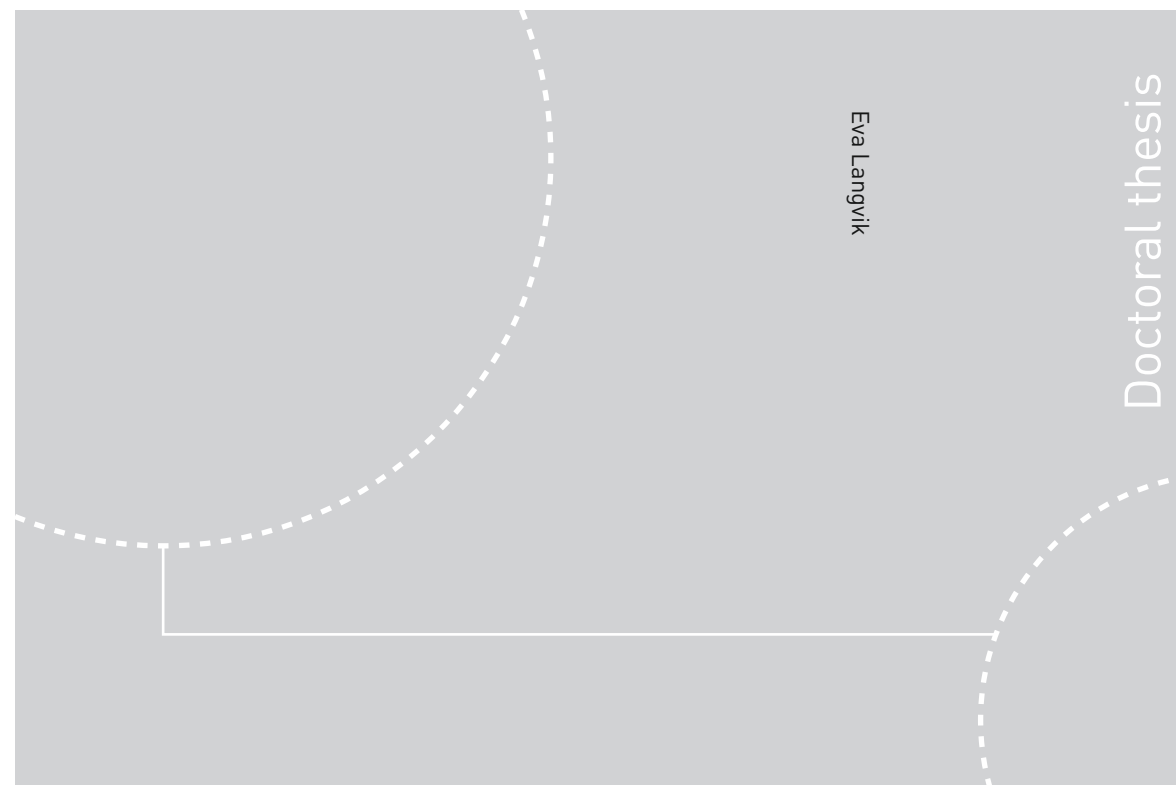


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Eva Langvik

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Gender-specific risk profiles, personality, and the role of anhedonia
The North-Trøndelag Health Study (HUNT)

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Thesis for the Degree of
Philosophiae Doctor
Faculty of Social Sciences and
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Summary

Coronary Heart Disease (CHD) is the leading cause of death worldwide and there has been an increasing interest in primary prevention. The research field struggles to reach a unified agreement about the role of anxiety and depression as etiological variables, and the role of anxiety is especially unclear. Inconsistencies and contradictory findings can, to a large extent, be attributed to a lack of specificity in both predictors and outcome. Identifying psychological risk variables is an important step in reducing the number of deaths and disabilities due to CHD, especially among women where Myocardial Infarction (MI) often occurs asymptotically.

The overall goal of this thesis was to investigate if symptoms of anxiety and depression as measured by the Hospital Anxiety and Depression Scale, HADS (Zigmond & Snaith, 1983), can be used to screen for risk of an incident Myocardial Infarction. Incident MI is defined as the individual's first MI.

This thesis consists of three papers. Paper I and II were based on data from The Nord-Trøndelag Health Study (HUNT 2 and HUNT 3). Paper III was based on a sample of psychology students. In Paper I, the etiological and prognostic approach is combined to identify symptoms of depression and anxiety as causes of MI, and not merely consequences of MI. This was done by comparing symptoms of anxiety and depression before and after the experience of incident MI. Elevated symptoms of depression measured by HADS increased the risk of incident MI. Although limitations apply, having an MI did not have long-term adverse effects on the level of anxiety and depression symptoms, and time since MI was not a significant predictor of symptom level.

Furthermore, researchers have requested a focus on women and CHD. The aim of Paper II was to identify gender-specific psychological risk-profiles based on HADS to optimize

screening of MI-risk. Gender differences in the MI-risk estimate were identified: elevated HADS-D score was a significantly stronger predictor of incident MI among women compared to men. History of depression was a significant predictor of MI among men, but not women. This emphasizes the need for gender-specific psychological risk profiles. Elevated symptoms of anxiety measured by HADS represented a reduced risk of having an incident MI among both men and women.

In Paper III, the aim was to focus on the content in the HADS, and how the anxiety and depression dimension in the instrument were related to more general emotional dispositions. The dimensions in HADS presented high test-retest stability and a strong relationship to the personality traits neuroticism and extroversion. The two dimensions in HADS could be differentiated by the specific relationship between the depression scale, positive affect and extroversion. The results supported that HADS-D represent an anhedonic subtype of depression.

The findings in this thesis have implications for the research field on psychological variables and CHD as well as the practice of efficient risk-screening. It further substantiates the role of personality in symptom reporting.

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List of papers included in the thesis

The thesis is based on three articles referred to by their Roman numeral.

- I. Langvik, E. & Hjemdal, O. (2015). Symptoms of depression and anxiety before and after myocardial infarction: The HUNT 2 and HUNT 3 Study. *Psychology, Health & Medicine*, 20, 560-569.

- II. Langvik, E. & Nordahl, H. M. (2014). Anhedonic depression, history of depression, and anxiety as gender-specific risk factors of myocardial infarction in healthy men and women: The HUNT study. *Health Psychology Open*, DOI: 10.1177/2055102914557658

- III. Langvik, E., Hjemdal, O., & Nordahl, H. M. (2016). Personality traits, gender differences and symptoms of anhedonia: What does the Hospital Anxiety and Depression Scale (HADS) measure in nonclinical settings? *Scandinavian Journal of Psychology*, 57, 144–151.

Abbreviations

CHD	Coronary Heart Disease
CVD	Cardiovascular Disease
<i>d</i>	Cohen's <i>d</i>
DSM	Diagnostic and Statistical Manual of Mental Disorders
HADS	Hospital Anxiety and depression Scale
HADS-A	HADS anxiety scale
HADS-D	HADS depression scale
HUNT	The Nord-Trøndelag Health Study
ICD-10	International Classification of Diseases, 10 th Revision
MI	Myocardial Infarction
NEO FFI	The NEO Five factor Inventory
OR	Odds ratio
PANAS	Positive and Negative Affect Scale
SBP	Systolic blood pressure
WHR	Waist-hip ratio
WC	Waist Circumference

Introduction

Cardiovascular disease (CVD) is the most common cause of death in Norway (National Health Institute, 2014). Identifying psychological risk variables is an important step in reducing the number of deaths and disabilities due to CVD. The research field struggles to reach a unified agreement on the role of anxiety and depression as etiological variables, due to lack of specificity in measurement (Suls & Bunde, 2005; Davidson, 2012; Batelaan, ten Have, van Balkom, Tuithof, & de Graaf, 2014; Cohen, Edmondson, Kronish, 2015). To understand the role of symptoms of anxiety and depression in predicting Myocardial Infarction (MI) in the general population, we need to (1) identify symptoms of depression and anxiety as *causes* of MI, not only consequence of MI. Furthermore, (2) it is important to identify gender-specific psychological risk-profiles in order to optimize screening of MI-risk. To identify the optimal screening tool and understand the relationship between psychological symptoms and MI, (3) there is a need to focus on the content in the specific instrument used, and how specific symptoms are related to more general emotional dispositions.

Depression and cardiovascular diseases

CVD includes two major sub-types: Coronary heart disease (CHD) and cerebrovascular disease (stroke). In CHD, the blood flow to the heart is reduced causing an inadequate amount of oxygen to reach the heart tissue. CHD can cause angina (chest pain), Myocardial Infarction (MI) and sudden cardiac death. Based on the 10th Revision of the International Classification of Diseases (ICD-10), Myocardial Infarction represents an acute heart failure (ICD-10 code 121-122). In Europe and North America, coronary heart disease (CHD) is the leading cause of death in the adult population (Yusuf et al., 2004), and several risk factors (e.g. smoking, hypertension, cholesterol and diabetes) have been established as effective

predictors (Wilson, A'Agistino, Levy, Belanger, Silbershatz, Kannel, 2005). The link between psychological variables and CVD is one of the most studied mind-body connections, where the role of depression has received most attention. Chronic psychological stress, post-traumatic stress, and anxiety have also been studied with regards to epidemiologic evidence and underlying mechanisms (Cohen, Edmondson, & Kronish, 2015). Depression continues to be subject to inquiry; both concerning incident CVD and mortality due to CVD (Carney, Freedland, & Sheps, 2004; Mykletun, Bjerkeset, Dewey, Prince, Overland, & Stewart, 2007) and as a prognostic factor in CVD patients (e.g. Huffman, Celano, & Januzzi, 2010; Doyle, Conroy, McGee, Delaney, 2010). While the prognostic studies focus on patients with existing coronary heart disease (CHD), the etiologic approach, on the other hand, focuses on whether depression is a risk factor for incident coronary heart disease in the general population. A substantial amount of the research on depression and CVD focuses on e.g. reinfarction and mortality in CVD patients (e.g. Doyle et al., 2015; Cohen et al., 2015), or depression in MI patients (e.g. Hanssen, Nordrehaug, Eide, Bjelland, & Rokne, 2009; Benyamini, Roziner, Goldbourt, Drory, & Gerber, 2013). The etiological approach has received less attention, unfortunately. However, integrating the two approaches could be beneficial. A review of studies examining the contribution of depression to the onset of coronary diseases has concluded that depressive symptoms contribute as a significant independent risk (Wulsin & Singal, 2003). A more recent systematic review and meta-analysis of depression and risk for CVD (Van der Koy, Hout, Marwijk, Marten, Stehouer, & Beekman, 2007) support the possible link, but emphasize that solid evidence for this relationship is not yet established, as the findings are inconsistent. A large meta-analysis of 54 observational studies concludes that depression is not established as an independent risk factor for CHD (Nicholson, Kuper, Hemingway, 2006). Two more recent reviews on the evidence of depression being a risk factor for CVD conclude that the evidence is not sufficient to suggest that depression is an

independent causal risk factor for incident CVD or CHD (Stampfer, Hince & Dimmit, 2012; Hare, Toukhsati, Johansson, Jaarsma, 2014).

However, both previous and current research propose a relationship between depression and CVD, a notion further supported by the inclusion of both anxiety and depression as risk factors in guidelines on CVD prevention (Gan et al., 2014; Perk et al., 2012; Glozier, et al. 2014). A review of prospective studies on depression as a risk factor of CHD points to substantial heterogeneity in risk estimate, especially those where self-report depression scales have been applied (Gan, et al., 2014). To improve the understanding of the nature of the relationship between symptoms of depression and CHD, one should aim at a high level of specificity in both predictor and outcome. Frequently, the literature does not differentiate between stroke and CHD, and hence CVD will be addressed as a general category several times in this introduction. However, the outcome of interest in this thesis is CHD, specifically Myocardial Infarction. Furthermore, there are different subtypes of depression, and some may be more relevant than others in this particular context.

The aim of this study is to address the role of anhedonic depression, which can be considered a specific depression sub-type, and an independent risk factor of incident MI when other risk factors as well as anxiety are included in the equation. In addition, the role of dispositional factors in terms of personality traits will be addressed in order to explore the complex relationship between affect and cardiovascular health, as it is suggested that personality and psychopathology share common biological and environmental developmental processes (Clark, 2005).

What causes Myocardial Infarction? Traditional and established risk factors

This thesis focuses on psychological variables, namely the self-report of symptoms of anxiety and depression using a specific instrument; the Hospital and depression scale; HADS (Zigmond and Snaith, 1983). Here, the HADS anxiety and depression subscales are investigated as independent risk factors of Myocardial Infarction (MI). Many studies included in meta-analysis of the relationship between depression and MI do not adjust for other risk factors (Nicholson et al., 2006), but depression can only be established as an independent risk factor when all major traditional risk factors are included and controlled for. Several risk scores has been developed. The Framingham risk score (Anderson, Odell, Wilson, & Kannel, 1991) and the European Society of cardiology systematic coronary risk evaluation (SCORE system) (Conroy, Pyorala, & Fitzgerald, 2003) both include six major risk factors of CHD, i.e., gender, age, systolic blood pressure (SBP), cholesterol, history of diabetes and smoking. The INTERHEART study investigated cases of first MI from 52 different countries, identified nine modifiable risk factors along with gender and age globally associated with MI. These were apolipoprotein (ApoB, or “bad cholesterol”) levels, smoking, hypertension, diabetes, abdominal obesity, psychosocial factors, dietary factors, physical exercise, and alcohol consumption. Several other factors are associated with increased risk of MI, such as family history of heart disease and physical activity, but these factors work to a large extent through the other major risk factors (Wilson et al., 1998). In the development of the INTERHEART modifiable risk score, the final version did not include psychosocial variables like stress and depression, as they did not improve discrimination (McGorrian et al., 2011). This advocates a further investigation of the role of depression as an independent risk factor.

Is depression a cause or effect of MI, or simply a correlate to other risk factors?

