

## Symptoms of anxiety and depression and risk of atrial fibrillation—The HUNT study

Tingting Feng<sup>a,\*</sup>, Vegard Malmo<sup>b,c</sup>, Lars E. Laugsand<sup>b,d</sup>, Linn B. Strand<sup>a</sup>, Lise T. Gustad<sup>b,e</sup>, Hanne Ellekjær<sup>f,g</sup>, Jan P. Loennechen<sup>b,c</sup>, Kenneth Mukamal<sup>h</sup>, Imre Janszky<sup>a,i,j</sup>

<sup>a</sup> Department of Public Health and Nursing, Norwegian University of Science and Technology, Trondheim, Norway

<sup>b</sup> Department of Circulation and Medical Imaging, Norwegian University of Science and Technology, Trondheim, Norway

<sup>c</sup> Clinic of Cardiology, St. Olavs Hospital, Trondheim, Norway

<sup>d</sup> Department of Emergency Medicine, St. Olavs Hospital, Trondheim, Norway

<sup>e</sup> Department of Medicine, Levanger Hospital, Nord-Trøndelag Hospital Trust, Levanger, Norway

<sup>f</sup> Stroke Unit, Department of Internal Medicine, St Olav's Hospital, Trondheim, Norway

<sup>g</sup> Department of Neuromedicine and Movement Science, Norwegian University of Science and Technology, Trondheim, Norway

<sup>h</sup> Department of Medicine, Beth Israel Deaconess Medical Center, Boston, MA, USA

<sup>i</sup> Department of Neurology, Medical School, University of Pécs, Pécs, Hungary

<sup>j</sup> Institute of Behavioural Sciences, Semmelweis University, Budapest, Hungary

### ARTICLE INFO

#### Article history:

Received 6 September 2019

Received in revised form 6 November 2019

Accepted 13 November 2019

Available online 14 November 2019

#### Keywords:

Atrial fibrillation

Depression

Anxiety

### ABSTRACT

**Background:** Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia. Anxiety and depression may activate the autonomic nervous system which is likely to play an important role in the etiology of AF. However, little is known about the association between symptoms of anxiety and depression and risk of AF.

**Objective:** This study aimed to assess the association between symptoms of anxiety and depression and risk of AF. **Methods:** In a population-based study, 37,402 adult residents were followed for incident AF from 2006 to 2008 until 2015. Participants were classified according to data on anxiety and depression symptoms. Cox proportional regression models were used to adjust for common AF risk factors.

**Results:** During a median follow-up of 8.1 years, 1433 (3.8%) participants developed AF. In comparisons with no anxiety symptoms, the multivariable-adjusted hazard ratios (HRs) were 1.1 (95% CI: 0.9–1.5) for mild to moderate anxiety symptoms and 1.0 (95% CI: 0.8–1.4) for severe anxiety symptoms. In comparisons with no depression symptoms, the multivariable-adjusted HRs were 1.5 (95% CI: 1.2–1.8) for mild to moderate depression symptoms and 0.9 (95% CI: 0.6–1.3) for severe depression symptoms. Recurrent anxiety/depression symptoms were not associated with increased AF risk.

**Conclusions:** In this large, population-based study, we found no evidence of an association between symptoms of anxiety or severe depression and AF risk, even for recurrent anxiety or depression symptoms. An unexpected association of symptoms of mild to moderate depression with increased AF risk requires confirmation in other studies. Our findings add to the sparse literature on symptoms of anxiety and depression and risk of AF.

© 2019 The Authors. Published by Elsevier B.V. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

## 1. Introduction

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia and is associated with increased risk of mortality and stroke as well as increased health care costs [1]. To be able to better prevent and treat AF, it is important to identify its modifiable risk factors [2]. Symptoms of depression and anxiety have been relatively strongly

\* Corresponding author at: Department of Public Health and General Practice, Faculty of Medicine, Norwegian University of Science and Technology, NO-7489 Trondheim, Norway.

E-mail address: [tingting.feng@ntnu.no](mailto:tingting.feng@ntnu.no) (T. Feng).

associated with cardiac diseases, including coronary heart disease [3], acute myocardial infarction [4] and heart failure [5]. Furthermore, depression and anxiety may activate the autonomic nervous system [6] which is likely to play an important role in the etiology of AF [7]. However, only limited research has explored the effect of psychological distress on AF onset [8,9]. Therefore, the aim of this large population-based study was to assess the prospective association of symptoms of anxiety and depression with AF risk.

## 2. Methods

### 2.1. Study population

All 93,860 residents  $\geq 20$  years of age in Nord-Trøndelag County in Norway were invited to participate in the third Nord-Trøndelag Health (HUNT 3) study from October 2006 to June 2008. Of these, 50,804 participants (54%) answered questionnaires and underwent a clinical examination. Holmen et al. have described the HUNT study in more detail [10].

We excluded 1598 participants from the analysis who had a history of AF at baseline and 11,804 participants with missing response for depression or anxiety symptoms, although we tested the inclusion of participants with missing data in imputation analyses described below. Details about inclusions are provided in eFig. 1.

