve episode door. Deze prevalentie is ongeveer 3 keer hoger dan die in de algehele bevolking. Depressie na een hartinfarct gaat gepaard met een 2 tot 2,5 keer verhoogd risico op het krijgen van nieuwe hartproblemen of vervroegd overlijden. Hoewel we de afgelopen twee decennia een duidelijke opmars hebben gezien van onderzoek naar depressie en CHZ, blijven verschillende fundamentele vragen onbeantwoord. In dit proefschrift zijn de potentiële effecten van depressie op de hartprognose bij patiënten met CHZ nader in kaart gebracht. Het eerste doel van dit proefschrift was om de relatie tussen somatische en cognitieve depressieve symptomen en de hartprognose te onderzoeken. Het tweede doel van dit proefschrift was een relatief nieuw mechanisme te onderzoeken dat ten grondslag zou kunnen liggen aan de associatie tussen depressie en de hartprognose. Het laatste doel van dit proefschrift was om de link tussen depressie en CHZ te verbreden en om positieve emoties aan het prognostische model toe te voegen.

Somatische versus cognitieve depressieve symptomen en prognose

In het eerste deel van dit proefschrift hebben we ons gericht op de associatie tussen depressieve symptomen en de hartprognose. Omdat gerandomiseerde studies hebben gevonden dat het behandelen van depressie niet resulteerde in een verbetering van de hartprognose, kan geconcludeerd worden dat depressie geen causaal effect heeft op nieuwe hartproblemen of vervroegd overlijden. Echter, als mogelijke alternatieve verklaring kan de heterogeniteit van depressie genoemd worden. Het is mogelijk dat alleen bepaalde vormen van depressie cardiotoxisch zijn of dat alleen bepaalde vormen van depressie goed reageren op behandeling. Het is belangrijk om de patiënten met het hoogste risico op een ongunstige hartprognose te identificeren omdat zij veel baat zouden kunnen hebben bij mogelijke interventiestrategieën. Het onderscheid tussen symptoom dimensies van depressie kan daarom van belang zijn. In *hoofdstuk 2* zijn de verschillende relaties onderzocht tussen dimensies van depressieve symptomen en ziekte-ernst en hartprognose bij patiënten die een hartinfarct hebben doorgemaakt. Depressieve symptomen zijn gemeten bij 473 hartinfarct patiënten aan de hand van de Beck Depression Inventory. Er werd onderscheid gemaakt tussen somatische depressieve symptomen, zoals vermoeidheid en eetproblemen en cognitieve depressieve symptomen, zoals depressieve stemming en concentratieproblemen. De resultaten lieten zien dat de somatische, maar niet de cognitieve depressieve symptomen waren geassocieerd met de ernst van de hartziekte en de hartprognose. De bevindingen bevestigden eerdere studies die aantoonden dat somatische depressieve symptomen geassocieerd zijn met de ernst van de hartziekte, maar ook dat somatische symptomen een onafhankelijk effect hebben op de hartprognose, terwijl cognitieve symptomen dat niet hebben.

In hoofdstuk 3 zijn de verschillende effecten van individuele depressieve symptomen op de hartprognose beschreven. We hebben ervoor gekozen de onderzoeksvraag te bestuderen in een populatie van 1019 patiënten met stabiele CHZ, omdat in deze groep de depressieve symptomen minder vertroebeld zijn door klachten die vaak worden ervaren na een acuut cardiaal event. Depressieve symptomen zijn gemeten met de Patient Health Questionnaire. Na controle voor demografische factoren en risicofactoren voor CHZ, was elk somatisch symptoom geassocieerd met een 14% toegenomen risico op nieuwe hartproblemen of vervroegd overlijden. Vermoeidheid, eetproblemen en slaapproblemen waren het sterkst geassocieerd met nieuwe hartproblemen of vervroegd overlijden. Daarentegen waren cognitieve depressieve symptomen niet significant geassocieerd met de hartprognose.