It is uncertain whether “emotional triggers could initiate a paradigm shift in preventive cardiology, or whether acute emotional triggers are either intractable catalysts for or merely an epiphenomenon of MI” (Edmondson, Newman, Whang & Davidson, 2011, p. 300). Symptoms of depression vary with age (Faravelli, Scarpato, Castellini, & Sauro), gender (Faravelli et al., 2013; Altemus, Sarvaiya, & Epperson, 2014), obesity (e.g. Svenningsson, Björkelund, Marklund & Gedda, 2011), hypertension (Meng, Chen, Yang, Zheng, & Hui, 2012), health behaviors like smoking and drinking (Benyamini et al., 2013) and health status, like being a cardiac patient (Doyle et al., 2015). A recent clinical review by Hare and colleagues (2014) points to the important distinction between depression being a risk factor, versus a risk marker, of CVD. It is argued that the causal relationship between depression and CVD is not established and that many different mechanisms might be biologically plausible (e.g. genetic linkage to serotonin transporter mechanism, platelet function) as well as behavior aspects like poor adherence to medical treatment (Baune, Stuart, Wersching, Heindel, Arolt, & Berger, 2012; Edmondson et al., 2013). Some have argued that the association is reversed; i.e., that there is a cardiovascular contribution to the etiology of depression (Åberg et al., 2012). Although there is a general agreement that depression is associated with worsened prognoses in cardiac patients (e.g. Cohen et al., 2015), the communication between the prognostic and etiological field has been scarce. Leung and colleagues (2012) have made a request for studies that separate pre-morbid and post-morbid depression in MI patients. Very few studies take into account that elevated symptoms of depression might represent a more dispositional tendency to experience negative emotions, a tendency that is closely linked to personality trait. Lack of consistent findings on the effect on treatment of depression in order to improve prognosis in cardiac patients (Vieweg, Hasnain, Lesnefsky, & Pandurangi, 2011; Thombs et al., 2013) might suggest that depression is more important as a risk marker of

CVD, but equivocal results are lacking within the field. Several meta-studies and reviews on the role of depression as an etiological factor in the development of CVD (e.g. Nicholson et al., 2006; Stamfer et al., 2012) have reached the same conclusion: Heterogeneity in measurement and lack of control of confounding variables prevent firm conclusions.

What do depression scales measure?

The European guidelines on cardiovascular disease prevention in clinical practice (Perk et al., 2012) recommend that anxiety and depression be included in the risk assessment of CHD. However, the guidelines do not specify what types of screening or instruments to apply. Although a clinical diagnostic interview is considered the golden standard, self-report measures of depression are both more cost-effective and easy to administrate. It is beyond the scope of this study to make a thorough discussion of the diagnostic criteria of depression (e.g. DSM-V vs DSM-IV, and ICD-10); therefore, the focus is on how and why some self-report scales of depression might be better at detecting risks than others. Snaith (1993) has addressed the question outlined in the heading and concluded that “The measurement of depression is as confused as the basic construct of the scale itself” (Snaith, 1993, p. 296).

In the prognostic field, the inaccurate measurement of depression has been suggested as the reason treatment of depression fails to improve the prognosis of MI patients (Vieweg et al., 2011; Thombs et al., 2013). In the etiological approach, inconsistent operationalization of depression might explain the substantial heterogeneity and, at times, conflicting findings.

Different types of depressive symptoms and clusters differ in their prognostic value in persons with CHD and hence, considering depression as a multidimensional disorder in research on CHD has been requested (Schaffer, Whang Shimbo et al., 2012; Hawkins, Callahan, Stump, & Stewart, 2013; Stewart et al., 2012; Doyle et al., 2010; Baune et al., 2012). To detect risk of recurrent CHD, the use of more specific sub-types, or intermediary phenotypes of

depression have been suggested (Shaffer et al., 2012). The confusion in the operationalization of depression has hampered the research on the link between depression and CVD (e.g. Davidson, 2008; Davidson et al., 2005). During the last half decade there has been a significant increase in the literature addressing the inconsistencies and problematic issues concerning depression measurement (Chen, Eaton, Gallo, & Nestadt, 2000; Fried, Nesse, Zivin, Guille & Sen, 2014; Fried, 2015; Fried & Nesse, 2015). In the recent meta-analysis by Gan and colleagues (2014) on prospective studies on depression and the risk of CHD, the suggestion for further research emphasizes that investigators should strive to improve the standardization of depression measurement. Fried and Nesse (2015) point to how depression is treated as a homogeneity unit, although few would agree that it is. Adding up different symptoms into one categorical unit labeled “depressed” has hampered the research on depression for understanding the risk factor of depression and developing effective treatment.

The dissatisfaction with the non-specificity of major depression has led many to propose more specific depressive subtyping models. Subtyping depression is a promising attempt to overcome the non-specificity of major depression, and this has an implication for treatment-specification (Baumeister & Parker, 2012). Fried (2015) argues that the focus on syndromes instead of symptoms has slowed down research on depression, and that the clear-cut “depressed vs. non-depressed” is based on the unweighted adding of diverse symptoms (e.g. sad moods, fatigue, anhedonia, sleep disturbance). The category “depressed” constitutes a rather heterogeneous group with a substantially different although overlapping, symptomatic profile. Furthermore, the substantial overlap between depression and anxiety adds to the complexity.

Anxiety and CVD

Comorbidity of anxiety and depression, both in terms of symptom reporting and diagnosis is prevalent from childhood (Cummings, Caporino, & Kendall, 2014). Although the status of anxiety as a risk factor of CVD is not as established as depression (Albus, 2010; Cohen et al., 2015), the European guidelines of CVD prevention suggest screening of anxiety and depression to identify those at risk (Perk et al., 2012). During the last decade, there has been an increased focus on the connection between anxiety and the development of CHD (Roest, Martens, Jonge, & Denollet, 2010; Tully, Cosh & Baune, 2013; Batelaan et al., 2014). However, as with depression, the various conceptualizations of anxiety have hampered the understanding. Seldenrijk and colleagues (2015) recommends a focus on diagnostic subtypes of both depression and anxiety in predicting CVD risk. The meta-analysis by Roest and colleagues (2010) is probably the most cited in the research on anxiety as a risk factor of incident CHD. However, it has been pointed out that the meta-analytic estimate was not adjusted for depression (Cohen et al., 2015). In the work by Janszky and colleagues (2010), early onset of anxiety was more important than early onset of depression. The sample consisted of men only, and depression was operationalized by the category “psychotic and neurotic depression” (ICD-10).

While some have found that worry and generalized anxiety disorder (GAD) is associated with mortality (Tully et al., 2011; Watkins et al., 2013), other studies have demonstrated that symptoms of anxiety are negatively associated with CHD mortality (Meyer, Buss, & Herrmann-Lingen, 2010; Mykletun et al., 2007; Walters, Rait, Petersen, Williams, & Nazareth, 2008). Further, generalized anxiety disorder (GAD) has been found to predict superior outcome after acute coronary syndrome (Parker, Hyett, Hadzi-Pavlovic, Brotchie, & Walsh, 2011). In CHD patients, elevated symptoms of anxiety operationalized by HADS (Zigmond & Snaith, 1983) were positively associated with survival and reduced the risk of

cardiac events (Meyer, Hussein, Lange, & Herrmann-Lingen 2015). Other studies have found that anxiety is not associated with CHD events when depression has been controlled for (Versteeg et al., 2013). To understand the role of anxiety as well as depression as risk factors of incident CVD, the level of specificity in the predictors and outcome needs to be high. The control of confounding variables and established risk factors also need to be included, and both measures of anxiety and depression should be included to rule out the possibility of comorbid confusion. Watson and colleagues (1995) note that in regard to anxiety and depression scales, there seems to be little consistency in which the respective scales of different symptoms should be associated with, and that many scales that measure depression include symptoms that are more appropriate to anxiety and vice versa. In addition, comorbidity between anxiety and depression varies depending on the specific anxiety disorder (Cummings et al., 2014). Methods that can adequately differentiate between depression and anxiety are crucial (den Hollander-Gijsman et al., 2012) and understanding the shared and distinctive features of the two constructs is important.

The Tripartite model of anxiety and depression and HADS

In 1991, Clark and Watson proposed the tripartite model of anxiety and depression. In the tripartite model, symptoms are grouped into three subtypes: The two basic dimensions, negative affect (NA) and positive affect (PA), and a third factor, physiological hyperarousal. In this model, a general dimension that represents negative affect is common for both anxiety and depression, while a lack of positive affect; anhedonia, is specifically related to depression. Somatic tension; physiological hyperarousal, is specific to anxiety (Fig 1.). This tripartite model gives an account of the symptom overlap and diagnostic comorbidity between anxiety and depression and has made significant contributions to understanding anxiety, depression and general mood disorders. Clark and Watson (1991) argue that the different combinations

of these three scales will facilitate differentiation of depression and anxiety disorders in patients. This tripartite model posits that anxiety and depression share a common component of negative affect, but can be differentiated by low positive affect associated with depression. The structure of the model has been validated in different samples across age and health status (Watson et al., 1995). Although it has received criticism due to a lack of specificity within anxiety and depression disorders (e.g. den Hollander-Gijsman et al., 2012), it provides a useful theoretical framework for understanding how to discriminate between anxiety and depression in self-report scales (Dunbar, Ford, Hunt, & Der, 2000).

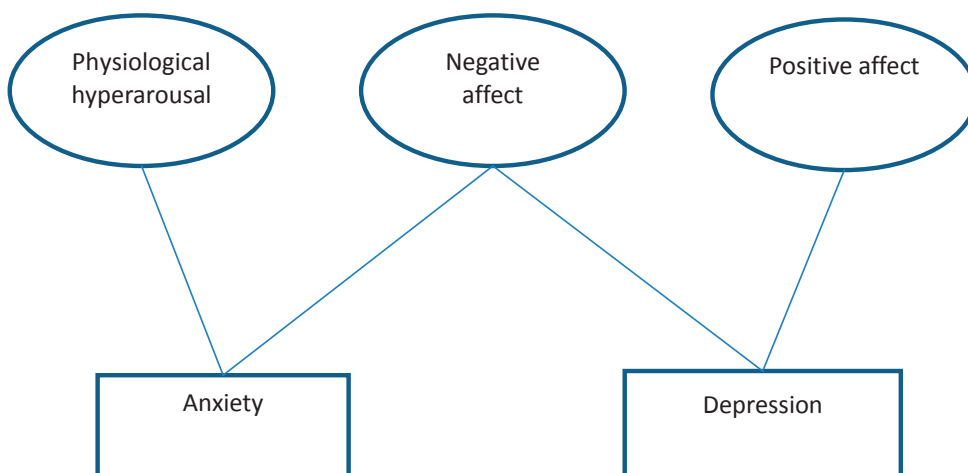


Figure 1. The tripartite model of anxiety and depression (Clark & Watson, 1991)

The Hospital Anxiety and Depression Scale

Few measures of symptoms of anxiety and depression have received the same amount of attention as the Hospital and Anxiety Depression Scale (HADS). In an updated literature review, Bjelland and colleagues (2002) concluded that the concurrent validity of HADS is good to very good, based on the available correlations between HADS and instruments like BDI, general health questionnaire (GHQ), Spielberg State and Trait Anxiety Inventory (STAI), and Montgomery-Aasberg Depression Rating Scale (MADRS). However, several analyses, review articles and meta-analysis have been performed since then. While Bjelland and colleagues (2002) conclude that HADS presents satisfactory structural properties, others claim that the factorial structure of HADS is unclear, depending on the statistical methods applied and characteristics of the sample (Caci, Baylè, Mattei, Dossios, Robert & Boyer, 2003; Cosco, Doyle, Ward & McGee, 2012). In 2012, Coyne and Sunderen wrote an article entitled “No further research needed: abandoning the Hospital and Anxiety Depression Scale.” The article was a comment to the 10-year systematic review of HADS made by Cosco and colleagues (2012). The main argument for abandoning HADS was that the review concluded that the psychometric properties of HADS varied across samples and the statistical approach applied. Others have argued that the HADS is important (Doyle, Cosco, Conroy 2012; Norton, Sacker & Done, 2012). Compared to BDI, HADS-D identifies fewer cases of depression in MI patients (Bush et al., 2005), and the accuracy of HADS-D in detecting depression in groups in general has been questioned (Nowak et al., 2014). Recent large-scale studies advocate that HADS should be used as a general measure of distress instead of two separate measures of anxiety and depression (Norton, Cosco, Doyle, Done, & Sacker, 2013; Burns, Höfer, Curry, Sexton, & Doyle, 2014). Further, the cross-cultural validity of HADS has been questioned because some of the items are not transferable culturally or geographically (Maters, Sanderman, Kim, & Coyne, 2013).

However, some have argued that there is a need to focus on the content in HADS (Doyle, Cosco, & Conroy, 2012; Straat, van der Ark, & Sijtsma, 2013). Despite wide criticism (e.g. Coyne, & van Sonderen 2012), HADS has received renewed attention in the field of cardiac research (e.g. Doyle, McGee, Harpe, Shelley & Conroy, 2006; Damen, Pelle, Boersma, Serruys, Domberg & Pedersen, 2012; Pelle, Pedersen, Erdman, Kazemier, Spiering, Domburg, & Denollet, 2011; Gustad, Laugsand, Janszky, Dalen, & Bjerkeset, 2013; Meyer et al., 2015).

Few studies have directly questioned the content validity of the HADS scale, although the dominant focus on anhedonia in the depression sub-scale has been noted: “important components of depression, such as hopelessness, guilt, and low self-esteem, are not assessed because the HADS-D focuses mainly on anhedonia” (Mykletun, Stordal, Dahl, 2001, p. 543). While the HADS anxiety scale contains items that are concerned with worrying, restlessness and panic attacks, the HADS depression scale focuses on anhedonic depression, i.e., lack of positive affect. Clark and Watson (1991) proposed that the anhedonic content in the HADS depression scale represents the “Low positive affect scale” in the tripartite model. In addition, using an abbreviated version of the HADS-D scale as a measure of reduced positive affect (anhedonia) has been observed in the prognostic approach (e.g. Denollet et al., 2007; Pelle et al., 2011; Damen et al., 2012).

Anhedonia

Anhedonia is a key feature in many psychiatric disorders, and is commonly thought of as reduced positive affect. Although viewed as a core symptom in the psychopathology of major depressive disorder, as well as included in diagnostic manuals, its measurement in depression has received little research attention (Nakonezny, Carmody, Morris, Benji, Kurian, & Trivedi, 2010). Anhedonia also refers to loss of interest and pleasure, and changes in reactivity to stimuli usually experienced as pleasurable. Rømer-Thomson and colleagues (2015) have

argued that anhedonia is more than a reduction in pleasure, and that anhedonia should be differentiated into impairments in pleasure, wanting and learning. Neuroscience can play an important role in the understanding of the concept (Der-Avakian & Markou, 2012), as different positive emotions have different physiological reactions (Kreibig, 2010). In research on depression and pharmacological treatment (anti-depressant), there has been an emerging interest in anhedonia (Kennedy & Cyriac, 2012; Di Giannantonio & Martinotti, 2012). The focus on different subtypes of depression, like anhedonia, has implications for treatment as well as diagnoses, as different antidepressants have unique effects on affect reward processes (McCabe, Mishor, Cowen, & Harmer, 2010; Kennedy & Cyriac, 2012).