### 2.2. Measures of depression and anxiety symptoms

The Norwegian version of the Hospital Anxiety and Depression Scale (HADS) was used to assess symptoms of anxiety (HADS-A) and depression (HADS-D) during the previous week [11]. The HADS is a valid and reliable instrument across various patient samples and settings [12]. It comprises 14 self-rated items, with seven items forming the Anxiety subscale (HADS-A) and seven items forming the Depression subscale (HADS-D) [13]. The HADS-A reflects symptoms of worry and tension, while HADS-D reflects symptoms of anhedonia and loss of interest. The items on the HADS-A subscale are: “(1) I feel tense or wound up; (2) I get a sort of frightened feeling as if something bad is about to happen; (3) Worrying thoughts go through my mind; (4) I can sit at ease and feel relaxed; (5) I get a sort of frightened feeling like butterflies in the stomach; (6) I feel restless and have to be on the move; (7) I get sudden feelings of panic.” The items on the HADS-D subscale are: “(1) I still enjoy the things I used to enjoy; (2) I can laugh and see the funny side of things; (3) I feel cheerful; (4) I feel as if I am slowed down; (5) I have lost interest in my appearance; (6) I look forward with enjoyment to things; (7) I can enjoy a good book or radio or TV program.” Each item on the questionnaire is scored from 0 (no symptom) to 3 (highest symptom level). Thus, participants can score between 0 and 21 for either symptoms of anxiety or depression. Participants were included in the subsequent analyses only if they answered all of the 14 items. The two subscales were divided into 3 categories: (1) having no symptoms of depression or anxiety (score  $< 8$ ), (2) having mild to moderate symptoms (score 8–10), and (3) having severe symptoms (score  $\geq 11$ ), respectively [14].

Among the 37,402 eligible participants in HUNT 3, 24,706 individuals had available information on HADS from the second wave of the HUNT Study (HUNT 2) conducted between 1995 and 1997 [10]. A combined burden of anxiety symptoms in HUNT 2 and 3 was categorized into 3 groups: (1) no anxiety symptoms (scoring  $< 11$  on HADS-A in HUNT 2 and 3), (2) anxiety symptoms at one time (scoring  $\geq 11$  on HADS-A in one of the HUNT studies), and (3) anxiety symptoms at both times (scoring  $\geq 11$  on HADS-A in both HUNT studies). A combined burden of depression symptoms in HUNT 2 and 3 was categorized into 3 groups: (1) no depression symptoms (scoring  $< 11$  on HADS-D in HUNT 2 and 3), (2) depression symptoms at one time (scoring  $\geq 11$  on HADS-D in one of the HUNT studies), and (3) depression symptoms at both times (scoring  $\geq 11$  on HADS-D in both HUNT studies).

### 2.3. Atrial fibrillation

From the baseline examination until November 30, 2015, AF diagnoses were retrieved from discharge registers at two hospitals that together serve the entire population of Nord-Trøndelag County. We used code I48 from the International Classification of Diseases Tenth Revision to screen for patients with possible AF. Medical records of these patients were then reviewed by experts, and AF was adjudicated based on electrocardiographic criteria recommended by the European Society of Cardiology [15]. Persons who only had an episode of AF within the first 7 days after cardiac surgery, during the acute phase of a myocardial infarction or during episodes of hemodynamic instability (e.g., sepsis or non-cardiac surgery) were not regarded as having incident AF. If information from medical records was insufficient for exact classification of the diagnosis, two physicians (HE and JPL) evaluated the available information separately. Only cases where both physicians concurred were regarded as AF. The rest were classified as possible AF and were not regarded as AF cases in the main analyses. The validation process is described in more detail elsewhere [16].

### 2.4. Covariates

A clinical examination was conducted by trained nurses. Height and weight were measured barefoot and wearing light clothing; height was measured to the nearest cm and weight to the nearest 0.5 kg. Body mass index was calculated as body weight in kilograms divided by the squared value of height in meters. Non-fasting blood samples were analyzed for glucose, triglycerides, high-density lipoprotein cholesterol (HDL-C) and high-sensitivity C-reactive protein (CRP) [10]. Self-reported data obtained at the baseline included smoking status (never, former, or current), alcohol consumption (abstainers, light drinkers, moderate drinkers, or heavy drinkers), physical activity (inactivity, moderate activity or high activity), occupation (desk work, light industry work, technicians or heavy physical work), and marital status (cohabitation or no cohabitation). Information on common chronic disorders was self-reported and included: angina pectoris, stroke, asthma, osteoarthritis, kidney disease, hyperthyroidism, rheumatoid arthritis, sarcoidosis, ankylosing spondylitis, cancer, epilepsy, chronic bronchitis, emphysema or COPD, psoriasis, diabetes, sleep apnea, acute myocardial infarction, and heart failure. Apart from self-report, information on history of acute myocardial infarction and heart failure was also retrieved from hospital registers [17].

