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Associations of depression and anxiety symptoms with cardiac function and cardiovascular disease in the general population

A linkage between the HUNT population study, hospital data and cause-of death register

Thesis for the degree of Philosophiae Doctor

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Norsk Sammendrag (Norwegian Summary)

Anslagvis rammes hvert år 10–30% av Norges og den vestlige verdens befolkning av en psykisk lidelse. I løpet av livet får mellom 30 og 50% en slik lidelse. De vanligste psykiske lidelsene er angst og depresjon, og disse tilstandene bidrar også til økt sykelighet og dødelighet ved flere somatiske sykdommer, inkludert hjerte-karsykdom (CVD). Hver tredje nordmann rammes av CVD i løpet av livet, og er i dag sammen med kreft vanligste årsak til død i Norge. Forskning antyder at angst- og depresjons-symptomer også bidrar til selve utviklingen av CVD, blant annet gjennom ugunstig livsstil (som røyking, alkohol, inaktivitet, og inntak av fet mat) som igjen øker blodtrykk, BMI og kolestrolnivå. De tre siste faktorene er noen av de viktigste faktorene bak inflammasjon og arteriosklerotiske prosesser som bidrar til CVD. Tidligere forskning har ikke tatt tilstrekkelig høyde for disse mellomliggende faktorene, slik at de underliggende mekanismene mellom psykisk helse og CVD fortsatt er noe uavklart. Helseundersøkelsen i Nord-Trøndelag (HUNT) er en stor befolkningsundersøkelse som har registrert mange av disse forklaringsvariablene som mangler i tidligere studier. Alle nordtrøndere over 20 år har blitt invitert til disse undersøkelsene (HUNT1, 1984–86; HUNT2, 1995–97; HUNT3, 2007–09), hvor det er gjort klinisk undersøkelser, blodprøvetaking og utfylling av spørreskjema. I spørreskjemaene ble det spurt om siste ukes symptomer på angst (HADS-A) og depresjon (HADS-D).

Sykehusene i Helse Nord-Trøndelag HF (HNT) i Levanger og Namsos har siden 1995 registrert opplysninger om diagnostikk, prøveresultater og behandling av alle pasienter med hjerteinfarkt (AMI) og hjertesvikt (HF). Det kardiologiske miljøet har kvalitetssikret denne informasjonen og validert diagnosene, og dermed sikret høy spesifisitet for diagnosene, før kobling med HUNT data.

Artikkel I og II undersøkte den prospektive sammenhengen mellom selvrapporterte symptomer på depresjon, angst og blandet angst og depresjon (MSAD) hos personer uten hjertesykdom i HUNT2, og utvikling av førstegangs hjerteinfarkt (AMI, artikkel I) og hjertesvikt (HF, artikkel II) fram til 31.12.2008. Endepunktene ble registrert både i sykehusjournaler og i Dødsårsaksregisteret. Artikkel I viste 20–30% økt risiko for fremtidig førstegangs AMI forbundet med symptomer på angst, depresjon og MSAD i HUNT2. Artikkel II viste at symptomer på depresjon, men ikke angst eller MSAD, ga ca. 40% økt risiko for å få diagnosen HF i løpet av oppfølgingsperioden.

I manuskript III studerte vi sammenhengen mellom angst- eller depresjonssymptomer og venstre hjertekammerfunksjon. Ett tilfeldig utvalg av friske HUNT3 deltagere uten hypertensjon, diabetes eller kjent klaffesykdom gjennomgikk ekkokardiografiundersøkelse. Vi fant ingen sammenheng mellom angst og depresjonssymptomer rapportert i HUNT3 og hjertefunksjon målt på samme tidspunkt.

Men summen av depresjonssymptomer fra HUNT2 og HUNT3 var assosiert med svekkelse av den diastoliske hjertefunksjonen i HUNT3, ca. 1 % svekkelse for hvert poeng/enhets økning på HADS-D skalaen, både for kvinner og menn Vi fant ingen slike sammenhenger for angstsymptomer.

Screening for angst- og depresjonssymptomer er en godt tolerert og ressursbesparende metode som kan brukes i de fleste kontekster. Våre resultater bekrefter at det er særlig viktig å vurdere depresjonssymptomene (alvorlighet og varighet) når det gjelder forebygging av CVD.

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Levanger, February 2015

Lise Tuset Gustad

List of abbreviations

ADI	Anxiety and Depression Index (used in HUNT1 as a crude anxiety and depression measure. Correlates well with HADS-T)
AMI	Acute Myocardial Infarction
BMI	Body Mass Index
CHD	Coronary Heart Disease
CVD	Cardiovascular Disease
e´	Peak mitral annular early diastolic velocity
Global strain	Left ventricular end-systolic global strain
Global strain rate	Left ventricular peak global strain rate
HADS-D	HADS- Depression symptoms
HADS-A	HADS- Anxiety symptoms
HADS-T	HADS-Total (the sum of HADS-A and HADS-D)
HF	Heart Failure
HUNT	Nord-Trøndelag Health Study.
LV	Left ventricle
MAPSE	Mitral Annular Plane Systolic Excursion
MSAD	Mixed symptoms of anxiety and depression (ADI and HADS-T)
S´	Peak mitral annular systolic velocity
ST	Speckle Tracking
TD	Tissue Doppler

List of studies

This thesis is based on two accepted papers and one study under review, which will be referred to in the text by their Roman numerals.

I. Gustad LT, Laugsand LE, Janszky I, Dalen H, Bjerkeset O. **Symptoms of anxiety and depression and risk of acute myocardial infarction: the HUNT2 study.** Eur Heart J. 2014: 35:1394–403.

II. Gustad LT, Laugsand LE, Janszky I, Dalen H, Bjerkeset O. **Symptoms of anxiety and depression and risk of heart failure: the HUNT study.** Eur J Heart Fail: 2014; 16:861–70.

III. Gustad LT, Bjerkeset O, Strand LB, Janszky I, Salvesen Ø, Dalen H. **Cardiac function and symptoms of depression and anxiety in a healthy population. The HUNT Study**. Under review.

1.0 Introduction

Depression is often characterized by symptoms of sadness, loss of interest, concentration, pleasure or appetite, guilt, negative thoughts and tiredness, whilst anxiety is more typically characterized by tension and worrying, often followed by physiological changes such as increased blood pressure, heart rate and sweating (1). These symptoms often represent indicators for underlying stress, both from internal and external factors, and they are highly prevalent in the general population. World-wide, approximately 400 million people are affected by depressive disorders and 272 million people by anxiety disorders (2). Further, there has been an increasing awareness that anxiety and depression disorders, but also anxiety and depression symptoms, could be linked to a broad spectrum of physical illnesses (2), including cardiovascular disease (CVD) (3-8).

CVD includes diseases of the heart and circulation (9). The focus in this thesis is on the influence of anxiety and depression symptoms on the development of acute myocardial infarction (AMI) and heart failure (HF) and on subclinical left ventricular (LV) dysfunction. Around 17.3 million people died from CVDs in 2008, representing 30% of all deaths in the world (10). WHO estimates that this number will increase to 23.3 million by 2030 (10). As CVD usually develops over decades and the progression rate is influenced by a variety of cardiovascular risk factors (11), it is crucial to identify modifiable risk factors early in this process. Today, the American Heart Association promotes a lifelong focus on seven health metrics; four health behaviours (healthy diet pattern, appropriate energy intake, physical activity and non-smoking) and three health factors (optimal blood lipids. blood pressure and glucose levels) in order to improve cardiovascular health (12).

Psychosocial factors like anxiety and depression, representing modifiable risk factors, have in the last decade been identified to be independent and highly prevalent risk factors for CVD (3-5, 8, 11, 13, 14). However, the nature of these associations remains controversial. The aim of this thesis is to contribute to a better understanding of the association of depression and anxiety symptoms with future AMI (paper I), HF (paper II) and present subclinical LV dysfunction (study III), controlling for potential confounders, including comorbid physical illnesses in a large population-based cohort.

2. Background

2.1 Cardiovascular Disease (CVD)

The strong interest for epidemiological research on CVD and CVD risk factors awoke in the mid-20th century, probably because most regions in the world then experienced a sharp rise in CVD mortality (15). **Figure 1** displays the trend of CVD mortality in Scandinavia between 1950 and 2000 as depicted by Mirzaei et al. 2009 (15)[1].

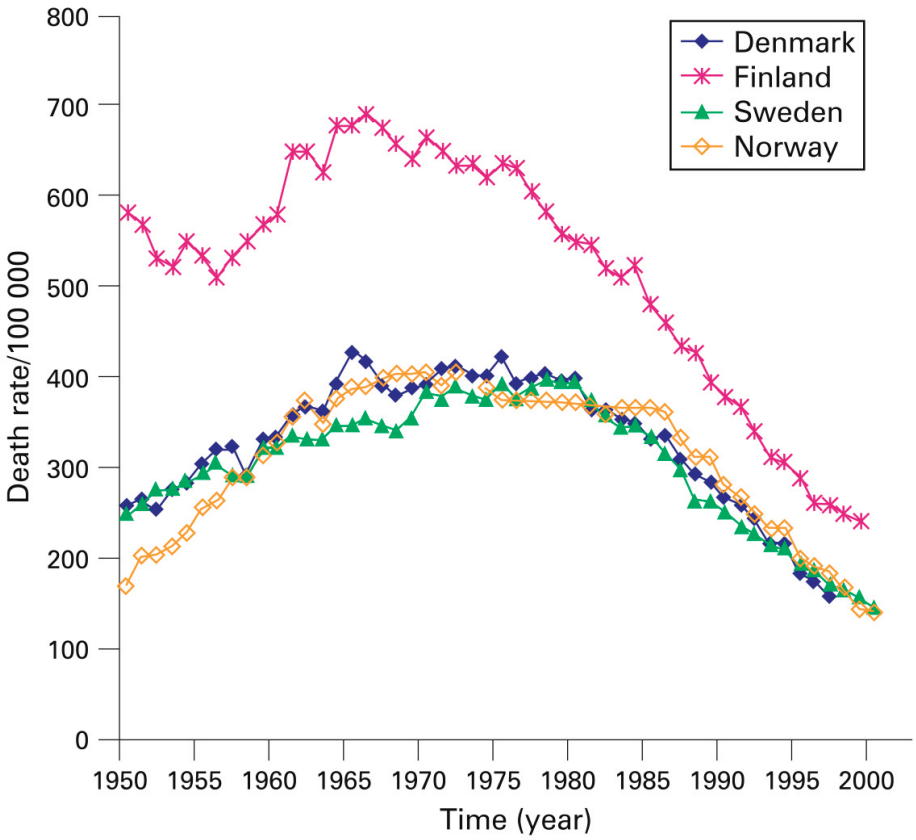

Figure 1: Age adjusted secular trend of CVD mortality in Scandinavia 1950-2000.

As Figure 1 shows, there was a peak in CVD mortality in Norway around 1970. The improved prognosis in established CVD after 1985 is mostly explained by the development of surgical and medical treatment (16). In most high-income countries universal access to and affordability of health services has lowered thresholds for

[1] Figure 1 is used with permission from Masoud Mirzaei.

diagnoses and treatment with preventive medications for hypertension and hyperlipidaemia (17). This has contributed to a lowered incidence of major CVD events and deaths compared to middle and low-income countries (17). Still, CVD is the leading cause of deaths in Norway; 5,975 men and 7,035 women died of CVD in 2012, accounting for 228/100,000 male inhabitants and 142/100,000 female inhabitants(18). In Europe, CVD is accounting for 42% of male deaths and 51% of female deaths (19). In Norway around 11–12% of patients with first acute myocardial infarction die within the first 30 days (20), which is a the lowest mortality rate in Europe (21, 22).

2.1.1 Acute Myocardial Infarction (AMI).

Development and diagnosis

Atherosclerosis, the main underlying condition that leads to AMI is caused by a chronic systematic inflammation in the large and medium size arteries and arterial walls (23, 24). The atherosclerotic process is strongly correlated to factors that can harm the endothelium such as adverse lipid profile, high blood pressure, and cigarette smoking. The pathological process of atherosclerosis develops over decades, beginning already in childhood. Initially, immune cells are attracted to support the reparation of injured sites in the endothelium (24). If the inflammatory response is not successful in removing the harmful agents, the endothelium becomes permeable for lymphocytes and monocytes that migrate into the deep layer of intima where they attract fatty Low-Density Lipoprotein (LDL) particles. The LDL particles are engulfed by the monocytes which forms large lipid-laden cells (foam cells) (25). The accumulation of these lipid-laden foam cells starts as fatty streak formation (23). This formation is the first pathological manifestation of the atherosclerotic process, and it is known to be reversible. As the atherosclerotic process is developing, more permanent manifestations includes development of thickened intima, development of plaque and plaque rupture, which initiate the development of a thrombus. This can cause occlusion to any or several of the coronary or any other arteries (23). The obstructed blood flow results in oxygen deprivation, which leads to myocardial ischemia and necrosis (AMI). The resulting AMI is diagnosed by a joint assessment of clinical history of chest pain, electrocardiogram and elevated biochemical markers (26). Atherosclerosis is also a prerequisite for acute coronary syndrome (ACS), including unstable angina, AMI and sudden cardiac death (27). In the vast majority of cases these sudden events are caused by plaque rupture, intracoronary thrombus formation and abrupt blood flow reduction (27).

Prevalence of and risk factors for AMI

AMI is amongst the most common reasons for hospitalization in Norway (28). In 2012, a total of 24,244 Norwegians were registered with a main diagnosis of AMI (28), which account for 0.6% of the 3,737,305 people in Norway aged ≥ 20 years at the time (29). The mean age for hospitalized patients with a main diagnosis of AMI in Norway is 68.1 (SD 13.1) years for men and 75.9 (SD 13.2) for women (21, 28).

Some of the most important risk factors for atherosclerosis and AMI are not modifiable, such as age, sex and genetic factors (14). Most other risk factors can be modified, including serum cholesterol, smoking habits, diabetes and hypertension (14). Also highly prevalent mental health conditions such as depression and anxiety symptoms are thought to represent such modifiable risk factors (14, 30).

A well-known example of modifying effects stems from World War 2, during which the Norwegian population had scarce recourses of fatty food and sugar. This led to weight loss in the population (31). Additionally, access to tobacco was limited. A steep decline of CVD deaths occurred in the 5 year war period, and the decline was observable in both genders across the adult age groups. Only a small part of this decline could be explained by changes in CVD nomenclature from an inter-Scandinavian to an International diagnosis of CVD deaths, applied by the Norwegian Statistical Central Bureau, in 1941 (31). In another example from Sweden, a 10.4% reduction of the populations' serum cholesterol levels (from 1986 to 2006) explained 39% of the reduced CVD mortality in the same time-period (32). However, despite a steady decline in AMI mortality since the 1980s (33), still around 12.5% of all deaths in Norway are due to CHD (34).

The development of effective treatment options has also improved the survival after AMI in high-income countries where preventive medication and revascularization are standard care (17). Still, there is an increased risk of stroke, sudden death and HF after AMI.

2.1.2 Heart Failure (HF).

Development and diagnosis of HF

In Europe AMI is the most common index event for HF development accounting for approximately 60% of HF events (35). Other known precursors for HF are hypertension, diabetes, cardiomyopathy, valvular disease and arrhythmias (36).

HF is defined as a syndrome characterized by elevated cardiac filling pressure and/or inadequate peripheral oxygen delivery, at rest or during stress, caused by cardiac

dysfunction (37, 38). In the development of HF, except HF initiated by AMI, the process of myocardial remodelling often starts long before the onset of HF symptoms (39). The progression of LV myocardial remodelling is a gradual and complex development that includes compensatory mechanisms driven forward by neuroendocrine activation and cytokine release (40). The remodelling process involves reorganization of myocytes, interstitial cells and vessels, leading to increased stiffness and/or impaired contractility of the myocardium (41). The HF diagnosis is often based on medical history and physical examination where symptoms including fatigue, breathlessness, ankle swelling, elevated jugular venous pressure, pulmonary crackles, displaced apex beat and objective evidence of cardiac dysfunction at rest plays an important role. The most frequently used diagnostic tests of HF include echocardiography, chest radiography and electrocardiography (ECG) (42). The newest guidelines also include measuring natriuretic peptide levels (43).

Prevalence and risk factors for HF

HF is a leading cause of morbidity, hospitalizations, disability and death across the world (42, 44). In Norway 30,230 (0.8% of the whole adult population) people were hospitalized with a main diagnosis of HF in 2012 (28). In Sweden, the estimated incidence of HF after adjusting for demographic variables was 3.7/1000 person years for women and 3.9/1000 person years for men (44). HF incidence and mortality has declined from 2006–2010 both in women and men. However, as HF is more prevalent in older age groups, the increasing longevity of the population keeps the HF prevalence stable (44). Elevated systolic blood pressure, impaired glucose tolerance, elevated blood lipids, and increased heart rate or decreased heart rate variability are strong risk factors for HF (45, 46). Other risk factors for HF include smoking, elevated levels of cholesterol, and alcohol abuse.

2.1.3 Subclinical left ventricular (LV) dysfunction.

Definition and prevalence

Normal data for the left ventricular (LV) systolic and diastolic function have recently been established in several population based studies using novel echocardiographic techniques, such as tissue Doppler Tracking (TD) and tracking of grey-scale speckles (Speckle-Tracking (ST)) (47-51). Detailed information about the normal LV systolic reference values by age-groups and sex and ethnicity obtained by these new techniques are recently published by Dalen et al (2010) and the EchoNoRMAL collaborators (2014) (47, 50).The LV function in the normal population follows a normal distribution

curve. This new knowledge may serve as a tool to identify early asymptomatic LV impairment (subclinical dysfunction) (52), even in sub-populations with normal conventional echocardiography findings (53). Early interventions in people with subclinical LV dysfunction may help prevent progression to overt HF (38). Asymptomatic LV systolic dysfunction was at least twice as common as symptomatic HF when TD was used to identify LV dysfunction (54). This underlines the importance of preventive strategies at an early stage of LV dysfunction. Among the most sensitive TD indices in order to detect subclinical LV dysfunction is peak mitral annular early diastolic velocities (e´) and LV end-systolic global strain (global strain), which have been shown to be related to different risk factors and diseases even though other indices of LV systolic and diastolic function have been less influenced (55-57).

Risk factors for subclinical LV dysfunction.

Treatment of asymptomatic LV dysfunction is thought to delay or prevent the progression to symptomatic HF. However little is known about potentially modifiable precursors for LV dysfunction. Traditional risk factors for CVD, such as hypertension, elevated cholesterol levels and high or low body mass index (BMI) are associated with subclinical LV dysfunction (56), i.e. the risk factors are negatively influencing cardiac function years before the presentation of clinical symptoms of HF. Further, low educational level was associated with subclinical cardiac dysfunction and future hospitalization for HF in a Danish study (58). One previous study suggested that depressive symptoms are associated with subclinical LV dysfunction (13). However, the sample included people with hypertension and diabetes mellitus which might suggest confounding; the physical disease might have caused both the depression and the LV dysfunction.

2.2 Anxiety and depression

Anxiety and depression are often expressed through and subtyped into psychological, somatic, functional and social symptoms (59, 60). A clinical diagnostic interview, which assesses a great variety of anxiety and depression symptoms, is the gold standard and is required to assess the presence of a clinical diagnosis of depressive or anxiety disorders (61). In large epidemiological studies however, the use of self-report instruments is more cost-effective and therefore the most widely used method (62). This was also the case for the current study. Thus, the main emphasis will be on symptoms of anxiety and depression and not diagnosis. However, in order to understand the difference, a brief overview of some of these diagnoses will follow.

2.2.1 Anxiety symptoms and disorders

Fear is a normal anxious state in the face of real danger, whilst the terms anxiety disorder or anxiety symptoms are often used to describe a more exaggerated, long-standing emotional and dysfunctional state (63). The 7-items HADS-Anxiety scale (HADS-A) used in this thesis, includes symptom report from the last week (64). Six of the HADS-A items mainly capture core anxiety symptoms of restlessness and worry, which are also necessary in order to diagnose a person with generalized anxiety disorder (GAD) (65, 66). In order to meet the criteria for GAD, however, these symptoms and additional somatic complaints such as fatigue, irritability, sleep disturbance, muscle tension and difficulty concentrating, must have persisted for most days over a longer period of time; one month according to the Diagnostic and Statistical Manual of Mental Disorders (DSM) III and six months from DSM III-R and following DSM versions (66, 67). At least one somatic symptom due to autonomic hyperarousal, such as palpitations sweating, trembling and dry mouth, is also essential in order to meet the diagnostic criteria of GAD (66). One HADS-A item assess the frequency of sudden panic during the last week on a Likert scale between "very often" to "not at all". Such sudden panic attacks are seen in panic disorder and specific phobias when exposed to the feared stimulus, e.g. spiders (68). However, the diagnosis of panic disorder involves repeated attacks of intense fear and worry, accompanied by physical symptoms due to sympathetic nervous system activation, such as increased heart rate, sweating, trembling or shaking, dyspnoea, hyperventilation, nausea or abdominal distress or chest pain (67, 68). Other common anxiety disorders are obsessive compulsive disorder, post traumatic stress disorders and social phobia (67). The severity of anxiety and depression disorders depends on symptom levels, persistence and functional impairment. Decreased functioning in social contexts, work and/or daily life activities is especially seen in those with moderate and severe symptom severity (67, 69). Of note, people with symptoms of anxiety as measured by HADS-A has been shown to be long lasting risk factors for onset, duration and recurrent episodes of sickness absence from work (70). Nevertheless, many people with anxiety disorders are able to maintain a high function both socially and in their jobs. Anxiety disorders in general and GAD in particular, are known to increase risk for subsequent depressive episodes (71, 72). In community samples one in three GAD patients also meet the criteria for depression and often patients with GAD present themselves to the doctor as depressed (73).

2.2.2. Depression symptoms and disorders

Depression symptoms are considered a normal reaction or adjustment to situations of great internal and/or external stress, but might represent depressive disorders if

symptoms persist each day for at least two weeks (74-76). Additionally, in order to meet the criteria for major depressive episode/disorder five out of the following nine symptoms must be experienced during the same two weeks; change in weight/ appetite, insomnia or hypersomnia, psychomotor retardation or agitation, loss of energy or fatigue, worthlessness or guilt, impaired concentration or indecisiveness; thoughts of death or suicidal ideation or attempts (77). Depressive disorders are rated as the fourth leading cause of disease burden accounting for 12% of years lived with disability world wide (78). The HADS-Depression questionnaire, which is used in this thesis, mainly mirrors core psychological depression symptoms during the last week; depressed mood or reduced pleasure response affect (anhedonia), as well as psychomotor retardation (64). People with depression symptoms, not only disorders, often report great functional impairment, e.g. high reports on the Hopkins Symptom Check list (HSC) showed high correlation with reduced working abilities and sleeping problems (69), and increases the odds of medical benefit receipt (79). Prospective studies using the HADS-D questionnaire has also found increased risk for disability pension (80).

2.2.3 Mixed anxiety and depression symptoms (MSAD)

Although anxiety and depression are characterized by somewhat different clinical features and symptoms, there is also great symptom overlap between these conditions (81, 82). Depression and anxiety often share functional symptoms, such as sleep disturbance, lack of energy and restlessness (60, 83, 84). These functional symptoms are prevalent also in CVD (85, 86). Further, depression and anxiety share social symptoms such as avoidance and social withdrawal or passiveness (60, 83). In accordance with this literature the HADS-A and HADS-D scales where highly inter-correlated in HUNT2, with a correlation coefficient 0.38 for the categorical approach and 0.51 when treating the scales as continuous variables (87). The overlap between anxiety and depression symptoms often increases with symptom severity (88-90), and mixed symptoms of anxiety and depression (MSAD) are often associated with poorer treatment outcomes and treatment response to anti-depressive medication (91), higher relapse incidence (92) and lower recovery rate compared to anxiety or depression alone (8, 93). However, the HADS depression scale is in some studies found to be more strongly associated with all-cause mortality than the combined effect of anxiety and depression symptoms (MSAD as measured by HADS-T) (94, 95).

