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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

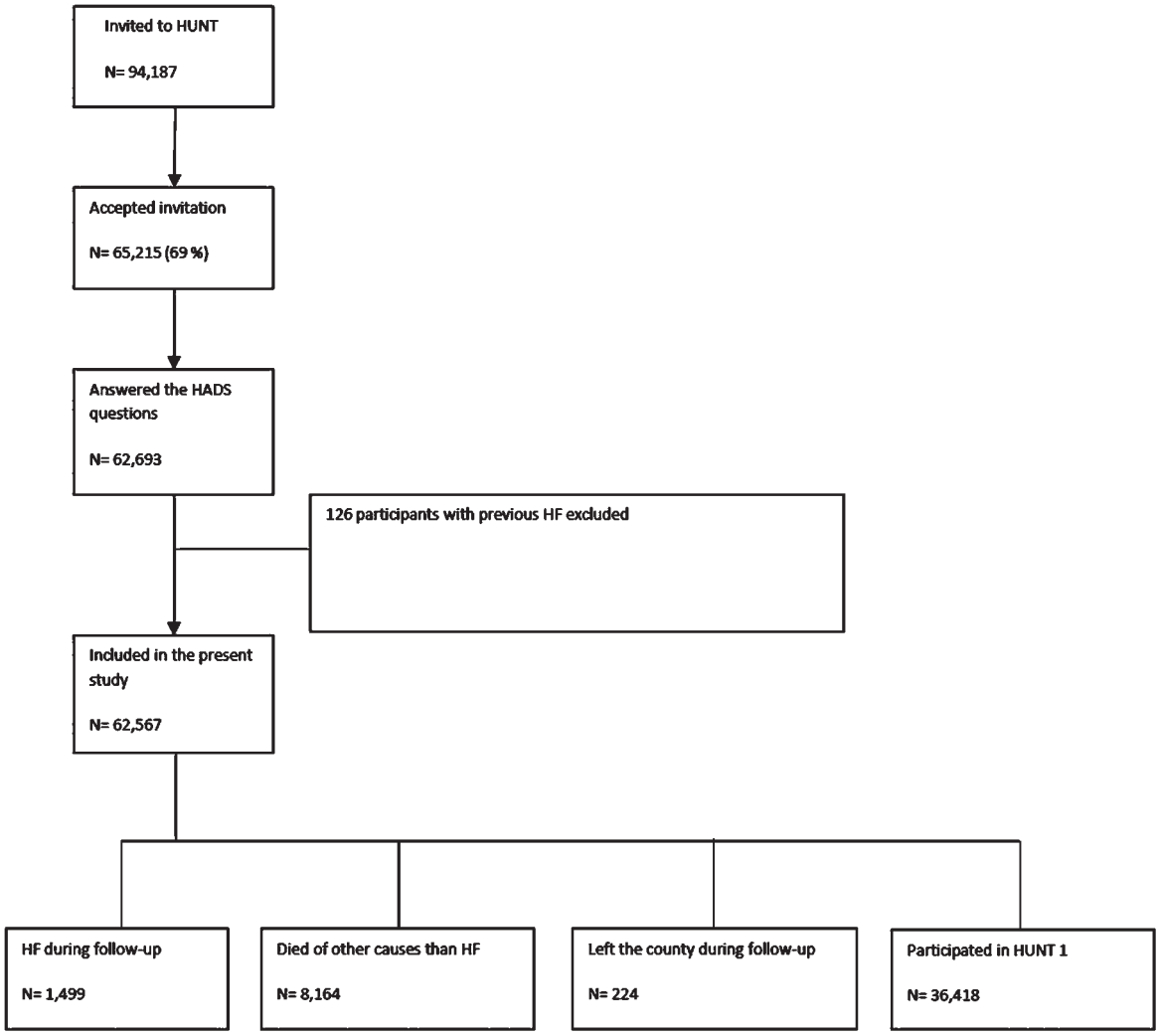

Figure 1 Flow chart of the heart failure (HF) study recruitment and follow-up.

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.

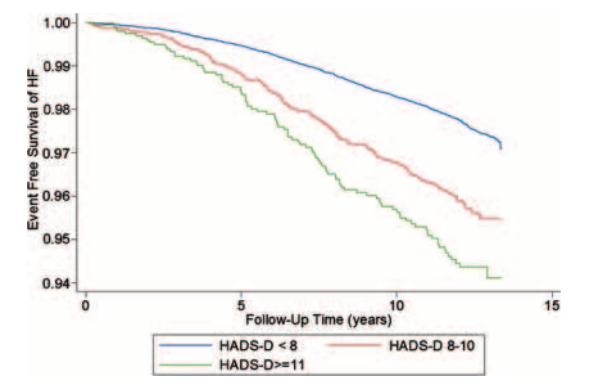

Figure 2 Kaplan–Meier curve of incident heart failure during follow-up according to depression category. HADS-D, Hospital Anxiety and Depression Scale, depression subscale.

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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