### 2.5. Statistical analyses

Baseline characteristics were presented as mean  $\pm$  standard deviation for continuous variables and percentages for categorical variables. Cox proportional regression models were used to assess the association of symptoms of depression and anxiety with subsequent risk of AF. Participants who reported no symptoms (i.e., scoring  $< 8$  on HADS-A or HADS-D) were regarded as the reference group. Time was defined as days from inclusion to either incident AF or censoring due to death from other causes ( $n = 2457$ ), emigration from the county ( $n = 82$ ) or end of follow-up. We calculated hazard ratios (HRs) and 95% confidence intervals (CI). We included age and sex in model 1; in addition, weight, height, smoking, occupation type, marital status, physical activity, and alcohol consumption were added as potential confounders in model 2. In further analyses, we also adjusted for chronic disorders, i.e., all diseases mentioned in the previous section were included in the regression models as part of a composite variable having the value of 1 in the presence of any of the condition and 0 otherwise (model 3) and for metabolic components (i.e., blood glucose, blood pressure, triglycerides, HDL-C and CRP) (model 4). We tested linear as well as quadratic trends for the associations of symptoms of anxiety and depression with AF risk. To explore dose-dependent associations, we presented the hazard ratios of AF in the form of smoothed curves where

symptoms of anxiety and depression were used as continuous variables [18].

In separate analyses, we assessed the relative risk of AF according to episodes of anxiety and depression symptoms in HUNT 2 and 3. Participants without symptoms in any of the HUNT studies were regarded as the reference group.

The proportional hazards assumption was tested by comparing –ln–ln survival curves and by performing tests on Schoenfeld residuals for each covariate. We found no violations of the proportionality assumption.

To assess effect modification, we conducted analyses stratified by age, sex, and chronic diseases.

In sensitivity analyses, we regarded possible or single-episode AF during follow-up as events. Furthermore, to address the possibility of reverse causation as an explanation for the observed associations, we excluded the first 2 years of follow-up and repeated the analyses. We also used multiple imputation with five imputations (mi command in Stata) to examine whether the complete-case approach yielded biased estimates [19]. Lastly, to assess to what extent symptoms of anxiety/depression may improve the ability of a multivariable model to predict a new-onset AF, we developed logistic regression-based multivariable prediction models with and without symptoms of anxiety/depression. We calculated the area under the ROC (receiver operating characteristic) curve (AUC) in these models [20]. All statistical analyses were conducted using Stata/MP 15.1 for Windows (College Station, TX: StataCorp LLC).

### 3. Results

#### 3.1. Baseline characteristics

Characteristics of participants with and without subsequent AF are presented in Table 1. During a median follow-up of 8.1 years (288,460 person-years), 1433 (3.8%) participants developed AF. Using a cutoff score of 11 and above for severe symptoms, 2.2% of the participants reported symptoms of depression and 4.9% reported symptoms of anxiety. The participants that developed AF were older and more likely

**Table 1**  
Baseline characteristics of participants in the total population according to atrial fibrillation vs. no atrial fibrillation during follow-up.

Variable	No. of subjects	Total population	AF during follow-up	No AF during follow-up
Total % (n)	37,402	%	3.8 (1433)	96.2 (35,969)
Variables, % (n)				
Female	21,122	56.5	41.5 (595)	57.1 (20,527)
Diabetes mellitus	1636	4.4	10.3 (148)	4.1 (1488)
Current smoker	6081	16.7	12.5 (173)	16.8 (5908)
Heavy drinkers	523	1.4	2.5 (35)	1.4 (488)
Technicians	7234	20.2	12.3 (164)	20.5 (7070)
Physically inactive	7470	20.3	24.1 (336)	20.1 (7134)
Cohabitation	22,798	61.0	64.7 (927)	60.9 (21,871)
Mean (SD)				
Age, years	37,402	53.4 (15.2)	70.1 (10.9)	52.8 (15.0)
Body mass index, kg/m <sup>2</sup>	37,289	27.2 (4.4)	28.2 (4.6)	27.1 (4.4)
HADS–depression score (HUNT 3)	37,402	3.3 (2.9)	4.0 (2.9)	3.3 (2.9)
HADS–anxiety score (HUNT 3)	37,402	4.0 (3.3)	3.7 (3.0)	4.0 (3.3)

AF: atrial fibrillation; HADS: Hospital Anxiety and Depression Scale.

to be men, inactive, heavy drinkers, and score higher on the HADS–D subscale.

#### 3.2. Relative risk of atrial fibrillation in relation to symptoms of anxiety and depression

Table 2 shows HRs for incident AF according to symptoms of depression and anxiety in HUNT 3. In comparisons with no symptoms of anxiety, the multivariable-adjusted HRs (model 2) were 1.1 (95% CI: 0.9–1.5) for symptoms of mild to moderate anxiety and 1.0 (95% CI: 0.8–1.4) for symptoms of severe anxiety, respectively. In comparisons with no symptoms of depression, the multivariable-adjusted HRs were 1.5 (95% CI: 1.2–1.8) for symptoms of mild to moderate depression and 0.9 (95% CI: 0.6–1.3) for symptoms of severe depression, respectively ( $P = 0.002$  for quadratic trend). Additional adjustment for chronic disorders or metabolic status did not materially change the estimates.

Fig. 1 presents the relative risks for atrial fibrillation in the form of a smoothed curve when symptoms of anxiety and depression were used as continuous variables. There was no clear sign of an increased risk for with symptoms of severe depression or anxiety in these analyses.