2.2.4 Anxiety and depression: Prevalence and risk factors

Mental disorders are common; studies indicate a lifetime prevalence of 25–50% and a 12- month prevalence of 10–30% (96-98) in the western world, and anxiety and depressive disorders are the most common of the mental disorders.. The 12-month prevalence for any mood disorder was estimated to be 4.2% in the European Study of the Epidemiology of Mental Disorders (ESEMeD) (96) and 10.0% in the National Co-morbidity Study (NCS) in the US. For any anxiety disorder the 12-month prevalence was found to be 6.4% in the ESEMeD (96) and 24.9% in the NCS (99). Both the NCS and the ESEMeD utilized the Composite International Diagnostic Interview (CIDI). However, the ESEMeD study used a new version CIDI 10, which is thought to yield less false positive assessments (96). Most studies find a higher prevalence of mental illness in urban compared to rural areas, bearing in mind that comparisons often are made across different studies using different instruments and methods (100). However, the estimated prevalence of major lifetime depression in Norway were quite similar for men living rurally 10.1%) compared to an urban residence (9.8%) but quite different when you compared between women; 19.6% prevalence in rural areas vs. 13.8% in urban areas (69). This estimation was calculated based on self-report on the 25-item Hopkins Symptom Check list (69). Thus, the prevalence of both anxiety and depression seems to differ considerably between different instruments and methods, study designs, study populations and countries.

Comorbidity between major depression and any anxiety disorders was 51% in the NCS (72). In the international WHO study on psychological disorders in primary health care 39% of the depressed cases had anxiety disorders and 44% of those with anxiety disorders had comorbid depression (101). Anxiety disorders often tend to occur earlier in life than depression and are a powerful predictor for depression and mixed symptoms of anxiety and depression (MSAD) later in life (102). Such clustering of psychosocial risk factor may act synergistically on the risk for subsequent of physical disease (82). MSAD is thus often associated with more severe illness, worse outcome and increased mortality compared to single conditions (103). In contrast, some studies using the HADS have found that especially HADS-Depression is a more powerful predictor of all-cause mortality than MSAD as measured by the sum of HADS-D and HADS-A (94, 95).

Further, depression is known to have an episodic nature (86). Recurrent major depressive episodes are predicted by younger age of onset, family history of depression, previous episodes (especially severity and duration of depression symptoms), residual symptoms, smoking, comorbid anxiety disorders and ongoing stress and difficulties in life, including substance abuse (104, 105). Limited evidence suggests that recurrent

depression has considerably stronger association with AMI than single depressive episodes (8, 106, 107).

Risk factors for anxiety and depression symptoms are many, and below we highlight a few risk factors which also represent risk factors for CVD, making confounding by those factors possible.

Sociodemograpic risk factors for anxiety and depression symptoms

Age: Anxiety disorders often manifest earlier in life than mood disorders, often already in adolescence, with median age of onset at 14 years (97). Mood disorders, depression being the most common, have a median age of onset at 30 years (97). Kessler et al (2012) found that age is associated with 37% of 12-month prevalence of psychiatric disorders (99).

Sex: In general, anxiety and depression disorders are more prevalent in women than men (98, 100, 108). One study speculated if the hormonal difference across genders could explain the higher prevalence (109) as the increased oestrogen-levels in puberty may activate a genetic vulnerability for mental health problems in females (110). However, the gender difference may also arise due to adaptive behavioural differences. Girls often take on different social roles, and have different patterns regarding cognition and affection towards others. But responsibility for others and caretaking is also thought to result in fear of rejection and self- criticism, key features of anxiety and depressive disorders (110). Sex differences in childhood exposures that predispose for anxiety and depression is also seen, with more females being exposed to abuse and neglect (110).

Marital and Socioeconomic Status: Singlehood, divorce, separation or widowing is associated with increased anxiety and depression prevalence (111). It is however, uncertain if people that are married or cohabitating have lower prevalence of psychiatric morbidity than the never married (111). A social class gradient is also observed with higher rates of mental health problems in people with lower education, lower income, and unemployment (111).

Traditional cardiovascular risk factors and correlation with anxiety and depression symptoms

The nature of the observed prospective association between anxiety and depression with CVD, i.e. whether anxiety and depression is a causative factor or only correlate, is largely unknown. Below is an attempt to present the conflicting conclusions for the main cardiovascular risk factors:

BMI. Cross-sectional data shows a positive association of depression and anxiety symptoms with BMI (112). A large US study (n= 177,047) found an association between mental health problems and BMI even when adjusting for demographics, psychosocial and lifestyle (113). In a large prospective follow-up study those with baseline anxiety and depression symptoms had larger weight change and increased risk of incident obesity in the follow-up period than those without anxiety and depression symptoms (114). The relationship is thought to be bidirectional; obesity may cause depression through inflammatory activity (115), social stigma or decreased activity (113), while anxiety and depression may also cause obesity through inactivity, binge eating or medication (112). Finally, common causes can lead to both increased BMI and depression, such as childhood abuse or bullying (113).

Hypertension: One cross-sectional study found that high systolic blood pressure levels increased the odds for a high self-report scoring on the panic item in HADS (116). The CARDIA study pointed out that depression severity increased with increasing blood pressure levels (117), yet the trend for anxiety severity did not reach statistical significance (p 0.09). One prospective follow-up study found that high symptom levels of anxiety and depression predicted lower blood pressure at follow-up (118). Conversely, another prospective follow-up from 19 countries found that both mood and anxiety disorders were risk factors in a dose-response manner for subsequent hypertension (119). However, the authors pointed out that important confounders for the observed risk could be alcohol, over-eating or a poor diet rich in salt and animal fat. Childhood abuse could also be common cause for both the mental disorders and hypertension (119).

Alcohol: Alcohol use may increase the risk of major depressive disorder and recent alcohol use and major depression is also strongly associated (120). Alcohol is often used as self-medication in persons with psychiatric disorders as it is associated with a temporarily alleviation of the anxiety and depression symptoms (121) and initially, alcohol enables sleep (122).

Smoking: Depression and anxiety disorders are associated with higher rates of cigarette smoking than the general population (115, 123, 124). It seems that smoking often is used to diminish negative effect associated with depression and anxiety symptoms (124). Nicotine initially increases dopamine levels, which engage feelings of reward. However, long term nicotine use decreases the dopamine levels (125). It is still unclear if depressive behaviour increases smoking or if cigarette smoking increases depression symptoms (115) even though two genetic study found no signs of a causal role of smoking in the development of depression and anxiety (126, 127).

Inactivity: People with anxiety and/or depression symptoms have greater odds of not meeting the recommended levels of exercise (128). However, the relationships

are bidirectional and regular activity also has the potential to decrease the risk for anxiety and depression symptoms (128, 129). In regards to underpinning mechanisms, physical inactivity may also explain some of the increased risk that is observed between poor diet and depression (130).

All the above described cardiovascular risk factors associated with depression and anxiety symptoms are associated with inflammatory activity and release of proinflammatory cytokines (115), which in turn are important drivers in the atherosclerotic process . Both anxiety and depression symptoms further represent a disorder of hyperarousal accompanied by a chronic activation of the stress response with increased activity in the hypothalamic-pituitary-adrenal axis (HPA) and the sympathetic nervous system (131). This stress reaction may lead to raised concentration of circulating catecholamine in the blood, leading to physiological changes such as increased heart rate, decreased heart rate variability, increased blood pressure, coronary vasoconstriction and increased platelet activity (131, 132).

Comorbid physical illness in anxiety and depression

Few studies have assessed the impact of anxiety disorders on function and outcome in physical illness (133). Several studies have shown that there is increased prevalence of major depression in people with chronic physical diseases, such as asthma, arthritis, diabetes and cancer (2, 78, 85, 86, 134, 135). Anxiety disorders are shown to be more prevalent in irritable bowel syndrome, asthma, cancer and CVD (133). Depressive or anxiety disorders that are comorbid with physical illness is suggested to cause greater decrements to health than each condition alone, i.e. there are signs of an interactive effect (78, 133). Of note, when inflammatory cytokines are released due to somatic disease, they are also shown able to induce depressive-like behaviour and symptoms, such as anhedonia, fatigue, anorexia and reduced social interaction (136, 137). Depressive symptoms especially are highly correlated with the overall disease burden from physical illness, and several common chronic disorders are also risk factors for AMI. As a result these are potential confounders.

2.3 Anxiety and depression symptoms in AMI, HF and subclinical LV dysfunction

Anxiety and depression disorders are highly prevalent conditions in people with established CVD. Up to 20–40% of patients with CHD (132, 138, 139) and up to 70% of hospitalized HF patients suffer from comorbid depression (140-142). Evidence is strong for increased morbidity and mortality when anxiety and/or depression disorders coexist with established CVD (30, 86, 141, 143-147). However, the causal relation between depression and anxiety symptoms with excess risk for mortality and morbidity

in established CVD is not agreed on (148). Mainly three causal pathways between depression symptoms and established CVD are mentioned; 1) depression symptoms may act like a marker of CVD disease severity; 2) shared risk factors such as smoking and inactivity explains both the CVD and the anxiety and depression symptoms; 3) a bidirectional relationship where the depression and CVD exerts direct effects on each other (148).

Meta analyses have found an increased CVD risk associated with anxiety and depression symptoms in initially healthy persons (3, 4). More specifically, results from prospective studies suggest that anxiety and depression disorders and symptoms are risk factors for future AMI (5, 149-154) and HF (155-157). One cross-sectional study has found association between depression symptoms and subclinical LV dysfunction (13). Previous studies cannot conclude to what extent the well-known cardiovascular risk factors explain the observed associations between mental health and CVD (3, 150). One meta-analysis of 54 observational studies showed a paucity of adjustments for even the well-known cardiovascular risk factors such as smoking and physical activity (3). This was found in most studies of the risk between depressive disorders or symptoms and future AMI (3).

Comorbid physical disorders are among the most overlooked confounders between mental health and CVD (85, 86). Especially depressive disorders and symptoms are highly correlated with the overall disease burden (85), and several common chronic disorders represent individual risk factors for AMI, HF (38, 158) and development of subclinical LV dysfunction (56). In the only previous study we found studying the association between depression symptoms and LV dysfunction, the sample included people with hypertension and diabetes, diseases known to be associated with depression (134). Thus the observed association between LV dysfunction and depression may be due to confounding from medical comorbidity.

Moreover, some studies suggest that recurrent depressive disorders have considerable stronger association with AMI than single depressive episodes (8, 106), yet the majority of studies assessed depression at one time-point only (159). To the best of our knowledge, no studies exist for recurrent depression symptoms and risk of HF and subclinical LV dysfunction. Still, relative little data are available on the prospective association between anxiety and risk of CVD, and similar methodological issues as those presented for depression apply to these studies as well (160).

The nature of the causal direction in these associations still remains controversial. One of the most challenging issues on the prospective association of anxiety and depression with CVD is reverse causality. One example is atherosclerosis, one of the main underlying pathophysiological mechanisms of AMI, which is known to develop over decades before presentation of the first clinical symptoms (159, 161).

However, almost all studies of depression and CVD risk included mainly middle aged or older adults, often with a short follow-up time (3, 155, 156, 162, 163). Thus, individuals free from clinical heart disease in the aforementioned prospective studies may not be free from atherosclerosis, which may facilitate depressive symptoms even before generating ischemia (161, 164). In HF, except HF initiated by AMI, the process of myocardial remodelling also starts long before the onset of HF symptoms (165). Some of the processes that contribute to the progression of HF, such as like pro-inflammatory cytokines (140), are known to give depression as well (115).

2.4 Aims

The main aims were to investigate the association between single and repeated measures of anxiety and depression and mixed anxiety and depression symptoms (MSAD) with future AMI (paper I), future HF (paper II) and present subclinical LV dysfunction (study III), controlling for potential confounders, including comorbid physical illnesses in a large population-based cohort.

3.0 Methods

3.1 Study setting, sampling and design

This thesis is based on data from the Nord-Trøndelag Health Study, http://www.ntnu.edu/hunt (166-168). Paper I and II additionally utilize endpoints for AMI and HF from the Hospital Registries in Nord-Trøndelag County and the National Cause of Death Registry.

Nord-Trøndelag County is located in the central part of Norway (**Figure 2**) and has 24 administrative municipalities (167). Around 127,000 people live in the county and net migration was about 0.3% per year in the period 1996-2000. In most respects, such as age distribution, morbidity and mortality, Nord-Trøndelag County is a relatively representative sample of the Norwegian population. There are two hospitals in the county, located in Levanger and Namsos. Both hospitals are managed by Nord-Trøndelag Hospital Trust (HNT), and these two hospitals serve the entire population in the county.

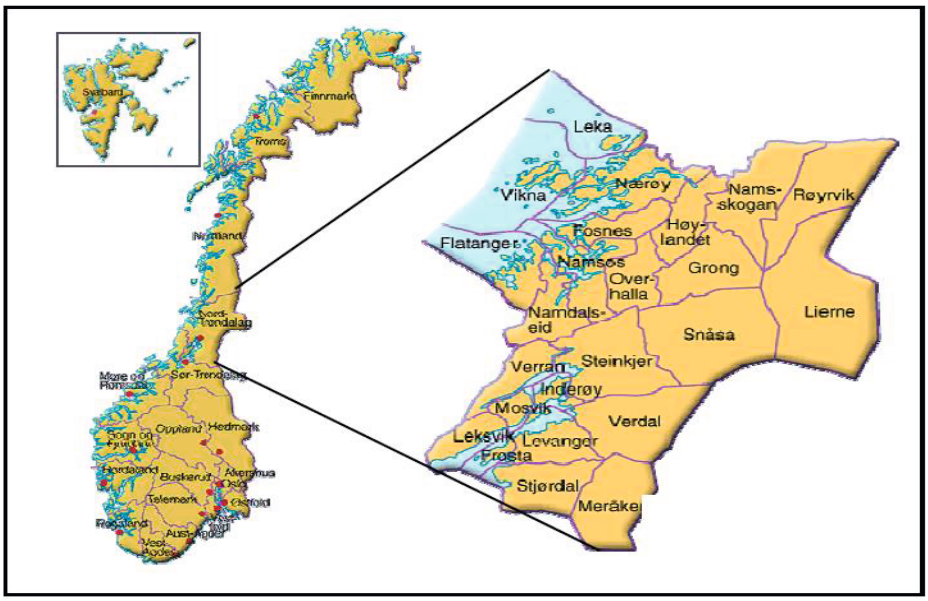

Figure 2: Map of Norway and Nord-Trøndelag County

3.2 The HUNT Study

HUNT is a population based general health survey and has to date been carried out in three waves. HUNT1 was conducted in 1984–86 (166), and new waves were carried out in 1995–97 and 2006–2008 (167, 168). In all three surveys the entire adult population (aged ≥ 20 years) was invited to participate. The participation rates have generally been decreasing, but compared to most epidemiologic studies the participation rate is overall high. Additionally, many of the subjects have participated in more than one of the waves. **Table 1** displays the eligible population and participation in HUNT1–3.

Health Survey	HUNT1	HUNT2	HUNT3
Year	1984–86	1995–97	2006–2008
Invited	86,404	94,187	93,860
Participated n, (%)	77,212 (89.4%)	65,212 (69.2%)	50,807 (54.1%)
Participated in previous HUNT , n	N/A	47,316 (HUNT1)	37,071 (HUNT2)

Table 1: Invitation and participation in HUNT1-3

All HUNT waves were approved by the National Directorate of Health and the Norwegian Data Inspectorate. All participants gave written consent before the baseline examination. Additional approval was given from the regional ethics committee and the HUNT data access committee for all three studies presented in this thesis.

All three studies included standardized clinical examinations performed by trained nurses, self-report on health related questionnaires http://www.ntnu.edu/hunt/data/que. In addition HUNT2 and HUNT3 collected blood samples from all participants (167, 168). The self-report questionnaires were extensive, and were distributed in a two-step procedure. Questionnaire 1 (Q1) was delivered by post together with a personal invitation to participate. The participants would fill in Q1 at home and bring it to the clinical examination. At the examination the attendees received Questionnaire 2 (Q2), which was taken home, filled in and returned in a prepaid envelope. The respondent rate was higher on Q1 than Q2 in all HUNT waves (169).

3.3 Study variables

Information on the clinical end-points (AMI in paper I and HF in paper II) were collected from the two hospitals in the county and from the National Cause of Death

registry. All other data came from the HUNT study. **Table 2** provides an overview of the sources of data used in the three studies.

Study	Baseline (clinical examination, laboratory data and self-report)	Anxiety and depression (self-report) prior to baseline	Outcome
I–II	HUNT2 (1995–97)	HUNT1 (1984–86)	Hospital and Cause of Death Registry (1995–2009)
III	HUNT3 (2006–2008)	HUNT2 (1995–97)	Echocardiography recordings (HUNT3)

Table 2: Overview of sources of data extraction in the different studies

3.3.1 Questionnaires

Anxiety and depression symptoms; The HADS Scale (all studies)

The Norwegian version of the HADS was available from Q1 in HUNT2 and from Q2 in HUNT3. The HADS instrument was originally developed by Zigmund and Snaith in 1983 to separate depression and anxiety symptoms from the symptoms caused by somatic illness (64). Functional and somatic symptoms of depression and anxiety that could be related to somatic diseases, such as fatigue, insomnia, dizziness were therefore not included in the scale. The HADS consists of two subscales, which assesses symptoms of anxiety (HADS-A) and depression (HADS-D) during the previous week. The 7 anxiety questions mirror symptoms of worry and restlessness, while the 7 depression items mirror core psychological depression symptoms of reduced pleasure response (anhedonia), depressed mood and psychomotor retardation. All questions have a 4-point Likert scale response option from 0 (no symptom) to 3 points (highest level). Both subscales thus range from 0 (no symptoms) to 21 points (highest symptom level). The HADS has shown good psychometric properties across various patient samples and settings (170).

Valid HADS response was defined as completed answer on 5 or more items on each subscale. Missing responses amongst those who filled in five or six items were replaced based on the sum of completed items multiplied by 7/5 or 6/5, respectively.

Operationalization of the HADS-D and HADS-A scores

In paper I and II we made an a priory decision about categorizing the participants according to their HADS-D and HADS-A scores, respectively, as having no symptoms of depression or anxiety (score <8), mild to moderate symptoms (score 8–10) and moderate to severe symptoms (score ≥11) (64). In paper II, the HADS-D and HADS-A variables were analysed as continuous variables, in addition to the categorical approach. In study III, the number of people whom scored above 8 and 11 on HADS-D and HADS-A were very few. Thus the HADS was treated solely as a continuous variable in the analysis.

In paper I and II, a combined HADS total score (HADS-T) for assessing the impact of mixed symptoms of anxiety and depression (MSAD) was calculated by the sum of valid HADS-A and HADS-D scores. In the literature, a wide range of different HADS-T cut-offs have been used (170). We categorized the participants into three groups: no MSAD (score <15), mild to moderate MSAD (score between 15 and 18) and severe MSAD (score ≥19) The latter cut-off was associated with psychiatric help-seeking, self-report of lifetime major depressive disorder, daily impairment because of lifetime mental problems and with having chronic somatic disease in a 4 year follow-up study arising from the HUNT population (171).

Repeated anxiety and depression symptoms

Many of the HUNT participants had participated in more than one wave of the study. This enabled us to assess whether two incidents of elevated anxiety and depression symptom scores, ten years apart, increased the risk for AMI, HF and subclinical LV dysfunction, compared to high levels in one wave only or normal levels at both waves.

Anxiety and depression symptoms prior to HUNT 2, (paper I and II).

HUNT1 (Q1) used a crude 4-item Anxiety and Depression Index (ADI-4), which is not suitable to distinguish between anxiety and depression. ADI-4 showed a high correlation (0.83) with the HADS-T score in HUNT2 and is an acceptable indicator for MSAD (sensitivity 0.51, specificity 0.93) (172) in our studies.

Two ADI questions have a 4-point Likert Scale; calmness ranging from almost all the time (1) to never (4) and nervousness ranging from never (1) to almost all the time (4). The last two ADI questions about mood and vitality have a 7-point Likert scale ranging from very happy/ strong and fit (1) to very downhearted/tired and worn out (7).

A variable to indicate the combined burden of MSAD in HUNT1 and HUNT2 was created in three categories of never, one or two episodes. MSAD in HUNT2 was defined as cut-off ≥19 on the HADS-T scale. Episode of MSAD in HUNT1 was defined by scoring in the upper quartile on ADI, i.e. a cut-off at ≥14 points. "Never MSAD" was defined as a scoring <14 on ADI in HUNT1 and <19 on HADS in HUNT2. "MSAD once" was defined as scoring above cut-off in one of the studies, while "MSAD twice" included those scoring above cut-off in both studies.

*Anxiety and depression symptoms prior to HUNT3 (study III)***.**

We treated the HADS scales from HUNT2 and HUNT3 as continuous variables and added each participant's HADS-D and HADS-A scores in order to assess risk with additive symptom levels from two waves.

Demographic and sosioeconomical variables

Education was categorized as low (≤9 years), medium (10 to 12 years) or high (>12 years) level (all studies).

Cohabitation status was dichotomized as living with a partner or alone in paper I and II. In study III cohabitation status was categorised into never married, married or living with partner, or separated/divorced/widowed.

Common chronic disorders (paper I and II). Participants self-reported if they had (or had ever had) cancer, asthma, diabetes mellitus, other endocrine disorders (hypothyreosis, hyperthyreosis, goitre and thyroiditis), musculoskeletal disorders (osteoporosis, fibromyalgia, and arthrosis/arthritis), autoimmune disease (Bechterew disease, rheumatoid arthritis), epilepsy or any other chronic disorders.

Life style factors

Smoking habits were self-reported and categorized as current, previous or never smoking (all studies).

Physical activity was defined as light if it didn't involve sweating or feeling of breathlessness, while hard physical activity was defined by sweating or breathlessness. In paper I and II the participants were categorized as inactive (less than 1 hour of hard activity and less than 3 hours of light physical activity per week), moderately active (1–3 hours of hard activity or >3 hours of light activity per week), and as physically active (>3 hours of hard physical activity per week). In study III, we used a validated index for leisure-time physical activity, calculated as a product of exercise frequency, exercise intensity and training session duration (173).

Alcohol (paper II) was categorized as abstainers, very light drinkers (0–1 drinks per day), light to moderate drinkers (1–2 drinks per day) or moderate to heavy drinkers (>2 drinks per day).

3.3.2 Clinical examination

Trained nurses performed the clinical examinations at baseline after a standardized protocol in all three HUNT waves (166-168).

Systolic and diastolic blood pressures (all studies) were measured three times after the participant had been seated for at least two minutes with the cuff on, with cuff size adjusted for arm circumference. All blood pressure measurements were performed with the Dinamap 845XT (Criticon) based on oscillometry. The average of the second and third measurement was used in the analyses.

Heart rate was measured using the above described Dinamap (paper I and II). The first heart rate recording was in average two beats per minute (bpm) lower than the second and third measurement and was thus used in order to mirror resting heart rate. In study III, we used the average heart rate during echocardiography as recorded by the high-end scanner (Vivid 7, version BT06; GE Vingmed Ultrasound AS, Horten, Norway).

Body mass index (BMI) (all studies) was computed as weight (in kg) divided by the square of the height (in meters). Height was measured without shoes to the nearest 1.0 cm and weight with light clothing to the nearest 0.5 kg.

3.3.3 Laboratory measurements

A non-fasting whole blood sample was drawn from each participant, and the time between last meal and the venepuncture was recorded. Serum was separated by centrifugation at the screening site and immediately placed in a refrigerator (4°C). The samples were sent (same day or following Monday for samples drawn on Friday) for analyses at the central laboratory at Levanger Hospital, Norway, where they used a Hitachi 911 Autoanalyzer, applying reagents from Boehringer Mannheim, Germany.

Serum total cholesterol (paper I and II) was measured by an enzymatic colorimetric cholesterol esterase method. The day-to-day coefficient of variation for total cholesterol was 1.3% to 1.9% (167).

Serum creatinine (paper II) was measured by the Jaffé method, and the day-to-day variation was on average 3.5% (167).

3.3.4 Definition and ascertainment of CVD (HUNT2, papers I and II).

Among the people that participated in HUNT2 some had experienced CVD events prior to baseline, and these were excluded from our studies. In paper I we excluded people with previous history of CVD; that is previous AMI, self-reported angina or stroke (n= 4,734). In paper II we excluded people with previous HF (n=126). After participating at the baseline examination in HUNT2, the participants were followed up for a first AMI (paper I) and incident HF (paper II) until December 31, 2008, by linkage with medical records in the two hospitals in Nord-Trøndelag County or by death certificates from the National Cause of Death Registry.

AMI was diagnosed according to the European Society American College Cardiology Consensus Guidelines (26, 174). Criteria for AMI included: (1) Certain symptoms according to case history information, (2) specified changes in the blood levels of cardiac enzymes and (3) specified ECG changes (26, 174, 175). The hospital AMI diagnosis is found to be approximately 100% correct according to the guidelines (176). Deaths from AMI were defined as ICD codes no 410 in the 9th revision and codes I21 and I22 in the 10th revision.