Analyses die tot dusver zijn gedaan om de relatie te onderzoeken tussen somatische en cognitieve depressieve symptomen en de hartprognose zijn gebaseerd op zelfrapportage, waaronder de Beck Depression Inventory en de Patient Health Questionnaire. Daarom zijn in *hoofdstuk 4* de associaties tussen individuele depressieve symptomen en de hartprognose geanalyseerd op basis van een gestructureerd diagnostisch interview. Ten eerste hebben we bevestigd dat, na controle voor confounders, somatische depressieve symptomen geassocieerd zijn met een toegenomen risico op nieuwe hartproblemen of vervroegd overlijden. Ten tweede hebben we gevonden dat, in tegenstelling tot eerdere studies die zelfrapportage hebben gebruikt, cognitieve depressieve symptomen gemeten met een interview in multivariate analyses ook geassocieerd zijn met een significant toegenomen risico op nieuwe hartproblemen of vervroegd overlijden. Deze associatie was echter minder sterk dan die met somatische depressieve symptomen. Deze bevindingen suggereren dat de associatie tussen depressieve symptoom dimensies en de hartprognose mogelijk afhankelijk is van het meetinstrument waarmee de depressie wordt bepaald. Meer onderzoek is nodig om de relatie tussen depressieve symptoom dimensies gemeten met een vragenlijst en een diagnostisch interview en de hartprognose in verschillende patiënten populaties te evalueren.

Telomeerlengte als een mogelijk mechanisme

Hoewel veel studies een verband hebben gevonden tussen depressie en CHZ, is relatief weinig bekend over de onderliggende mechanismen die dit verband kunnen verklaren. Het is belangrijk om nieuwe mechanismen te identificeren die kunnen verklaren hoe depressie leidt tot een slechte hartprognose bij CHZ patiënten. Inzicht in deze mechanismen kan mogelijk in de toekomst leiden tot verbetering van de hartprognose bij deze patiënten. Recent is een korte telomeerlengte geïndiceerd als een mogelijk mechanisme dat bij kan dragen aan een slechtere hartprognose bij depressieve patiënten. Telomeren zijn de uiteinden van chromosomen en worden gezien als een maat voor biologische veroudering.

In *hoofdstuk 5* hebben we onderzocht of depressie geassocieerd is met telomeerlengte of telomeerverkorting bij patiënten met stabiele CHZ. Telomeerlengte was in deze groep gemeten in leukocyten. In een groep van 952 patiënten met stabiele CHZ hebben we gevonden dat depressie geassocieerd is met een 71% grotere kans op het hebben van kortere telomeerlengte tijdens de start van de studie. Dit impliceert dat de leukocyten van depressieve patiënten 2.3 jaar ouder waren, vergeleken met patiënten die niet depressief waren. Depressie was echter niet voorspellend voor telomeerlengte verandering over tijd. Tevens konden we in deze studie niet bevestigen dat toegenomen biologische veroudering van de cellen een mechanisme is dat bijdraagt aan de slechtere prognose die geassocieerd is met depressie.

In *hoofdstuk 6* is in een relatief gezonde groep mensen uit de bevolking (n = 911) onderzocht of depressie verandering in telomeerlengte over tijd voorspelt. Eerder is gebleken dat angst een belangrijke onafhankelijke risicofactor is voor een slechte hartprognose en vervroegd overlijden. Daarom hebben we ons in dit hoofdstuk gericht op de relatie tussen zowel angst als depressie en telomeerlengte over tijd. Deze studie heeft aangetoond dat angst voorspellend is voor telomeerlengte gemeten tijdens follow-up. Deze associatie was niet te verklaren door negatieve gebeurtenissen in het leven, leefstijlfactoren, opleidingsniveau en het gebruik van antidepressiva. In tegenstelling tot eerdere bevindingen, hebben we geen associatie gevonden tussen depressie en telomeerlengte verkorting over tijd. Hoe angst kan leiden tot toegenomen telomeerlengte verkorting en of dit mechanisme verklarend kan zijn voor de toegenomen mortaliteit die gepaard gaat met angst moet verder onderzocht worden.