Table 3 shows the HRs for AF according to episodes of symptoms of anxiety and depression in HUNT 2 and 3. Participants with recurrent symptoms of anxiety or depression did not have higher relative risks of incident AF compared to those without symptoms of anxiety or depression at any of the HUNT studies.

#### 3.3. Effect modification

Overall, we found limited evidence of major effect modification by age, sex, or chronic disease (eTables 1–3). In general, the HRs tended to be higher among younger individuals, men, and participants without chronic disease.

#### 3.4. Sensitivity analyses

We documented 1165 AF cases after the second year of follow-up. Exclusion of the first 2 years of follow-up had little effect on the results (eTable 4). The results were also consistent with the main analyses when possible or single-episode AF events ( $n = 99$ ) were regarded as AF during follow-up. Finally, when we performed multiple imputation, the results were similar to those in the primary analysis (eTable 5).

#### 3.5. AF identification ability of prediction models with and without symptoms of anxiety and depression

The AUC in the multivariable-adjusted logistic regression model without symptoms of anxiety and depression was 0.8504, while AUC in the logistic regression model with symptoms of anxiety and depression was 0.8504 and 0.8506, respectively. Thus, adding symptoms of anxiety/depression to the model did not improve its ability to distinguish between patients with AF and no AF.

### 4. Discussion

In this large, population-based study, we found no evidence of an association between severe symptoms of depression and AF risk, even when symptoms of depression were recurrent. We also found no association of symptoms of anxiety with AF risk. Unexpectedly, only symptoms of mild to moderate depression were associated with an increased AF risk.

Only four previous studies have assessed the prospective association of symptoms of anxiety or depression with AF risk, and all had potential limitations in their assessments of exposure or outcome, and none had repeated measures of symptoms of anxiety or depression. In the Framingham Offspring study which had a relatively small sample size

**Table 2**

Hazard ratios (95% confidence intervals) for atrial fibrillation during follow up according to symptoms of anxiety (HADS-A) and depression (HADS-D) in HUNT 3.

	Model 1	Model 2	Model 3	Model 4
Events/person-years	1433/288,460	1235/266,671	1186/256,765	1205/260,753
HADS-A				
0–7	Reference	Reference	Reference	Reference
8–10	1.0 (0.8–1.3)	1.1 (0.9–1.5)	1.1 (0.8–1.4)	1.1 (0.8–1.4)
≥11	1.1 (0.8–1.4)	1.0 (0.8–1.4)	1.0 (0.7–1.4)	1.1 (0.8–1.5)
P for linear trend	0.5092	0.7865	0.9603	0.6695
P for quadratic trend	0.8193	0.5454	0.5736	0.7501
HADS-D				
0–7	Reference	Reference	Reference	Reference
8–10	1.3 (1.0–1.6)	1.5 (1.2–1.8)	1.4 (1.1–1.7)	1.5 (1.2–1.8)
≥11	0.9 (0.7–1.3)	0.9 (0.6–1.3)	0.8 (0.6–1.2)	0.8 (0.6–1.2)
P for linear trend	0.6503	0.4552	0.3942	0.3648
P for quadratic trend	0.0371	0.0021	0.0070	0.0014

HADS-D and HADS-A score: &lt;8: no symptoms of depression or anxiety, 8–10: mild to moderate symptoms, ≥11: severe symptoms.

Model 1: adjusted for age and sex.

Model 2: Model 1 + weight, height, smoking status, occupation, marital status, physical activity and alcohol consumption.

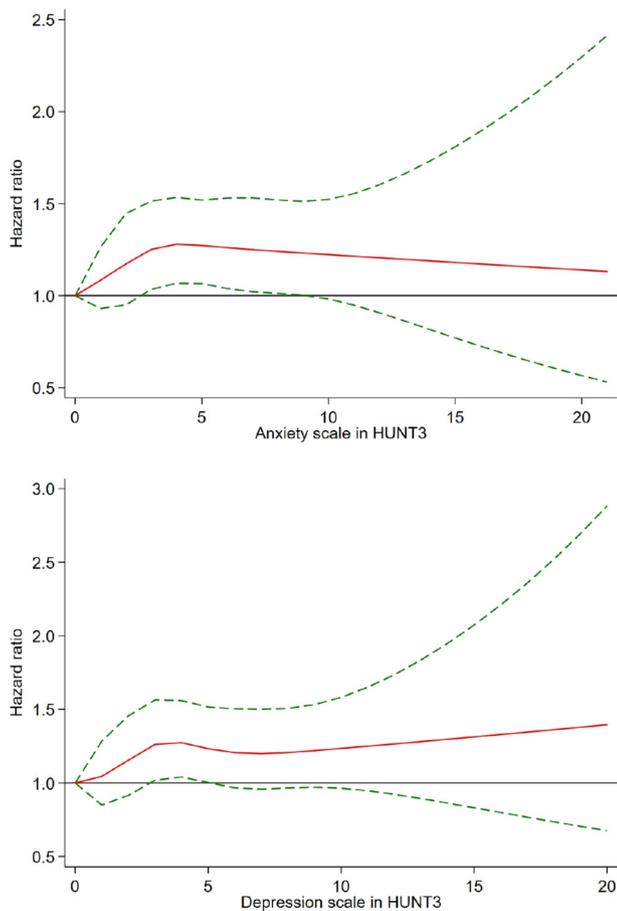
Model 3: Model 2 + chronic disorders.