Hospital criteria for HF was defined and diagnosed according to the current European Society of Cardiology Guidelines (177). Criteria for HF included symptoms and signs of HF and additionally echocardiography, radiological examination and biochemical measurements. The overall quality of the hospitals discharge diagnosis of HF is generally high in Nordic countries (178, 179). In order to increase specificity we only extracted primary hospital diagnoses as recommended (178). Deaths from HF were defined as ICD-9 code 428 and ICD-10 codes I50.0, I50.1 and I50.9.

3.3.5 The echocardiography study (HUNT3, study III).

Within the HUNT3-study, the Echocardiographic study was conducted in a random selection of 1,296 subjects free from known CVD, diabetes or hypertension. The random selection process took place when the participants attended a baseline clinical examination at the study centres and the echocardiographic examinations were performed at this visit. Thirty individuals were excluded from the normal reference population due to echocardiographic findings that could interfere with LV function, and thus, 1,266 healthy subjects were included in the analyses.

Acquisition, analyses and reproducibility of the echocardiography study.

All echocardiography examinations were conducted by an experienced cardiologist (HD) and the participants were examined in the left lateral decubitus position with a high-end Vivid 7 scanner (version BT06; GE Vingmed Ultrasound AS, Horten, Norway) using a phased-array transducer (M3S and M4S). All the presented echocardiographic measurements were available in ≥ 96% of the random selection (180). All echocardiographic data were stored digitally and analysed subsequently (50, 56, 180, 181).

Left ventricular (LV) function was assessed by several well-established echocardiographic indices of systolic and diastolic longitudinal function. The LV end-systolic global strain (global strain) refers to percentage longitudinal shortening of LV myocardium during systole, and LV peak global strain rate (global strain rate) reflects the maximal speed of global strain. Both indices are presented as the average of segmental values when assessed in a 16 segment model of the LV (180). We used customized software (GcMat; GE Vingmed Ultrasound, Norway) with a combination of Tissue Doppler (TD) for tracking along the ultrasound beam and Speckle Tracking (ST, trace grey-scale speckles) for tracking perpendicular to the ultrasound beam (56).

Peak mitral annular systolic velocity (S') and peak mitral annular early diastolic velocities (e') were measured in the base of the LV wall by pulsed waved TD and the average of the septal, lateral, anterior, and inferior locations was used in the analyses. Correspondingly, mitral annular plane systolic excursion (MAPSE) was measured as the average of the total systolic cumulative excursion of the same locations Ejection fraction (EF) was analysed by calculation of end-diastolic and end-systolic LV volumes from tracings in the four and two chamber view (56).

The reproducibility of the echocardiographic measures has been described elsewhere by Thorstensen et al (2010) (181). Briefly the inter-observer mean errors were 4–8% and intra-observer mean errors were 2–5% for indices of LV function (56).

Figure 3 [2]below depicts; **A)** 4-chamber view where regions of interest are localized at the segmental borders of the left ventricle in the customized software (GcMat; GE Ultrasound) with a combination of tissue Doppler for tracking along the ultrasound beam (orange boxes) and speckle tracking for tracking perpendicular to the ultrasound beam (white boxes). **B)** End-systolic strain refers to average of segmental strain in a 16 segment model of the left ventricle. Strain is calculated as the percentage systolic longitudinal shortening of myocardial segments (difference between L0 and L) in a segmental model of the LV myocardium during systole. **C)** Strain curves for the six segments shown in A. **D)** Zoom in of basal and mid-ventricular segments of the septal wall with end-systolic strain values. Blue curves are segmental values, green curves illustrate the average value.

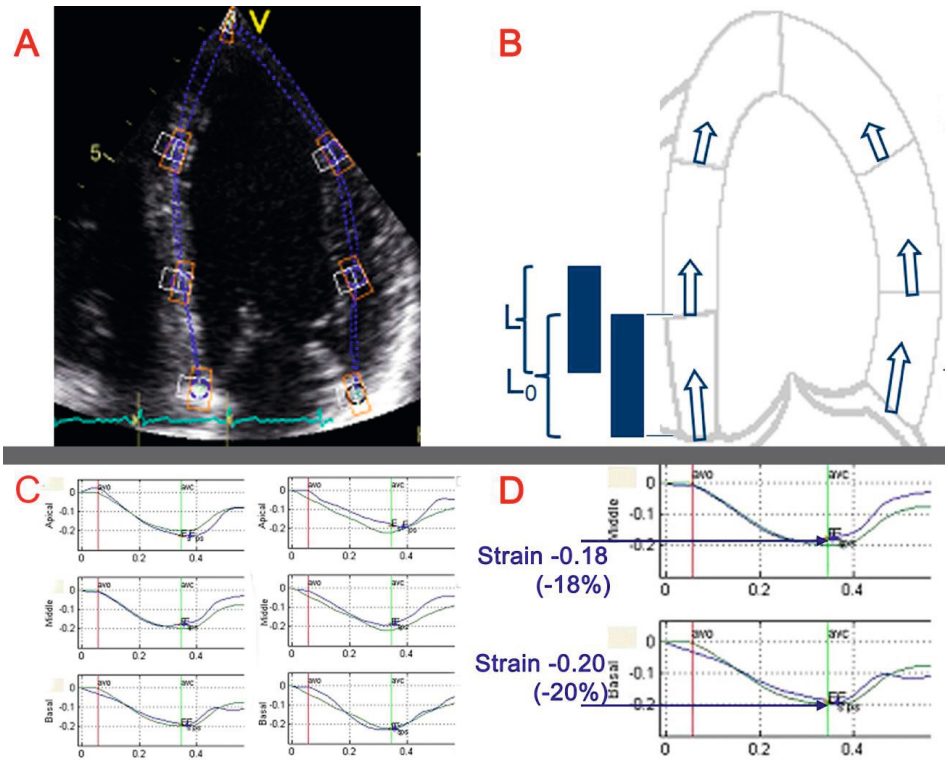

Figure 3: A: 4 chamber view of regions of interest. B: End systolic strain. C: Strain curves. D: Strain curves.

[2] Fgure 3 is made by Håvard Dalen, January 2015.

[3]**Figure 4** illustrates; **A)** The left ventricle as shown in a 4-chamber view. Red lines perpendicular to the ultrasound beam (measured at *) illustrate the sampled volume for Tissue Doppler assessed myocardial velocities located at the basal part of the septal wall. **B)** Tissue Doppler velocity curve assessed from the same region as illustrated above. ECG is shown as green line at bottom. Measurements of peak mitral annular systolic (S'), early diastolic velocities (e') (and late (atrial (a')) diastolic velocity) are marked by arrows.

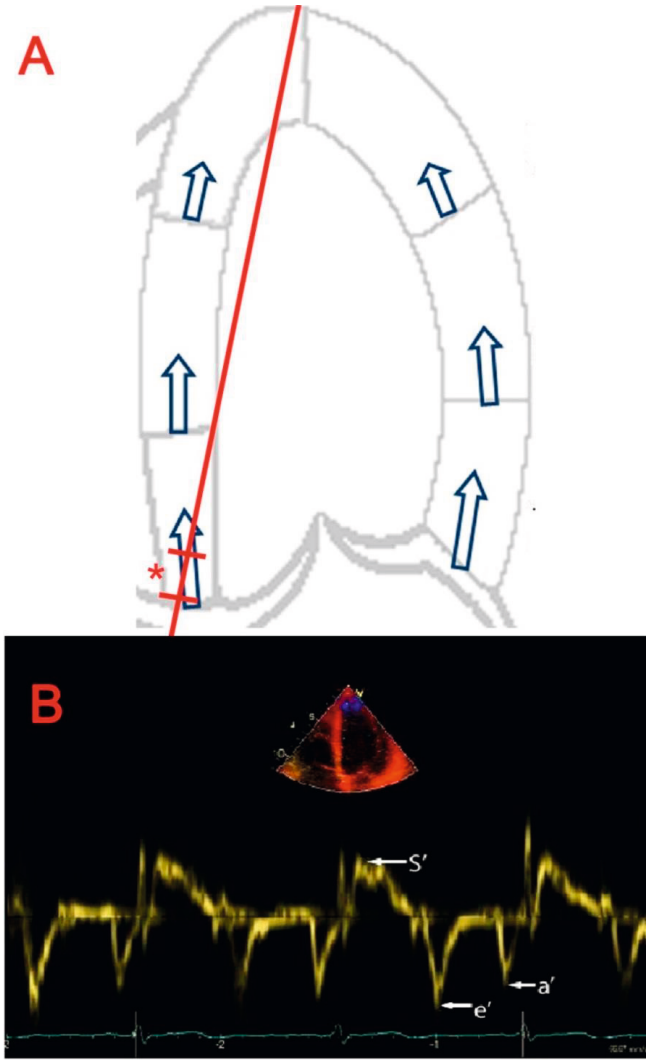

Figure 4: A) The left ventricle in a 4 chamber view. B) Tissue Doppler velocity curves.

[3] Figure 4 is made by Håvard Dalen, January 2015.

3.4 Statistical analyses.

All statistical analyses were conducted with Stata IC/12.1 for windows (© Stat Corp LP).

3.4.1 Prospective analysis (papers I and II).

Comparisons among those who developed AMI (paper I) and HF (paper II) during follow-up and those who did not were made by two-sided t-test for continuous variables, and χ^2 test for categorical data.

We used Cox proportional hazard models to examine the association of depression and anxiety symptoms and subsequent risk for AMI (paper I) and HF (paper II). We calculated hazard ratios (HRs) and 95% confidence intervals (CIs). Paper II estimated the risk per unit increase on the different HADS-scores. Both articles categorised the anxiety and depression symptoms and the highest categories, i.e. ≥ 11 on each scale, were compared with the rest of the categories. For test of trends, we assigned a numeric value of 0 to 2 to the HADS categories, with 0 having no, 1 having moderate and 2 having severe anxiety or depression symptoms, treating the categories as a continuous variable. In a separate analysis, we calculated the risk for AMI (paper I) and HF (paper II) associated with the presence of MSAD in HUNT1 and HUNT2 when those without symptoms of MSAD in both of the surveys constituted the reference group.

The associations between symptoms of anxiety and depression with AMI (paper I) and HF (paper II) were assessed in different multivariable models. We included sex and age as potentially confounding factors in our models. In model 2 education and marital status were added in order to adjust for potentially socioeconomic confounders. Established cardiovascular risk factors such as resting heart rate, high blood pressure, low physical activity, high BMI, smoking, dyslipidaemia, diabetes mellitus, serum-creatinine (paper II), and alcohol intake (paper II) may act both as a confounding and mediating factors for the association of anxiety and depression symptoms with cardiovascular risk. We therefore modelled the data both with (model 3) and without (model 1 and 2) these factors in the analyses. In paper II we also tested whether AMI prior to baseline (model 4) and AMI during follow-up (model 5) influenced our estimates of the association of anxiety and depression with HF. AMI during follow-up was included as a time-dependent variable.

We conducted several stratified analyses to assess whether the association of anxiety and depression and risk for AMI could be modified by other factors. We investigated the potential effect modification by sex, age (dichotomized at age 50 and age 65), body mass index (BMI; dichotomized at ≥ 35 kg/m^2), total cholesterol (dichotomized at 6.5 mmol/L), education (dichotomized at 12 years), blood pressure

(systolic blood pressure dichotomized at >140 mm Hg, diastolic at >90 mm Hg), smoking status (current versus no current smoking), alcohol consumption (paper II; heavy drinking/no heavy drinking) and previous AMI (paper II yes/no). We also formally tested the homogeneity of stratum-specific relative risks. For these tests of interaction, we used the trend variable as defined above.

We performed several sensitivity analyses to assess the robustness of our findings. In paper II we analysed the risk restricted to diabetic patients. In both papers we excluded participants with cancer, asthma, diabetes mellitus, other endocrine disorders, musculoskeletal disorders, and autoimmune diseases or other reported chronic disorders and repeated the Cox analysis in the population without chronic disease. We also restricted the analysis to AMI cases (paper I) and HF cases (paper II) that were confirmed at the hospital, thus cases whose AMI/HF diagnosis were based on death certificates alone were excluded from the analyses. Finally, in order to address the possibility of reverse causation as an explanation for possible associations, we excluded the first five years of follow-up and repeated the analyses. All sensitivity analyses were run in the full multi-variable model (paper I: model 3; paper II model 5).

We tested the proportionality of hazard using log-log curves and formal tests of interaction with time or log-time. There was no evidence against the proportionality assumption in our models.

3.4.2 Cross-sectional analysis (study III).

Clinical echocardiographic data followed a normal distribution and is presented as mean (SD). Characteristics by gender is presented as mean (SD) for continuous variables and as numbers (%) for categorical data. Associations of symptoms of depression and anxiety with LV function were estimated by multivariate linear regression analyses with the different LV function indices as dependent variables as all LV function indices were mutually correlated (r 0.21–0.61, all $p<0.001$). The LV function measures were log transformed, and the partial-regression coefficients are presented as the percentage difference in LV function per specified 5 units difference in HADS-score with the corresponding 95% confidence intervals.

Spearman correlations were performed between all HADS-scores and LV function data. All our linear regression models were adjusted for age and heart rate during echocardiography as a potentially confounding factor for the association of depression symptoms with cardiac function. In model 2, we added potential socioeconomic confounders (education and marital status), and in model 3 established cardiovascular risk factors such as blood pressure, BMI, smoking and physical activity index were included. We investigated the potential effect modification by sex and age (dichotomized at age 50). We found signs of effect modification of gender with global strain ($p=0.019$), thus we stratified all our analysis by sex.

We tested our models for violations of linear assumptions, including variance and normally distributed residuals, and the linear fit was tested with and without polynomials. We found no serious violations for using the linear line approach.

3.5 Ethical considerations.

All the studies were approved by the Norwegian Directorate of Health, the Norwegian Data inspectorate, the Regional Committee for Medical Research Ethics and the Data Access Committees at HUNT and HNT.

4. Main Results

4.1 Paper I: "Symptoms of anxiety and depression and risk of myocardial infarction: the HUNT 2 study".

In paper I, we examined the prospective risk associated with anxiety and depression symptoms and future risk of first incident AMI. Baseline data on anxiety and depression symptoms, sociodemographic variables, health status including cardiovascular risk factors and common chronic disorders were registered for 57,953 adult men and women free of cardiovascular disease.

Results: The cohort was followed up during a mean (SD) 11.4 (2.9) years for a first AMI from baseline, through 2008. A total of 2,111 incident AMIs occurred either identified at hospitals or by the National Cause of Death Registry. The multi-adjusted hazard ratios (HR) were 1.31 (95% CI 1.03–1.66) for severe symptoms of depression and 1.25 (95% CI 0.99–1.57) for anxiety. Two episodes of mixed symptoms of anxiety and depression (MSAD), reported ten years apart, increased the risk of AMI by 52% (95% CI 1.11–2.08). After exclusion of all AMIs occurring during the first five years of follow-up, the association of severe depression symptoms with AMI risk attenuated to a HR of 1.14 (95% CI 0.83–1.57). Relative risk for AMI with severe anxiety symptoms and MSAD weakened to 1.14 (95% CI 0.74–1.75) and 1.38 (0.79–2.40), respectively, when participants with chronic disorders were excluded.

4.2 Paper II: "Symptoms of anxiety and depression and risk of heart failure; the HUNT study."

In this HUNT2 study 62,567 adult men and women free of known HF, were included.

Results: The cohort was followed for incident HF from baseline throughout 2008. A total of 1,499 cases of HF occurred during a mean follow-up of 11.3 years (SD= 2.9), either identified in hospital registers or by the National Cause of Death Registry. We found no excess risk for future HF associated with symptoms of anxiety symptoms or MSAD at baseline. Risk with two episodes of MSAD in both HUNT1 and HUNT2 was associated with a HR of 1.47 (95% CI 1.04–2.01) which was partly explained by AMI before follow-up (HR 1.21, 95% CI 0.76–1.93). For depression symptoms, the multi-adjusted hazard ratios for HF were 1.07 (95% CI 0.87–1.30) for moderate symptoms and 1.41 (95% CI 1.07–1.87) for severe symptoms (p for trend 0.026). Established cardiovascular risk factors, AMI prior to baseline and adjustment for incident AMI as a time-dependent covariate during follow-up had little influence on the estimates. The evidence for a dose-response relationship between depression symptoms and future was confirmed in the analysis using the risk per unit HADS score, and we found no evidence of effect modification due to reverse causality or confounding from common chronic disorders.

4.3 Study III: "Cardiac function and symptoms of depression and anxiety in a healthy population. The HUNT study"

In study III we examined the associations of single and repeated self-reported depression and anxiety symptoms on the Hospital Anxiety and Depression Scale (HADS) with sensitive indices of LV systolic and diastolic function based on Tissue Doppler (TD) and Speckle Tracking (ST) in a healthy population. The study originated from the third wave of the Nord-Trøndelag Health Study. A random selection of 1266 persons who where free from known cardiovascular disease, hypertension and diabetes at baseline underwent echocardiography. In the echocardiography population 1034 had filled in the HADS questionnaire in HUNT3, and 700 of them had participated and had valid HADS responses in HUNT2 (1995–1997) ten years earlier.

Results: Baseline depression and anxiety symptoms were not associated with a reduction in LV indices in HUNT3. However, a 5 unit increase in the additive HADS-D scores from HUNT2 and HUNT3 but not the additive anxiety symptoms, where associated with a reduction in early diastolic annular velocity (e´); -5.5% (95% CI -9.6,-1.5) for women and -5.0% (95% CI -8.6, -1.3) for men.

5 Discussion

The main findings in this thesis are:

- Self-reported symptoms of depression and anxiety, especially if recurrent, were moderately associated with risk of incident AMI. Results indicate that these associations might partly reflect reverse causation or confounding from common chronic diseases.
- Depression symptoms but not anxiety or MSAD, were associated with increased risk for HF in a dose-response manner. The increased risk could not be fully explained by cardiovascular or socioeconomic risk factors, or by comorbid AMI.
- The additive sum of depression symptoms from HUNT2 and HUNT3 were associated with lower LV diastolic function measured by echocardiography among healthy participants in HUNT3.

5.1 Strengths and limitations

Below we discuss the methodological strengths and limitations of the thesis, especially the typical sources of error relevant to epidemiological studies.

5.1.2 Random error

The observed associations in epidemiological studies may be due to chance or unexplained variability in data (182). Random error in epidemiological data can be caused by any factors that randomly affect the data, like sampling error, biological variation or measurement errors (182). The opposite of random error is precision (182) and the measure of precision in studies I–III is the 95% confidence interval (CI). A large sample size is a preferred way to reduce random error and thus increase precision in an epidemiological study (182). Paper I and II both include very large sample sizes compared to most prior research in this field, with over 57,000 persons included in each study. The large sample size in these studies also allowed us to perform sensitivity analysis in sub-groups of the sample. Study III describes a study performed in a in a random subsample (n=1,266) of the HUNT3 population. As a consequence, some of the effect measures, especially in the 700 persons that had valid anxiety and depression scores from HUNT3, were less precise as illustrated by wide CIs.

5.1.3 Validity (lack of systematic error)

Internal validity

The presence of systematic errors may lead to incorrect results. Little systematic error reflects high internal validity and if so, the internal validity will not improve significantly by increasing the sample size. There are three types of systematic errors, which need to be carefully considered in study design and analysis: selection bias, information bias and confounding (182).

Selection bias is a distortion that results from erroneous selection of the participants in the study (182). That is, a selection bias would occur if the participants had a different association between the exposure, i.e. anxiety and depression symptoms and the outcome, i.e. CVD, than those who in theory could have been eligible(183). The HUNT2 study, baseline for paper I and II, had an overall high participation rate of 71.2% (167, 169). However, the attendance rate differed between age groups and the participation rate was lowest among the age group 20–29 (49%) (167, 169). The HUNT 2 non-participation study showed that health related mechanisms were unlikely reasons for not participating in the younger age groups (167). Thus it is unlikely that we would have gained different results by recruiting more young people. More importantly, the age groups 40-79 had a very high participant rate of 77–85% and our Cox models did not show a potential effect modification by age.

The follow-up period (paper I and II) may also potentially introduce selection bias in prospective studies, as health related conditions often lead to an inability to continue the participation (182). However, loss of follow-up in this study is minimal due to; 1) use of health registries which track the individuals disease profile by a unique 11 digit identification number given to each Norwegian citizen at birth; 2) the population in Nord-Trøndelag has a high residential stability (less than 0.3% net migration/year) (167), which ensure that we find most of the participants diagnosis in the hospital registries and; 3) data from Statistics Norway allows us to censor those few who moves out of the county.

In HUNT3 (study III) the attendance rate dropped to 54%, and a separate non-participating study was carried out (184). This study showed that depression symptoms, and to a lesser degree anxiety symptoms, were more prevalent in non-participants than participants (184). Further studies should include more patients with higher burden of anxiety and depression symptoms in order to evaluate the influence on LV function in such a population.

Information bias occurs due to systematic errors in measurements of exposure, covariates or in classification of the outcome variables. The measurement error can be differential or non-differential (182).

Differential misclassification occurs if the misclassification of the exposure depend on the outcome (or vice versa) and can lead to either exaggeration or underestimation of the effect (182). *Recall bias* is one example of differential misclassification. Recall bias is likely to happen in any study that relies on subject memory (182). An advantage with using the HADS (study I–III) and ADI (paper I and II) parameters from the HUNT questionnaires is that the demands on subject memory is low, as the respondents were instructed to report how they had felt during the last week for HADS (185), and in the present moment for three of the ADI-items and during the last month for the item nervousness (172). In order to assess association of repeated anxiety or depression symptoms with CVD risk we utilized the dataset from the previous HUNT wave for those who had participated both times. Another option for paper I and II would have been to use the 5-items assessing lifetime depressive episode which was included at baseline in HUNT2 (but not in HUNT3): ”During your life, have there been periods of 2 consecutive weeks or more when you: 1) felt sad, depressed or down; 2) had appetite problems or ate too little, 3) felt weak (adynamic) or lacked energy; 4) really reproached yourself or felt worthless or 5) had problems concentrating or had difficulty making decisions”. However, although these items represent DSM-IV criteria of major depression, this could have introduced recall bias and we therefore chose to use data from HUNT1 to avoid this.

Non-differential misclassification occurs if the misclassification of exposure is unrelated to the outcome (or vice versa) and typically leads to an underestimation of the effect, i.e. closer to the null than the true effect (182). Using self-report instruments people often tend to present themselves in a favourable light, e.g. people tend to under-report smoking and alcohol use, while exercise frequency often is over-reported (186). In contrast, some studies argue that self-report provide a feeling of anonymity which increase reliable data of anxiety and depression symptoms (186). In paper I and II which encompassed a large proportion of the normal population in Nord-Trøndelag, the prevalence for HADS depression and anxiety symptoms defined as the highest cut-off ($\geq$11) were comparable to the estimates from a psychiatric interview approach in the general European population (187).

For screening, assessment of severity and decision making purposes it is common, and often necessary, to categorize continuous variables in order to help identify which patients are in need for follow-up for their anxiety and depression symptoms (170, 188). This was also the main approach in this thesis. In general the downside of categorizing continuous variables is high, including loss of information with reduced power to detect a relation between the variable and an outcome measure (182). However, in paper II the use of the continuous HADS scale supported the findings from the categorical approach, and the findings from paper I have recently

been supported by another study from HUNT using the continuous HADS-D scale in assessing association with AMI risk (189).

There is also a possibility for misclassification in the identification and ascertainment of AMI (paper I), HF (paper II) and interpretation of the echocardiography recordings (study III). However, the reproducibility of the echocardiographic LV measures was high with an inter-observer mean error between 4–8% and an intra-observer mean error between 2–5% (56). Also, the overall quality of the diagnosis of AMI and HF at the time of hospital discharge is high in Nordic countries and in the mid-Norway region (176, 178, 190). The quality of the HF registries appears slightly less precise than the AMI registries because there is no unequivocal definition for HF. For this reason we used only the primary diagnosis for HF as recommended (178). Nevertheless, the choice of including only primary diagnosis of HF leads to a possible underestimation of the true incidence. However, our main purpose was to ensure the most valid diagnosis, not give precise estimates on HF incidence in the general population. As the HF diagnosis had approximately 100% specificity, low sensitivity does not lead to bias of the risk ratios, just decreasing the precision (182). In short, to include only primary diagnosis of HF may decrease power, yet preserves validity. Additionally, sensitivity analysis including endpoints from hospital registries only (paper I and II) showed similar effects as the main analysis, and therefore it seems unlikely that the lower reliability of the National Cause of Death registries could have explained the effects.