Positive emotions, Anhedonia and CVD

Positive and negative states are dependent although not bipolar opposites (Barrett & Russel, 1999). Although marginalized compared to negative emotions, the idea that positive emotions are good for the heart has a long history. Fredrickson (1988) points to how positive emotions build social, intellectual, psychological and physical resources. Of physical resources, the impact of positive emotions on immune function has shown that positive emotional style predicts resistance to experimental exposure to virus (Cohen, Alper, Doyle, Treanor, & Turner, 2006). Recent research on amygdala activation suggests that a high level of positive affect does not reflect a neglect of negative stimuli, but is rather associated with being better equipped to notice and respond appropriately to both opportunity and threat (Cunningham & Kirkland, 2014). Cardiovascular health is affected as positive emotions have shown to speed recovery from the cardiovascular stress-responses caused by negative emotions (Fredrickson & Levenson, 1998). Fredrickson (2000) points to the undoing effect of positive emotions, as experimental induced positive emotions made the participant return faster to baseline levels of blood pressure, heart rate and peripheral vasoconstriction. In a prospective study, positive psychological well-being was associated with a reduced risk of CHD (Boehm, Peterson,

Kivimaki, & Kubzansky, 2001) and longevity in general (Diener & Chan, 2011). Shaffer and colleagues (2012) address the importance of research on different depression phenotypes, and emphasize the role of anhedonic depression in the association between depression and CHD. In the search for specific symptom clusters of depression as risk factors of CHD, anhedonia was the second most important after the somatic cluster (Hawkins, 2013).

Anhedonia has received attention both as a prognostic (Denollet, Pedersen, Daemen, de Jaegere, Serruys, van Domburg, 2007; Leroy, Loas, & Perez-Diaz, 2010; Damen et al., 2013) and an etiological factor (Davidson, Mostofsky, & Whang, 2010). The HADS (Zigmond & Snaith, 1983) include no somatic markers, but has been suggested as superior to other measurement scales of depression in CHD research because of its focus on anhedonia (Doyle, et al., 2012). Recent research has pointed out that positive affect was protective against a 10-year incident of coronary heart disease when controlling for depression (Davidson et al., 2010). In regard to stroke, the items of the Center for Epidemiological Studies Depression scale (CES-D) that measure positive affect significantly predicted risk of stroke, whereas the remaining items of the scale, i.e., negative affect, did not (Ostir, Markides, Peek, & Goodwin, 2001). Anhedonia has been found to be a predictor of severe cardiac events after acute coronary syndromes (Leroy et al., 2010) and after coronary-artery stent implantation (Denollet et al., 2007) and among CHD patients, reduced positive affect (anhedonia) is associated with mortality (Damen, Pelle, Boersma, Serruys, Domburg, & Pedersen, 2013). In the studies mentioned above, anhedonia has been operationalized by four out of seven of the items in the depression scale in HADS, and has provided support for the idea that anhedonia is independently associated with MI or death in patients with heart conditions. These findings from the prognostic approach strongly advocate an investigation of the role of anhedonic depression symptoms as predictors for an elevated risk of having an incident MI.

Although linked to psychiatric disorders, trait anhedonia is also observed dimensionally in healthy individuals, where trait anhedonia was related to limbic and paralimbic systems involved in reward processing (Keller et al., 2013). Reward-dependence and positive affect is a central aspect of anhedonia, as well as being core components within personality psychology. Positive affect is also closely linked to more stable dispositions in experiencing positive emotions and reward dependence, and personality traits represent stable, emotional tendencies that can predict both frequencies, intensity as well as more pathogen emotional experiences (Watson & Naragon-Gainey, 2014; Watson, Stasik, Ellickson-Larew, & Stanton, 2015). More recent studies move beyond the prior emphasis on negative affect, and show how positive affect in children is associated with internalizing problems (Wang & Saudino, 2015). Personality traits are important in the study of symptoms of depression as a risk factor of MI, as personality is linked to psychopathology (Ormel et al., 2013) as well as treatment-outcome (Takahashi et al., 2013).

Personality, depression and coronary heart disease

Several researchers have advocated the importance of focusing on specific aspects of depression and anxiety to understand their contribution to the development of CVD (Baune et al., 2012; Batelaan, 2014; Hawkins et al., 2013, Shaffer; et al., 2012). However, positive and negative affect as specific aspects of specific types of anxiety and depression are closely linked to more dispositional tendencies in emotions (Clark, 2005; Watson & Naragon-Gainey, 2014). The acknowledgement of more general dispositions has a long history, but the inconsistency in research on both anxiety and depression as risk factors of Myocardial Infarction (MI) has caused researchers to take a second look at broader dimensions of dispositional affect as a psychological risk factor of CHD (Suls & Bunde, 2005; Edmondson et al., 2013; Jokela, Pulkki-Råback, Elovainio, & Kivimäki, 2013; Roest et al., 2010).

The dominant model within trait theory is the five factor model of personality (McCrae & John, 1992; McCrae & Costa, 2008; McCrae, 2010). In this model, five broad dispositions, neuroticism, extroversion, openness to experience, agreeableness and conscientiousness, reflect basic tendencies in feeling, thinking and acting in certain ways. Personality traits influence both frequency and intensity of positive and negative emotions (Ching et al., 2014). While the *trait* approach describes dimensional aspects of personality, the *typology* approach focuses on the distribution of individuals into distinct categories. In the 1950s, the Type A personality was introduced as typology characterized by aggressiveness, impatience, excessive competitiveness and time urgency (Friedmann & Rosenman, 1959). Although 50 years of research has failed to support Type A personality as a risk factor of CVD, it continues to linger in the research field as well as in the public opinion. A recent large-scale study applying different measures of Type A assessment concluded that there is no evidence to support the Type A as a CVD risk factor (Smigelskas, Zemaitiene, Julkunen, & Kauhanen, 2015). Hostility has received somewhat more elevated status in the research field and has also been found to be a precursor to the development of depression (Stewart, Fitzgerald, Kamarck, 2010). Further, a promising replacement of the Type A personality was made by the introduction of the type D personality, a composite of two sub-factors, i.e. social inhibition and negative affect (Denollet, 2000). A review of the prognostic value of Type D in cardiac samples concludes that the effect sizes have probably been overestimated (Grande, Romppel, & Barth, 2012). As an etiologic factor, Type D has received less attention, but in a recent study, the Type D personality construct failed to be successfully associated with incident CHD (Larson, Barger & Sydeman 2013). However, the sub-component of Type D, namely social inhibition, along with anger-personality has been associated with coronary artery plaque in CHD-free populations (Compare, et al. 2014). The Type D personality is related to the personality traits in the five factor model, where social inhibition shows a strong negative

relationship to extroversion, and a more moderate positive relationship to neuroticism (De Fruyt & Denollet, 2002). In a recent analysis of three cohort studies, neuroticism was associated with cardiovascular diseases, especially CHD (Jokela et al., 2013). However, Lee and colleagues (2014) found that low extroversion was more important than high neuroticism in constituting a risk of incident CHD. A meta-analysis by Richardson and colleagues (2012) has concluded that perceived stress is associated with increased risk of incident CHD. Given the strong link between personality and stress-processes (Ferguson, 2013; Friedman & Kern, 2014; Hervas & Vazquez, 2011), stable dispositions should be given more attention in the study of the etiology of CHD. This is further supported by recent research in psychophysiology concluding that cardiovascular responses to psychological stress represent stable individual traits (Dragomir, Gentile, Nolan, & D'antonio, 2014).

Personality traits are associated with acute major depression across the age spectrum (Weber et al., 2012). Different models have been proposed to explain the relationship between personality traits and psychopathology, but can, according to Klein and colleagues (2011), be divided into three groups, where the first group views personality and depression as having similar causal influences, although they do not causally influence each other. In the second group, consisting of what is referred to as the predisposition and pathoplasticity model, personality has a causal effect on the onset, or the maintenance of depression in terms of vulnerability and predispositions (etiopathogenesis). In the third group, (concomitants/consequence), depression is suggested to have a causal influence on personality, and is also referred to as the “scar” hypothesis, in which depression causes personality alteration (Ormel et al., 2013). Neuroticism has received substantial attention in the study of depression as vulnerability-factor, sharing the same genetic background (Ormel et al., 2013; Clark, 2005). Shared genetic contribution is still under investigation, and Hirvonen and colleagues (2015) have found that neuroticism is correlated to serotonin receptor binding

in healthy individuals. Extroversion has received less attention, but more recently, a focus on different aspects of extroversion and psychopathology has emerged (Watson et al., 2015).

Ormel and colleagues (2013) has reviewed the evidence for the different models and concluded that none of the models can fully explain the relationship observed between neuroticism and common mental disorders like anxiety and depression, although the common cause model and vulnerable-model have received the most empirical support, whereas the opposite is the case for the scar-model.

The five-factor model has received exhaustive support (McCrae, 2010). However, recent physiological approaches to personality have also focused on a more general meta-trait, where negative and positive affect represent basic overarching dispositions referred to as stability and plasticity, respectively (DeYoung, 2010). Stability is closely related to neuroticism and serotonin, while extroversion represents the plasticity meta-trait and is related to dopaminergic activity (DeYoung, 2010). Another physiological approach to personality is the Behavioral Activation System (BAS) and Behavioral Inhibition System (BIS) that represent two general motivational systems that underlie behavior and affect (Gray, 1981) as well as responses to reward and punishment (Carver & White, 1994). BIS/BAS has also been suggested as a theoretical model that can explain the comorbidity of anxiety and depression as BIS-sensitivity is associated with both anxiety and depression, whereas low BAS-sensitivity is specific to depression with anhedonic symptoms (Cummings et al., 2013, p. 822).

Neuroticism is strongly correlated with symptoms of depression and anxiety (Ormel et al., 2013; Jylhä & Isometsä, 2006), and large meta-analysis confirms the strong association between neuroticism, distress, and anxiety disorders (Kotov, Gamez, Schmidt, & Watson, 2010). Extraversion on the other hand is negatively associated with depression (Jylhä & Isometsä, 2006) and mental disorders (Kotov et al., 2010; Watson & Naragon-Gainey, 2014).

In addition, a recent study by Watson and colleagues (2015) has investigated the relationship between extroversion and psychopathology on the facet level, and found that positive emotionality, a facet representing extroversion, is especially strongly linked to depressive symptoms and diagnosis. Gender differences in personality are small but consistent across cultures (Costa, Terracciano, and McCrae, 2002); women tend to score higher on neuroticism compared to men. Given the gender differences in psychological variables like depression, anxiety and personality traits, focusing on gender-specific psychological risk factors of MI is warranted.

Women and coronary heart disease

According to Wenger (2012), women have been “understudied, underdiagnosed and undertreated” (p. 604) in cardiac research. Women have been marginalized in the research field in general (Orth-Gomer, Schneiderman, Vaccarino & Deter, 2015), and studies focusing on psychological risk profiles in particular have been lacking (Naqvi, Naqvi, & Merz, 2005). In women, symptoms of Myocardial Infarction are more atypical, as they are less likely than men to experience chest pain before an MI compared to men; however, they are significantly more likely to experience dizziness, fatigue, and pain located in the neck, jaw and right-arm (Coventry, Finn, & Bremner, 2011). Although several risk-factors are common, some, like hormone therapy, oral contraceptives, menopause, preeclampsia, and polycystic ovary syndrome, are unique for women (for an overview, see Tan, Gast, & van der Schouw 2010). Although unquestionably important, the scope of this thesis is not risk factors unique for women, but rather psychological variables that are common in men and women, constituting differentiated risk-estimates. The impact of non-traditional risk factors of CHD in women is of special interest given the increased prevalence of psychological risk factors like anxiety and depression among women (Metha, Wei, Wenger, 2015). Furthermore, because cardiac events are more likely to occur asymptotically (i.e. without experiencing symptoms), the

focus on risk factors is even more crucial for women. Traditional risk-factors like being overweight, smoking and diabetes, as well as psychological factors, show differential risk impact on men and women (Lloyd et al., 1996; Tan et al., 2009). Although the biological aspect, including how sex hormones affect neurotransmitters like serotonin and dopamine (Barth, Villringer, & Sacher, 2015), are important, social variables are also relevant. Möller-Leimkühler (2007) points to studies showing that women in high control-high demand jobs, in typically male-dominated occupations, and combined work-family demands, are at a higher risk of having an MI. An interaction between neuroticism and socio-economic status (SES) has been observed as a gender specific risk factor of cardiac mortality (Hagger-Johnsen et al., 2012). In the study by Hagger-Johnsen and colleagues (2012), women with low SES and high neuroticism were at a higher risk of cardiac mortality, whereas for those with high SES, high neuroticism predicted a reduced risk of mortality. This pattern was not observed in men. In addition, women tend to report more stress and symptoms of exhaustion than men, and more work-family demand (Wiegner, Hange, Björkelund & Ahlberg, 2015), emphasizing the role of the social context.

Although most of the literature concerning symptoms of depression as risk factors of CVD has not performed separate analysis for men and women, there are some exceptions. In a Finnish study, symptoms of depression predicted all-cause mortality in both genders, but CVD events only in women (Haukkala, Kontinen, Uutela, Kawachi, & Laatikainen, 2009). In another study, depressive symptoms were an independent risk factor for CHD in women but not in men (Mendes de Leon et al., 1998). However, in a French population-based study, depressive mood predicted cardiovascular mortality only for men (Lemogne et al., 2012). These findings emphasize the importance of both screening for depression in general and the particular focus on the gender-specific role of depression in preventive heart intervention. Changing practices by healthcare providers designed to reverse the trend of late referral and

late intervention may substantially reduce the number of women disabled and killed by CHD each year (Wenger, 2003). According to the European guidelines on cardiovascular disease prevention in clinical practice (Perk et al., 2012), it is crucial to include psychosocial factors in the risk assessment of CHD, but no gender-specific risk factor regarding anxiety and depression is presented, and the guidelines lack specification regarding types of screening or instruments to apply.