Model 4: Model 2 + metabolic components (i.e., blood glucose, blood pressure, triglycerides, high-density lipoproteins and C-reactive protein.).

( $n = 3682$ ) and a 10-year follow-up [9], symptoms of anxiety in men (HR: 1.1; 95% CI, 1.0–1.3) had a weak association with AF risk while there was no such an association in women (HR: 1.0; 95% CI, 0.8–1.3). In the Multi-Ethnic Study of Atherosclerosis ( $n = 6644$ ) [21], symptoms of depression were associated with higher AF risk (HR: 1.3; 95% CI, 1.0–1.7). However, few details of these results are available, since these were published only as an abstract. Furthermore, both the Framingham Offspring study and the Multi-Ethnic Study of Atherosclerosis used instruments (i.e., the Tension and Symptoms of Anxiety Scales [9]

and Depression Scale of Epidemiologic Studies [22], respectively) that include somatic symptoms. Consequently, the potential overlap of somatic symptoms caused by physical illness with that of psychological distress limited the ability of these studies to examine the genuine effects of core psychological and cognitive symptoms of anxiety and depression on AF risk. On the other hand, our study used the HADS scale, which replaces somatic symptoms with non-somatic alternatives [11]. Thus, in our study, we were able to examine the association of core psychological and cognitive symptoms of anxiety and depression with AF risk. In the Women's Health Study [8], symptoms of depression was unrelated to AF risk (HR: 1.0; 95% CI, 0.8–1.3). The Mental Health Inventory-5, which has similar features as HADS in terms of exclusion of somatic symptoms, was used to assess symptoms of depression [8]. However, AF events were self-reported in this study, which would tend to lower the specificity of the AF diagnoses. A Danish matched cohort study compared AF risk in all Danes initiating antidepressant medication ( $n = 785,254$ ) with that in a 1:5-matched sample from the general population [23]. The study defined depression as the condition within the month before initiation of antidepressant medication. Substantially increased AF risk was observed even before antidepressant medication (HR = 3.18; 95% CI: 2.98–3.39) and within the first month (4.29; 95% CI: 3.94–4.67) after antidepressant initiation, but AF risk decreased 6–12 months after antidepressant initiation (HR = 1.11; 95% CI: 1.06–1.16). However, antidepressant medication is only a proxy for depression and these medications have common indications beyond depression as well [24], such as pain or insomnia. For example, a study conducted in five European countries showed that between 1.1 and 7.4% of prescribed antidepressants were used for sleeping disorders [24]. Another European study found that 25% of prescribed antidepressants were used for chronic pain [25]. Furthermore, the study retrieved AF diagnosis from registers without further manual verification, which could have resulted in misclassification.

Our study revealed an unexpected inverted U-shaped association between symptoms of depression and AF risk, which is inconsistent with the limited previous research. The underlying mechanism is unclear. Depression may lead to increased inflammation [26], oxidative stress [27] and sympathetic activation which in turn could increase the risk for AF. However, depression has also been associated with parasympathetic suppression [28], which might actually reduce AF risk, thus potentially explaining the null effects of symptoms of severe depression. It is also possible that the null effect for symptoms of anxiety and severe depression may be related to cardiac effects of different antidepressant medications. Selective serotonin reuptake inhibitors (SSRIs) seem to have a cardio-protective profile [29]. SSRIs have been documented to improve glucose metabolism, dyslipidemia, and reduce inflammatory markers, which may contribute to reduced AF risk [30]. In the



**Fig. 1.** Smoothed curve for hazard ratios of atrial fibrillation and symptoms of anxiety and depression at baseline (adjusted for sex, age, height, smoking status, level of education, marital status, physical activity and alcohol consumption).

**Table 3**  
Episodes of symptoms of anxiety and depression in HUNT 2 and 3, and risk for atrial fibrillation.

	Model 1	Model 2	Model 3	Model 4
Episodes of anxiety				
Events/person-years	1064/197,659	941/185,194	905/178,283	919/181,398
No anxiety	Reference	Reference	Reference	Reference
Anxiety at one time	1.2 (0.9–1.6)	1.1 (0.9–1.5)	1.1 (0.8–1.4)	1.2 (0.9–1.6)
Anxiety at two times	0.9 (0.5–1.6)	1.0 (0.5–1.9)	0.9 (0.5–1.8)	1.0 (0.5–2.0)
P for linear trend	0.6947	0.8987	0.8585	0.9624
P for quadratic trend	0.2050	0.5131	0.7950	0.5304
Episodes of depression				
Events/person-years	1189/209,075	1039/194,757	998/187,170	1015/190,694
No depression	Reference	Reference	Reference	Reference
Depression at one time	1.2 (0.9–1.6)	1.2 (0.9–1.6)	1.1 (0.8–1.6)	1.2 (0.9–1.6)
Depression at two times	0.9 (0.4–1.9)	0.9 (0.4–2.0)	0.9 (0.4–2.1)	0.8 (0.3–1.9)
P for linear trend	0.8137	0.7818	0.8480	0.5888
P for quadratic trend	0.3748	0.3898	0.4934	0.2843

Model 1: adjusted for age and sex.