Confounding arises when the exposure and outcome share a common cause (191). Confounding can lead to overestimation, underestimation and even cause an association in the opposite direction of the true effect (182). One way to increase the knowledge about confounding is to visualize the hypothetical relations among variables of interest in directed acyclic graphs (DAGS) (191). Age and sex are examples of variables that based on our subject matter knowledge are confounders in studies I–III; both CVD and symptoms of depression and anxiety increase with age and differs by sex. Both variables (age and sex) must be directed to depression and the outcome (AMI in paper I, HF in paper II, subclinical LV dysfunction in study III). A statistical model that only includes such verified confounders are the best for analysing causality (182). When one adjusts or condition on such confounders in the statistical model, confounding caused by those variables is removed from the estimates (191).

In study III we included average heart rate during echocardiography as a third covariate in model 1 because the interpretation of the echocardiographic recordings is pulse dependent. However, since increased heart rate during clinical procedures such as echocardiography may be an exaggerated physiological response associated with depression and anxiety symptoms (192), heart rate could be a mediator between the

exposure and outcome. This could have led to an underestimation of the effect of anxiety and depression symptoms on subclinical heart dysfunction.

Residual confounding in observational studies can not be ruled out due to missing information on factors that could have a confounding effect (193). Even though our adjustments were extensive compared to most prior research in the same area (3), we lacked information on important potential confounders such as dietary patterns, neurohormonal stress levels and inflammatory activity. These factors are all associated with both the exposure (115, 137, 194) and the outcome (12, 17, 195). However, it is not clear whether these factors represents confounders, mediators or are part of a loop-feedback mechanism in the observed associations (115, 140). In order to largely affect the gained estimates the unmeasured confounders must also be unrelated to the other factors that were already included in the analyses (182). However, inflammation is associated with smoking, BMI, lipids and alcohol (115), and diet is associated with BMI, lipids and hypertension (196). Thus, theoretically these variables would not largely influence the estimates.

Among the most overlooked confounders between anxiety and depression symptoms with CVD risk are comorbid physical disorders (85, 86). Depressive symptoms are highly correlated with the overall disease burden, and several common chronic disorders are also risk factors for AMI, HF (193) and subclinical LV dysfunction (51). In paper I and II we handled this problem with performing sensitivity analysis where those with comorbid physical disease were excluded. In study III, the inclusion criteria for the echocardiography study excluded many comorbid conditions, see **Figure 5.** In **Figure 5** the grey arrows indicate the inclusion criteria and the random selection for the echocardiography study and blue arrows represent the sources of data extraction for one and sum of two reports of anxiety and depression symptoms.

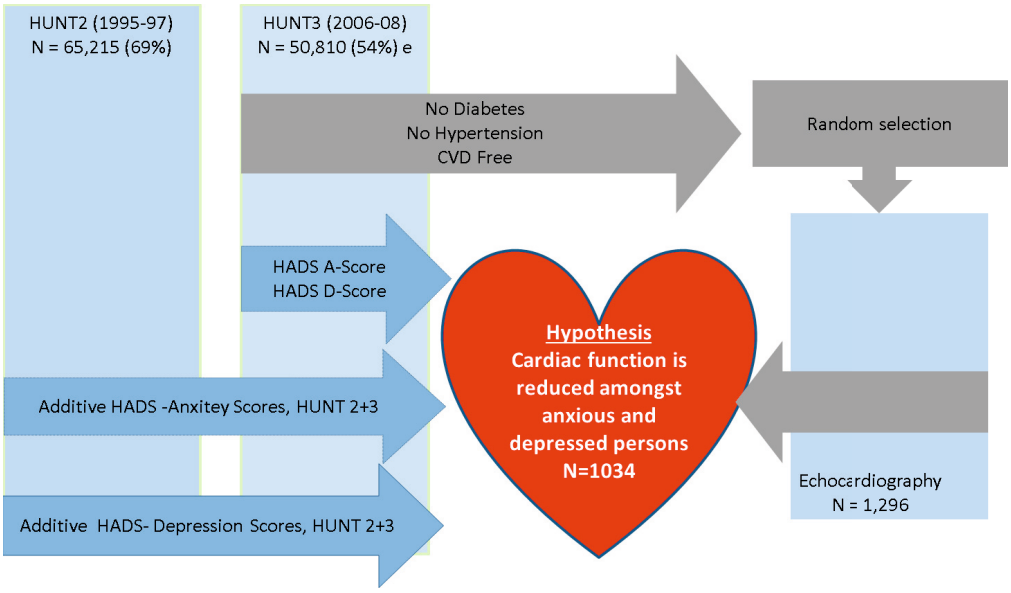

Figure 5: Sources of selection for the echocardiography study and data extraction for one and two reports of anxiety and depression symptoms.

External validity

External validity refers to generalizability, that is to what extent findings apply to other populations (182). Differences in prevalence of anxiety and depression symptoms, CVD risk factors and CVD rates may vary between study settings, countries and cultures. Moreover, the somewhat low participant rate (52%) and the health related reasons for non-participating in the oldest (>70) group (166, 167), makes it necessary to be cautious about inference from our results to the elderly population. Nevertheless, it is little reason to believe that the effect of depression and anxiety on CVD would be radically different in other populations.

5.2 Comparison with previous studies.

Although anxiety and depression symptoms tend to overlap, these conditions have to date mostly been investigated separately in terms of risk of AMI, HF and subclinical LV dysfunction. A meta-analysis of 23 prospective studies of risk associated with a wide range of anxiety measures for future AMI, found a pooled relative risk 1.26 (95% 1.15–1.38) (4), which is close to our estimates. To the best of our knowledge no

studies exist on the association between anxiety symptoms and subclinical LV dysfunction, and we found only one prospective study of anxiety disorders and HF (197): a large (n=236,079) study of American war veterans, where a HR 1.19 (95% CI 1.10–1.28) of associated with anxiety disorders was found (197). This point estimate is also comparable to the 1.17 (95% CI 0.90–1.51) risk of future HF found in participants with a score ≥ 11 on the HADS-Anxiety scale in our study.

Also for depression, the majority of studies is undertaken on risk for future AMI, whilst we found only five studies for the prospective risk associated with HF (155-157, 162, 163) and one cross-sectional study (13) on the association with subclinical LV dysfunction. For depression and risk of future AMI, a meta-analysis including 54 prospective studies reported a pooled effect of 1.95 (95% CI 1.51–2.51) on fatal and non-fatal AMI (3), which is considerably higher than our estimates. Some prospective studies have also found a lack of effect between depression and AMI and HF (3, 157, 162). Studies using self-report instruments have generally found smaller effects than studies relying on clinical diagnosis or psychiatric interviews (3), which might indicate a dose-response effect of anxiety and depression symptoms with risk for CVD. People with present psychiatric disorders, e.g. people with major depressive disorder generally score higher on self-rating scales compared to those who do not fill the diagnostic criteria. However, defining optimal cut-offs for identifying depressive disorders with high specificity is challenging (170, 198). Thus, some studies using self-report might have failed to detect a relation due to sub-optimal cut offs for their exposure. This dose-response effect, i.e. the higher levels of anxiety and depression levels the higher CVD risk, is confirmed in studies of future AMI and HF risk, and in the cross-sectional association of subclinical LV dysfunction (8, 13, 155, 189, 199, 200).

Unfavourable socioeconomic and behavioural lifestyles may be a link between depression symptoms and increased CVD risk. These traditional cardiovascular risk factors were inadequately controlled for in most previous studies and it is still not clear to which extent these factors explain the observed association between depression symptoms and CVD (3). Depression, but not as much anxiety symptoms, is often strongly associated with traditional risk factors for AMI, HF and subclinical LV dysfunction, such as lower educational level, physical inactivity, unhealthy diet, obesity, smoking, medical adherence and poorer lifestyle (58, 115, 140, 201, 202). Some of these behaviours associated with depressive symptoms are factors that negatively influence the cardiovascular health (12, 14). In our studies of risk for AMI (paper I) and HF (paper II), people in the most severe symptom category of anxiety and depression symptoms both had a more unfavourable socioeconomic and cardiovascular risk profile. However, even if cardiovascular risk factors explained some of the risk associated with anxiety symptoms for AMI and all of the risk for HF, they did not explain the risk associated with depression symptoms for AMI and HF. In addition, the above

mentioned unhealthy behaviours are suggested to be sources of an inflammatory process with release of proinflammatory cytokines that can cause depression (115, 203), and the inflammatory process reciprocally are part of the pathophysiological processes that cause HF, AMI and subclinical LV dysfunction (52, 140, 161, 204, 205). Unfortunately, we did not have data on inflammation or proinflammatory cytokines on all participants, so we were unable to test if this was a potential confounder in the observed associations.

The risk associated with number of episodes of anxiety and depression symptoms is another dose-response issue, and several studies report that repeated episodes contribute to a higher risk for AMI than single episodes (8, 150, 152, 206, 207). To best of our knowledge no study was found for assessing risk associated repeated anxiety and depression symptoms with future risk for HF or the presence of subclinical LV dysfunction. People who experience recurrent episodes of anxiety and depression might be exposed to a prolonged biological stress response, which in turn lead to increased CVD risk (195). However, as we did not have data on biological stress markers, we were not able to test if this could have been confounders for the observed associations. One can also hypothesize that a single measurement could reflect a normal reaction to stressful events, whilst multiple episodes may better capture anxiety and depressive disorders (208), such as bipolar disorders, known for poorer adherence with lifestyle and medical advice (209). In our studies repeated MSAD constituted a higher risk of AMI and HF. In study III, repeated high levels of depression symptoms was linearly associated with lower LV function among participants free from diabetes, hypertension and CVD. However, the increased associated with MSAD for AMI (paper I) was partially explained by comorbid physical disease and with previous AMI for HF (paper II).

Our sensitivity analysis suggested a higher risk in the first five years of follow-up regarding depression symptoms with risk for AMI (paper I) but not for HF (paper II) in those with depression symptoms at baseline. This might, for AMI; reflect reverse causation, which might be harder to detect for HF since the outcome is manifesting in average 5.9 years later than the AMI diagnosis. The possibility that both depressive symptoms and subsequent CVD are caused by subclinical pathological processes, e.g. atherosclerosis in the case of AMI, is among the greatest challenges on the prospective association between depression and CVD (85, 86). One possible pathway is the depressogenic actions of the increased inflammatory activity (210, 211). Inflammation is known to be one of the initiating pathophysiological processes behind arteriosclerosis (24), a driver in the LV myocardial remodelling (40) and neuroimaging and neuropathology studies has also found that depression can arise from a cerebrovascular origin (203).

6 Conclusion and future perspectives

The results of this thesis contribute to the understanding of the risk associated with anxiety and depression symptoms for development of future CVD. HADS-Anxiety symptoms were only a moderate risk factor for AMI and not for HF or LV dysfunction. HADS-Depression symptoms were a moderate risk factor for future AMI (paper I) and HF (II), and the increased risk was not explained by traditional cardiovascular risk factors.

Repeated HADS-Depression symptoms, but not repeated HADS-Anxiety symptoms, were associated with subclinical LV diastolic dysfunction at baseline (study III). Repeated episodes of MSAD were risk factors for AMI (paper I) and HF (paper II). We had some indications that the increased risk with MSAD was explained by coexisting chronic disease (paper I) and by previous AMI (paper II).

Sensitivity analysis indicated that the observed risk associated with depression symptoms could be explained by reverse causation for future AMI (paper I) but not HF (paper II). It might be harder to detect reverse causality with increased HF risk since the outcome is manifesting in average 5.9 years later than the AMI diagnosis.

Strategies for screening, early prevention, and improved treatment of depressive and anxiety symptoms might have the potential to reduce development of CVD, and should therefore be carried out both in primary care settings and in specialist services. Also, better treatment of anxiety and depression could contribute to increased adherence to medical and behavioural advice in persons at risk of CVD or with established CVD.

Finally, future research should assess the unexplained pathophysiological links, such as unhealthy dietary patterns, use of psychotropic drugs, neurohormonal stress, proinflammatory cytokines, and shared genetic disposition, which could explain the underpinning mechanisms linking depression symptoms and CVD.

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Paper I

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Symptoms of anxiety and depression and risk of acute myocardial infarction: the HUNT 2 study

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Aims The nature of the association of depression and anxiety with risk for acute myocardial infarction (AMI) remains unclear. We aimed to study the prospective association of single and recurrent self-reported symptoms of anxiety and depression with a risk of AMI in a large Norwegian population based cohort.

Methods and results In the second wave of the Nord-Trøndelag Health Study (HUNT2, 1995–97) baseline data on anxiety and depression symptoms, sociodemographic variables, health status including cardiovascular risk factors and common chronic disorders were registered for 57 953 adult men and women free of cardiovascular disease. The cohort was followed up during a mean (SD) 11.4 (2.9) years for a first AMI from baseline through 2008. A total of 2111 incident AMIs occurred, either identified at hospitals or by the National Cause of Death Registry. The multi-adjusted hazard ratios were 1.31 (95% CI 1.03–1.66) for symptoms of depression and 1.25 (CI 0.99–1.57) for anxiety. Two episodes of mixed symptoms of anxiety and depression (MSAD), reported 10 years apart, increased the risk for AMI by 52% (11–108%). After exclusion of the first 5 years of follow-up, the association of depression symptoms with AMI risk was attenuated. Relative risk for AMI with anxiety symptoms and MSAD weakened when participants with chronic disorders were excluded.

Conclusion Self-reported symptoms of depression and anxiety, especially if recurrent, were moderately associated with the risk of incident AMI. We had some indications that these associations might partly reflect reverse causation or confounding from common chronic diseases.

Keywords Depression • Anxiety • Prospective • Risk • Acute myocardial infarction • Epidemiology

Introduction

Depression and anxiety, both highly prevalent conditions in the general population, are associated with elevated risk for acute myocardial infarction (AMI).[1–7] However, the nature of this association remains controversial.

One of the greatest challenges in the research on the prospective association of anxiety and depression with AMI is that atherosclerosis, one of the main underlying pathophysiological mechanisms of AMI, is known to develop during decades before the first clinical symptoms.[8] However, almost all studies of depression included middle aged or older adults, often with a short follow-up time.[9] Thus, individuals free from clinical heart disease in the aforementioned prospective studies may not be free from atherosclerosis, which may facilitate depressive symptoms even before generating ischaemia.[8,10]

Furthermore, in most previous reports, the well-known cardiovascular risk factors were inadequately controlled for, and it is not clear to what extent these factors explain the observed association between depression and AMI.[1,9,11] Among the most overlooked confounders are comorbid physical disorders.[12] Depressive symptoms are highly correlated with the overall disease burden, and several common chronic disorders are also risk factors for AMI. Moreover, depression is known to have an episodic nature,[13] yet in the great majority of previous studies, depression was assessed only once. Some studies, however, suggest that recurrent depression has considerably stronger association with AMI than single depressive episodes.[14]

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Further, anxiety and depression are often considered separate psychopathological conditions, yet they share common symptoms and often overlap.[15] Still, relatively little data are available on the prospective association between anxiety and risk for cardiovascular disorders (CAD), and similar methodological concerns as those presented for depression apply to these studies as well.[16] Therefore, the aim of this study was to investigate the prospective association of single and recurrent self-reported symptoms of anxiety and depression with the risk of AMI controlled for potential confounders, including comorbidities in a large population-based cohort.

Methods

Study population and setting

All adult citizens in Nord-Trøndelag County, Norway, received a postal invitation to participate in the second wave of the Nord-Trøndelag Health Study (HUNT 2, 1995–97, http://www.ntnu.edu/hunt, last accessed 28 July 2013). In total, 94 187 individuals were invited and 65 215 (69%) participated in the HUNT 2 study. The participants filled in questionnaires (http://www.ntnu.edu/hunt/data/que, last accessed 28 July 2013) and attended a baseline clinical examination. Details about the study have been published elsewhere.[17,18] Of the participants in HUNT 2, 47 316 also attended the first wave of the HUNT Study (HUNT 1, 1984–86).[19]

This study was approved by the regional ethics committee for research, by the National Directorate of Health, the Norwegian Data Inspectorate, and the HUNT data access committee. All participants gave written consent.

Exposure: depression and anxiety symptoms

The HUNT self-report questionnaire included a Norwegian version of the Hospital Anxiety and Depression Scale (HADS),[20] which assesses core psychological symptoms of anxiety (HADS-A) and depression (HADS-D) during the last week. The seven anxiety questions mirror symptoms of worry and tension, while the seven depression items mirror mainly symptoms of anhedonia and loss of interest. All questions have a 4-point Likert scale response option from 0 (no symptom) to 3 points (highest symptom level). The HADS has shown good psychometric properties across various patient samples and settings.[21]

In total, 62 685 (96.1%) of the HUNT 2 participants had a valid HADS response, defined as response on 5 or more items on one subscale. Missing response among those who filled in five or six items were replaced based on the sum of completed items multiplied by 7/5 or 6/5, respectively. Both subscales range from 0 (no symptoms) to 21 points.

We categorized the participants according to their HADS-D and HADS-A scores, respectively, as having no symptoms of depression or anxiety (score < 8), having mild to moderate symptoms (score 8–10), and having severe symptoms (score ≥ 11).[22] A combined total score (HADS-T) for assessing the impact of mixed symptoms of anxiety/depression (MSAD) was calculated by summing up valid HADS-A and HADS-D scores. We categorized the participants into three groups: no MSAD (score < 15), mild to moderate MSAD (score between 15 and 18), and severe MSAD (score ≥ 19).[21]

In HUNT 1 (1984–86), the Anxiety and Depression Index (ADI-4) was included. ADI-4 is an acceptable indicator for MSAD (sensitivity 0.51, specificity 0.93) and showed a high correlation (0.83) with the HADS-T score.[23] ADI has been used as a crude baseline measure of MSAD in HUNT 1.[23] ADI consists of four questions, two tapping into general anxiety and two into depression. Two of the questions have four response categories: nervousness ranging from never (1) to almost all the time (4) and calmness which range from almost all the time (1) to never (4). The two other questions had seven response categories; mood, ranging from very downhearted (7) to very happy (1) and vitality ranging from very strong and fit (1) to very tired and worn out (7).

In total, 32 963 of the participants in the present study had valid MSAD scores both in HUNT 1 (ADI-4) and HUNT 2 (HADS-T). A variable to indicate the combined burden of MSAD in HUNT 1 and HUNT 2 was created in categories of never, one, and two episodes. MSAD in HUNT 2 was defined as cut off ≥ 19 on the HADS-T scale. We then defined previous episode of MSAD in HUNT 1 by scoring in the upper quartile on ADI, cut-off at ≥ 14 points. 'Never MSAD' was as defined as a scoring < 14 on ADI in HUNT 1 and < 19 on HADS in HUNT 2, 'MSAD once' was defined as scoring above cut-off in one of the studies, while 'MSAD twice' included those scoring above cut-off in both studies.

Follow-up and outcome ascertainment

A total of 4734 participants were excluded at baseline because they reported a history of previous myocardial infarction ($n = 1944$), angina pectoris ($n = 2978$), or stroke ($n = 1120$). The remaining 57 953 participants were included in this study, and *Figure 1* summarizes the recruitment of the participants.

Participants were followed-up for a first AMI from enrolment in HUNT 2 study until 31th of December 2008, either identified at the two hospitals in Nord-Trøndelag County or by the National Cause of Death Registry.[24]

Acute myocardial infarction was diagnosed according to the European Society of Cardiology/American College of Cardiology consensus guidelines.[5] Criteria for AMI included: (i) specific clinical symptoms according to case history information, (ii) changes in blood levels of cardiac enzymes, and (iii) specified ECG changes. Fatal AMI incidents that never reached the emergency units at the hospitals were identified in the National Cause of Death Registry by the International Classification of Diseases codes (code no. 410 in the 9th revision and codes I21 and I22 in the 10th revision). During mean (SD) 11.4 (2.9) years of follow-up, 231 participants who left the county, and 6409 participants who died from other causes than AMI, were censored at the time of event (emigration or death) in the statistical analyses (see *Figure 1* , flow chart).

Covariates

Demographic factors

Cohabitation status was dichotomized as living with a partner or alone. Education was categorized as low ($\leq$ 9 years), medium (between 10 and 12 years), or high (over 12 years).

Life style factors

Smoking habits were self-reported and were categorized as current, previous, or never smoking. Physical activity was defined as light if it did not involve sweating or feeling of breathlessness, while hard physical activity was defined by sweating or breathlessness. The participants were categorized as inactive (less than 1 h of hard activity and less than 3 h of light physical activity per week), moderate active if they reported 1–3 h of hard activity or >3 h of light activity per week, and as physically active if they reported >3 h of hard physical activity per week.

Chronic somatic disorders

Participants self-reported if they had (or had ever had) cancer, asthma, diabetes mellitus, other endocrine disorders (hypothyreosis, hyperthyreosis, goitre, and thyroiditis), musculoskeletal disorders (osteoporosis, fibromyalgia, and arthrosis/arthritis), autoimmune disease (Bechterew disease, rheumatoid arthritis), epilepsy, or other chronic disorders (replying yes to the question 'do you have or ever had any other chronic disease' and no to the questions regarding previous specified diagnosis of chronic disease).

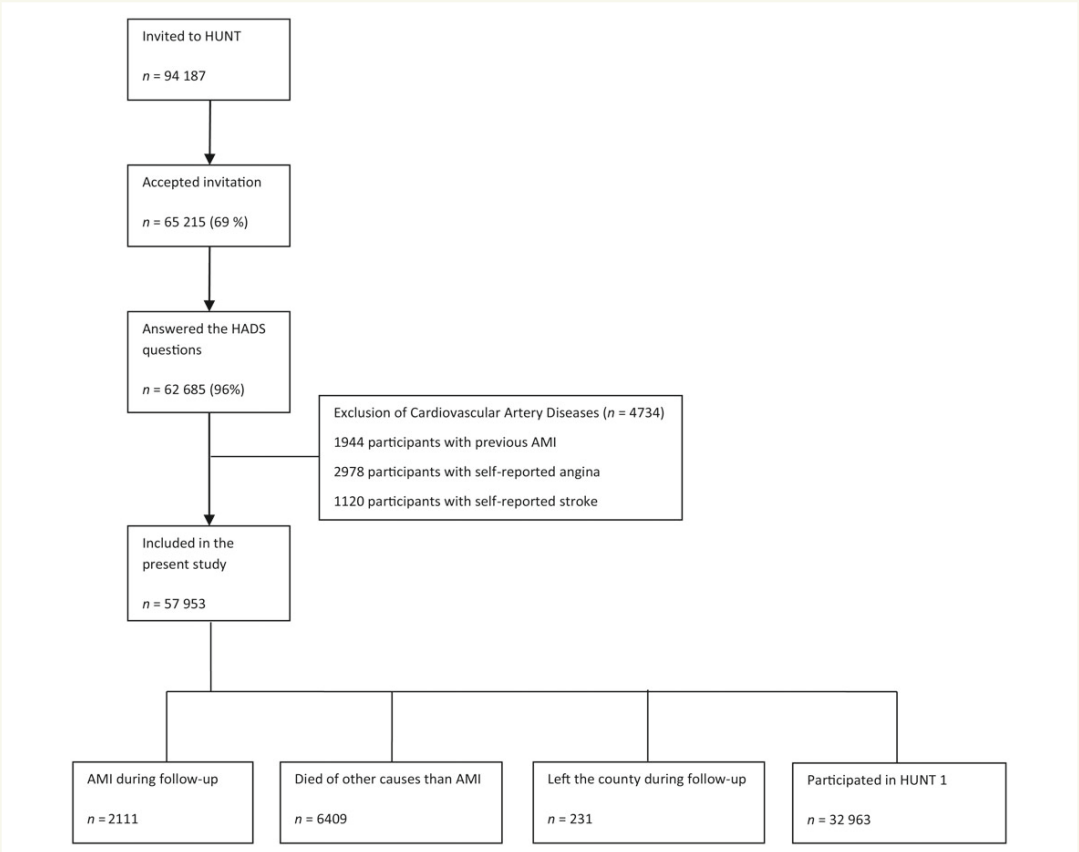

Figure 1 Flow chart for the participants.