Several reviews on the relationship between depression and CHD (e.g. Wulsin & Singal, 2003; Nicholson, Kuper, & Hemingway, 2006; Van der Koy, Hout, Marwijk, Marten, Stehouer, & Beekman, 2007; Stampfer et al., 2012) and prospective studies (e.g. Hawkins et al., 2013; Gustad et al., 2013) strongly support that there is an association between depression and CHD. However, separate analyses for men and women are lacking. Among women, there has been an increased prevalence of coronary heart disease, and the role of depression as a gender-specific factor is unclear (Naqvi et al., 2005). Women with depressive symptoms have been found to have higher CRP levels (a risk factor of the development of CHD) compared to men with depressive symptoms, suggesting the importance of giving clinical attention to women with high cardiac risk when they experience depressive mood (Azar, Nolan & Stewart, 2011).

Gender differences in anxiety and depression

Prevalence, incidence, and morbidity risk of depressive disorders are higher in females than in males (Piccinelli & Wilkinson, 2000). The lifetime prevalence of affective disorders among women is almost doubled compared to men (Faravelli et al., 2013), and for major depression, the prevalence ratio is even worse for women (Delisle, Beck, Dobson, Dozois, & Thombs, 2012). Considerable cross-country differences exist, and compared to other European countries, the level of depressive symptoms is lowest in Norway (Van de Velde, Bracke & Levecque, 2010).

Gender differences vary across sub-groups of depression (Baune, Adrian, Arolt & Berger, 2006). Different measures of depression tend to display differentiated gender differences (Salokangas, Vaahtera, Pacriev, Sohlman, & Lehtinen, 2002), and in some self-report instruments, the differences are reversed, i.e., men have a higher score on depression (Stordal, Kruger, Dahl, Kruger, Mykletun, & Dahl, 2001; Nortvedt, Riise, & Sanne, 2006). At the symptom level, different gender subtypes can be identified (Alexandrino-Silva, Wang, Viana, Bulhoes, Martins, & Andrade, 2013), and this might have implications for understanding the depression–CHD relationship. Dysthymia, characterized by chronic lack of enjoyment, depressive mood, loss of interest and drive, with a long duration (at least two years), with depression symptoms milder than major depression, presents gender differences of a smaller magnitude than unipolar major depression (Baune et al., 2006). Gender differences in the tendency to report somatic symptoms has been suggested as an explanation of gender differences in depression, but have recently been found to be of less importance (Delisle et al., 2012). Scales that measure anhedonia do not present gender differences in the general population or patient groups (Snaith, Hamilton, Morley, Humayan, Hargreaves & Trigwell, 1995; Nakonezny et al., 2010), suggesting that lack of expected gender differences in HADS-D might be due to the anhedonic content in the scale. A large-scale systematic review of depression in MI patients by Doyle and colleagues (2015) showed that women were more depressed than men, but the prognostic value of depression was more important for men than women, addressing the importance of treating women and men as different populations in cardiac research on psychological risk factors.

Gender differences in depression differ from gender differences in CHD, suggesting that the association between depression and CHD is gender specific (Low, Thurston, & Matthews, 2010). This discrepancy might be explained by the reduction in the risk of affective disorder for women after menopause (Faravelli et al., 2013). However, more research is needed on the

gender-specific link between depression and CVD (Orth-Gomer & Deter, 2015). Gender differences might be linked to treatments of depression and their effectiveness in men and women (Naqvi et al., 2005), and depression might systematically vary with other risk factors in different ways in men and women. In recent years, waist-hip ratio (WHR) has emerged as a superior predictor of CVD compared to, for example, body mass index (BMI) (de Koning, Merchant, Pogue, & Anand, 2007), and WHR seems to be a stronger predictor in women compared to men (Möller-Leimkühler, 2007), although others find a similar strength of association in men and women (de Koning et al., 2007). It has been pointed out that women and men with CHD represent different populations, and that the practice of using men as references should be reconsidered (Wenger, Shaw, & Vaccarino, 2008).

Aims and objectives

To understand the role of symptoms of anxiety and depression in predicting Myocardial Infarction (MI) in the general population, we need to (1) identify symptoms of depression and anxiety as causes of MI, not only consequences of MI. Further, (2) it is important to identify gender-specific psychological risk-profiles in order to optimize the screening of MI-risk. To identify the optimal screening tool and understand the relationship between psychological symptoms and MI, (3) there is a need to focus on the content in the specific instrument used, and how specific symptoms are related to more general emotional dispositions.

Paper I

The aim of paper I was to identify a dose-response relationship between symptoms of anxiety and depression, and the risk of incident MI. Further, to compare the role of anxiety and depression as both predictor of, and outcome after MI. This was done by combining the

etiological approach with the prognostic approach, focusing on symptoms of anxiety and depression before and after incident MI. More specifically, the following research questions were formulated:

1. Do elevated symptoms of depression in a population free of CHD at baseline increase the risk of incident MI?
2. How are levels of anxiety and depression affected by having an MI?
3. Is the level of anxiety and depression in patients with a history of MI affected by time since the MI?

Paper II

The aim of paper II was to identify a gender-specific psychological risk estimate of having a fatal or non-fatal MI. The objective was to investigate whether elevated symptoms of depression or history of depression provide the best risk estimate for men or women, respectively. In addition, to follow up on the findings in Paper I, the possibility of elevated levels of anxiety-symptoms measured by HADS as a cardioprotective factor was investigated.

1. Are there gender differences in incident MI risk-estimate based on the HADS-depression scale?
2. Does history of depression offer a more efficient tool for detecting MI risk than HADS?
3. Do elevated symptoms of anxiety measured by HADS represent a reduced risk of having an MI among both men and women free of CHD at baseline?

Paper III

To identify the optimal screening tool and understand the relationship between psychological symptoms and MI, there is a need to focus on the content in the specific instrument used, and how specific symptoms are related to more general emotional dispositions. The aim of paper III was to investigate the validity of HADS as a measure of anhedonic depression. To explore the relationship between HADS-A and HADS-D and trait and state positive affect to understand the content in the scales, gender differences were of special interest. The research questions outlined included:

1. How are the anxiety and depression scales in HADS related to negative and positive affect?
2. Can the personality traits neuroticism and extraversion predict symptoms of anxiety and depression measured by HADS?
3. Can anhedonia explain contradictory gender differences observed in HADS-D?

Method

The papers in this thesis are based on two sources of data. Paper I and II utilize longitudinal data collected through the HUNT study (HUNT 2 and 3). The sample in paper III consists of psychology students enrolled at The Norwegian University of Science and Technology (NTNU). The instruments and measurement procedures will be described in the next section, followed by a presentation of the different analyses applied.

Instruments

This study made use of self-report of psychological variables, self-report and clinical assessment of health-variables. To identify cases of incident Myocardial Infarction, self-report and register-data by linkage to the mortality-register were used.

Self-reported measures

Diabetes

In HUNT 2, the participants were asked to answer the question “Do you have diabetes?” by checking “yes” or “no.”

Smoking

Smoking was self-reported and operationalized as numbers of years of daily smoking.

HADS

The Hospital Anxiety and Depression Scale. The Hospital Anxiety and Depression Scale (Zigmond & Snaith, 1983) includes 14 items that indicate the way the respondent has felt over a two-week period prior to measurement (Table 1.). The HADS usually operationalize anxiety and depression by cut-off scores (≥ 8), but in papers I and III, the computed indexes were treated as continuous variables.

Table 1. Item order and label in the Hospital Anxiety and Depression Scale

Item number	Item text	Scale content
1	I feel tense or wound up	Anxiety
2	I still enjoy the things I used to enjoy	Depression
3	I get a sort of frightened feeling as if something awful is about to happen	Anxiety
4	I can laugh and see the funny side of things	Depression
5	Worrying thoughts go through my mind	Anxiety
6	I feel cheerful	Depression
7	I can sit at ease and feel relaxed	Anxiety
8	I feel as if I'm slowed down	Depression
9	I get a sort of frightened feeling like 'butterflies' in the stomach	Anxiety
10	I have lost interest in my appearance	Depression
11	I feel restless as if I have to be on the move	Anxiety
12	I look forward with enjoyment to things	Depression
13	I get sudden feelings of panic	Anxiety
14	I can enjoy a good book or radio or TV show	Depression

History of depression/major depressive episode

In an extended part of the HUNT 2, the participants were instructed to indicate whether, during their life, there had been periods of two consecutive weeks or more when they “felt depressed, sad, and down,” “had appetite problems or ate too little,” “felt weak (adynamic) or lacked energy,” “really reproached yourself and felt worthless,” or “had problems concentrating or had difficulty making decisions.” Participants were classified as having

experienced a depressive episode if they answered yes to the question, “During your life, have there been periods of two consecutive weeks or more when you had at least three of the above-mentioned problems simultaneously?”

PANAS

The Positive and Negative Affect Schedule (PANAS) consists of two 10-item mood scales that measure the two dominant affect structures, and were developed by Watson, Clark and Tellegen (1998). PANAS offers a variety of instructions depending on the concept of interest; i.e. trait or state positive and negative affect. In this current study, the respondents were instructed to report how they have felt over a two-week period prior to measurement. PANAS has shown very good psychometric properties in the general population, with a high internal consistency and construct validity (Crawford & Henry, 1999).

NEO FFI: Extroversion and neuroticism

Costa and McCrae developed the NEO Personality Inventory Revised (NEO PI R) to operationalize the five factor model of personality traits. The short form, the NEO Five-factor Inventory (NEO FFI), consists of 60 items representing the domains Neuroticism, Extroversion, Agreeableness, Openness to Experience, and Conscientiousness. In this study, the Extroversion and Neuroticism domain were operationalized by 24 items with a five-point Likert scale ranging from 1 (“strongly disagree”) to 5 (“strongly agree”). The psychometric properties of NEO FFI are well documented (Costa & McCrae, 1992; Martinsen, Nordvik, & Østbø, 2011).

Clinical measures

Cholesterol

Total serum cholesterol was measured applying an enzymatic colorimetric cholesterol esterase method (Holmen et al., 2003).

Blood pressure

At HUNT 2, the participants' systolic blood pressure (SBP) was measured by specifically trained nurses, using a cuff adjusted for arm circumference. SBP was measured three times, and a mean was calculated from the second and third observations to ensure reliable measurements.

Waist circumference and Waist/hip ratio

Waist and hip circumferences were measured with a steel band to the nearest 1.0 cm with the participant standing and with the arms hanging relaxed. The waist circumference was measured horizontally at the height of the umbilicus, and the hip circumference was measured at the thickest part of the hip (Holmen et al., 2003).

In Paper II, the waist/hip ratio (WHR) was applied instead of waist circumference, i.e., the hip circumference was divided on the waist circumference to calculate the ratio. Cut-off scores were calculated based on The International Diabetes Federation (IDF). WHR was used instead of WC in Paper II as they provide recommendations that are gender, population, and geography specific. For Europeans, the recommended cutoff scores are .80 for women and .94 for men to identify central obesity (Alberti, Zimmet & Shaw, 2006).

Register data

Fatal MI

The mortality data were obtained from the National Mortality Register by combining the mortality database and the HUNT data by means of an 11-digit personal identity number. In the mortality registry, diagnoses are encoded according to International Classification of Diseases, 10th Revision (ICD-10). MI mortality in this study encompasses ICD-10 codes I21-9, unspecified acute MI, and I22-9 subsequent MI (within four weeks of a preceding MI) with an unspecified location, with the majority of cases being I21-9. Non-fatal MI was indicated by self-report in the HUNT 3 study as a “yes” or “no” response to the question, “Have you ever had or do you have Myocardial Infarction?”

The HUNT Study

The Nord-Trøndelag Health Study (The HUNT Study) is a collaboration between HUNT Research Centre (Faculty of Medicine, Norwegian University of Science and Technology NTNU), Nord-Trøndelag County Council, Central Norway Health Authority, and the Norwegian Institute of Public Health. HUNT is one of the largest health studies ever performed and is thoroughly described by Holmen and colleagues (2003). It is a unique database of personal and family medical histories collected during three intensive studies. HUNT 1 was carried out in 1984-1986 to establish the health history of 75,000 people. The succeeding HUNT 2 was carried out in 1995-1997 and focused on the evolution of the health history of 65,049 people. HUNT 3 was completed in June 2008 and 48,289 people participated (52% participation rate). The data was collected by means of questionnaires, interviews, clinical examinations and the collection of blood and urine samples.

Sample and procedure

Paper I

In Paper I, participants free of CHD at baseline (HUNT 2) were included in the study. History of MI and past or present angina was applied as exclusion criteria, leaving us with 62,919 eligible candidates of whom 28,859 also participated in HUNT 3. Within this group, 770 participants reported a current or prior incident of non-fatal MI during the follow-up period. Men were overrepresented in the MI-group where only 32.21 percent were women. The mean age was 46.97 (13.04).

Paper 2

As in Paper I, participants free of CHD at baseline (HUNT 2) were included in the study. History of MI and past or present angina was applied as exclusion criteria. The inclusion criteria in Sample II also included a response to “history of depressive episode.” The mean age of women was 43.12 (13.07) and men 43.61 (12.90). Of the 41,248 participants meeting the inclusion criteria, 242 women and 580 men had an MI (fatal or non-fatal). In all 41.7 percent of the fatal/non-fatal MI group was women. A total of 23066 of the participants in Sample II also constitute a substantial part of Sample I (28,859). Differences in sample sizes are due to different inclusion criteria (e.g. valid HADS-score at HUNT 3 in Sample I) and the use of mortality register in Sample II.

Paper III

HADS were administered along with FFI, and PANAS to a Norwegian sample of undergraduate students (N = 350) at the department of psychology; NTNU. The instruments were distributed through an open link on the intranet Web page. Eight weeks later, a new link was posted on the Web site. Because of theoretical relevance and drop-out concerns, only the “big two” of the five factors in the FFM, i.e. Extroversion and Neuroticism, were included.