Positief affect en prognose

Hoewel de impact van negatieve emoties op de prognose uitgebreid is onderzocht, zijn er weinig studies die zich richten op positieve emoties. In *hoofdstuk 7* hebben we gekeken of positief affect geassocieerd is met toegenomen overleving bij patiënten met stabiele CHZ. Positieve affectiviteit geeft onder andere weer hoe enthousiast, energiek en alert een persoon is. De resultaten lieten zien dat elke standaard deviatie toename in de positief affect score geassocieerd is met een 16% afgenomen risico op mortaliteit bij een gemiddelde follow-up duur van 7 jaren. Na controle voor ernst van de hartziekte en depressieve symptomen, bleef positief affect geassocieerd met een toegenomen overlevingsduur. Biologische variabelen vormden ook geen verklaring voor deze associatie. Echter, de associatie tussen positief affect en overleving was niet langer significant na controle voor fysieke activiteit. Deze bevindingen suggereren dat de toename in overleving, geassocieerd met positief affect, mogelijk bereikt kan worden met behulp van gedragsinterventies die ook fysieke training bevorderen.

Concluderende opmerkingen

Het algemene doel van dit proefschrift was om inzicht te krijgen in de associatie tussen depressie en de hartprognose bij patiënten met CHZ. Het eerste deel van dit proefschrift ondersteunt het concept van depressie als een heterogeen syndroom, waarbij bepaalde aspecten van depressie sterker geassocieerd zijn met de hartprognose dan andere aspecten. Verder onderzoek naar onderliggende pathofysiologische processen is nodig om te begrijpen waarom vooral somatische symptomen bijdragen aan een slechtere prognose in CHZ patiënten. Vervolgonderzoek dat zich richt op de verschillende associaties tussen symptoom dimensies van depressie en de hartprognose zou kunnen leiden tot effectieve behandelstrategieën die de prognose van CHZ patiënten kunnen verbeteren. Het tweede deel van dit proefschrift richtte zich op biologische veroudering als mogelijk mechanisme onderliggend aan de relatie tussen psychopathologie en een slechte medische uitkomst. Verder onderzoek is nodig om de exacte rol van telomeerlengte vast te stellen. Dit kan bijdragen aan verbeterde kennis van geestelijke gezondheid als een onderdeel van gezond ouder worden. Tenslotte hebben we in dit proefschrift het belang laten zien van andere factoren dan depressie, zoals positief affect. Zo bleek dat in tegenstelling tot depressie, positief affect was geassocieerd met een langere overleving. Daarom zou een uitgebreidere aanpak tot behandeling meer succesvol kunnen zijn teneinde de prognose van patiënten met CHZ te verbeteren.

Concluderend laat dit proefschrift zien dat nieuwe perspectieven op de relatie tussen depressie en CHZvan belangzijn. Deze perspectieven hebben betrekking op de heterogeniteit van depressie, de onderliggende mechanismen, en andere psychosociale factoren. Beter inzicht in de mentale staat van CHZ patiënten kan leiden tot effectievere interventies om de medische uitkomsten te verbeteren.

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Petra

About the author

Petra Hoen was born on July 29, 1986 in Groningen, the Netherlands. In 2004, she graduated from secondary school (Gymnasium) at the Maartenscollege in Groningen. Subsequently, she began studying Medicine at the University of Groningen. She developed a special interest in Psychosomatic Medicine, and participated in a research project at the Interdisciplinary Center Psychopathology and Emotion regulation under the supervision of Prof. Dr. Peter de Jonge. This project resulted in an MD/PhD trajectory in 2008, the results of which are presented in this thesis. In 2010, Petra went to the USA for two months to work on one of her PhD projects under the supervision of Dr. Mary A. Whooley at the VA Medical Center. In 2011, she went to Tilburg University in the Netherlands for a research collaboration under the supervision of Prof. Dr. Johan Denollet. She further developed her skills as a researcher by presenting her work at national and international conferences. In October 2012, she will start her final clinical rotation at the department of Neurology of the University Medical Center Groningen. In 2013, she will receive her Master's degree in Medicine.

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