Clinical examination

Blood pressure, heart rate, weight, height, waist, and hip circumference were measured by specially trained nurses after a standardised protocol. Heart rate, and systolic and diastolic blood pressure were measured after the participant had been seated for at least 2 min with the cuff on, and the size of the cuff was adjusted for arm circumference.[17] All blood pressure and heart rate recordings were performed using a Dinamap 845XT (Criticon) based on oscillometry and involved automatically three recordings at 1 min intervals. The first heart rate recording was in average 2 bpm lower than the second and third measurement and was thus used in order to mirror resting heart rate. For blood pressure, the value decreased for each recording, thus we used the average of the second and third measurements in our analysis. Height was measured without shoes to the nearest 1.0 cm and weight with light clothing to the nearest 0.5 kg.[17] Body mass index (BMI) was computed as weight (in kg) divided by the squared value of height (in metres).

Blood sampling and laboratory measurements

A non-fasting whole blood sample was drawn from each participant, and the time between last meal and the venepuncture was recorded. Serum was separated by centrifugation at the screening site and immediately placed in a refrigerator (4°C). The samples were sent (same day or following Monday for samples drawn on Friday) for analyses at the central laboratory at Levanger Hospital, Norway, where they used a Hitachi 911 Autoanalyzer, applying reagents from Boehringer Mannheim. Serum total cholesterol was measured by an enzymatic colorimetric cholesterol esterase method. The day-to-day coefficient of variation for total cholesterol was 1.3–1.9%.[17]

Statistical analysis

Comparisons of continuous variables among those who developed AMI during follow-up and those who did not were made by two-sided *t*-test, and the χ^2 test was used to compare categorical data. We used Cox proportional hazard models to examine the association of depression and anxiety symptoms and subsequent risk for AMI. We calculated hazard ratios (HRs) and 95% confidence intervals (CIs). For test of trends, we assigned a numeric value of 0 to 2 to the HADS categories, with 0 having no, 1 having moderate, and 2 having severe anxiety or depression symptoms, treating the categories as a continuous variable. In a separate analysis, we calculated the risk for AMI associated with the presence of MSAD in HUNT 1 and HUNT 2 when those without symptoms of MSAD in both of the surveys constituted the reference group.

We adjusted all our models for sex and age as a continuous variable. In the second adjustment model, we added education and marital status as potentially confounding factors in our models. Established cardiovascular risk factors such as resting heart rate, high blood pressure, low physical activity, high BMI, smoking, dyslipidemia, and diabetes mellitus may act both as confounding and mediating factors for the association of depression and anxiety with the AMI risk. We therefore analysed the data both with and without the factors included in the analyses. We conducted several stratified analyses to assess whether the association of anxiety and depression and the risk for AMI could be modified by other factors.

We investigated the potential effect modification by sex, age (dichotomized at age 50 and age 65), BMI (dichotomized at $\geq$35 kg/m^2), total cholesterol (dichotomized at 6.5 mmol/L), education (dichotomized at 12 years), blood pressure (systolic blood pressure dichotomized at >140 mm Hg, diastolic at >90 mm Hg), and smoking status (current vs. no current smoking). We also formally tested the homogeneity of stratum-specific relative risks. For these tests of interaction, we used the trend variable as defined above.

We present event-free survival curves using the Kaplan–Meier method according to symptom categories.

We performed several sensitivity analyses to assess the robustness of our findings. First, we excluded participants with cancer, asthma, diabetes mellitus, other endocrine disorders, musculoskeletal disorders, and autoimmune diseases or other reported chronic disorders. We also restricted the analysis to AMI cases that were confirmed at the hospital, thus cases whose AMI diagnosis were based on death certificates alone were excluded from the analyses. Finally, in order to address the possibility of reverse causation as an explanation for possible associations, we excluded the first 5 years of follow-up and repeated the analyses. All sensitivity analyses were run with adjustments for socioeconomic status and traditional cardiovascular risk factors (Model 3).

We tested the proportionality of hazard using log–log curves and formal tests of interaction with time or log-time. There was no evidence against the proportionality assumption (all $P > 0.10$).

Statistical analyses were performed in Stata IC/12.1 for windows (© Stata Corp LP).

Results

Characteristics of the study population, by AMI status, are shown in *Table 1*. Among the 59 953 participants, 2111 (3.5%) had a first AMI during follow-up. Of these, 1632 cases were diagnosed at a hospital and 479 cases were registered by the National Cause of Death Registry alone.

Table 1 Baseline characteristics of participants in the total population and according to AMI vs. no AMI during follow-up

Variable	No. of subjects	Total population	AMI during follow-up	No AMI during follow-up	*P*-value
Total % (*n*)	57 953	%	3.6 (2111)	96.7 (55 854)	
Variables, % (*n*)					
Male sex	26 551	45.8	62.5 (1312)	45.2 (25 239)	<0.0001
Diabetes mellitus	1292	2.2	8.3 (176)	2.0 (1 116)	<0.0001
Smoking					<0.0001
Never	26 669	46.2	34.0 (714)	46.6 (25 955)	
Former	13 748	23.8	28.0 (608)	23.6 (13 140)	
Current	17 334	30.0	36.0 (775)	29.8 (16 569)	
Physical activity					<0.0001
Inactive	20 333	38.1	46.9 (796)	37.8 (19 537)	
Moderately active	27 574	51.7	46.5 (788)	51.9 (26 786)	
Physically active	5434	10.2	6.6 (112)	10.3 (5322)	
Living alone	23 009	39.8	35.9 (757)	39.9 (22 252)	<0.0001
Education					<0.0001
≤9 years	18 930	33.7	63.2 (1468)	32.8 (17 763)	
10–12 years	25 311	45.1	27.3 (632)	45.7 (24 765)	
>12 years	11 857	21.1	9.0 (133)	21.5 (11 661)	
Mean (SD)					
Age, years	57 953	47.7 (16.3)	64.9 (12.7)	47.0 (16.0)	<0.0001
Body mass index, kg/m^2	57 498	26.2 (4.1)	27.4 (4.0)	26.2 (4.1)	<0.0001
Systolic blood pressure, mmHg	57 586	123.5 (21.1)	153.9 (23.5)	135.8 (20.7)	<0.0001
Diastolic blood pressure, mmHg	57 586	79.9 (12.0)	87.1 (12.7)	79.7 (11.9)	<0.0001
Resting heart rate, bpm	57 673	71.6 (13.0)	73.4 (13.5)	71.6 (13.0)	<0.0001
Total cholesterol, mmol/L	57 644	5.8 (1.2)	6.7 (1.2)	5.8 (1.2)	<0.0001
HADS—depression score	57 819	3.4 (3.0)	4.1 (3.0)	3.4 (3.0)	<0.0001
HADS—anxiety score	57 023	4.2 (3.3)	3.9 (3.4)	4.3 (3.3)	<0.0001
HADS—total score	56 889	7.6 (5.6)	8.7 (5.8)	8.6 (5.4)	0.3555
ADI score (HUNT 1)	32 963	13.5 (1.2)	13.6 (1.3)	13.5 (1.2)	0.0036

Using the highest cut off (≥11), the prevalence rates of HADS-defined anxiety and depression were 5.2 and 3.0, respectively. These estimates were comparable with the corresponding values (6.4 and 4.2%) found in the general European population.[25]

In our study, women reported higher symptom levels of anxiety and MSAD, while depression symptom levels were the same in both genders.

A total of 2111 participants had a first AMI during a mean (SD) follow-up of 11.4 (2.9) years. The prevalence of current smoking, diabetes, physical inactivity, and low education was higher among those who developed AMI during follow-up.

Table 2 presents the HRs for AMI in relation to symptoms of anxiety, depression, and MSAD. Risk for AMI was moderately elevated for participants reporting symptoms of depression, anxiety, and MSAD. The point estimates were fairly robust in multivariable models for socioeconomic and cardiovascular risk factors. Additional adjustment for resting heart rate in model 3 did not alter these results considerably (data not shown). Symptoms of anxiety were associated with higher risks for non-fatal AMI (HR 1.33, 95% CI 1.03–1.71) than for fatal AMI (HR 0.93, 95% CI 0.70–1.24), and this pattern was similar regarding symptoms of depression and MSAD (data not shown).

Figures 2–5 show Kaplan–Meier curves for event-free survival according to symptom categories and number of subjects at risk for each 2.5 years of follow-up.

Table 3 displays the HRs for AMI according to the presence of MSAD combining data from HUNT 1 and 2. In the study population, 48.4% ($n = 15\,657$) reported no episodes of MSAD, 48.9% ($n = 15\,770$) reported one MSAD episode, and 2.7% ($n = 884$) experienced two MSAD episodes. There was a trend towards higher HRs in those with two episodes of MSAD compared with those who did not report MSAD at HUNT 1 or HUNT 2 and HRs were 30% higher than for those reporting MSAD only in HUNT 2.

Sensitivity analyses

Table 4 presents the multivariable adjusted HRs for AMI in relation to depression, anxiety, and MSAD in different sensitivity analyses.

There were 1582 AMI cases among 49 330 participants that completed the questionnaire on common chronic somatic disorders. Of these, 13 515 persons (27.4%) reported to have at least one chronic disease. The frequency of chronic disorders was: diabetes mellitus $n = 902$, other endocrine disorders $n = 1998$, autoimmune diseases $n = 1330$, muscle/skeletal disorders $n = 4184$, asthma $n = 3898$, cancer $n = 1323$, epilepsy $n = 652$, and 'other chronic disorders' $n = 1793$. After exclusion of common chronic disorders, the effect sizes were generally attenuated (*Table 4*). No single group of chronic disorders appeared to be responsible for this effect.

When we restricted follow-up to AMI cases that were confirmed in hospital (1632) events, we obtained similar or even higher hazard ratios for anxiety, depression, and MSAD than in the main analyses.

After the fifth year of follow-up, we observed 1443 AMI events. Exclusion of the first 5 years substantially weakened the observed association between depression and AMI risk. Risk for AMI associated with anxiety symptoms and MSAD remained fairly stable (*Table 4*).

Discussion

In this large population-based cohort study, participants with symptoms of anxiety, depression and mixed symptoms (MSAD) had a 20–30% increased risk for first AMI. Participants reporting two episodes of MSAD, 10 years apart, had >50% increased risk for AMI. All effects were robust to extensive adjustments for socioeconomic and

Table 2 Hazard ratios (95% confidence intervals) for AMI during follow up according to symptoms of depression (HADS-D) and anxiety (HADS-A) and mixed anxiety/depression symptoms (MSAD measured by HADS-T) in HUNT 2 (1995–97)

Variable		Model 1	Model 2	Model 3
HADS-D	Events/person-time	2096/656 582	1896/636 445	1561/590 365
0–7		Reference	Reference	Reference
8–10		1.08 (0.94–1.24)	1.03 (0.88–1.19)	0.91 (0.77–1.09)
≥11		1.32 (1.07–1.61)	1.25 (1.01–1.56)	1.31 (1.03–1.66)
P for trend		0.008	0.074	0.253
HADS-A	Events/person-time	2012/648 777	1847/630 642	1533/586 848
0–7		Reference	Reference	Reference
8–10		1.02 (0.87–1.20)	1.00 (0.84–1.18)	0.91 (0.76–1.00)
≥11		1.30 (1.06–1.60)	1.30 (1.06–1.61)	1.25 (0.99–1.57)
P for trend		0.027	0.049	0.309
HADS-T	Events/person-time	1997/647 414	1836/629 490	1528/586 132
0–12		Reference	Reference	Reference
15–19		1.02 (0.85–1.21)	1.00 (0.83–1.20)	0.87 (0.70–1.07)
≥19		1.26 (1.04–1.51)	1.24 (1.02–1.51)	1.22 (0.98–1.51)
P for trend		0.032	0.066	0.345

HR indicates hazard ratio; CI, confidence interval; AMI, acute myocardial infarction.
Model 1: adjusted for calendar age and sex. Model 2: Model 1 + marital status, education.
Model 3: Model 2 + smoking, physical activity, body mass index, total cholesterol, diabetes mellitus, systolic blood pressure.

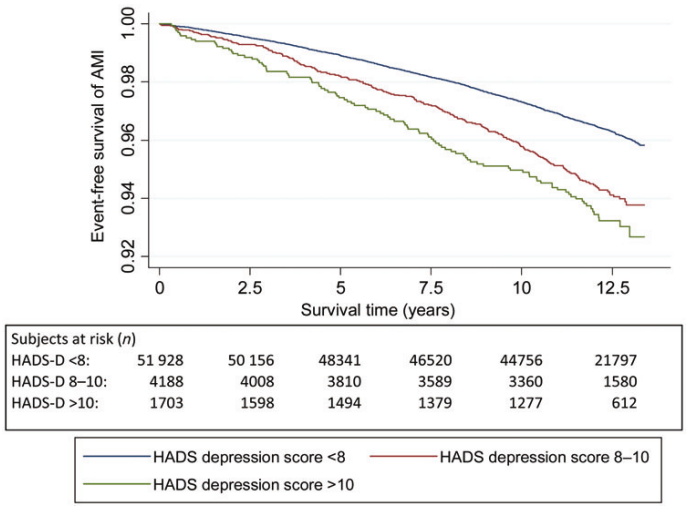

Figure 2 The Kaplan–Meier curve of incident acute myocardial infarction and subjects at risk during follow-up according to HADS-Depression symptom categories.

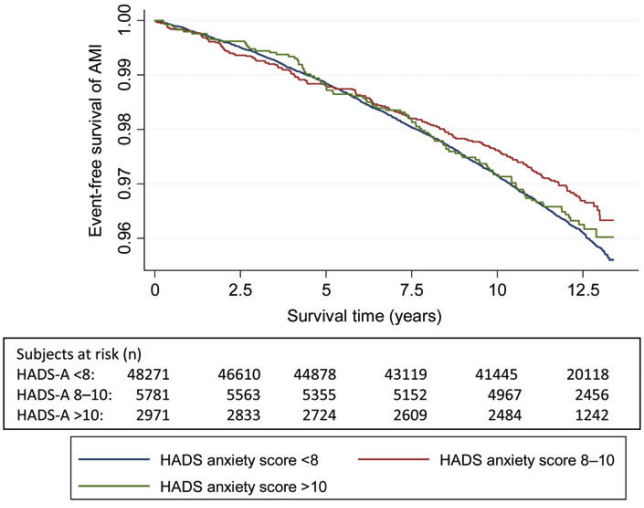

Figure 3 The Kaplan–Meier curve of incident acute myocardial infarction and number of persons at risk during follow-up according to HADS-Anxiety symptom categories.

traditional cardiovascular risk factors. For depression symptoms, the effect was only evident the first 5 years of follow-up, which raises a possibility for a reverse causation. For anxiety symptoms and MSAD, AMI risk attenuated with exclusion of participants with co-existent chronic physical illnesses at baseline, which probably reflects confounding.

Comparisons with previous studies

Although anxiety and depression symptoms tend to overlap, these conditions have to date mostly been investigated separately in terms of risk for AMI.[10] A recent meta-analysis of 23 prospective studies including a wide range of anxiety measures, found a pooled effect-size associated with incident cardiac heart disease of 1.26

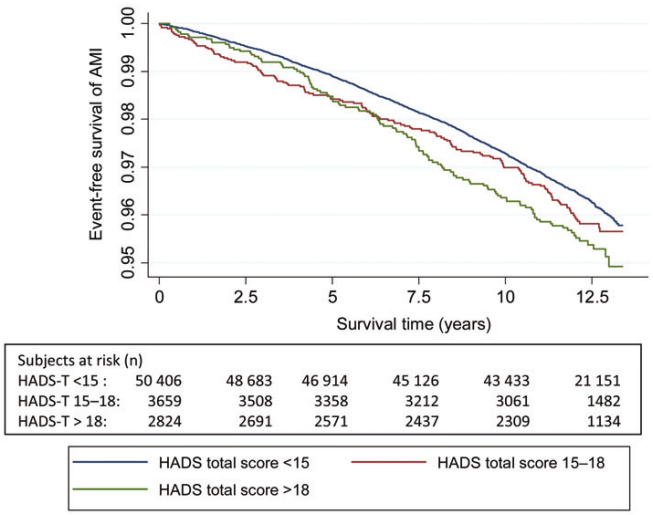

Figure 4 The Kaplan–Meier curve of incident acute myocardial infarction and number of persons at risk during follow-up according to HADS-Total symptom categories.

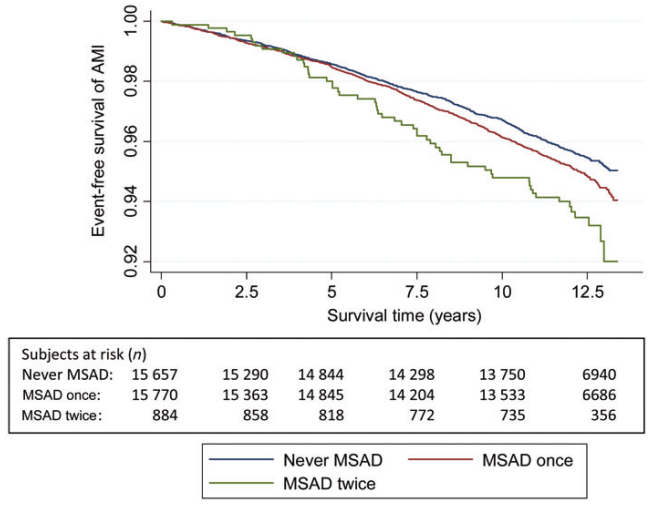

Figure 5 The Kaplan–Meier curve of incident acute myocardial infarction and number of persons at risk during follow-up according to mixed anxiety and depression symptom categories in HUNT 1 and 2.

(95% 1.15–1.38).[26] Only 22% of the anxiety studies included in the meta-analysis consisted of both men and women.[26] In our study, the relative risks for AMI in relation to anxiety and depression symptoms were similar in the two sexes and the overall effect was comparable to previous studies.[26]

For depression, another meta-analysis including 21 prospective studies reported a pooled effect of 1.95 (95% CI 1.51–2.51) on CAD death and AMI,[9] considerably higher than the point estimates found in our study. We can think of several explanations for this discrepancy; first, studies using self-report instruments have generally

Table 3 The association between episodes of mixed symptoms of anxiety and depression (MSAD) in HUNT 1 and 2, and risk of subsequent acute myocardial infarction

Number of episodes MSAD Events/person years	Model 1 1491/372 505	Model 2 1368/361 051	Model 3 1145/333 405
Never MSAD ($n = 15\,657$)	Reference	Reference	Reference
MSAD once ($n = 15\,770$)	1.07 (0.97–1.19)	1.06 (0.96–1.19)	1.02 (0.99–1.14)
MSAD twice ($n = 884$)	1.63 (1.24–2.19)	1.65 (1.24–2.20)	1.52 (1.11–2.08)
P for trend	0.009	0.016	0.184

Results presented as HR's (95% CIs).
Model 1: adjusted for calendar age and sex.
Model 2: Model 1 + marital status, education.
Model 3: Model 2 + smoking, physical activity, body mass index, total cholesterol, diabetes mellitus+ systolic blood pressure.

found smaller effects than studies relying on clinical diagnosis or psychiatric interviews.[9] Second, adjustment for cardiovascular risk factors and comorbid physical illness(es) was limited in most previous studies. Third, large population-based studies tended to report lower point estimates than smaller studies probably due to publication bias.[9] Finally, we shall emphasize that previous studies used diagnostic interviews or self report instruments that included a wide depressive symptom spectrum, such as sleep problems, lack of energy and disturbed appetite. These symptoms greatly overlap with symptoms of common physical illnesses, including subclinical coronary artery disease.[13] As a result, the genuine contribution of core psychological and cognitive symptoms of anxiety and depression to cardiovascular morbidity has been uncertain. Importantly, the tool used in the current study, i.e. HADS, was originally designed for detection of anxiety and depression in patients with physical illness, and systematically excludes somatic symptoms which can mimic heart disease.[22] Hence, our study is one of the first to link core psychological and cognitive symptoms of anxiety and depression to a moderately increased AMI risk. Nevertheless, by using this approach, some participants with predominantly somatic symptoms of depression might go undetected. As a consequence, we are likely to have underestimated, rather than overestimated, the association between depression and AMI in our study.

Most studies confirm that comorbid anxiety and depression are associated with more severe illness, worse outcome, and increased mortality compared with single conditions.[27] This was not confirmed in our study, as we found no excess risk for AMI associated with MSAD in HUNT 2.

Limited previous evidence suggested that information on anxiety or depressive symptoms provided by repeated measures enable a considerably better risk prediction when compared with the information derived from a single measurement.[1,3,28,29] Our study supports these earlier findings and suggests that persistent or recurrent symptoms might be associated with increased cardiovascular risk. One can hypothesize that a single measurement could reflect a normal reaction to stressful events, while multiple episodes may better capture anxiety and depressive disorders,[30] such as bipolar disorders, known for poorer adherence with lifestyle and medical advice.[31]

Our sensitivity analysis regarding depressive symptoms, but not anxiety or mixed symptoms, indicate a higher risk for AMI in the first 5 years of follow-up. This might reflect a reverse causation. The possibility that both depressive symptoms and subsequent AMI are caused by subclinical manifestations of atherosclerosis is among the greatest challenges for research on the prospective association between depression and AMI.[12,13] Individuals free from clinical heart disease included in prospective studies may not be free from atherosclerosis, which is known to develop during decades before first symptoms.[8,10] Thus, individuals free from clinical heart disease included in prospective studies may not be free from atherosclerosis. Atherosclerosis may facilitate depressive symptoms even before generating cardiac ischaemia creating a spurious association between depression and atherosclerosis. One possible pathway is the depressogenic actions of the increased inflammatory activity.[32,33] Moreover, neuroimaging and neuropathology studies suggest that late onset depression often has a cerebrovascular origin.[34] Cerebral atherosclerosis may thus facilitate depressive symptoms even before coronary atherosclerosis generates cardiac ischaemia.

Several epidemiological findings supported the reverse causality hypothesis. Studies with a shorter follow-up generally show stronger association with AMI.[9] In the PRIME study, depressive symptoms were associated with coronary heart disease only in the first 5 years of follow-up,[35] a finding which is confirmed in our study. There were some studies with null findings which were conducted in young populations, where vascular depression and subclinical CAD are less likely. In a study of healthy US army personnel 39–45 years of age,[36] no correlation was found between depression and subclinical coronary artery disease identified by electron-beam computed tomography. Further, in a large prospective cohort study of men who were 19–21 years old at baseline, only anxiety but not depression was associated with future CAD risk.[37]

While adjustment for established cardiovascular risk factors was extensive in several studies regarding anxiety,[26] many prospective studies of depression and AMI risk failed to adjust even for well-known cardiovascular risk factors such as smoking and physical activity.[9] Furthermore, comorbid physical disorders are among the most overlooked confounders in previous prospective studies of anxiety or depression and subsequent heart disease.[12] Depressive symptoms are highly correlated with the overall disease burden, and several common chronic disorders are risk factors for AMI.[13] In the present study, AMI risk in participants with symptoms of anxiety and MSAD at baseline was attenuated considerably after excluding all participants with comorbid chronic diseases from the analysis. In

Table 4 Risk for acute myocardial infarction associated with symptoms of anxiety and depression in sensitivity analyses

	Exclusion of all chronic diseases[a]	Restriction to hospital verified AMI	Exclusion of first 5 years of follow-up
HADS—depression			
Events/ person years	768/384 975	1228/51 442	1082/341 485
Cut off 8–10	0.95 (0.74–1.23)	0.94 (0.44–1.15)	0.96 (0.78–1.18)
Cut off ≥11	1.25 (0.81–1.91)	1.33 (1.02–1.75)	1.14 (0.83–1.57)
P for trend	0.632	0.203	0.673
HADS—anxiety			
Events/person years	762/384 068	1209/586 848	1060/345 716
Cut off 8–10	1.08 (0.82–1.43)	0.97 (0.79–1.19)	0.87 (0.69–1.10)
Cut off ≥11	1.14 (0.74–1.75)	1.33 (1.03–1.71)	1.32 (1.00–1.73)
P for trend	0.439	0.099	0.321
HADS—total			
Events/person years	761/383 732	1205/586 132	1057/339 216
Cut off 15–19	0.75 (0.53–1.05)	0.89 (0.70–1.31)	0.80 (0.61–1.05)
Cut off ≥19	1.07 (0.72–1.58)	1.27 (1.00–1.61)	1.23 (0.95–1.59)
P for trend	0.559	0.202	0.563
MSAD (HUNT 1 and 2)			
Events/person years	587/204 678	908/333 405	787/27 215
One episode MSAD	0.93 (0.79–1.09)	1.07 (0.93–1.22)	1.06 (0.92–1.23)
Two episode MSAD	1.38 (0.79–2.40)	1.81 (1.29–2.52)	1.75 (1.21–2.53)
P for trend	0.688	0.022	0.053

MSAD, mixed symptoms of anxiety and depression.
[a]Joint effect of persons that reported asthma, diabetes, other endocrine disorders, musculoskeletal disorders, autoimmune diseases, epilepsy, cancer, and other chronic diseases.

contrast, the excess AMI risk in those with depression symptoms and recurrent MSAD was more robust throughout these analyses.