The participants were instructed to create a personal code that should be used to match the participant's responses from the two surveys. In all, the 160 participants in Sample II were identified with responses in both surveys. Women were overrepresented in both sample one and two; 75.5 and 70.0 percent, respectively. The time span between the two points of measurement ranged from 35 to 66 days, with a mean of 50.95 ($SD=6.65$) days. The mean age was 22.13 ($SD = 4.30$) and in the follow-up sample, the mean age was 22.18 years ($SD = 4.45$).

Analysis

Analysis of dropouts and missing data

In the HUNT study, a thorough investigation of completers versus drop-outs has been performed. According to Langhammer and colleagues (2012), participation in HUNT 2 and HUNT 3 is associated with better mental and physical health. Participation depended on age, sex and type of symptoms and diseases. Among non-participants, the prevalence of cardiovascular diseases, diabetes and psychiatric disorders were higher, based on data extracted from general practice. Furthermore, registry data showed that the non-participants had lower socioeconomic status and a higher mortality than the participants (Langhammer et al., 2012).

Logistic regression

The goal of paper I and II was to investigate differences in risk, and the results from a logistic regression analysis were regarded as the best way to produce easily, interpretable estimate. Logistic regression is a robust analysis that served this purpose very well. It is not the time that is the main interest in this study, and in an analysis in which outcome is simply treated as binary, logistic regression is informative and easily interpretable. Furthermore, in the self-

reported MI-group (HUNT 3), the time of MI was not reported in several cases. In this situation, it is advantageous to treat the outcome variable as binary.

Hierarchical, block-wise regression

Hierarchical block-wise hierarchical linear regression was used in papers I and III. Before running the analysis, the data was pre-analyzed to ensure none of the assumptions were violated. All indicators were within the established criteria (e.g. VIF <10).

Test of bivariate association and group differences

In all three papers, t-test and chi-square test were used to test the significance of group differences and association between categorical variables.

Significance testing of differences in risk estimate

Post-hoc analysis applying the formula suggested by Paternoster, Brame, Mazerolle, and Piquero, (1998) were used to test the significance of the differences in risk estimate in Paper II.

Ethical considerations

The Regional Committee for Ethics in Medical Research has considered and approved this research project (reference in REK: 2010/393). The protocols for HUNT 2 and HUNT 3 were approved prior to this specific study. A specific request for approval was made for the linkage to the mortality register applied in Paper II. All participants in the HUNT 2 and HUNT 3 study gave their written consent. In Sample III, informed consent was assured by informing the student that participation was absolutely voluntary and that they were able to withdraw from the study at any time, without any questions being asked. As Sample III consists of responses made to an anonymous online survey, the protection of the participants was considered to be within standards.

Results

Paper I. Symptoms of depression and anxiety before and after myocardial infarction: The HUNT 2 and HUNT 3 study

In Paper I, a request in the research field to treat depression as a continuous variable was met. Further, few, if any, had measured symptoms of anxiety and depression before and after an MI. Although a few studies had asked MI patients about past history of depression, the general view in the prognostic approach was that symptoms of depression, mainly, and to a lesser extent, anxiety, were directly attributed to the experience of having a heart attack. In this study, 28,859 participants with no prior CHD (MI or Angina) and with a valid score on HADS in HUNT 2 and HUNT 3 participated. Of those, 770 reported that they had a Myocardial Infarction during the five to eight years' time-span between HUNT 2 and HUNT 3. The results demonstrated a dose-response positive relationship between symptoms of depression and the risk of having an MI, where a one unit increase in symptoms of depression increased the risk of having an MI (OR 1.01) more than one year of daily smoking, one unit increase in systolic blood-pressure (e.g. 122 to 123) or one cm wider waist-circumference. Anxiety, on the other hand, was negatively associated with MI risk, although the risk estimate (OR .96) was not significant. The symptom-level of anxiety at baseline was significantly lower in the MI-group compared to the non-MI group, warranting further investigation of the role of anxiety. The long-term stability coefficient observed between HADS-scores at HUNT 2 and HUNT 3 suggested that symptoms of anxiety (r .57) and depression (r .54) measured by HADS represent more stable dispositions. Regression analysis showed that a substantial part of the variation in HADS-A and HADS-D scores at HUNT 3 could be predicted by baseline symptom levels at HUNT 2 (R^2 = .34 and .30, respectively). In the total sample, MI only marginally predicted the symptom-level of depression (β .01, p < .05). In the MI-group, the time since MI was not a significant predictor of level of anxiety and depression. In sum, the

results suggest that symptoms of depression measured by HADS are important in the etiology of MI, and that symptoms of depression among MI patients might represent a more general and stable disposition that is best considered as the cause of MI rather than the consequence. Furthermore, symptoms of anxiety presented a reversed relationship to MI and should be subject to further inquiry.

Paper II. Anhedonic depression, history of depression, and anxiety as gender-specific risk factors of myocardial infarction in healthy men and women: The Hunt study

In Paper II, the search for a gender-specific relationship between different measures of depression and MI identified that HADS-D was significantly better at identifying women at risk of MI than men. Significantly more women had a history of depression ($\Phi .16, p < .001$) and elevated symptoms of anxiety ($\Phi .07, p < .001$). More men had elevated symptoms of depression (HADS-D ≥ 8); however, although significant the difference was marginal. Women with a HADS-D score of or above 8 were more than twice as likely to have an fatal/non-fatal MI, even after controlling for traditional factors, symptoms of anxiety and history of depression (OR=2.31). HADS-D was not a significant predictor of MI among men in the adjusted model. Symptoms of anxiety as a cardioprotective factor were supported, as elevated symptoms of anxiety (HADS-A ≥ 8) significantly reduced the risk of having an MI in both men (OR = .65) and women, (OR = .55) although the effect-size was somewhat stronger for men. In the total sample, a history of depressive episode was a significant predictor of MI in the adjusted model (OR = 1.29). Gender-specific analysis showed that a depressive episode was a significant predictor among men (OR = 1.44) but not women. The results confirmed that gender differences in risk estimate are important. Depression measured by HADS presented rather contradictory results considering the literature on gender differences in depression. Depression measured by HADS has a specific focus on anhedonia; a symptom aspect that might be more cardio-toxic than other symptom-clusters, especially for women. To summarize the findings, there is a need to treat men and women as separate populations in the research on depression as an etiological factor of depression. HADS-D is suggested as a simple and effective tool for identifying women at risk of having an MI.

Psychological tools for screening should be gender-specific, and the role of anxiety as a risk factor in the development of MI should be reconsidered or perhaps reversed.

Paper III: Personality traits, gender differences and symptoms of anhedonia: What does the Hospital Anxiety and Depression Scale (HADS) measure in nonclinical settings?

In Paper III, the aim was to understand why HADS-D predicts MI in patients free of CHD at baseline whereas an opposite trend is observed for HADS-A. In Papers I and II, the anhedonic content in the depression scale is suggested as a reason for its superiority in detecting those at risk, but the literature relating HADS to measures of positive affect is scarce. The results from Paper I suggested that the dimensions in HADS represent more stable dispositions; Paper II suggested that gender differences in HADS was in need of further investigation. In this study, the results showed that HADS-A was strongly linked to both state and trait negative affect, and that neuroticism measured at T1 predicted a substantial part of the variance in HADS-A at time 2 ($R^2 = .44$). Neuroticism and extroversion predicted HADS-D at T2 ($R^2 = .35$). The results were congruent with the tripartite model of anxiety and depression. The results indicated that positive affect differentiated the anxiety and depression scale in HADS, but also that HADS-D is only relatively moderately associated with negative affect. Gender differences were as hypothesized; women had a significantly higher score on all instruments measuring negative affect (PANAS-Negative affect, Neuroticism, HADS-A), but a lower score on HADS-D. No significant gender differences were observed on extroversion and PANAS-positive affect. The anhedonic content in the HADS-D scale was suggested as an explanation of the reversed gender differences in depression observed when HADS is used in non-clinical samples.

Discussion

Personality traits represent a stable tendency in the experience of positive and negative affect. These differences are expected to persist through life, and beyond major life events like having a heart attack. The prognostic approach to depression in CHD/CVD patients seems to have overlooked contributions from the etiological approach. Depression as a risk factor of mortality in CHD/CVD patients should incorporate the role of depression as a general risk factor of mortality, as the risk estimates of all-cause mortality are stronger than those observed for cardiovascular events in MI patients (Doyle et al., 2015). In Paper I, elevated symptoms of depression constituted an independent risk of having an MI, even when controlling for the major risk factors and symptoms of anxiety. Although the American Heart Association has recommended screening for depression in cardiac patients, others are critical, as the benefits in terms of reduced symptoms or improved prognoses has received marginal support (Thombs et al., 2013; Vieweg et al., 2011). Among the participants, having an MI did not affect the level of symptoms of anxiety and depression, a finding consistent with other studies on the long-term psychological effect of MI (e.g. Hanssen et al., 2009), but at the same time contradicts others (e.g. Doyle et al., 2015). Furthermore, time since MI was not a predictor of symptom-level anxiety and depression in the MI-group, a finding that strengthened the role of depression as a risk factor more than being a prognostic factor caused by having an MI. It might be that screening for depression to identify the risk of MI would be a better way of using resources.

While Paper I confirmed the symptoms of anhedonic depression predicting MI, Paper II compared HADS-D to other measures of depression as potential tools for detecting those at risk of incident MI. Paper II followed up on the results from Paper I, where symptoms of anxiety at baseline were significantly lower in the MI group compared to those that suffered from a heart attack in the succeeding years. Gender-differences in risk estimate based on

HADS-D further called for the understanding of gender differences in HADS and how personality traits and individual differences in experiencing positive and negative affect could account for them, as the level of symptoms of anxiety and depression measured for five to eight years had a substantial impact on the current level of symptoms of anxiety and depression in both the MI and non-MI group (Paper I). Several researchers in the field of cardiac research have addressed the need to focus on how depression and anxiety are operationalized in order to understand their role as risk factors of MI (e.g. Davidson, 2008; Davidson, Rieckmann, & Rapp, 2005; Schaffer et al., 2012; Baune et al., 2012). Inconsistencies in the measurement of depression and anxiety are not only important for understanding the link between psychological variables and CVD, but for the diagnosis and treatment of depression in general (Fried & Nesse, 2015). Together, the results from this study suggest that HADS-D represents a specific, anhedonic subtype of depression, closely linked to dispositional tendencies in experiencing positive affect.

Anxiety as a cardioprotective factor?

In Paper I, the level of symptoms of anxiety was significantly higher in the MI group compared to the non-MI group. Anxiety was associated with a lower risk of having a non-fatal MI, but the risk estimate (OR) was not significant when controlling for the established risk factors (i.e. smoking, age, gender, hypertension, central adiposity, and diabetes). In Paper II, anxiety was operationalized by the cut-off score; a stronger manipulation of the variable and predicted reduced risk of fatal/non-fatal MI. Others (e.g. Janszky et al., 2010) have found that anxiety is an independent risk of CVD/CHD; therefore, the findings from this study should be treated with caution. It is also important to consider a potential curve-linear effect between symptoms of anxiety and the risk of MI. However, Meyer and colleagues (2015) found in a sample of stable CHD-patients that the highest quartile of HADS-A (≥ 10) was most strongly associated with reduced mortality. Although this study does not rule out the

possibility of a positive relationship between specific subtypes of anxiety (e.g. panic disorder or social phobia) and specific CVD outcome, the results from this current study strongly suggest that an elevated score on HADS-A does not constitute an elevated risk of having an MI in the general population. On a more general, theoretical level, anxiety can be both adaptive and maladaptive (Nesse, 1999). Anxiety and depression have been found to have an inverse association with health behavior in MI patients (Benyamini et al., 2013), and although not directly transferable to healthy populations, it might be that those reporting more anxiety have a higher risk-perception and hence live a more healthy life, attending to symptoms. However, anxiety as a health-promoting factor has received marginal support (Tully et al., 2011); and perhaps the most plausible explanation for inconsistent findings of anxiety as a risk factor of MI is heterogeneity in measurement of anxiety and heterogeneity in outcome variable. Further, Cohen and colleagues (2015) argue that some anxiety scales assess somatic symptoms (e.g. irregular heartbeat and chest pain) which may be symptoms of cardiovascular abnormalities rather than symptoms of anxiety (p. 4). As HADS do not contain somatic symptoms, this could be a possible explanation of inconsistencies, and why HADS-A did not predict MI in this study. As noted by Baatelan and colleagues (2014), different anxiety disorders have differential impacts on the onset of cardiovascular disease. Panic disorder, with symptoms that mimic those of acute heart failure, predicts the onset of CHD events (Walters et al., 2008). However, as the etiology is still controversial, Tully and colleagues (2015) have outlined a systematic review to further investigate the link between panic disorder and incident CHD. The results from this review can probably inform and guide future research on the subject.

Comparing different Axis I lifetime diagnosis, neither panic disorder, generalized anxiety disorders, obsessive-compulsive disorder (OCD) nor social phobia were significant predictors of CHD whereas depression was (Lee et al., 2014). Both GAD and OCD were associated

with lower risk (not significant) while social phobia and panic was, although not statistically significant, associated with higher risk of CHD. A framework for differentiating the specific anxiety disorders, and moreover, symptoms of anxiety and depression, is by focusing on their relation to personality. Neuroticism is strongly related to all internalization-disorders and symptoms of anxiety and depression, while extroversion, on the other hand, is specifically related to depression, but also to social phobia (Watson et al., 2015; Kotov et al., 2010). The results from Paper III demonstrated that HADS- A and HADS-D has a strong relationship to neuroticism and negative affect, and that what differentiates HADS-A and HADS-D is their relation to extroversion; a unique predictor of symptoms of depression but not anxiety when HADS was applied.

Positive emotionality and cardiovascular health: Anhedonia and MI, the role of extroversion

Although the role of Type A personality has been questioned, and perhaps rather dismissed (e.g. Smigelskas, 2015), personality, and more specifically, dispositional affect continues to be of interest in cardiac research (e.g. Roest et al., 2010; Lee et al., 2014; Jokela et al., 2013). Neuroticism has been central not because of its link to depression (Kotov et al., 2010; Ormel et al., 2013; Naragon-Gainey & Watson, 2014; Watson & Naragon-Gainly, 2014) but also as a direct risk factor of CVD (Jokela et al., 2013). The role of extroversion has until recently received less attention, but it is now recognized as having a specific relation to depression (Watson & Naragon-Gainly, 2014; Watson et al., 2015) and as being a more important predictor of CHD than neuroticism (Lee et al., 2015). Reduced positive affect predicts prognoses in cardiac patients (Denollet et al., 2007; Pelle et al., 2011; Damen et al., 2012) and the study by Davidson and colleagues (2010) demonstrated that positive affect protects against CHD, even when controlling for depression. The same is the case for positive psychological well-being (Boehm, Peterson, Kivimäki, & Kubzansky, 2012). Given the

relationship between HADS-D and positive affect, and moreover, the prospective link between extroversion and HADS-D observed in Paper III, the results from Paper I and Paper III support the role of positive affect as a cardioprotective factor. The strong relationship between neuroticism, negative affect and HADS-A observed in Paper III further strengthens the argument that neuroticism/negative affect is less important as a risk factor of MI, as an elevated score on HADS-A was associated with a reduced risk of having an MI.