Model 2: Model 1 + weight, height, smoking status, occupation, marital status, physical activity and alcohol consumption.

Model 3: Model 2 + chronic disorders.

Model 4: Model 2 + metabolic components (i.e., blood glucose, blood pressure, triglycerides, high-density lipoproteins and C-reactive protein).

aforementioned Danish study, AF risk was high 30 to 15 days before antidepressant medication initiation and after the first month of medication [23]. The association gradually attenuated over the following 6–12 months (HR = 1.11; 95% CI: 1.06–1.16). The attenuation of the association could reflect the possibility that depression-related AF may be a time-dependent event and that AF risk might decrease after an initial higher-risk period [23]. In our study, we did not have information about when depression may have started nor whether our participants were medicated, which limited our ability to explore the reason for the null association between symptoms of depression and AF risk.

Additionally, one can speculate that the higher AF risk among those with symptoms of mild/moderate depression – when compared to those without symptoms of depression and to those with symptoms of severe depression – might be due to differential help-seeking behaviors and differential detection rate of AF. Also, a prior study examining the effects of depression and antidepressant therapy on the risk of mortality and cardiovascular diseases showed that individuals with the most severe depression benefited most from antidepressant therapy regarding mortality and cardiovascular diseases, and those who had only mild depression showed no cardiovascular risk reduction [31]. Thus, individuals with symptoms of severe depression in our study may have adhered more regularly to antidepressant treatment compared to those with symptoms of mild to moderate depression, which might explain the observed null association between symptoms of severe depression and AF risk.

#### 4.1. Strengths and limitations

The strengths of our study derive from the population-based design, the homogeneity of the population (eliminating confounding by racial differences in AF risk) [32], its high stability (<0.3% net migration/year), the uniformly organized health care system which was equally available for every citizen and the relatively high response rate. Comprehensive data including those on a wide range of chronic disorders allowed us to thoroughly characterize participants and minimize confounding. We had data on repeated assessments of symptoms of anxiety and depression, which offered a unique opportunity to examine how AF risk was related to changes in symptoms of anxiety or depression over time. Furthermore, careful verification of AF diagnoses ensured the minimization of the misclassification of endpoints.

Some limitations warrant discussion. First, we relied on a self-reported scale to measure symptoms of anxiety and depression and lacked a clinician-administered interview to establish psychiatric diagnoses. While the HADS has been documented to be a valid and reliable instrument for screening among a wide variety of patient samples and

the general population, its ability to differentiate between anxiety and depression and its capability as a case-finder (i.e., to identify cases of clinical depression/anxiety) are imperfect [33,34]. This may have led to some misclassification of symptoms of depression and anxiety. Coronary heart disease is generally more strongly associated with anxiety and depression when these conditions are clinically diagnosed than when self-reported questionnaires alone are used [35]. Thus, the association between anxiety/depression and AF risk might be stronger if clinical interviews were available. Second, we lacked data on antidepressant medication. Third, the average HADS scores on symptoms of anxiety were generally lower compared to other studies in Norway and other European countries [33,36–38]. It might be possible that individuals with substantial anxiety symptoms were less prone to participate in the study. Fourth, we did not have updated information of symptoms of anxiety and depression during follow-up after baseline. This could lead to measurement error if participants changed their psychological status during follow-up. Because information on symptoms of anxiety and depression was gathered before diagnosis of AF, any misclassification would be expected to be unrelated to the outcome, i.e., non-differential misclassification [39]. Because non-differential misclassification tends to lead to weakening/dilution of the measure of association, i.e., a “bias towards the null”, it might explain the null association observed between symptoms of severe depression and AF risk. However, we had two measurements on HADS at or before baseline, and even recurrent symptoms of depression or anxiety were not associated with AF risk. In a previous study conducted in the same population, symptoms of depression and anxiety as measured by HADS were prospectively associated with both myocardial infarction and heart failure [4,5]. Lastly, AF can be occult and we only identified AF cases that came to clinical attention. Therefore, under-detection of AF, particularly when paroxysmal, is likely to exist in our findings. However, the consequence of under-detection, namely lower sensitivity, is generally less threatening to the validity of an epidemiological study than is lower specificity [16,39]. Nonetheless, this may have precluded us from identifying a true association between depression or anxiety and risk of AF if one exists.

#### 5. Conclusion

In this large, population-based study, we found no evidence of an association between symptoms of anxiety or severe depression and AF risk, even for recurrent symptoms of anxiety or depression. An unexpected association of symptoms of mild to moderate depression with increased AF risk requires confirmation in other studies.

## Declaration of competing interest

None of the authors have any conflicts of interest.

## Acknowledgements

The HUNT study is a collaboration between the Faculty of Medicine and Health Sciences, Norwegian University of Science and Technology, the Nord-Trøndelag County Council and the Norwegian Institute of Public Health. All laboratory analyses were performed and financed by the Health Trust of Nord-Trøndelag. We thank the Department for Research and Development, and clinicians at the Medical Department, Nord-Trøndelag Hospital Trust, Norway, for extracting the data from the patient registers.