Strengths and limitations

Compared with prior studies, we had an ample statistical power to address the prospective association between symptoms of depression and anxiety, and the risk for AMI. The population-based nature of the study, the high stability (less than 0.3% net migration/year), and relatively high genetic and socioeconomic homogeneity of the population[17] along with reliable hospital and register information covering the entire county, ensured close to complete follow-up and minimized the possibility for the misclassification of endpoints or for a selection bias.[24] Moreover, in contrast to many previous studies, we could extensively control for potentially confounding factors.

Yet, the present work has some important limitations. Attendance in HUNT 2 was generally high, but considerably lower in the age group of 70 years and older.[19] Further, we had no information on treatment for depression. SSRIs, the most commonly used medication for anxiety and depression, are known to reduce platelet adhesion[38] and increase BMI[39] and therefore are potential mediators for the observed associations. However, in the present study, it was not possible to separate the effect of depression and its eventual treatment.

Conclusion

Our findings indicate that self-reported core psychological symptoms of depression and anxiety, especially if recurrent, are moderately associated with the AMI risk. We had some indication that these associations might partly reflect reverse causation (depression) or confounding from common chronic diseases (anxiety and mixed anxiety and depression).

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Paper II

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Symptoms of anxiety and depression and risk of heart failure: the HUNT Study

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Aims Symptoms of anxiety and depression often co-exist with cardiovascular disease, yet little is known about the prospective risk for heart failure (HF) in people with symptoms of depression and anxiety. We aimed to study these prospective associations using self-reported symptoms of anxiety, depression, and mixed symptoms of anxiety and depression (MSAD) in a large population sample.

Methods and results In the second wave of the Nord-Trøndelag Health Study (HUNT 2, 1995–1997), Norway, baseline data on symptoms of anxiety and depression, socio-demographic variables, health status including cardiovascular risk factors, and common chronic somatic diseases were registered for 62 567 adults, men and women, free of known HF. The cohort was followed for incident HF from baseline throughout 2008. A total of 1499 cases of HF occurred during a mean follow-up of 11.3 years (SD = 2.9), identified either in hospital registers or by the National Cause of Death Registry. There was no excess risk for future HF associated with symptoms of anxiety or MSAD at baseline. For depression, the multi-adjusted hazard ratios for HF were 1.07 (0.87–1.30) for moderate symptoms and 1.41 (1.07–1.87) for severe symptoms (*P* for trend 0.026). Established cardiovascular risk factors, acute myocardial infarction (AMI) prior to baseline, and adjustment for incident AMI as a time-dependent covariate during follow-up had little influence on the estimates.

Conclusion Symptoms of depression, but not symptoms of anxiety or MSAD, were associated with increased risk for HF in a dose–response manner. The increased risk could not be fully explained by cardiovascular or socio-economic risk factors, or by co-morbid AMI.

Keywords Depression • Anxiety • Prospective • Risk • Heart failure • Epidemiology

Introduction

Heart failure (HF) is often co-prevalent with symptoms of depression[1–8] and anxiety,[3,9] and symptoms of depression have been found to worsen the course and prognosis of established HF.[2,3,10]

Ischaemic heart disease (IHD), like acute myocardial infarction (AMI), is the main cause of HF in Europe and accounts for ~60% of HF.[11] Other known precursors for HF are hypertension, diabetes, cardiomyopathy, heart valve disease, and arrhythmias.[12] In the development of HF, except HF initiated by AMI, the process of myocardial remodelling often starts long before the onset of HF symptoms.[13] As HF is a major and increasingly important public health problem, it is crucial to search for modifiable risk factors in the aetiology of HF.[14] It is plausible that symptoms of depression and anxiety represent such modifiable risk factors as they have been found to influence behavioural risk factors for HF, such as obesity, reduced physical activity, alcohol abuse, and smoking.[1,15] Furthermore, neurohormonal stress associated with symptoms of depression and anxiety is known to regulate blood pressure, heart

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rate, proinflammatory cytokines, and circulating catecholamine levels, which in turn promote HF.[1,16]

However, the prospective evidence supporting a link between symptoms of depression and future HF arise from small studies of elderly people, and the results are conflicting.[4–8] To the best of our knowledge, only one study, among US veterans, has investigated the risk for future HF with symptoms of anxiety.[17] We therefore aimed to investigate the prospective association of self-reported symptoms of anxiety and depression with risk for future HF in a large population-based study, taking into account a large number of established cardiovascular risk factors, previous and/or incident AMI, several chronic somatic disorders, and previous symptoms of anxiety and depression.

Methods

Study population and setting

All adult citizens in Nord-Trøndelag County, Norway, received a postal invitation to participate in the second wave of the Nord-Trøndelag Health Study (HUNT 2, 1995–1997, http://www.ntnu.edu/hunt). In total, 94 187 individuals were invited, and 65 215 (69%) participated in the HUNT 2 study. The participants attended a baseline clinical examination and gave self-report on standardized questionnaires (http://www.ntnu.edu/hunt/data/que). Details of the HUNT study have been published elsewhere.[18,19]

The study was approved by the regional committee for medical and health research ethics, by the National Directorate of Health, and by the Norwegian Data Inspectorate.

Exposure: symptoms of anxiety and depression

Participants self-reported symptoms of anxiety and depression using a Norwegian version of the Hospital Anxiety and Depression Scale (HADS),[20] which assesses core psychological symptoms of anxiety (HADS-A) and depression (HADS-D) during the previous week.

Seven depression questions mirror symptoms of anhedonia and loss of interest, and seven anxiety questions mirror mostly symptoms of worry and tension. We included all participants that responded to ≥5 items on one subscale ($n = 62\,693$). For those who filled in only five or six items on the HADS-A and -D subscales, missing scores were substituted based on the sum of completed items multiplied by 7/5 or 7/6, respectively.[21] All HADS questions have a 4-point Likert scale, ranging from 0 (no symptom) to 3 (highest symptom level); thus the subscales range from 0 points (no symptoms) to 21 points, which allows calculation of risk per unit increase in the HADS.[21] In addition, recommended cut-offs were used to categorize the participants as not depressed or anxious (score <8), moderately depressed or anxious (score between 8 and 11), and severely depressed or anxious (score ≥11).[22] Mixed symptoms of anxiety and depression (MSAD) were calculated by summing up valid HADS-A and HADS-D into HADS-total scores (HADS-T) and categorized into no MSAD (score <15), moderate MSAD (score between 15 and 18), and severe MSAD (score ≥19).[23]

Previous symptoms of MSAD were available for 36 418 participants that also attended HUNT 1 (1984–1986) and filled in the 4-item Anxiety and Depression Index (ADI-4). ADI-4 has a high correlation (0.83) with the HADS-T score from HUNT 2 and is an acceptable indicator for MSAD (sensitivity 0.51, specificity 0.93).[24] Two ADI questions have a 4-point Likert scale: calmness, ranging from almost all the time (1) to never (4); and nervousness, ranging from never (1) to almost all the time (4). The last two ADI questions about mood and vitality have a 7-point Likert scale ranging from very happy/strong and fit (1) to very downhearted/tired and worn out (7). We categorized symptoms of MSAD in HUNT 1 by scoring on the upper quartile on ADI-4, i.e above a score of 14. Symptoms of MSAD in HUNT 2 were defined as a score ≥19 on the HADS-T subscale. A variable to indicate the combined burden of MSAD in HUNT 1 and 2 was created in categories of never (no symptoms of MSAD in HUNT 1 or 2), one (MSAD symptoms in one of the HUNT waves), and two episodes (MSAD symptoms in both HUNT waves).

Outcome ascertainment

After baseline, the participants were followed up for a first incident of HF until 31 December 2008, identified either by linkage with medical records at the two hospitals in Nord-Trøndelag county or by the National Cause of Death Registry.[25] A total of 126 participants were excluded because their medical records indicated HF before they participated at baseline. Therefore, 62 567 people were included in the analyses, as displayed in *Figure 1*. Heart failure was defined and diagnosed according to the current European Society of Cardiology (ESC) Guidelines.[26] The overall quality of the hospital discharge diagnosis of HF is generally high in Nordic countries.[27,28] In order to increase specificity, we only extracted primary diagnoses as recommended.[27] Deaths due to HF were extracted from the National Death Registry. We used International Classification of Diseases (ICD) 9 code 428 and ICD codes I50.0, I50.1, and I50.9 to identify HF.[25] Having 100% specificity and low—but non-differential—sensitivity leads to no bias of the risk ratio. Even a slight decrease in specificity, even if non-differential, might lead to a severe bias. Therefore, in brief, our decision to include only primary diagnosis decreases our power, but preserved our validity.[29]

During an average of 11.3 years of follow-up, 8164 participants who died of causes other than HF and 224 who left the county were censored at time of death or emigration (see *Figure 1*).

Covariates

Demographic and lifestyle factors

Cohabitation status was dichotomized as living with a partner or alone. Education was categorized as low (≤9 years), medium (between 10 and 12 years), or high (over 12 years).

Smoking habits were self-reported and were categorized as current, previous, or never smoking. We categorized the participants according to self-reported alcohol consumption as abstainers, very light drinkers (0–1 drinks per day), light to moderate drinkers (1–2 drinks per day), or moderate to heavy drinkers (>2 drinks per day). Physical activity was reported as light or hard, defined respectively as activity excluding or including sweating or feelings of breathlessness. The participants were categorized as inactive (<1 h of strenuous activity and <3 h of light physical activity per week), moderately active (1–3 h of strenuous activity or >3 h of light activity per week), and as physically active (>3 h of strenuous physical activity per week).

Common chronic somatic diseases

The participants reported their medical history (yes/no) regarding previous cardiovascular diseases (myocardial infarction, stroke, or angina

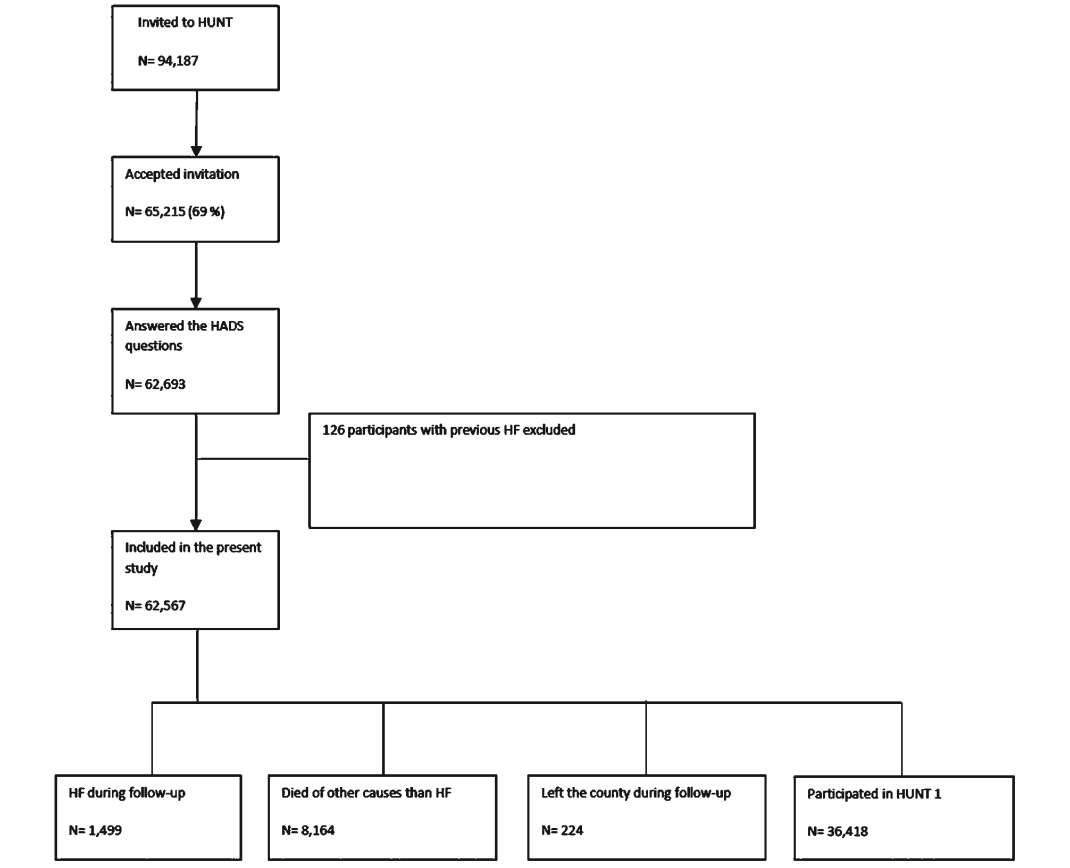

Figure 1 Flow chart of the heart failure (HF) study recruitment and follow-up.

pectoris), cancer, asthma, diabetes mellitus, other endocrine disorders (hypothyreosis, hyperthyreosis, goitre, or thyroiditis), musculoskeletal disorders (osteoporosis, fibromyalgia, or arthrosis/arthritis), autoimmune disease (Bechterew disease or rheumatoid arthritis), epilepsy, or other chronic disease. Those who answered 'yes' to one or more of these questions were categorized as having a chronic disease.

Clinical examination

Clinical examinations were performed by trained nurses according to a standardized protocol and included measurements of blood pressure, heart rate, weight, height, and waist and hip circumference. Heart rate, and systolic and diastolic blood pressures were measured after the participant had been seated for at least 2 min with the cuff on, with cuff size adjusted for arm circumference.[30] Blood pressure and heart rate measurements were performed with the Dinamap 845XT (Criticon) based on oscillometry and automatically involved three recordings at 1-min intervals. The first heart rate recording was on average 2 b.p.m. lower than the second and third measurement and was thus used in order to mirror resting heart rate. For blood pressure, the value decreased for each recording, thus we used the average of the second and third blood pressure readings. Height was measured without shoes to the nearest 1.0 cm and weight with light clothing to the nearest 0.5 kg.[30] Body mass index (BMI) was computed as weight (in kg) divided by the squared value of height (in metres).

Blood sampling and laboratory measurements

A non-fasting whole blood sample was drawn from each participant, recording the time between the last meal and the venepuncture. Serum was separated by centrifugation at the screening site and immediately placed in a refrigerator. The samples were sent (the same day, or the following Monday for samples drawn on Friday) for analyses at the central laboratory at Levanger Hospital, Norway, where a Hitachi 911 Autoanalyzer was used, applying reagents from Boehringer Mannheim, Germany. Serum total cholesterol was measured by an enzymatic colorimetric cholesterol esterase method and serum creatinine by the Jaffé method. The day-to-day coefficient of variations were 1.3–1.9% for total cholesterol and 3.5% for creatinine.[8]

Statistical analysis

We used Cox proportional hazard models to examine the associations of symptoms of depression and anxiety with subsequent risk for HF and hazard ratios (HRs) with 95% confidence intervals (CIs). All the models were analysed both using a categorical approach and estimating risk per unit increase on the different HADS scores. For test of trends between increasing anxiety and depression symptom level, a numeric value of 0–2 was assigned to the HADS categories, with 0 having no, 1 having moderate, and 2 having severe symptoms of anxiety or depression, treating the categories as a continuous variable. In a separate analysis, we calculated the risk for HF associated with the presence of MSAD in HUNT 1 and HUNT 2 when those without symptoms of MSAD in both of the surveys constituted the reference group.

We used directed acyclic causal graphs to summarize visually hypothetical relationships among variables of interest.[29] Model 1, adjusted for age as a continuous variable and sex, is the best for assessing causality. Models 2–5 include variables that may act as both confounding and mediating factors for the association of depression and anxiety with HF risk. Model 2 included potentially socio-economic confounders, such as education and marital status. In model 3, established cardiovascular risk factors such as high heart rate, high blood pressure, low physical activity, high BMI, smoking, dyslipidaemia, alcohol intake, diabetes mellitus, and serum creatinine were added. Model 4 tested whether AMI prior to baseline data collection influenced the estimates. Finally, the full multivariable model tested if AMI during follow-up influenced the estimates, and included AMI during follow-up as a time-dependent variable (model 5). For the 2522 non-responders on the HADS questionnaire, we examined HF incidence and the distribution of the variables included in the statistical models.

Several stratified analyses were conducted to assess whether the association of anxiety and depression and risk for HF could be modified by other factors. We investigated the potential effect of modification by sex, age (dichotomized at age 50 and age 65), BMI (dichotomized at $\geq$35 kg/m^2), total cholesterol (dichotomized at 6.5 mmol/L), education (dichotomized at 12 years), blood pressure (systolic blood pressure dichotomized at >140 mmHg, diastolic blood pressure at >90 mmHg), smoking status (current vs. no current smoking), alcohol consumption (heavy drinking vs. no heavy drinking), and previous AMI (yes/no). We also formally tested the homogeneity of stratum-specific relative risks. For these tests of interaction, we used the trend variable as defined above.

Several sensitivity analyses were performed to assess the robustness of our findings. First, as AMI is a known risk factor for HF and is also associated with depression and anxiety symptoms, we performed an additional analysis restricted to those without known AMI at baseline. Next, we analysed the risk restricted to diabetic patients. Thereafter, we excluded participants with one or more of the following co-morbid physical illnesses: previous myocardial infarction (AMI), stroke, angina pectoris, cancer, asthma, diabetes mellitus, other endocrine disorders, musculoskeletal disorders, autoimmune diseases, and other chronic diseases.

Secondly, in additional analysis, we restricted cases to those HF cases that were confirmed at the hospital; thus, cases whose HF diagnosis were based on death certificates alone were excluded from the analyses.

Finally, in order to address the possibility of reverse causation as an explanation for possible associations, we excluded the first 5 years of follow-up and repeated the analyses. All sensitivity analyses were run in the full multivariable model including previous AMI and adjustment for incident AMI during follow-up as a time-dependent covariate.

We tested the proportionality of hazard using log–log curves and formal tests of interaction with time or log-time. There was no evidence against the proportionality assumption in our models. Statistical analyses were performed in Stata IC/12.1 for Windows (©Stata Corp LP).

Results

Characteristics of the study population at baseline, by HF status during follow-up, are shown in *Table 1*. Among those who did not respond to the HADS questionnaire, the HF incidence in the 11.4 years was 8.7%, probably mainly because they were older (mean 66.4 years) at baseline, and in addition had a more unfavourable cardiovascular risk profile, including higher blood pressure on average, than the total study population. Among the 63 567 study participants, 1499 participants (2.4%) developed HF during an average of 11.3 years (SD 2.9) of follow up. Of these, 1245 HF cases were diagnosed and included in the hospital registers, and 254 were registered by the National Cause of Death Registry alone. The participants that developed HF were older at baseline examination and more likely to have diabetes, higher systolic and diastolic blood pressure, be inactive, to live alone, have lower education, be alcohol abstainers, and score higher on the HADS-D subscale. They also had a higher incidence of incident AMI (14%) during follow-up, compared with those who did not develop HF (2.5% incident AMI).

Using the highest cut-off (HADS $\geq$11), the prevalence rates were 3.2% and 5.1% for depression and anxiety symptoms, respectively. This estimate is comparable with the prevalence of diagnosed depression and anxiety disorders in the general population in Europe.[31] These participants were more likely to be female, less educated, inactive, current smokers, alcohol abstainers, and report a history of previous AMI than those in the reference group.

Table 2 presents the age- and sex-adjusted HRs and several multivariable adjusted HRs for incident HF in relation to symptoms of depression, anxiety, and MSAD. There was no excess risk for future HF associated with symptoms of anxiety in the crude model, adjusted for sex and age (HR 1.17, 95% CI 0.90–1.15). For MSAD, the moderately increased risk for HF observed in model 1 (HR 1.34, 95% CI 1.04–2.07) was explained by traditional cardiovascular factors in model 3 (HR 1.09, 95% CI 0.81–1.46). For depression, the age- and sex-adjusted HRs for HF were 1.11 (0.95–1.30) for moderate symptoms and 1.46 (1.19–1.80) for severe symptoms (*P* for trend 0.000). These associations for severe symptoms were only slightly attenuated after further adjustments for socio-economic status, an established cardiovascular risk factor (HR 1.37, 95% CI 1.04–1.81). Additional adjustment for previous and time-dependent incident AMI during follow-up did not further attenuate the risk for HF associated with severe symptoms of depression (HR 1.41, 95% CI 1.07–1.87). The results from the analysis using the risk per unit HADS score approach did not differ from the categorical approach; taking HADS-D as an example, with a 1.03 increased risk associated with each unit rise in HADS-D

Table 1 Baseline characteristics of the participants according to heart failure during follow-up

	n	HF during follow-up, % (*n*)	No HF during follow-up, % (*n*)
Total	62 567	2.4 (1499)	97.6 (61 068)
Variable			
Sex (male)	62 567	50.6 (759)	46.7 (28 559)
Diabetes mellitus	62 448	12.7 (188)	2.6 (1562)
Smoking	62 344		
Never	28 313	45.4 (674)	45.4 (27 639)
Former	15 675	32.7 (485)	24.9 (15 190)
Current	18 356	21.9 (1485)	29.6 (18 030)
Physical activity	56 993		
Inactive	22 255	60.9 (676)	38.6 (21 579)
Moderately active	29 109	34.7 (385)	51.4 (28 724)
Physically active	5629	4.4 (49)	9.9 (5580)
Living alone	62 425	43.9 (659)	39.4 (24 007)
Education	60 270		
≤9 years	21 629	71.6 (942)	35.1 (20 687)
10–12 years	26 443	22.4 (295)	44.4 (26 148)
>12 years	12 198	5.9 (78)	20.6 (12 120)
Alcohol	58,986		
Abstainer	23 640	71.2 (975)	39.3 (22 665)
Light drinker	27 298	23.7 (325)	46.8 (26 973)
Moderate drinker	6196	3.8 (52)	10.7 (6144)
Heavy drinker	1852	1.2 (17)	3.2 (1835)
Previous myocardial infarction	1871	21.7 (322)	2.5 (1549)
Myocardial infarction during follow-up	1739	14.0 (210)	2.5 (1529)
Variables, mean (SD)	*n*	Mean (SD)	Mean (SD)
Age, years	62 567	73.6 (9.7)	48.7 (16.6)
BMI, kg/m^2	61 956	27.9 (4.6)	26.3 (4.1)
Heart rate, b.p.m.	62 235	73.3 (14.6)	71.3 (13.1)
Systolic BP, mmHg	62 152	156.6 (25.9)	136.9 (21.2)
Diastolic BP, mmHg	62 152	85.5 (12.1)	80.0 (12.0)
Total cholesterol, mmol/ L	62 216	6.4 (1.3)	5.9 (1.3)
HDL cholesterol, mmol/L	62 195	1.3 (0.4)	1.4 (0.4)
Triglycerides, mmol/L	62 215	2.1 (1.2)	1.7 (1.1)
Serum creatinine, mmol/L	62 214	97.6 (22.6)	87.5 (15.0)
HADS-Depression score	62 414	4.6 (3.5)	3.5 (3.3)
HADS-Anxiety score	61 335	3.8 (3.4)	4.3 (3.3)
HADS-Total score	61 182	8.4 (6.0)	7.7 (5.6)
ADI-Total score in HUNT 1	36 418	13.6 (1.3)	13.5 (1.2)

ADI, Anxiety and Depression Index; BMI, body mass index; BP, blood pressure; HADS, Hospital Anxiety and Depression Scale; HF, heart failure.

score, a person with a score of 8 will have 1.03^9 times, i.e 30%, increased risk compared with a person that scores 0. *Figure 2* shows the Kaplan–Meier curves for incident HF according to depression symptom categories; depressive symptoms were associated with higher risk for HF in a dose–response manner consistently during the follow-up.

Table 3 displays the risk for HF with MSAD in HUNT 1 and 2. Those who reported MSAD in both HUNT 1 and 2 had an HR of 1.47 (95% CI 1.04–2.07) for HF in model 1 compared with those who did not experience MSAD in any of the health surveys. This relative risk for HF was, however, largely explained by cardiovascular risk factors (HR 1.18, 95% CI 0.73–1.87). Further adjustments for previous AMI and time-dependent incident AMI during follow up did not lead to further attenuation.