The relationship between positive affect and CHD is probably more complex than portrayed so far in this study and in others. It might be that positive emotions work by their effect on buffering negative emotions and stress. In terms of cardiovascular reaction caused by negative emotions, extroversion is important in the experience of happiness and especially in rewarding situations that are social (Wilkowsky & Ferguson, 2014). The results from paper III clearly showed that neither HADS-D nor extroversion is identical with low positive affect. A more differentiated view of what is referred to as anhedonia (e.g. Rømer-Thomson et al., 2015) and knowledge about how extroversion is related to anhedonia and reward processes (Smillie, 2013) is important in future research. Extroversion might buffer the negative effects of neuroticism, and hence low extroversion might represent vulnerability when combined with neuroticism. This is consistent with the undoing hypothesis offered by Fredrickson and colleagues (1998; 2000) and their findings of positive emotions having a clear and consistent effect of undoing cardiovascular effects of negative emotions (i.e. blood pressure, heart rate and peripheral vasoconstriction). The recent focus on how positive affect is associated with prosocial behavior and internalizing problems in children (Wang & Saudino, 2015), and how positive affect moderates responses to positive and negative stimuli (Cunningham & Kirkland, 2014), can contribute in understanding the link between positive affect and depression. The fact that gender differences in positive affect and anhedonia is marginal to

non-existent (Costa et al., 2001; Snaith et al., 1995; Nakonezny et al., 2010) emphasizes the distinct features of anhedonia compared to other symptoms of depression.

Gender differences in depression and risk of MI

Women are overrepresented both in terms of diagnosis and higher symptom-level of depression (Piccinelli & Wilkinson, 2000; Alexandrino-Silva et al., 2013). In line with this, Paper II showed that, compared to men, women had significantly more often a history of depression ($\Phi = .16$). However, except from the post-MI group in Paper II, men were significantly more depressed than women in the samples used in Papers I, II, and III using HADS-D. Gender differences in depression vary across age (Faravelli et al., 2013; Altemus, et al., 2014), sub-type (Baune et al., 2006; Salakangas et al., 2002; Alexandrino-Silva et al., 2013) and symptom profile (Delisle et al., 2012). Paper III compared gender differences in negative and positive affect and personality trait associated with symptom reporting. The results from Paper III supported the idea that the reversed gender differences in depression could be, at least partly, explained by the focus on anhedonia in the HADS-D dimension. Consistent with other findings (e.g. Haukkala et al., 2009; Mendes de Leon et al., 1998), symptoms of depression were a stronger predictor of MI in women compared to men. Although not significant, there was a trend of symptoms of anxiety being more cardioprotective among men than women. History of depression was also a significant predictor of MI among men, but not women. HADS-D was a significant predictor of MI in men only when not controlling for other risk-factors, but was a very strong predictor (OR = 3.68/2.31 unadjusted/adjusted) of incident MI among women. As symptoms of MI in women differ from those in men, and that MI in women are more likely to occur asymptotically (Coventry et al., 2011), the search for effective ways of screening is crucial. The results from this study strongly suggest that HADS can serve that mission.

Is HADS still important?

In 2012, Coyne and Sonderen called for the abandonment of the Hospital Anxiety and Depression Scale based on the 10-year systematic review by Cosco and colleagues (2012). The results from Paper III adds to the debate regarding the validity of HADS-D as a general measure of depression due to the moderate relationship between HADS-D and neuroticism, compared to HADS-A. Also, in Paper II, history of depression was more strongly related to HADS-A than HADS-D. The reversed gender differences observed in Papers II and III further advocates cautious use of the instrument. So why is HADS still important? An elevated score on HADS-D represents a strong predictor of MI among women free of CHD at baseline. Using HADS-D to identify those at risk and providing interventions that reduce the risk could, therefore, save lives. Martin (2005) has asked what HADS measures in a psychiatric setting. To understand the role of psychological variables in the etiology of CHD, the timely question is, what does it measure in a general population? This study contributes to this understanding and emphasis that HADS-D measure an anhedonic subtype of depression that reflects dispositional tendencies. The content in HADS-D imposes both limitations and possibilities for future use of HADS. The request for more specific measurement of depression in research on the etiological link between depression and CHD (Doyle et al., 2010; Hawkins et al., 2013) suggest that HADS (Zigmond & Snaith, 1983) has a future within cardiac research. While Papers I and II give a clear answer to *why* HADS is still important; Paper III offers an answer on *how* HADS is important.

Heterogeneity, comorbidity and complexity as reasons for inconsistency in findings

In a substantial part of the research on depression and CVD, the outcome-variable has consisted of a non-specific CVD incident category comprising MI, stroke as well as other

coronary or vascular conditions. However, the biological mechanism representing these relationships may vary substantially for coronary versus vascular incident. A CVD outcome variable might be comprised of both fatal/non-fatal CHD and stroke events. Jokela and colleagues (2013) found that extroversion was negatively associated with CHD-mortality (not significant), but also that extroversion was significantly and positively associated with increased stroke-mortality. In the study by Lee and colleagues, only CHD incidents were the outcome variable. This emphasizes the importance of being specific both in terms of predictors and outcome, and hence the results from this study should not be generalized to CVD events in general.

Anxiety has been found to be associated with reduced mortality (Mykletun et al., 2007). Further, while panic disorders increase the hazard of MI for those less than 50 years, it reduced CHD-mortality at all ages (Walters et al., 2008). Future studies could benefit from investigating differences in non-fatal and fatal events as anxiety and depression have a general effect on mortality not limited to CVD events (Mykletun et al., 2007). Although a request for a more specific measurement of depression and anxiety has been made by several researchers (e.g. Baatelan et al., 2014; Baune et al., 2012; Davidson, 2012; Tully et al., 2015), focus on high specificity in the outcome variable should be an aim, as well as gender-specific analysis. The comorbidity of anxiety and depression further dilute the picture. The nature of comorbidity is yet unknown and whether anxiety precedes depression or vice versa is still debated (Cummings et al., 2014). In Paper II, symptoms of anxiety measured at HUNT 2 were a stronger predictor of depression measured at HUNT 3 than depression measured at HUNT 2 was of anxiety at HUNT 3. This indirectly supports the idea that anxiety precedes depression, at least at symptom level, and can explain why anxiety diagnosis received at a younger age predicts CVD events in later life (i.e. Janszky et al., 2010). Regardless, the relationship between symptoms of depression and CHD is complex, and dispositions in experiencing

negative and positive affect and stress-proneness interacts with life circumstances. The environmental influences should not be overlooked and stressful life events are found to interact with the relationship between personality and symptom-reporting (Hundt et al., 2007). Furthermore, the findings of how neuroticism interacts with socioeconomic status (Hagger-Johnsen et al., 2012) suggest that neuroticism might be cardioprotective for those having the resources to attend to health worries, whereas the opposite is the case for those less fortunate in terms of income and education. The combination of traits is also important, and the combination of high neuroticism and low extroversion is important in explaining symptom reporting (Watson & Naragon-Gainey, 2014). The biologically-based brain system BIS and BAS (closely related to neuroticism and extroversion) jointly predicts symptoms of anhedonic depression, especially encounters with stressful life events (Hundt et al., 2007). However, in terms of mental disorders, like major depression, other personality traits, especially conscientiousness, are important (Kotov et al., 2010). The way personality influences health is complex. Personality traits dynamically influence health, directly through bodily sensations and symptom reporting as well as mortality, and more indirectly by the means of social cognition, health behavior and coping (Ferguson, 2013). Recent advances in the physiological approach to personality, like the study of personality and cardiovascular reactivity (Jonassaint et al., 2009; Kelly-Hughes, Wetherell & Smith, 2014), other physiological correlates (Brouwer, van Schaik, Korteling, van Erp & Toet, 2015), and brain structure (DeYoung et al., 2010) as well as function (Cunningham & Kirkland, 2014) might be a promising approach to better understand the link between personality and CHD.

Broad dispositions or specific sub-types of depression and anxiety

While arguing the importance of broad disposition, the need to focus on specific sub-types or phenotypes of anxiety depression is emphasized in cardiac research (e.g. Doyle et al., 2010;

Hawkins, et al., 2013; Baatelan et al., 2014; Tully et al., 2015). Although the focus on both broad dispositions apparently contradicts the request for focusing on specific symptom clusters, this might not be the case. Negative and positive affect is viewed as two dominant higher-order dimensions (Watson & Tellegen, 1985), while at the same time being operationalized as specific symptom clusters (Hawkins et al., 2014). In more recent theories on the organization of human personality, it has been suggested that the traits in the five factor model can be organized under these two basic dimensions, namely positive and negative affect (DeYoung, 2010).

Given the strong relationship between HADS-A, neuroticism, negative affect and history of depression observed in Papers II and III, the reversed relationship between HADS-A and MI is somewhat surprising, especially since perceived stress is associated with cardiac events (Katsarou et al., 2014) and the role of neuroticism in both symptom reporting and common mental disorders (Kotov et al., 2010). However, a recent meta-analysis of prospective studies has concluded that depression, measured by self-report as well as clinical diagnosis; represents an increased risk of CHD (Cohen et al., 2015; Gan et al., 2014). While the differentiation of negative affect into e.g. anxiety, disgust, depression and hostility has a long history, positive emotions seem to be less differentiated (Egloff et al., 2003). However, the different items HADS-D representing positive affect or anhedonia, have been found to have differentiated prognostic value (Denollet et al., 2007), addressing the need of specificity in predictors. At the same time, broad personality dimensions have been found to predict CHD events (Lee et al., 2014; Jokela et al., 2013). An established view is the differentiation of both positive and negative emotions in terms of activation vs. deactivation and pleasantness vs. unpleasantness (Barrett & Russell, 1999). Different models exist; however, the tripartite model of Clark and Watson (1991) can best account for the relationship between positive and negative affect in terms of related, but not bipolar dimensions, as the negative correlation

between positive and negative affect varies from non-existent, weak to moderate (Barrett & Russell, 1999). Future cardiac research should aim at integrating broad dispositions as well as specific symptom clusters. The focus on anhedonia is one of many ways to unravel the psychological etiology of CHD.

Anhedonia as a risk of incident MI: implications for screening and treatment

Papers I and II showed that symptoms of depression measured by HADS-D increased the risk of an MI, although the risk estimate was not significant for men when controlling for all of the established risk factors. Treatment of depression with selective serotonin reuptake inhibitors has been found to diminish neural processing of reward stimuli (McCabe et al., 2010).

Impairment in reward processes is a central component in anhedonia (Römer-Thomson et al., 2015), and it is likely that antidepressants other than SSRI would be more suitable for the pharmacological treatment of anhedonia. Agomelatine, one of the most recent antidepressants, affects both the release of noradrenaline and dopamine, and has been suggested to be superior to other pharmacological treatments of symptoms of anhedonia, and of major depression in general (De Berardis et al., 2015; Kennedy & Cyriac, 2012). Furthermore, the role of dispositional anhedonia might also have implications for depression treatment in general as Takahashi and colleagues (2013) suggest that the personality trait (low) reward dependence is a risk factor for treatment-resistant depression. A randomized controlled study of internet-based cognitive behavioral therapy as a treatment of anxiety in depression in MI patients using HADS as the main measure is outlined (Norlund, Olsson, Burell, & Held, 2015). Although not directly transferable to a general population, the forthcoming results from this study can inform the development of effective treatment of anhedonia.

Limitations

The results from Paper I suggest that having an MI did not significantly impact the level of symptoms of anxiety and depression on a long-term basis, but the conclusions based on these results call for caution. Analyses of the participation in the follow-up HUNT 2 and HUNT 3 conclude that participation is associated with survival, socioeconomic status and symptoms (Langhammer et al., 2012). Therefore, those severely depressed after MI were less likely to participate in HUNT 3. Furthermore, the results cannot be transferable to a short-term effect of having MI due to the long duration since MI. In Samples I and II, the sample size is very large. This means that the statistical power is very high, higher than the recommended standard criteria of .80 (Cohen, 1992). To counter this, effect sizes were included in all results. It should be noted that the effect size in Paper I is small (OR 1.04). However, it is important to remember that symptoms of depression were operationalized as a continuous variable, and that even a change from “Not at all” to “Not often” would constitute a change in risk estimate. The effect size of HADS-D operationalized as $HADS \geq 8$ logically shows a much stronger effect. The relatively moderate correlation between neuroticism and depression measured by HADS, could also, in part, be explained by somewhat low internal consistency in the dimension and the skewness in the distribution of the variable. In Paper III, the sample consisted of university students, and there should be some caution regarding generalization. However, the gender differences observed in HADS presented the same pattern as the community sample applied in Paper II. It should also be mentioned that this study does not directly address the impact of personality traits on risk of MI, and the role of extroversion as a risk factor of MI is suggestive and indirect more than empirically documented in this study.

Future research

Heterogeneity in type of sample, predictors, assessment and outcome is why firm conclusions about anxiety and depression as risk factors of CVD cannot be yet drawn. It has been argued

that gender should be included in all investigative CVD models (Orth-Gomer & Deter, 2015). Waist-hip ratio is a strong physical risk indicator where gender-specific cut-off scores are being applied. It is time to move forward in regards to psychological variables, as well. Men and women do not represent an identical population, neither in regards to biological aspect nor psychological profiles. In the future, a clearer distinction should be made on general population versus CVD patients. To understand the role of psychological variables in the etiology of CVD, large-scale prospective studies on subjects free of CVD at baseline should be encouraged. The role of dispositional affect should be incorporated as stable tendencies not only might represent an independent risk factor in the etiology of CVD but also represent vulnerability and resilience toward several psychological conditions known to be associated with risk on CVD. Measurement that is specially designed to measure anhedonia (Leventhal et al., 2006) should be applied in the future research to increase knowledge about the role of anhedonia as a risk factor of MI. Furthermore, CVD as an outcome should not be treated as one single outcome. The relationship between specific psychological variables relates in differentiated ways to specific outcomes. Focusing on more specific outcomes allows more accurate investigation. There is reason to suggest that it would be wise to separate fatal and non-fatal outcomes given the general relationship between depression, anxiety and mortality. Most importantly, the operationalization of anxiety and depression is crucial.