## Funding

Grants are from Norwegian Heart and Lung Association and Liaison Committee for Education, Research and Innovation in Central Norway. The funding sources had no role in the study design, in the collection, analysis and interpretation of data, in the writing of the report, or in the decision to submit the article for publication.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ijcard.2019.11.107>.

## References

- [1] P.A. Wolf, J.B. Mitchell, C.S. Baker, W.B. Kannel, R.B. D'Agostino, Impact of atrial fibrillation on mortality, stroke, and medical costs, *Arch. Intern. Med.* 158 (1998) 229–234.
- [2] D.H. Lau, S. Nattel, J.M. Kalman, P. Sanders, Modifiable risk factors and atrial fibrillation, *Circulation* 136 (2017) 583–596.
- [3] R.M. Carney, K.E. Freedland, Depression and coronary heart disease, *Nat. Rev. Cardiol.* 14 (2017) 145.
- [4] L.T. Gustad, L.E. Laugsand, I. Janszky, H. Dalen, O. Bjerkeset, Symptoms of anxiety and depression and risk of acute myocardial infarction: the HUNT 2 study, *Eur. Heart J.* 35 (2013) 1394–1403.
- [5] L.T. Gustad, L.E. Laugsand, I. Janszky, H. Dalen, O. Bjerkeset, Symptoms of anxiety and depression and risk of heart failure: the HUNT study, *Eur. J. Heart Fail.* 16 (2014) 861–870.
- [6] S.D. Kreibitz, Autonomic nervous system activity in emotion: a review, *Biol. Psychol.* 84 (2010) 394–421.
- [7] P.-S. Chen, L.S. Chen, M.C. Fishbein, S.-F. Lin, S. Nattel, Role of the autonomic nervous system in atrial fibrillation: pathophysiology and therapy, *Circ. Res.* 114 (2014) 1500–1515.
- [8] W. Whang, K.W. Davidson, D. Conen, U.B. Tedrow, B.M. Everett, C.M. Albert, Global psychological distress and risk of atrial fibrillation among women: the Women's Health Study, *J. Am. Heart Assoc.* 1 (2012), e001107.
- [9] E.D. Eaker, L.M. Sullivan, M. Kelly-Hayes, R.B. D'Agostino Sr., E.J. Benjamin, Tension and anxiety and the prediction of the 10-year incidence of coronary heart disease, atrial fibrillation, and total mortality: the Framingham Offspring Study, *Psychosom. Med.* 67 (2005) 692–696.
- [10] J. Holmen, K. Midtjell, Ø. Krüger, A. Langhammer, T.L. Holmen, G.H. Bratberg, et al., The Nord-Trøndelag Health Study 1995–97 (HUNT 2): objectives, contents, methods and participation, *Norsk Epidemiologi.* 13 (2003) 19–32.
- [11] A. Mykletun, E. Stordal, A.A. Dahl, Hospital Anxiety and Depression (HAD) scale: factor structure, item analyses and internal consistency in a large population, *BrjPsychiatry.* 179 (2001) 540–544.
- [12] I. Bjelland, A.A. Dahl, T.T. Haug, D. Neckelmann, The validity of the Hospital Anxiety and Depression Scale: an updated literature review, *J. Psychosom. Res.* 52 (2002) 69–77.
- [13] M.A. Annunziata, B. Muzzatti, G. Altoe, Defining hospital anxiety and depression scale (HADS) structure by confirmatory factor analysis: a contribution to validation for oncological settings, *Ann. Oncol.* 22 (2011) 2330–2333.
- [14] A. Zigmond, R. Snaith, The hospital anxiety and depression scale, *ActaPsychiatrScand.* 67 (1983) 361–370.
- [15] A.J. Camm, P. Kirchhof, G.Y. Lip, U. Schotten, I. Savelieva, S. Ernst, et al., Guidelines for the management of atrial fibrillation, *Eur Heart J* 31 (19) (2010) 2369–2429.
- [16] V. Malmø, A. Langhammer, K.H. Bønna, J.P. Loennechen, H. Ellekjaer, Validation of self-reported and hospital-diagnosed atrial fibrillation: the HUNT study, *Clin Epidemiol.* 8 (2016) 185.
- [17] B. Morkedal, L.J. Vatten, P.R. Romundstad, L.E. Laugsand, I. Janszky, Risk of myocardial infarction and heart failure among metabolically healthy but obese individuals: HUNT (Nord-Trøndelag Health Study), Norway, *J Am Coll Cardiol.* 63 (2014) 1071–1078.
- [18] L.A. Sleeper, D.P. Harrington, Regression splines in the Cox model with application to covariate effects in liver disease, *J. Am. Stat. Assoc.* 85 (1990) 941–949.
- [19] D.B. Rubin, Multiple imputation for nonresponse in surveys, *Wiley Series in Probability and Statistics*, 1987.
- [20] M.J. Pencina, R.B. D'Agostino Sr., R.B. D'Agostino Jr., R.S. Vasan, Evaluating the added predictive ability of a new marker: from area under the ROC curve to reclassification and beyond, *Stat. Med.* 27 (2008) 157–172.