We found no statistical evidence for any effect modification for any of the stratified variables including sex, age, education, smoking status, BMI, total cholesterol, physical activity, and blood pressure.

Sensitivity analysis

Supplementary material online, *Table S1* presents the multivariable adjusted HRs for HF in relation to symptoms of depression, anxiety, and MSAD in different sensitivity analyses.

A total of 52 202 participants completed the questionnaire on common chronic somatic disease. Of these, 16 072 reported having at least one chronic somatic disease. Diabetes was six-fold more prevalent in those who later developed HF, and this warranted a separate analysis; in the 1750 diabetic participants, ≥11

Table 2 Hazard ratios (95% confidence intervals) for heart failure during follow-up according to symptoms of depression and anxiety, and mixed symptoms of anxiety and depression in HUNT 2 (1995–1997).

Variable		Model 1	Model 2	Model 3	Model 4	Model 5
HADS-D	Events/person-years	1492/703 766	1310/679 612	905/597 200	900/596 685	900/596685
0–7		Reference	Reference	Reference	Reference	Reference
8–10		1.11 (0.95–1.30)	1.10 (0.93–1.30)	1.07 (0.87–1.32)	1.07 (0.87–1.31)	1.08 (0.88–1.33)
≥11		1.46 (1.19–1.80)	1.51 (1.21–1.89)	1.38 (1.04–1.83)	1.41 (1.06–1.86)	1.41 (1.07–1.87)
P for trend		0.000	0.001	0.034	0.028	0.023
	Risk per unit increase in the HADS-D scale	1.03 (1.02–1.05)	1.03 (1.02–1.05)	1.03 (1.01–1.05)	1.03 (1.01–1.05)	1.03 (1.01–1.05)
HADS-A	Events/person-years	1366/693 483	1224/671 888	869/593 199	864/592 694	864/592694
0–7		Reference	Reference	Reference	Reference	Reference
8–10		1.12 (0.93–1.34)	1.15 (0.95–1.40)	0.88 (0.69–1.13)	0.88 (0.69–1.13)	0.90 (0.70–1.15)
≥11		1.17 (0.90–1.15)	1.07 (0.80–1.43)	0.95 (0.67–1.35)	0.98 (0.69–1.40)	1.00 (0.70–1.43)
P for trend		0.105	0.221	0.431	0.560	0.643
	Risk per unit increase in the HADS-A scale	1.01 (0.99–1.03)	1.01 (0.99–1.02)	1.01 (0.99–1.03)	1.01 (0.99–1.03)	1.01 (0.99–1.03)
HADS-T	Events/person-years	1359/691 950	1219/670 617	868/592 540	869/592 035	863/592035
0–15		Reference	Reference	Reference	Reference	Reference
15–19		1.09 (0.90–1.33)	1.17 (0.91–1.37)	1.18 (0.92–1.49)	1.15 (0.90–1.46)	1.16 (0.91–1.48)
≥19		1.34 (1.04–2.07)	1.31 (1.04–1.66)	1.10 (0.82–1.48)	1.18 (0.87–1.58)	1.20 (0.89–1.61)
P for trend		0.018	0.015	0.248	0.151	0.114
	Risk per unit increase in the HADS-T scale	1.01 (1.00–1.02)	1.01 (1.00–1.02)	1.01 (0.99–1.02)	1.01 (1.00–1.02)	1.01 (1.00–1.03)

HADS, Hospital Anxiety and Depression Scale. HADS-T, was calculated by summing up valid HADS-A and HADS-D into HADS-total scores.
Model 1: adjusted for calendar age and sex.
Model 2: model 1 + marital status, education.
Model 3: model 2 + smoking, physical activity, body mass index, total cholesterol, diabetes mellitus, resting heart rate, systolic blood pressure, alcohol, serum creatinine.
Model 4: model 3 + previous myocardial infarction.
Model 5: model 4 + time-dependent adjustment for acute myocardial infarction during follow-up.

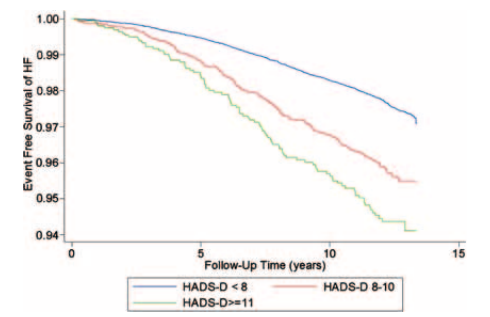

Figure 2 Kaplan–Meier curve of incident heart failure during follow-up according to depression category. HADS-D, Hospital Anxiety and Depression Scale, depression subscale.

in depression score constituted a 70% (95% CI 1.03–2.80) higher risk than for those who scored <8. This high risk in the diabetic population was mainly explained by cardiovascular risk factors in model 3, where the risk dropped to 23%. After exclusion of all common chronic somatic diseases, 305 were diagnosed with HF during follow-up, and the risk of HF in people free of chronic diseases related to symptoms of depression slightly increased. Of special interest, the risk associated with symptoms of depression, after excluding participants with self-reported previous AMI before HUNT 2 ($n = 1253$), was only reduced by ~10% (HR 1.33, 95% CI 0.88–2.01) in the full multivariable model including adjustment for time-dependent incident AMI during follow-up.

When follow-up was restricted to HF events confirmed in hospitals (1073 events) and HF cases emerging after the first 5 years of follow-up (692 events), the risk for HF related to symptoms of depression remained virtually unchanged. The risk for HF associated with MSAD in HUNT 2 and repeated MSAD in HUNT 1 and 2 was elevated in hospitalized confirmed HF compared with the total HF sample, and lower after exclusion of the first 5 years of follow-up.

Discussion

In this large prospective study of a general population free from known HF at baseline, we found that symptoms of depression, but not those of anxiety or MSAD, were associated with a dose–response increased risk for incident HF. This risk remained essentially unchanged after adjustment for demographic variables, established cardiovascular risk factors, previous AMI, and time-dependent adjustment for incident AMI during follow-up. The

Table 3 Hazard ratios (95% confidence intervals) for heart failure during follow-up according to episodes of mixed symptoms of anxiety and depressionin HUNT 1 and HUNT 2.

No. of episodes of MSAD	Model 1	Model 2	Model 3	Model 4	Model 5 651/29616
Events/person-years	1021/406071	910/392 118	654/344 334	651/29 616	
Never MSAD	Reference	Reference	Reference	Reference	Reference
MSAD once	1.12 (0.98–1.27)	1.09 (0.95–1.24)	1.03 (0.88–1.20)	1.05 (0.89–1.22)	1.05 (0.90–1.23)
MSAD twice	1.47 (1.04–2.01)	1.53 (1.06–2.20)	1.30 (0.83–2.06)	1.21 (0.76–1.93)	1.21 (0.76–1.93)
P for trend	0.018	0.048	0.441	0.426	0.385

MSAD, mixed symptoms of anxiety and depression.
Model 1: adjusted for calendar age and sex.
Model 2: model 1 + marital status, education.
Model 3: model 2 + smoking, physical activity, body mass index, total cholesterol, diabetes mellitus, resting heart rate, systolic blood pressure, alcohol, serum creatinine.
Model 4: model 3 + previous myocardial infarction.
Model 5: model 4 + time-dependent adjustment for acute myocardial infarction during follow-up.

association also remained robust in several additional sensitivity analyses.

Comparison with previous studies

Previously, the association between anxiety symptoms and future HF has been investigated in one study of American veterans, where the authors found a 1.19 (95% CI 1.10–1.28) increased age-adjusted hazard associated with anxiety disorders and post-traumatic stress disorder.[17] This point estimate is comparable with the 1.17 (95% CI 0.90–1.15) hazard for future HF associated with a score of ≥11 on the HADS-A subscale in our study. The US study has a larger sample size, with 236 079 participants, which may explain the difference in precision between the two studies.

Symptoms of depression and risk for future HF have mostly been investigated in smaller studies and/or in selected samples, and conclusions have been conflicting.[4–8,17] Two studies found negative results between symptoms of depression and HF: the first of these was the 'Established population for epidemiologic studies of the elderly' (EPESE, $n = 1749$), conducted in 1999.[5] However, in that study, Chen *et al.* seem to have discarded symptoms of depression as a risk factor for HF based on *P*-values from χ^2 and *t*-statistics, which do not account for time to event. The second negative results were reported in 2011 from 'The cardiovascular health study (CHS)' population, who at baseline were on average 79 years old but free of HF ($n = 4114$). Afro-American people reported more depression (30%) compared with white people (18.7%) in the CHS study, yet the distribution of confirmed HF events between the ethnic groups was not reported. Based on well known differences in health status and access to health services across ethnical groups in the USA, this is a limitation of the otherwise well performed study.[32] In contrast, we had a homogenous study population from Norway, where healthcare coverage is universal, and free healthcare system access exists across socio-economic groups.[32]

Conversely, three small-scale studies with potential methodological problems reported increased risk for HF with depressive symptoms. 'The Finland, Italy and Netherlands Elderly' (FINE study), which included only men ($n = 799$), found a 1.16 increased hazard for each five steps in the Zung depression rating scale.[6] Another study, 'the Systolic Hypertension in the Elderly Program' in the USA, had short follow-up of 4538 persons above 65 years with hypertension,[4] i.e inclusion of only persons predisposed for HF,[7] found a 2.59 increased risk for future HF. The third study, also from EPESE, found a 52% increased risk for future HF associated with symptoms of depression, but only for the women in the sample. In contrast, our study included a large community sample with both sexes and long follow-up which allowed for exclusion of the first 5 years of follow-up, which increases the possibility of detecting reverse causation. Further, we used statistical models that allowed for time to event and we tested our model carefully for violations against the proportionality of hazard assumptions.

Unfavourable socio-economic and behavioural lifestyles may be a link between symptoms of depression and increased HF risk. Symptoms of depression, but not as much symptoms of anxiety, are often strongly associated with traditional risk factors for HF, such as lower education, physical inactivity, unhealthy diet, obesity, and poorer lifestyle.[1,33,34] Some of these behaviours associated with lowered mood, such as inactivity, obesity, and smoking, are also suggested to be sources of an inflammatory process that can cause HF, and reciprocally also cause depression.[35] In our study, people with the most severe symptoms of anxiety and depression had a more unfavourable socio-economic and cardiovascular profile. However, the adjustment for socio-economic factors and established cardiovascular risk factors only attenuated the relative risks in relation to symptoms of anxiety and MSAD, but not for depressive symptoms.

Ischaemic heart disease is a major cause of HF, and IHD is closely linked to symptoms of depression.[36–38] However, in our analyses, cardiovascular risk factors and AMI prior to baseline explained only 10–13% of the risk point estimate for HF in association with depressive symptoms. Time-dependent adjustment for incident AMI during follow-up did not attenuate the risk any further. Other chronic somatic diseases did not explain the association either, and the risk for HF associated with symptoms of depression increased when we excluded these chronic disorders. In diabetic patients, for example, the crude risk for HF associated with depression symptoms was high (70%) but, after adjustment for cardiovascular

risk factors, only a 23% increased risk remained. It is well known that over a certain amount of time, the strength of the effect of a given factor on disease occurrence may change because the prevalence of its causal complement in various mechanisms also changes.[29] It is therefore likely that participants with chronic diseases such as diabetes have different distributions of the other component causes, i.e cardiovascular risk factors, compared with the general population.

Strengths and study limitations

The large sample size and the life span perspective, together with long follow-up are amongst the most important strengths of this study. Furthermore, the HUNT catchment area has a low net migration (<0.3% net migration/year) and close to complete follow-up at the local hospitals.

Nevertheless, the study also has some important limitations. Similar to other prospective studies of risk for HF associated with symptoms of depression, we did not assess depression and anxiety disorders, but relied on self-reported symptoms. The HADS questionnaire, which was used in HUNT, does not mirror somatic depressive symptoms such as fatigue, weight loss, and insomnia, which greatly overlap with HF symptoms.[15,22] However, by using this approach, some depression cases with predominantly somatic symptoms may go undetected. Thus, it is more likely that our estimate for the association between symptoms of depression, anxiety, and MSAD with future HF is underestimated than overestimated. Even though we found no evidence of excess risk for HF in participants who reported symptoms of anxiety and depression in HUNT 1, ten years prior to baseline, compared with those who did not, our study cannot conclude whether there is a dose–response relationship between the number of episodes of symptoms of anxiety and depression, and HF risk.

Further, depressive symptoms have been shown to be associated with low adherence to treatment, drug, and medical advice.[1,39–42] The Norwegian prescription registry was established in 2004, and the HUNT 2 study does not have access to reliable data about all participants' medications. It is important to distinguish treatment by tricyclic antidepressant which are known to cause adverse cardiovascular effects from by selective serotonin reuptake inhibitors (SSRIs) that are associated with effects that are favourable in lowering cardiovascular risk.[43] Therefore, poor medical adherence might be a potential mechanism that remained undetected in our study. However, in the only large-scale study of risk for HF with major depressive disorder, the observed age-adjusted risk of 1.21 (1.13–1.28) increased to 1.56 with adjustment for psychotropics.[17] The same US study also found a protective effect of psycotropics for symptoms of anxiety and MSAD, where the point estimate increased from 1.19 to 1.46 and 1.24 to 1.74, respectively. Also for depressive symptoms, other studies indicate that treatment including psychotropics[44,45] protects depressed persons for future cardiovascular disease risk rather than confounding the relationship.

Increased neurohormonal stress activity and inflammation have also been linked to development of depression.[1] Symptoms of depression may in turn up-regulate and worsen the neurohormonal regulation of heart rate, blood pressure, and obesity, which are all central mechanisms in the development of HF.[1,16,46–48] In contrast, anxiety symptoms showed a weaker association with future HF in the current cohort. It may be hypothesized that low intensity anxiety, such as worry and tension, as measured by HADS-A, activates proinflammatory cytokines or neurohormonal stress activity less than diagnostic categories of anxiety, such as panic disorders and agoraphobic disorder. These latter conditions manifest with intense physiological activation and are found to increase overall morbidity.[49] Furthermore, symptoms of anxiety often act as a precursor for depressive symptoms, and of the two conditions depression is often found to be the largest driving factor in mortality studies.[39] Unfortunately, the HUNT study did not analyse markers of increased neurohormonal activity, and inflammatory activity was only analysed for a small subpopulation; therefore, we were not able to test these hypothetical links between depressive symptoms and future HF.

Identification and ascertainment of HF diagnostics might be misclassified. However, the overall quality and reliability of the hospital discharge registers of HF is high in Nordic Countries.[27,50] In line with Nordic recommendations and to ensure optimal precision, only those with a primary diagnosis of HF were included in the analyses.[25,27,50] From January 1995 to December 2008, a total of 1958 patients (≥18 years of age) were diagnosed with HF in the two hospitals of Nord-Trøndelag County. Of these, only 29 (1.6%) were diagnosed outside the Departments of Internal Medicine/Cardiology. Thus, 98.4% of the total HF patients received their hospital diagnosis in a setting where cardiologists were central in the diagnostics, ensuring a high sensitivity and specificity. Data from the Cause of Death Registry have somewhat lower reliability than the hospital discharge register of the HF diagnosis,[25] as many of these deaths are probably sudden. However, even if we do not know which proportion of the deaths were sudden, we obtained essentially the same effect by restricting the study to hospital-verified HF cases, and therefore it seems unlikely that the lower reliability of HF deaths could explain our findings.

Conclusion

Symptoms of depression, but not symptoms of anxiety or MSAD, were associated with increased risk for HF in a dose–response manner in this general population sample. The increased risk could not be directly explained by established cardiovascular risk factors or by prevalent or incident AMI. Prevention and treatment strategies for depressive symptoms might have the potential to reduce development of cardiovascular disease, including HF, and should therefore be carried out on a population level and in primary care settings, not only in patients with established HF or cardiovascular disorders. In both community[51] and hospital samples,[52] anxiety often co-exists and worsens the course of depressive symptoms, and it is recommended to consider both conditions when planning appropriate management strategiesl.[53]

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Supplementary Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Risk for HFAssociated with Symptoms of Anxiety and Depression in Sensitivity Analyses.

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Table S1. Risk for HFAssociated with Symptoms of Anxiety and Depression in Sensitivity Analyses.

	Exclusion of All Chronic somatic diseases	Restriction to Hospital Verified HF (1073 events *
HADS-D		
Events/ person-years	212/ 373909	656/597292
Cut off 8–10	1.25 (0.81–1.91)	0.99 (0.77–1.27)
Cut off ≥11	1.57 (0.79–3.08)	1.46 (1.05–2.01)
P for trend	*0.114*	*0.084*
CONTINOUS SCALE	*1.05 (1.01–1.10)*	*1.02 (1.00–1.05)*
HADS-A		
Events/ person years	207 (373069)	629/ 593291
Cut Off 8–10	0.73 (0.39–1.39)	0.89 (0.67–1.18)
Cut off ≥11	0.75 (0.24–2.38)	1.04 (0.69–1.55)
P for trend	*0.337*	*0.742*
CONTINOUS SCALE	*1.01 (0.96–1.06)*	*1.01 (0.98–1.03)*
HADS-T		
Events/ person years	207/ 372784	628/592632
Cut Off 15–19	1.30 (0.76 – 2.14)	0.98 (0.72–1.32)
Cut Off ≥19	0.81 (0.29–2.18)	1.25 (0.89–1.74)
P for trend	*0.811*	*0.305*
CONTINOUS SCALE	*1.02 (0.99–1.05)*	*1.01 (1.00–1.02)*
MSAD (HUNT 1 and 2)		
Events /person years	157/200695	467/344398
One episode MSAD	1.09 (0.79–1.50)	1.11 (0.92–1.34)
Two episode MSAD	1.22 (0.30–5.02)	1.34 (0.79–2.27)
P for trend	0.533	0.166

*Joint effect of persons that reported previous myocardial infarction, previous other coronary disease like diabetes, other endocrine disorders, musculoskeletal disorders, autoimmune diseases, epilepsy, cancer and analysis are preformed in model 5 with adjustment for startage, sex, Marital Status, Education, Smoking, Total Cholesterol, Diabetes Mellitus, Systolic Blood pressure, se-Creatinine, Alcohol, Previous myocardi adjustment for myocardial infarction during follow up.

Paper III

Cover Page

Full title:

Cardiac function and symptoms of depression and anxiety in a healthy population. The HUNT Study.

Brief title: Cardiac function and depression and anxiety.

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Abstract

Aims

Symptoms of anxiety and depression often co-exist with heart failure, yet little is known about the association with left ventricular (LV) subclinical dysfunction. We aimed to study the associations of single and repeated self-reported depression and anxiety symptoms on the Hospital Anxiety and Depression Scale (HADS) with sensitive indices of LV systolic and diastolic function based on Tissue Doppler (TD) and Speckle Tracking (ST).

Methods and results

In the third wave of the Nord-Trøndelag Health Study (HUNT3, 2006-2008) 50,810 (54% of invited) participated at a baseline examination. A random selection of 1296 persons whom where free from known cardiovascular disease, hypertension and diabetes at baseline underwent echocardiography. Of these, 1034 had answered the HADS questionnaire in HUNT 3 and 700 had additionally answered the HADS in HUNT2 (1995–1997) ten years earlier. Baseline depression and anxiety symptoms were not associated with a reduction in LV indices. A 5 unit increase in the additive depression scores from HUNT2 and HUNT3, but not additive anxiety score, where associated with a reduction in early diastolic annular velocity (e´); -5.5% (95% CI -9.6%, -1.5%) for women and -5.0% (95% CI -8.6%, -1.3%) for men.

Conclusion

The additive effect of two repeated depression scorings indicates lower LV diastolic function measured by e´ at follow-up among healthy participants. Thus, long lasting depression symptoms should be taken into account when discussing subclinical LV dysfunction.

Key words: Echocardiography, Epidemiology, Risk factors, Depression, Anxiety

Introduction

Even though depression and anxiety symptoms are associated with increased risk for CVD (1-6) little is known about their influence on subclinical cardiac dysfunction. Decades ago the hypothetical link between depression symptoms and left ventricular (LV) subclinical dysfunction was disregarded based on no association with ejection fraction (7), a measure which today is acknowledged with limited ability to reveal subtle LV dysfunction (8). However, novel methods of assessing LV function, including assessment of tissue velocities and deformational changes of the myocardium through the cardiac cycle, have been shown to be sensitive in detecting subtle subclinical dysfunction related to specific diseases or conventional risk factors such as age, BMI, non HDL cholesterol (9-11). To the best of our knowledge, no study exists on the association between anxiety symptoms and subclinical cardiac dysfunction measured by echocardiography or magnetic resonance imaging, and only one study with symptoms of depression. That one study included people with hypertension, diabetes and metabolic syndrome (12). Subclinical cardiac disease or the presence of cardiovascular risk factors may trigger inflammatory activity or neurohormonal actions that trigger both the depressive symptoms (13-15) and cause the process of early LV remodeling. Thus, the positive associations of depression symptoms with LV dysfunction in the Korean study may to some degree reflect reverse causality (12).

Therefore, the aim of this study was to investigate cross sectional associations with single and repeated anxiety and depression symptom levels with sensitive indices of LV systolic and diastolic function based on Tissue Doppler (TD) and Speckle Tracking (ST) echocardiography in 1034 Norwegian healthy adults who participated in the third wave of the Nord-Trøndelag Health Study (HUNT3).

Methods

Study population and setting

All 93,210 adult citizens aged ≥20 years in Nord-Trøndelag County, Norway, received a postal invitation to participate in the third wave of HUNT (HUNT3, 2006–2008, http://www.ntnu.edu/hunt). In total, 48,289 (52%) people participated. Within the HUNT3 study, the Echocardiographic study was conducted in a random selection of 1266 subjects free from known CVD, diabetes or hypertension. The random selection process took place when the participants attended a baseline clinical examination at the study centres and the echocardiographic examinations were performed at this visit. The study size for the echocardiography study was based on suitability in order to obtain normal reference values of the different LV indices by age groups (9, 16-18). The participants also gave self-report on standardised questionnaires (http://www.ntnu.edu/hunt/data/que) in the HUNT3 study

Earlier, in the second wave of the HUNT study (HUNT2), which was conducted in 1995-1997, 95,147 persons were invited and 65,215 (69%) participated. Details about the HUNT study have been published by Krokstad et al. (2013) (19). The study was approved by the regional committee for medical and health research ethics, and by the HUNT Publication Board.

Exposure: Symptoms of anxiety and depression.

At the examination the attendees received Questionnaire 2 (Q2), which was taken home, filled in and returned in a prepaid envelope. On Q2, the participants reported symptoms of anxiety and depression during the last week using the Norwegian version of the HADS. Seven depression questions mainly mirror depressed mood or reduced pleasure response affect (anhedonia), as well as psychomotor retardation (HADS-D), and seven anxiety questions mirror mostly symptoms of worry and restlessness (HADS-A) (20). Each subscale have a 4-point Likert scale, ranging from 0 (no symptom) to 3 (highest symptom level), which add up to a score range from 0 to 21 points. Valid HADS-D and HADS-A scores where defined if 5

or more of the questions were answered on each subscale. Missing response among those who filled in 6 or 5 items where replaced based on the sum of completed items multiplied by 7/6 or 7/5, respectively. In total, 1034 persons from the echocardiographic study (544 women) had valid HADS symptom scores from baseline in HUNT3 and thus constitute the study population in this study (see Figure 1 Flow chart).

Insert Figure 1 Flow chart about here

Previous HADS symptoms were available for 700 individuals (357 women, i.e 68 %) from their participation in HUNT2. We summed each participants´ HADS-D and HADS-A scores from HUNT2 and HUNT3 in order to reflect the additive sum of depression (HADS-D^A) and anxiety symptom scores (HADS-A^A) from both waves. We used the observed score range for all HADS-measurements in the statistical models, i.e a theoretical range of 0-21 for HADS-A and HADS-D in HUNT3 and 0-42 for the additive score of depression and anxiety symptoms in HUNT2 and HUNT3.

Covariates

Demographic and lifestyle factors

Demographic and lifestyle factors were assessed from the baseline examination, in HUNT3. Marital status was categorized into never married, married or living with partner, or separated/divorced/widowed.

Education was categorized as low (≤ 9 years), medium (10 to 12 years) or high (> 12 years). Smoking habits were categorized as current, previous or never smoking. A validated index for leisure-time physical activity was calculated as a product of exercise frequency, exercise intensity and training session duration (21).