Conclusion

The conclusions from this study can be summarized in the following way. Elevated symptoms of depression measured by HADS increases the risk of incident MI. Although limitations apply, having an MI does not have long-term adverse effects on the level of symptoms of anxiety and depression, and time since MI was not a significant predictor of symptom level. Second, there were gender differences in the MI-risk estimate based on HADS-D. A HADS-D score above seven was a significantly stronger predictor of incident MI among women than

men. History of depression was a significant predictor of MI among men, but not women, further emphasizing the need for gender-specific psychological risk profiles. Elevated symptoms of anxiety measured by HADS represented a reduced risk of having an incident MI among both men and women. Finally, HADS presented a relationship to positive and negative affect consistent with the tripartite model of anxiety and depression. The dimensions in HADS presented high test-retest stability and a strong relationship to the personality traits neuroticism and extroversion. The results supported that the HADS depression subscale represents an anhedonic type of depression, and that the anhedonic content in the depression subscale can account for the reversed gender differences in depression observed in this and other samples.

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Paper I

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Paper II

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Anhedonic depression, history of depression, and anxiety as gender-specific risk factors of myocardial infarction in healthy men and women: The HUNT study

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Abstract

This prospective study examines gender-specific psychological risk factors of myocardial infarction. Out of 41,248 participants free of coronary heart disease at baseline, 822 cases of myocardial infarction were identified in the Nord-Trøndelag Health Study or the mortality register. The participants completed the Hospital Anxiety and Depression Scale. Cholesterol, blood pressure, and waist-hip ratio were measured by medical staff. Smoking, diabetes, non-fatal myocardial infarction, and history of depressive episode were self-reported. Anhedonic depression (Hospital Anxiety and Depression Scale-D ≥ 8) was a significant predictor of myocardial infarction in women but not in men. Gender difference in risk estimate based on Hospital Anxiety and Depression Scale-D was significant ($p < .01$). History of depressive episode was a significant predictor of myocardial infarction in men. Symptoms of anxiety (Hospital Anxiety and Depression Scale-A ≥ 8) reduced the risk of having a myocardial infarction.

Keywords

anxiety, depression, gender, myocardial infarction, risk

Women have been marginalized in the field of cardiac research, and studies focusing specifically on women's psychological risk profiles are lacking (Naqvi et al., 2005; Wenger, 2003). Coronary heart disease (CHD) in women does not present or manifest the same way as in men; symptoms of myocardial infarction (MI) are more atypical and cardiac events more likely to occur asymptotically. Women are less likely to experience chest pain before an MI than men, but significantly more likely to experience neck pain, nausea, right-arm pain, dizziness, jaw pain and fatigue (Coventry et al., 2011). Furthermore, women typically experience a heart attack later in life than men and hence have more comorbid conditions, and they are also less likely to be diagnosed and treated efficiently (Low et al., 2010; Möller-Leimkühler, 2007). The European guidelines on cardiovascular disease (CVD) prevention in clinical practice (Perk et al., 2012) emphasize the inclusion of psychosocial factors in CHD risk assessment. However, the guidelines offer no gender-specific risk profile in regard to anxiety and depression.

Several reviews about the relationship between depression and CHD (e.g. Nicholson et al., 2006; Stampfer et al., 2012; Van der Kooy et al., 2007; Wulsin and Singal, 2003) and prospective studies (e.g. Gustad et al., 2013; Hawkins et al., 2013) strongly support that there is an association between depression and CHD. Among women, there has been an increased prevalence of CHD, and the role of depression as a gender-specific factor is still unclear (Naqvi et al., 2005). In a Finnish study, symptoms of depression predicted cardiovascular mortality only in women (Haukkala et al., 2009). In another study, depressive symptoms were an independent risk factor for CHD in women but not in men (Mendes de Leon et al., 1998), and depressive symptomatology has been found

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to be more important in predicting CVD in women than in men (Lloyd et al., 1996). In contrary, a French population-based study found that depressive mood predicted cardiovascular mortality for men only (Lemogne et al., 2012). These findings emphasize the importance of both screening for depression in general and a focus on the gender-specific role of depression in preventive heart interventions.

Women and men represent different populations, and therefore, the practice of using men as references should be reconsidered (Wenger et al., 2008). Prevalence, incidence, and morbidity risk of depressive disorders are higher in females than in males (Piccinelli and Wilkinson, 2000). Different measures of depression tend to display differentiated gender differences (Salokangas et al., 2002), and in some self-report instruments, the differences are reversed, that is, men have a higher score on depression (Nortvedt et al., 2006; Stordal et al., 2001). At the symptom level, different gender subtypes can be identified (Alexandrino-Silva et al., 2013), and this might have implications for understanding the depression–CHD relationship. Gender differences in depression differ from gender differences in CHD, suggesting that the association between depression and CHD is gender specific (Faravelli et al., 2013; Low et al., 2010).

In medical practice as well as in the research field addressing depression and CHD, a variety of operationalizations of depression exist (Davidson, 2012; Davidson et al., 2005; Stampfer et al., 2012). The relationship between affective disorders and CHD seems to vary in strength by subtype (Baune et al., 2012). The treatment of depression as a unidimensional construct in the research field has left several questions unanswered regarding symptom clusters (Hawkins et al., 2013) and whether some aspects or subtypes of depression are more cardiotoxic than others (Doyle et al., 2010). Furthermore, different symptomatic profiles of depression have been identified in men and women (Alexandrino-Silva et al., 2013), so including gender-specific analysis is important in understanding the role of depression as a risk factor of CHD. It is also possible that gender-specific strategies could improve the predictive power of a psychological risk profile, but prospective studies are needed to identify gender-specific risk profiles.

Shaffer et al. (2012) address the importance of research on different depression phenotypes and emphasize the role of anhedonic depression in the association between depression and CHD. Recent research on MI has emphasized the role of anhedonia (reduced positive affect and loss of interest and pleasure and lack of reactivity to usually pleasurable stimuli) as independently associated with MI (Davidson et al., 2010; Denollet et al., 2007). Anhedonia, which refers to the reduced or lost capacity to experience pleasure, is a feature of major depressive disorder (Di Giannantonio and Martinotti, 2012). An emphasis on the distinction between depressive syndromes and symptoms and the examination of the predictive ability of different operationalization has also been requested (Davidson et al., 2005).

Although the study of psychological risk factors of CHD has mainly focused on depression, there is a growing amount of literature on the link between anxiety and the development of CHD (Batelaan et al., 2014; Roest et al., 2010; Tully et al., 2013). However, the heterogeneity in assessment of anxiety imposes major limitations in the investigation of the impact of anxiety (Batelaan et al., 2014). Generalized anxiety disorder (GAD), but not symptoms of anxious arousal, has been found to predict mortality in CHD patients (Tully et al., 2011). In another study, symptoms of anxiety predicted mortality in CHD patients independent of symptoms of depression (Watkins et al., 2013). In a study of middle-aged women, a three-item measure of symptoms of anxiety predicted fatal cardiovascular incidents (Denollet et al., 2009). In contrast, the study by Mykletun et al. (2007) showed that symptoms of anxiety were negatively associated with cardiovascular mortality. Similarly, others have documented that higher anxiety scores are associated with reduced mortality (Meyer et al., 2010). Furthermore, GAD has been found to predict superior outcome after an acute coronary syndrome (Parker et al., 2011). Other studies have found that symptoms of anxiety are not associated with CHD events when controlling for depression (Versteeg et al., 2013). Furthermore, gender differences in anxiety are highly prevalent, and comorbidity between the disorders is higher among women (McLean et al., 2011). It is therefore important to include measures of anxiety in the search for a gender-specific psychological risk profile.

The European guidelines on CVD prevention (Perk et al., 2012) do not specify how depression should be measured and offer no gender-specific recommendations. This study addresses the value of using simple psychological screening tools in order to identify men and women at risk of having an MI based on their psychological profile.

Although highly comorbid in psychiatric clinical samples, the comorbidity rates between anxiety and depression in CHD patients are substantially lower (Tully and Cosh, 2013). This is also the conclusion made by Hek et al. (2011): Comorbid depression and anxiety are less prevalent in older adults, while current anxiety disorders are substantially related to past depression. In this prospective, population-based study, a unique linkage between a large health survey, clinical assessment, and the national mortality register is utilized. This enables the investigation of the roles of anhedonic depression, depressive episode, and anxiety as gender-specific risk factors of MI.

Method

Study design and participation

The Nord-Trøndelag Health Study (The HUNT Study) is collaboration between the HUNT Research Centre (Faculty of Medicine, Norwegian University of Science and Technology

NTNU), the Nord-Trøndelag County Council, the Central Norway Health Authority, and the Norwegian Institute of Public Health. HUNT is one of the largest health studies ever conducted and is described in Holmen et al. (2003). It is a large database of personal and family medical histories collected during three intensive studies over two decades. HUNT1 was carried out from 1984 through 1986 to establish the health history of 75,000 people. The succeeding HUNT2 was carried out from 1995 through 1997 and focused on the evolution of the health history of 65,049 people. HUNT3 was completed in June 2008, and 48,289 people participated (52% participation rate). Data were collected by means of questionnaires, interviews, clinical examinations, and collection of blood and urine samples.

Of the 65,049 people who participated in HUNT2, those with a history of MI or reported current or previous incidents of angina were excluded from the analyses. Participation in the HUNT3 study or identification in the mortality register was used as the inclusion criteria, resulting in 41,248 candidates for this study. A total of 573 participants in the HUNT3 study (2.5%) reported that they currently or prior to the examination had a non-fatal MI. According to the mortality register, 249 were classified with mortality due to MI, that is, having a fatal MI. The Regional Committee for Ethics in Medical Research approved the protocols for HUNT2, HUNT3, and for this specific study, including the linkage to the mortality register. All participants in this study gave their written consent.

Measurement of depression and anxiety

The Hospital Anxiety and Depression Scale (HADS; Zigmond and Snaith, 1983) includes 14 items with a 4-point scale indicating how the respondent has felt over a 2-week period prior to measurement. HADS has been found superior to other depression scales when measuring cardiotoxic symptoms, as HADS focuses mainly on anhedonia (Doyle et al., 2012). However, HADS does not include somatic symptoms, a symptom cluster identified as important in relation to CHD (Hawkins et al., 2013).

The HADS anxiety scale contains items that cover worrying, restlessness, and panic attacks. It has been proven to have good clinical value and case-finding abilities (Olsson et al., 2005). In the depression subscale, the dominant focus is on anhedonia (Mykletun et al., 2001). In this study, a Norwegian translation of HADS was used (Mykletun et al., 2001). A score on HADS-A and HADS-D ≥ 8 on the respective scales was used as an indicator of case-level anxiety and depression (Bjelland et al., 2002).

Depressive episode

In an extended part of the HUNT2, the participants were instructed to indicate whether, during their life, there had been periods of two consecutive weeks or more when they “felt depressed, sad, and down,” “had appetite problems or

ate too little,” “felt weak (adynamic) or lacked energy,” “really reproached yourself and felt worthless,” or “had problems concentrating or had difficulty making decisions.” Participants were classified as having experienced a depressive episode if they answered yes to the question, “During your life, have there been periods of two consecutive weeks or more when you had at least three of the above-mentioned problems simultaneously?”

Hypertension, cholesterol, waist-hip ratio

Participants' systolic blood pressure (SBP) was measured by specifically trained nurses using a cuff adjusted for arm circumference in HUNT2. SBP was measured three times, and a mean was calculated from the second and third observations to ensure reliable measurements. Total serum cholesterol was measured applying an enzymatic colorimetric cholesterol esterase method (Holmen et al., 2003). Waist and hip circumferences were measured with a steel band to the nearest 1.0 cm with the participant standing and with the arms hanging relaxed. The waist circumference was measured horizontally at the height of the umbilicus, and the hip circumference was measured at the thickest part of the hip (Holmen et al., 2003). The International Diabetes Federation (IDF) has also provided recommendations for cut-offs for waist circumference and waist-hip ratio. The recommendations are gender, population, and geography specific. For Europeans, the recommended cutoff scores are .80 for women and .94 for men to identify central obesity (Alberti et al., 2006).

Diabetes and smoking

Smoking was self-reported and operationalized as numbers of years of daily smoking. Diabetes was also self-assessed by answering yes or no.

End point: fatal and non-fatal MI

The mortality data were obtained from the National Mortality Register by combining the mortality database and the HUNT data by means of an 11-digit personal identity number. In the mortality registry, diagnoses are encoded according to International Classification of Diseases, 10th Revision (ICD-10). MI mortality in this study encompasses ICD-10 codes I21-9, unspecified acute MI, and I22-9 subsequent MI with unspecified location, with the majority of cases being I21-9. Non-fatal MI was indicated by self-report in the HUNT3 study as a “yes” or “no” response to the question, “Have you ever had or do you have myocardial infarction?”

Statistical analysis

Independent-samples *t*-test and χ^2 were conducted to compare the groups on the baseline characteristics at HUNT2. Logistic regressions were applied to investigate the effect

Table 1. Demographic and baseline risk factors in MI (822) versus non-MI group (40,426) sorted by gender (N=41,248).