- [21] P.K. Garg, W.T. O'Neal, A.V.D. Roux, A. Alonso, E. Soliman, S. Heckbert, Depressive symptoms and risk of incident atrial fibrillation: the multi-ethnic study of atherosclerosis, *Circulation* 137 (2018) AMP60.
- [22] R.N. Carleton, M.A. Thibodeau, M.J. Teale, P.G. Welch, M.P. Abrams, T. Robinson, et al., The center for epidemiologic studies depression scale: a review with a theoretical and empirical examination of item content and factor structure, *PLoS One* 8 (2013), e58067.
- [23] M. Fenger-Grøn, M. Vestergaard, H.S. Pedersen, L. Frost, E.T. Parner, A.R. Ribe, et al., Depression, antidepressants, and the risk of non-valvular atrial fibrillation: a nationwide Danish matched cohort study, *Eur. J. Prev. Cardiol.* 26 (2) (2018) 187–1952047487318811184.
- [24] V. Abbing-Karagapian, C. Huerta, P. Souverein, F. De Abajo, H. Leufkens, J. Slattery, et al., Antidepressant prescribing in five European countries: application of common definitions to assess the prevalence, clinical observations, and methodological implications, *Eur J Clin Pharmacol.* 70 (2014) 849–857.
- [25] Verhaak PF, de Beurs D, Spreuuenberg P. What proportion of initially prescribed antidepressants is still being prescribed chronically after 5 years in general practice? A longitudinal cohort analysis. *BMJ open.* 2019;9:e024051.
- [26] G.E. Miller, E. Blackwell, Turning up the heat: inflammation as a mechanism linking chronic stress, depression, and heart disease, *Curr. Dir. Psychol. Sci.* 15 (2006) 269–272.
- [27] P. Palta, L.J. Samuel, E.R. Miller III, S.L. Zanton, Depression and oxidative stress: results from a meta-analysis of observational studies, *Psychosom. Med.* 76 (2014) 12.
- [28] J.M. Gorman, R.P. Sloan, Heart rate variability in depressive and anxiety disorders, *Am. Heart J.* 140 (2000) S77–S83.
- [29] M.H. Nezaefati, M. Vojdanparast, P. Nezaefati, Antidepressants and cardiovascular adverse events: a narrative review, *ARYA Atherosclerosis.* 11 (2015) 295.
- [30] M.H. Nezaefati, A. Eshraghi, M. Vojdanparast, S. Abtahi, P. Nezaefati, Selective serotonin reuptake inhibitors and cardiovascular events: a systematic review. *Journal of research in medical sciences: the official journal of Isfahan University of Medical, Sciences* 21 (2016).
- [31] H.T. May, T. Bair, B. Reiss-Brennan, S. Knight, J. Anderson, B. Horne, et al., The association of antidepressant and statin use to future death and incident cardiovascular disease varies by depression severity, *J. Am. Coll. Cardiol.* 65 (2015) A1443.
- [32] L. Mou, F.L. Norby, L.Y. Chen, W.T. O'Neal, T.T. Lewis, L.R. Loehr, et al., Lifetime risk of atrial fibrillation by race and socioeconomic status: ARIC Study (Atherosclerosis Risk in Communities), *Circ. Arrhythm. Electrophysiol.* 11 (2018), e006350.
- [33] M.W. Nortvedt, T. Riise, B. Sanne, Are men more depressed than women in Norway? Validity of the Hospital Anxiety and Depression Scale, *J. Psychosom. Res.* 60 (2006) 195–198.
- [34] A.J. Mitchell, N. Meader, P. Symonds, Diagnostic validity of the Hospital Anxiety and Depression Scale (HADS) in cancer and palliative settings: a meta-analysis, *J. Affect. Disord.* 126 (2010) 335–348.
- [35] I. Janszky, A. Ahlbom, J. Hallqvist, S. Ahnve, Hospitalization for depression is associated with an increased risk for myocardial infarction not explained by lifestyle, lipids, coagulation, and inflammation: the SHEEP Study, *Biol. Psychiatry* 62 (2007) 25–32.
- [36] A. Jöregården, L. Wettergen, L. von Essen, Measuring health-related quality of life in adolescents and young adults: Swedish normative data for the SF-36 and the HADS, and the influence of age, gender, and method of administration, *Health and Quality of Life Outcomes* 4 (2006) 91.
- [37] W. Häuser, K.-H. Janke, B. Klump, A. Hinz, Anxiety and depression in patients with inflammatory bowel disease: comparisons with chronic liver disease patients and the general population, *Inflamm. Bowel Dis.* 17 (2010) 621–632.
- [38] C. Bocéréan, E. Dupret, A validation study of the Hospital Anxiety and Depression Scale (HADS) in a large sample of French employees, *BMC Psychiatry.* 14 (2014) 354.
- [39] K.J. Rothman, S. Greenland, T. Lash, *Modern Epidemiology*, 1, Lippincott Williams & Wilkins Foundation for Alcohol Research & Education Level, Philadelphia, 2008 40.