Clinical examination

A clinical examination was performed by trained nurses at baseline examination in HUNT3 according to a standardised protocol (19). Systolic and diastolic blood pressures were measured three times after the participant had been seated for at least two minutes with the cuff on, with cuff size adjusted for arm circumference. All blood pressure measurements were performed with the Dinamap 845XT (Criticon) based on oscillometry. The average of the second and third measurement was used in the analyses. Height was measured without shoes to the nearest 1.0 cm and weight with light clothing to the nearest 0.5 kg. Body mass index (BMI) was computed as weight (in kg) divided by the squared value of height (in meters) (19).

Echocardiographic Acquisition, analyses and reproducibility

The participants waited at least one hour without smoking or eating at the study site before the echocardiography, and the mean time since last meal was 2.7 (SD 2.1) hours for women and 2.8 (SD 2.0) hours for men (9).All examinations were conducted by an experienced physician echocardiographer (HD) and the participants were examined in the left lateral decubitus position with a high- end Vivid 7 scanner (version BT06; GE Vingmed Ultrasound AS, Horten, Norway) using a phased-array transducer (M3S and M4S). All the presented echocardiographic measurements were available in ≥96% of the participants (16). All echocardiographic data were stored digitally and analysed subsequently (9, 16-18).

LV function was assessed by the several well-established echocardiographic indices of systolic and diastolic longitudinal function. LV end-systolic global strain (global strain) refers to percentage longitudinal shortening of the myocardium of the LV during systole, and LV peak global strain rate (global strain rate) to the respective maximal speed of global strain. Both indices are presented as the average of segmental values when assessed in a 16 segment

model of the LV (16). We used a customized software (GcMat; GE Vingmed Ultrasound, Norway) with a combination of TD for tracking along the ultrasound beam and ST (tracking of grey-scale speckles) for tracking perpendicular to the ultrasound beam (9). Further, peak mitral annular systolic velocity (S') and peak mitral annular early diastolic velocities (e') were measured in the base of the LV wall by pulsed waved TD and the average of the septal, lateral, anterior, and inferior locations was used in the analyses. Correspondingly, mitral annular plane systolic excursion (MAPSE) was measured as the average of the total systolic cumulative excursion of the same locations. Ejection fraction (EF) was analysed by calculation of end-diastolic and end-systolic LV volumes from tracings in the four and two chamber view (9). The average heart rate during echocardiography was used in the analysis.

The reproducibility of the echocardiographic measures has been described elsewhere (18). Briefly the interobserver mean errors were 4–8% and intraobserver mean errors were 2-5% for indices of LV function (9).

Statistical analysis

Clinical echocardiographic data followed a normal distribution and is presented as mean (SD). Characteristics by gender is presented in mean (SD) for continuous variables and as numbers (%) for categorical data. Associations of symptoms of depression and anxiety with LV function were estimated by multivariate linear regression analyses with the different LV function indices as dependent variables as all LV function indices were mutually correlated (r 0.21–0.61, all $p<0.001$). The LV function measures were log transformed, and the partial-regression coefficients are presented as the percentage difference in LV function per specified 5 units difference in HADS-score with the corresponding 95% confidence intervals.

Spearman correlations were performed between all HADS-measures and LV function measures. All our linear regression models were adjusted for age and heart rate during

echocardiography as a potentially confounding factor for the association of depression symptoms with cardiac function. In model 2, we added potential socioeconomic confounders (i.e. education and marital status), and in model 3 established cardiovascular risk factors such as blood pressure, BMI, smoking and physical activity index were included. We investigated the potential effect modification by sex and age (dichotomized at age 50). Previous research have found a consistent sex difference across normal values of LV function (9, 16-18), and wee found signs of effect modification of gender with global strain (p=0.019) thus we stratified all our analysis by sex.

We tested our models for violations of linear assumptions, including variance and normally distributed residuals, and the linear fit was tested with and without polynomials. We found no serious violations for using the linear line approach. All statistical analyses were performed in Stata IC/12.1 for Windows (© Stata Corp LP).

Results

Table 1 displays the characteristics of the study participants at baseline. Using the cut off which is recommended in order to ensure depression and anxiety symptom specificity, i.e a score ≥11 on the HADS-D and HADS-A, respectively, only 17 (1.6%) had depression and 30 (2.9%) had anxiety. Thus, in this sub population of HUNT, which is a random selection free from known CVD, diabetes and hypertension, the prevalence of anxiety and depression "caseness" is lower than in the total HUNT population (1, 2).

We found a negative correlation between the additive HADS-Depression scores from HUNT2 and HUNT3 with e´ (*r* -0.1628, p<0.001). Correlations between all echocardiographic measures and present depression scores and all anxiety scores were weak (*r* -0.05–0.04, all p values >0.09).

Table 2 shows that the point estimates for e´ were 2.53.2% lower per 5 units increase in HADS-Depression and HADS-Anxiety scores. For the additive HADS-D scores from HUNT 2 and 3, e´ was approximately 5% lower for women and men per 5 units of increase in HADS-D score. In contrast, additive anxiety symptoms had little impact on e´. The results from analyses after adjustment for socioeconomic status (Model 2) were similar to those in Model 1 (data not shown). Multivariable adjustment for age, education, marital status, systolic blood pressure, BMI, smoking, physical activity index and heart rate during echocardiography (Model 3) did not change the estimates substantially.

Table 3 shows that the additive depression symptoms from HUNT2 and HUNT3, but not additive anxiety symptoms, have a marginal negative influence on global strain in women, but not in men. The percentage differences of S´, global strain rate and MAPSE with symptoms of depression and anxiety are provided in Supplementary Table I and II, respectively. Both depression symptoms and anxiety symptoms are associated with marginal lower effect estimates for S´ and MAPSE. However, for the measures shown in S-Table I and II, the statistical evidence is weak and not of clinical importance.

Discussion

In the present study of healthy individuals, additive depression symptoms from two reports, ten years apart, indicated lower LV function at follow-up. The negative influence was most pronounced in e´, as well as in strain in women. Symptoms of anxiety and present depression symptoms were less associated with cardiac function. As the study population consisted of healthy individuals the effect is unlikely to be caused by reverse causality or existing disease.

Comparisons with previous studies

Strain and e' are among the most sensitive echocardiographic indices with respect to detect subtle LV dysfunction, and are linked to different CVD risk factors and manifest CVD even though other indices of LV systolic and diastolic function have been less influenced (9, 22, 23). To our knowledge only one echocardiography study using novel TD parameters has been published on the associations of LV diastolic function and depression symptoms (12). Unlike our study, the Korean study also included participants with cardiovascular risk factors, like hypertension, diabetes, metabolic syndrome and patients on antihypertensive medication (12). Such medical comorbidity can be important confounders in the observed association between depression symptoms and LV dysfunction (24). Further, subclinical cardiac disease or the presence of cardiovascular risk factors may trigger inflammatory activity or neurohormonal actions that mimic both the depressive symptoms (13, 15, 25) and cause the process of early LV remodeling (26). The association observed between depression symptoms and LV function in the Korean study could therefore reflect reverse causation. Thus, our study is the first to confirm that two reports of depression symptoms are associated with reduced LV function on a sub-clinical level. This finding supports our previous findings in the HUNT cohort of long lasting depression symptoms as a risk factor for myocardial infarctions and heart failure (1, 2).

Even though depression symptoms often are episodic, most studies only use one-off measures of depression. Limited previous evidence suggests that recurrent depression symptoms are associated with higher risk of cardiac disease than a single episode (2, 14, 27, 28). In the present study, the additive depression symptoms levels, measured twice in a ten years perspective, were correlated with LV subclinical dysfunction, but present depression symptoms and anxiety symptoms was not. Chronic stress, like long-lasting depression and anxiety symptoms, is previously found to be associated with neurohormonal and cytokine

release (29), and furthermore to modify the response to new stress events, i.e. creating a pattern of dysfunctional hormonal dynamics. Anhedonia, which is a core depressive feature measured by the HADS-Depression questionnaire, is previously described to produce such a chronic stress (30). It might be hypothesized that HADS anxiety questionnaire, which mirrors worries and tension, is less sensitive to neurohormonal stress and cytokine release than symptoms of anhedonia.

The influence of current and additive anxiety symptoms levels on all echocardiographic indices of LV function was less pronounced than for depression symptoms. Depression symptoms have most often been associated with a stronger risk for various CVD diseases, like AMI and HF, than anxiety symptoms (1-3, 31). Anxiety and depression symptoms are associated with different behavioral patterns, where individuals with anxiety more often seek and cohere with medical and lifestyle advice (32, 33). Furthermore, compared to anxiety symptoms depression symptoms are more strongly linked to an unfavorable lifestyle (32) which may trigger pro-inflammatory cytokines (34) which may increase the risk for both depression symptoms and early cardiac remodeling that can lead to cardiac diseases (26), like heart failure (29, 35, 36). However, the association we observed between additive depression levels and e´ was not fully explained by unfavorable life-style. Thus, long lasting high reports on depression symptoms should be taken into account when discussing subclinical LV dysfunction.

Strengths and Limitations

This study has apparent strengths, like inclusion persons free from CVD, diabetes and hypertension, in addition to extensive adjustment for potential confounders, which make medical comorbidity and reverse causality less likely to explain the observed association.

The study also has some important limitations. The participants were healthy both with respect to anxiety and depression, and the results may not necessarily be generalizable to other populations (46). Future studies should include more patients with higher burden of anxiety and depression symptoms in order to evaluate the influence on LV function in such a population.

Perspectives

Detection of subclinical cardiac dysfunction related to long-lasting anhedonic depression symptoms is important from a pathophysiological and clinical point of view as it contributes to the understanding of the vulnerability of depressed patients to CVD and, thus, may lead to an earlier identification and an improved prevention of CVD.

Further, a previous study from the echo population in HUNT3 allows us to compare the LV reduction associated with depression symptoms to traditional risk factors for CVD (9). A 5 unit higher additive HADS-Depression score from HUNT2 and HUNT3 gives similar detrimental effect of the cardiac function as 16 mm Hg and 13 mm Hg higher blood pressure in women and men, respectively. The corresponding values for age and non HDL cholesterol were 3.4 and 3.3 years and 2.8 and 1.1 mmol/L in women and men, respectively (9). Thus, compared to the associations of the well-known CVD risk factors on LV function, the effect size of repeated high levels of depression symptoms is not negligible.

It may be argued that diagnosing asymptomatic disease is only useful if it can lead to clinical action that slows or stops progression of disease (39). In light of our findings that recurrent depression symptoms is associated with lower cardiac function, it is interesting that both the SADHART and CREATE trial found that persons with previous history of depression symptoms were especially responsive to medical treatment (40, 41). Those who did not respond to cognitive behavioral treatment in the ENRICHED trial could receive

antidepressant drugs on a non-randomized basis, and those who did had a 42% lower incidence of death or recurrent MI (40). It is therefore plausible that depression symptoms represent a modifiable risk factor for CVD. In clinical practice anxiety and depression co-exists and it is advised to consider both conditions when planning treatment strategies (41). Furthermore, action directed to depression symptoms is often improving quality of life, which may be a standalone important target (41).

Conclusion

Repeated high levels of depression symptoms indicated lower LV function at follow-up among the healthy participant. The negative influence was most pronounced for diastolic function measured by early diastolic mitral annular velocity. Thus, long lasting depression symptoms should be taken into account when discussing subclinical LV dysfunction.

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Table 1 Characteristics of the Study Population at Baseline

Variable	N	Women	Men
		N (%)	**N (%)**
Sex (n)	1,034	544 (52.6)	490 (47.4)
Smoking	1,018		
Never		239 (44.6)	252 (52.2)
Former		163 (30.4)	124 (25.7)
Current		134 (25.0)	106 (21.9)
Marital Status	1,031		
Never Married		127 (23.5)	101 (20.7)
Married		327 (60.3)	321 (65.6)
Separated/ Divorced/Widowed		88 (16.2)	67 (13.7)
Education	1,025		
≥9 years		83 (15.4)	54 (11.1)
10-12 years		273 (50.7)	265 (54.4)
>12 years		182 (33.8)	168 (34.5)
		Mean (SD)	**Mean (SD)**
Age (years)	1,034	50.4 (14.1)	50.2 (13.4)
Body Mass index (kg/ m^2)	1,031	26.4 (4.0)	26.4 (3.8)
PAI index	906	0.7 (0.8)	0.7 (0.8)
Systolic blood pressure (mmHg)	1,024	127.3 (17.1)	135.0 (14.0)
Diastolic blood pressure (mm Hg)	1,024	71.3 (11.6)	78.1 (11.2)
Resting heart rate (bpm)	1,026	70.7 (11.2)	66.2 (11.1)
Total serum cholesterol (mmol/L)	1,028	5.6 (1.0)	5.6 (1.0)
HADS-Depression (0-21)	1,034	2.9 (2.8)	2.6 (2.5)
HADS-Anxiety (0-21)	1,034	3.7 (3.0)	3.5 (2.8)
Ejection Fraction (EF)	1,011	64.7 (10.1)	65.1 (9.6)
Mitral Annular Plane Systolic Excursion (MAPSE) (cm)	1,034	1.6 (0.3)	1.6 (0.2)
Global strain (%)	1,034	-17.4 (2.3)	-15.9 (2.2)
Global strain rate (s^{-1})	1,018	-1.0 (-0.1)	-1.0 (-0.1)
Systolic annular velocity (S´) (cm/s)	1,023	8.2 (1.2)	8.6 (1.4)
Diastolic annular velocity (e´) (cm/s)	1,023	11.9 (3.2)	10.7 (3.1)

Table 2. Percentage difference in e´ per 5 units increase in HADS-Depression, HADS-Anxiety, including additive sum of two reports HADS-D and HADS-A (HUNT 2 +3).

	Women				Men			
	Model 1 (n=459)		Model 3 (n=459)		Model 1 (n=459)		Model 3 (n=459)	
	N	% difference (95% CI)	N	% difference (95% CI)	N	% difference (95% CI)	N	% difference (95% CI)
HADS-D (0-21)	526	-2.5 (-7.1, 2.2)	442	-3.6 (-8.1, 0.8)	474	-2.6 (-8.0, 2.8)	402	-1.9 (-7.5, 3.6)
HADS-D^{A} (0-42)	343	-5.5 (-9.6, -1.5)	287	-4.0 (-8.2, 0.1)	332	-5.0 (-8.6, -1.3)	279	-4.3 (-7.9, -0.6)
HADS-A (0-21)	522	-2.9 (-7.1, 1.4)	442	-3.2 (-7.3, 0.9)	473	0.2 (-4.5, 5.0)	402	-0.8 (-5.8, 4.1)
HADS-A^{A} (0-42)	327	-0.9 (-4.5, 2.8)	273	-1.2 (-4.9, 2.5)	325	-0.6 (-4.1, 2.9)	274	-0.5 (-4.0, 3.0)

Model 1: Age, heart rate during echocardiography. Model 2: Model 1+ marital status and education. (data not shown). Model 3: Model 1+ 2+systolic and diastolic blood pressure, body mass index, smoking, and physical activity index.

Abbreviations: HADS-D^{A} :Additive score of HADS-D reports from HUNT2 + HUNT3. HADS-A^{A}: Additive score of HADS-A reports from HUNT2 + HUNT3

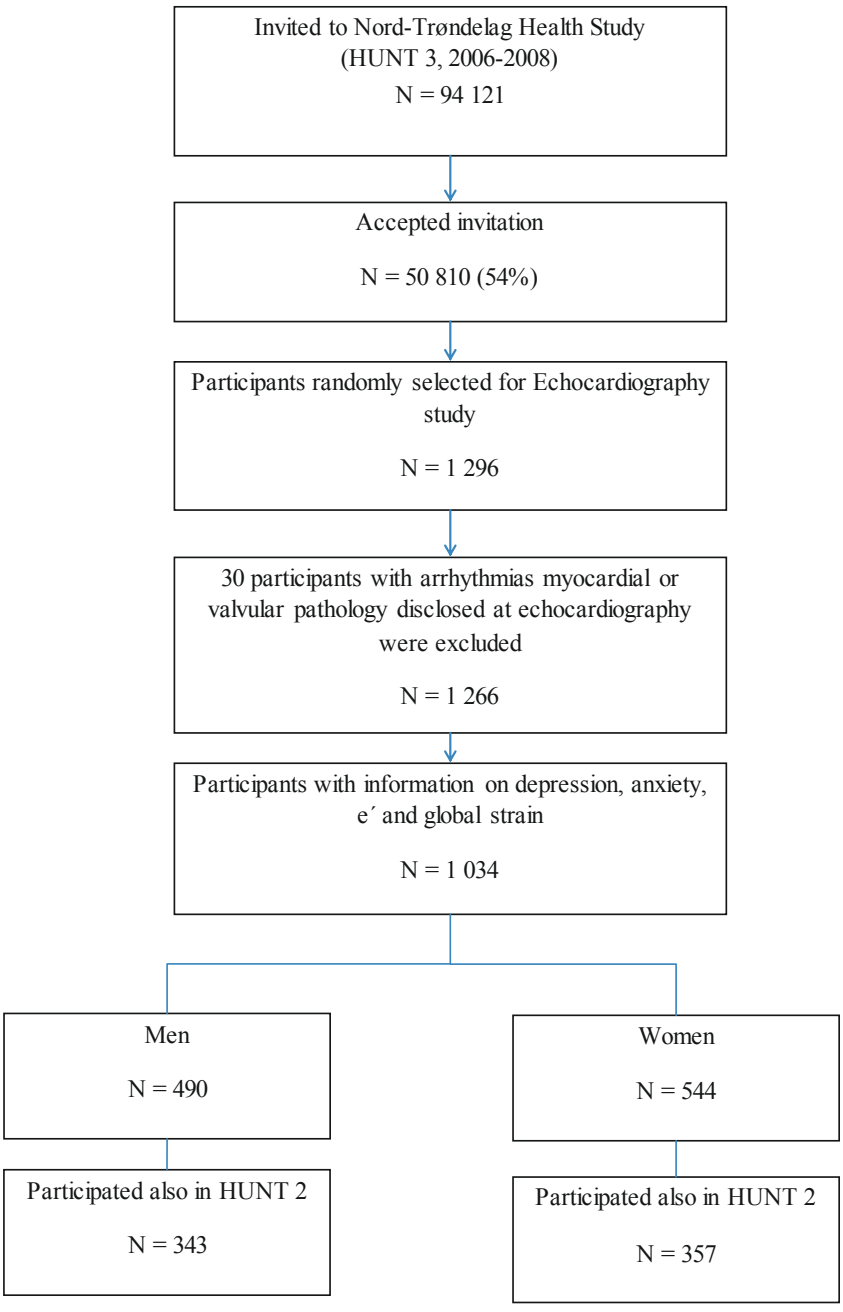
Table 3. Percentage difference in global strain per 5 unit rise in HADS-Depression, HADS-Anxiety, including additive sum of two reports HADS-D and HADS-A (HUNT 2 +3).

	Women				Men			
	Model 1 (n=459)		Model 3 (n=459)		Model 1 (n=459)		Model 3 (n=459)	
	N	% difference (95% CI)	N	% difference (95% CI)	N	% difference (95% CI)	N	% difference (95% CI)
HADS-D (0-21)	526	-1.1 (-3.3, 1.1)	445	-0.6 (-2.8, 1.7)	482	3.4 (-0.8, 6.0)	408	3.3 (-0.4, 6.1)
HADS-D^{A} (0-42)	326	-2.2 (-4.2, 0.1)	289	-0.3 (-3.6, 0.7)	336	-0.3 (-2.2, 1.7)	281	-0.0 (-2.1, 2.2)
HADS-A (0-21)	526	-0.8 (-2.8, 1.2)	445	-0.8 (-2.9, 1.3)	482	1.1 (-1.2, 3.4)	408	0.6 (-1.9, 3.2)
HADS-A^{A} (0-42)	329	-2.2 (-4.2, 0.8)	274	-1.3 (-3.3, 0.6)	329	-0.3 (-2.2, 1.3)	276	-0.6 (-2.6, 1.4)

Adjustments: Model 1: Age, heart rate during echocardiography. Model 2: Model 1+ marital status and education (data not shown). Model 3: Model 1+ 2+systolic and diastolic blood pressure, body mass index, smoking, and physical activity index.

Abbreviations: HADS-D^{A} :Additive score of HADS-D reports from HUNT2 + HUNT3. HADS-A^{A}: Additive score of HADS-A reports from HUNT2 + HUNT3

Figure 1: Flow Chart of Study Recruitment



Supplementary Table I. Percentage difference in secondary measures for LV function per 5 unit rise in present HADS-D (HUNT3), and additive HADS-D levels from HUNT2 and 3.

	Women				Men			
	Model 1		Model 3		Model 1		Model 3	
	N	% difference (95% CI)	N	% difference (95% CI)	N	% difference (95% CI)	N	% difference (95% CI)
S´								
HADS-D	525	-1.0 (-3.4, 1.5)	442	-1.2 (-3.8, 1.4)	481	-0.3 (-3.4, 2.7)	402	0,8 (-3.3, 3.4)
HADS-D^{A}	343	-1.3 (-3.4, 0.9)	287	-0.4 (-2.8, 2.0)	332	-1.0 (-3.3, 1.3)	279	-0.1 (-2.6, 2.4)
Global strain rate								
HADS-D	517	-0.4 (-2.5, 1.7)	438	0.2 (-2.6, 2.2)	475	0.6 (-1.7, 2.8)	403	0.5 (-2.0, 3.0)
HADS-D^{A}	339	0.1 (-1.9, 2.0)	284	0.1 (-2.1, 2.4)	330	0.6 (-1.1, 2.4)	277	0.8 (-1.1, 2.7)
MAPSE								
HADS-D	525	-0.5 (-3.2, 2.1)	444	-1.0 (-3.9, 1.9)	481	-0.3 (-3.4, 2.9)	407	-0.7 (-4.3, 2.9)
HADS-D^{A}	346	-1.7 (-4.1, 0.8)	289	-1.1 (-3.8, 1.6)	336	-0,9 (-3.3, 1.5)	281	-0.9 (-3.3, 1.6)

Adjustments: Model 1: Age, heart rate during echocardiography. Model 2 (not shown): Model 1+ marital status and education. Model 3: Model 1+ 2+systolic and diastolic blood pressure, body mass index, smoking, and physical activity index.

Abbreviations: HADS-D^{A} : Additive score of HADS-D levels from HUNT2 + HUNT3. HADS-A^{A}: Additive score of HADS-A levels from HUNT2 + HUNT3

Supplementary Table II. Percentage difference in secondary measures for LV function per 5 unit rise in HADS-Anxiety (HUNT3), and additive HADS-Anxiety levels from HUNT2 and HUNT3

	Women				Men			
	Model 1		Model 3		Model 1		Model 3	
	N	% difference (95% CI)	N	% difference (95% CI)	N	% difference (95% CI)	N	% difference (95% CI)
S´								
HADS-A	522	-1.5 (-3.7, 0.7)	442	-1.6 (-4.0, 0.8)	474	-1,4 (-4.1, 1.3)	403	-1.9 (-4.9, 1.1)
HADS-A^{A}	322	-0.3 (-2.3, 1.7)	269	-0,5 (-2.7, 1.7)	325	-1.8 (-4.0, 0.4)	274	-1.6 (-4.0, 0.7)
global strain rate								
HADS-A	517	0.1 (-1.8, 2.0)	438	0.8 (-1.4, 2.9)	474	0.7 (-1.2, 2.7)	403	1.2 (-1.1, 3.4)
HADS-A^{A}	339	0.2 (-1.5, 1.8)	284	0.3 (-1.6, 2.3)	323	1.1 (-0.5, 2.8)	272	1.8 (0.0, 3.6)
MAPSE								
HADS-A	525	-1.1 (-3.5, 1.3)	444	-0.7 (-4.4, 0.9)	480	-0.4 (-3.2, 2.3)	407	-1.1 (-4.2, 2.1)
HADS-A^{A}	329	-2.2 (-5.5, 1.2)	274	-1.2 (-3.6, 1.2)	329	-0.2 (-2.3, 1.9)	276	-0.1 (-2.5, 2.3)

Adjustments: Model 1: Age, heart rate during echocardiography. Model 2 (not shown): Model 1+ marital status and education. Model 3 Model 1+ 2+systolic and diastolic blood pressure, body mass index, smoking, and physical activity index.

Abbreviations: HADS-D^{A} : Additive HADS-D levels from HUNT 2 + HUNT 3. HADS-A^{A}: Additive HADS-A levels from HUNT 2 + HUNT 3