	Women (22,013)		<i>p</i> ≤	Men (18,413)		<i>p</i> ≤
	Non-MI (21,771)	MI (242)		Non-MI (17,833/17,759)	MI (580)	
Age	43.12 (13.07)	57.87 (9.31)	.001	43.61 (12.90)	55.81 (9.44)	.001
Systolic blood pressure	129.30 (19.02)	148.31 (23.94)	.001	136.93 (16.36)	146.73 (18.17)	.001
Total cholesterol	5.69 (1.24)	6.94 (1.20)	.001	5.72 (1.14)	6.50 (1.07)	.001
Diabetes (<i>n</i>)	251 (1.2%)	13 (5.4%)	.001	295 (1.7%)	22 (3.8%)	.001
WHR (<i>n</i>)	8001 (37.4%)	148 (61.7%)	.001	2702 (15.20%)	167 (28.8%)	.001
Smoking <i>N</i> years	9.85 (12.10)	19.37 (16.68)	.001	11.55 (13.72)	23.31 (15.57)	.001
Depression cutoff ≥8	1855 (8.5%)	52 (21.51%)	.001	1645 (9.2%)	69 (11.9%)	.03
Anxiety cutoff ≥8 (<i>n</i>)	3826 (17.6%)	43 (17.8%)	.94	2244 (12.6%)	47 (8.1%)	.001
Depressive episode (<i>n</i>)	6514 (29.9%)	83 (34.3%)	.14	2949 (16.5%)	111 (19.1%)	.10

MI: myocardial infarction; WHR: waist-hip ratio.
 χ^2 and *t*-test for bivariate association between MI and non-MI group.

on MI. The dependent variable was dichotomous (MI/non-MI). Separate analyses were performed for men and women to enable comparison of the risk predictor's gender-specific magnitude. The psychological variables were entered in Step 1, whereas the traditional risk factors were entered in Step 2 to adjust the model.

Results

In the total sample of 41,248 subjects, 822 of the participants had a fatal (249) or non-fatal (573) MI. Of those with a HADS-D score ≥ 8 (3621), 59.3 percent (2148) had a HADS-A score ≥ 8 , and 5.7 percent (2148) had a history of depressive episode. Compared to men, women reported higher prevalence of prior depressive episode (6597/22,013 vs 3060/18,413, $\chi^2=982.81$ (1), $\Phi=16$, $p<.001$). Women were overrepresented in the HADS-A ≥ 8 group as 1907 out of 2203 women had a HADS-A score equal or above 8, whereas the respective numbers for the men were 2291 out of 18,413 ($\chi^2=317.71$ (1), $\Phi=.07$, $p<.001$). Men were marginally overrepresented in the HADS-D >8 group; 1714 out of 18,413 men and 1907 out of 22,013 women had a HADS-D score ≥ 8 ($\chi^2=5.12$ (1), $\Phi=.01$, $p<.03$). Analysis between the outcome variable MI versus non-MI group and predictors performed by *t*-test and χ^2 showed significant associations and group differences related to all predictors except depressive episodes. The prevalence of elevated symptoms of anxiety was higher in the non-MI group, although this association was significant only for men. Prevalence of depression measured by HADS-D was significantly different in the MI versus the non-MI group in both men and women, whereas depressive episodes were not. There was a significant association between HADS-D and depressive episode ($\Phi=.25$, $p<.001$) and a significant association between HADS-D and HADS-A ($\Phi=.39$, $p<.001$). HADS-A and depressive episode had a significant positive association ($\chi^2=4498.32$ $\Phi=.33$, $p<.001$; Table 1).

Table 2 shows the results of the logistic regression. In the total sample, elevated symptoms of depression (>8) were a significant predictor of MI, whereas history of depression was not. After adjusting for the traditional risk factors (gender, cholesterol, waist-hip ratio, diabetes, smoking, and SBP), history of depressive episode emerged as a significant predictor along with symptoms of depression. A high score on anxiety (HADS-A >8) significantly reduced the risk of having an MI both in the unadjusted and adjusted model. In the separate analysis, history of depression was not a significant predictor of MI in the female sample. Elevated symptoms of depression increased the odds of having an MI, whereas the opposite was the case for anxiety. Higher score on HADS-A represented reduced risk of having an MI in the male sample, and the effect size (odds ratio (OR)) of this predictor was stronger compared to the female sample in both the unadjusted and adjusted model. History of depressive episode was a significant predictor of MI in men, and elevated symptoms of depression were a significant predictor only in the unadjusted model.

Post hoc analyses of risk differences

To investigate whether the gender differences in risk were statistically significant, the statistical approach suggested by Paternoster et al. (1998) was applied. In this procedure, a *Z*-score is calculated, and according to the results, there was a significant difference in risk estimate based on HADS-D; $Z=2.96$, $p=.002$. The difference in risk-based anxiety ($Z=.62$) and history of depression ($Z=1.57$) did not reach statistical significance.

Discussion

Women have been marginalized in the search for psychological risk factors for CHD, and prospective studies applying separate analyses for men and women have been

Table 2. Results of logistic regression.

Variables	OR (CI)	<i>p</i> <
Psychological variables (total sample)		
Unadjusted		
HADS-D ≥ 8	2.42 (1.93–3.02)	.001
HADS-A ≥ 8	.49 (.38–.63)	.001
Depressive episode	1.00 (.84–1.19)	.98
Adjusted		
HADS-D ≥ 8	1.41 (1.12–1.78)	.003
HADS-A ≥ 8	.61 (.50–.79)	.001
Depressive episode	1.29 (1.07–1.55)	.008
Psychological variables (women)		
Unadjusted		
HADS-D ≥ 8	3.68 (2.52–5.37)	.001
HADS-A ≥ 8	.59 (.40–.89)	.011
Depressive episode	1.02 (.75–1.37)	.92
Adjusted		
HADS-D ≥ 8	2.31 (1.57–3.40)	.001
HADS-A ≥ 8	.65 (.43–.98)	.038
Depressive episode	1.05 (.77–1.43)	.747
Psychological variables (men)		
Unadjusted		
HADS-D ≥ 8	1.66 (1.25–2.20)	.001
HADS-A ≥ 8	.45 (.32–.63)	.001
Depressive episode	1.36 (1.09–1.71)	.008
Adjusted		
HADS-D ≥ 8	1.11 (.83–1.48)	.500
HADS-A ≥ 8	.55 (.40–.78)	.001
Depressive episode	1.44 (1.14–1.82)	.002

CI: confidence interval; OR: odds ratio; HADS: Hospital Anxiety and Depression Scale.

requested (Low et al., 2010; Naqvi et al., 2005; Wenger et al., 2008). In this study, different psychological risk profiles among men and women were identified and support the assumption that the association between depression and CHD is gender specific (e.g. Faravelli et al., 2013; Low et al., 2010). Depression, especially symptoms of anhedonic depression as measured by HADS, seems to be a strong predictor of MI among women, whereas this specific instrument did not contribute in predicting MI among men after controlling for traditional risk factors. Post hoc analysis of differences in risk estimate showed that this difference was statistically significant. This is consistent with other findings of symptoms of depression being more important in predicting CHD in women than men (Lloyd et al., 1996). History of depressive episodes was more prevalent in women and was a significant risk predictor in men only; however, the gender difference in risk was not significant. Although HADS-D and depressive episodes were correlated ($\Phi = .25$), the strength of the relationship between do not suggest that these differences could be attributed to collinearity. It rather supports the view that men and women represent different populations when it comes to

understanding the link between depression and CHD (Wenger et al., 2008). The higher prevalence of history of depressive episodes in women might be the reason that it fails to differentiate those at risk of MI. The results support that gender differences in depression are important to incorporate in understanding the link between depression and CHD. Elevated symptoms of depression (HADS-D ≥ 8) were not more prevalent in women, and this is consistent with other studies using HADS (e.g. Nortvedt et al., 2006; Stordal et al., 2001). However, the results in this study are contrary to comparable samples where other measurements of depression have been applied (e.g. Mendes de Leon et al., 1998) and the general literature on gender differences (Piccinelli and Wilkinson, 2000). This suggests that HADS-D represents a distinct symptom cluster of depression that might be especially cardiotoxic for women. HADS does not include somatic symptoms, and HADS-D focuses mainly on anhedonia (Mykletun et al., 2001). Although the somatic cluster has been identified as the most important symptom cluster in predicting CHD (Hawkins et al., 2013), this study found that other symptom clusters of depression are relevant and that positive affect may be cardioprotective, especially for women. Hawkins et al. (2013) identified somatic clusters followed by positive affect as the most important symptom clusters predictive of CHD, but the analyses were not performed separately for men and women, and the role of specific symptom clusters as more cardiotoxic can only be understood by prospective studies including participants free of CHD at baseline. Furthermore, separate data analysis should be performed, not only controlling for gender (Low et al., 2010). The variable “Depressive episode” includes both somatic symptoms and lack of positive affect/depressed affect, and it might be that somatic clusters are more important for men than for women. A lifetime history of depressive episodes was a unique predictor of MI in men and not women in the adjusted models.

HADS does not include somatic symptoms, and this methodological aspect might be the reason why studies using HADS-A (e.g. Versteeg et al., 2013), including this study, do not find a positive association between anxiety and CHD. However, the study by Parker et al. (2011) using diagnostic criteria for GAD did find the same results as in this study, that is, anxiety being cardioprotective. Although distinctive conditions, the relationship between HADS-A and GAD is well documented (Olsson, et al., 2005)

It is important to differentiate between anxiety and depression as a prognostic factor in CHD groups and risk factor of CHD in healthy populations. While the prognostic studies focus on patients with existing CHD, the etiologic approach focuses on psychological factors as risk factors of CHD, and these represent two different approaches (Nicholson et al., 2006; Stampfer et al., 2012). As suggested by Parker et al. (2011), timing is of great importance, and both anxiety and depression might have quite different roles as etiological factors compared to prognostic

factors. However, the findings of this study of anxiety as a protective factor of MI in healthy subjects are consistent with studies of patients with acute coronary syndrome, where anxiety predicted superior 5-year outcomes (Parker et al., 2011). Men are more reluctant to self-refer to primary health care (Jeffries and Grogan, 2012), and this might be why the protective effect of anxiety is stronger for the male sample in this study. Although females were underrepresented, the review of seven etiological studies of initially disease-free individuals points to worry as being associated with fatal and non-fatal CHD (Tully et al., 2013). Limited knowledge about anxiety and CHD has been attributed to the assessment of anxiety, and worry has been found to have the strongest impact on the onset of CVD compared to panic and phobias (Batelaan et al., 2014). More knowledge about the association between depression and anxiety can be achieved through the focus on the differential impact of types of anxiety (Batelaan et al., 2014) informed by the focus on specific symptom cluster/phenotypes of depression (Hawkins et al., 2013; Shaffer et al., 2012). A higher level of specificity might be a promising approach toward a more comprehensive understanding of anxiety as a risk or protective factor of CHD in general and MI in particular for men and women.

Treatment of depression in CHD patients thus far has demonstrated only moderate effects (Baumeister et al., 2011), especially among women (Low et al., 2010). However, treatment of depression before the onset of CHD has been found to reduce the risk of CVD (Stewart et al., 2014). This points to the importance of primary prevention and suggests that addressing depression as a risk factor has more impact than the treatment of depression as a prognostic factor, and hence interventions should aim at screening those at risk. Effective and simple screening for depression in identifying CHD risk in non-cardiac patients could reduce the number of MI deaths among men and women. Screening for depression would have a positive impact regardless of its association with CHD as depression represents a major health problem (Möller-Leimkühler, 2007).

In the research on depression and CHD, depression has been treated as a unidimensional cluster, whereas more recent studies have demonstrated that particular depressive symptoms are stronger predictors (Hawkins et al., 2013), and the role of anhedonia has received particular attention (Davidson et al., 2010; Denollet et al., 2007; Shaffer et al., 2012). The implication of anhedonia as a specific cardiotoxic symptom is that this symptom cluster or depression subtype, or intermediary phenotype, should be more carefully addressed in the preventive strategies (Shaffer et al., 2012). It is also possible that the type of treatment has not been optimal for women (Low et al., 2010; Naqvi et al., 2005). In the research on anhedonia in major depression, agomelatine has shown promising results (Di Giannantonio and Martinotti, 2012). The potential of agomelatine to reduce the risk of CHD in patients with an anhedonic

depression subtype should be explored as a possible new intervention in prospective studies applying a gender-specific approach.

Efficient ways of identifying women with increased CHD risk due to psychological factors is necessary in order to develop effective prevention and intervention strategies (Low et al., 2010). This study suggests that HADS-D could be used to identify risk in women, whereas information about lifetime depression/depressive episode is more promising in identifying risk among men. Both represent simple and non-invasive approach that easily could be adopted by health personnel. Anxiety as measured by HADS-A is not a suitable screening tool in identifying risk, according to the results of this study, which is in line with other studies that have used HADS to explore the association between anxiety and CHD (Versteeg et al., 2013). Further research should address whether symptoms of anxiety might be protective of MI in a general population.

It has been argued that it is premature to conclude that depression in general is an independent causal risk factor for CHD (Stampfer et al., 2012). The findings from this study support this notion, as it seems that too little is known about the specific aspects of depression as a CHD risk factor in men and women. A general recommendation to screen for anxiety and depression (Perk et al., 2012) might have little benefit, as specific subtypes of depression differentiate in predictive power, and the role of anxiety is far from conclusive. In research on the link between depression and CHD, more attention should be given to measurement issues and levels of specificity. Gender differences in depression are important to incorporate, as well as a focus on specific aspects of depression symptom clusters and different anxiety diagnoses. The results of this study suggest that it would be useful to develop gender-differentiated screening tools for depression in preventive CHD care and that the role of anxiety as a risk factor needs to be re-evaluated or reversed.

Strengths and limitations

This study contributes to the existing literature in the following ways: (1) prospective study of a large community-based sample free of CHD at baseline; (2) it includes all the major risk factors; (3) separate analysis is applied for men and women (4); two different measures of depression are included as potential screening tools; (5) it includes measures of anxiety; and (6) it includes both fatal and non-fatal MI as end-point measures.

The most obvious limitations in this study are as follows: (1) the reliance on self-reporting measures for several variables, and (2) the measure of depressive episode is unspecific, as it does not ask when it occurred or whether there have been recurrent episodes. Furthermore, a depressive episode as described here does not imply a valid assessment of major depressive episode as diagnosed in the

Diagnostic and Statistical Manual of Mental Disorders (5th ed.; DSM-V). Although HADS has been found to be a reliable screening instrument of psychological stress, the factorial structure of HADS has been questioned (Martin et al., 2003).

This study indicates that men and women represent different populations in the investigation of psychological risk factors in the development of MI and that the association between depression, anxiety and CHD is gender specific. This study emphasizes the importance of screening for depression in women with no CHD at baseline. Symptoms of anhedonic depression measured by HADS-D might be a gender-specific risk factor of MI in women.

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Paper III

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