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Assessment of mental health trajectories before and after myocardial infarction, atrial fibrillation or stroke: analysis of a cohort study in Tromsø, Norway (Tromsø Study, 1994–2016)

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ABSTRACT

Objectives The increased survival rate of cardiovascular disease (CVD) implies a higher proportion of individuals who live with CVD. Using data from the Tromsø Study, we aimed to investigate mental health symptom trajectories before and after myocardial infarction, atrial fibrillation or stroke in a general population and to explore factors that contribute to the association.

Design Cohort study.

Setting Sample drawn from inhabitants of the municipality of Tromsø, Norway, who participated in the Tromsø Study (1994–2016).

Participants A total of 18 719 participants (52.3% women) were included, and of these 2098 (32.9% women) were diagnosed with myocardial infarction, 1896 (41.9% women) with atrial fibrillation and 1263 (42.9% women) with stroke.

Primary outcome measures Mental health symptoms were assessed using the Hopkins Symptom Checklist-10 and the Conor Mental Health Index.

Results The participants who were diagnosed with either myocardial infarction or stroke had a significant monotonous increase in mental health symptoms before myocardial infarction (p=0.029) and stroke (p=0.029) that intensified at the time of diagnosis. After the event, the study found a higher prevalence of mental health symptoms with a decline in symptom levels over time for myocardial infarction (p<0.001) and stroke (p=0.004), but not for atrial fibrillation (before: p=0.180, after: p=0.410). The risk of elevated mental health symptoms with myocardial infarction, atrial fibrillation and stroke was associated with sex (p<0.001), age (p<0.01), physical activity (p<0.001), diabetes (p<0.05) and other comorbidities (p<0.001).

Conclusion The study indicates that mental health problems among individuals with myocardial infarction, atrial fibrillation and stroke may have started to develop several years before the cardiovascular event and suggests that successful CVD rehabilitation may need to consider previous life factors. Future research is recommended to examine whether health promotion measures in a general population also create mental health resilience after a CVD event.

Strengths and limitations of this study

- ► The accelerated longitudinal design with 21 years of follow-up time allows us to link mental health trajectories to the onset of cardiovascular disease (CVD).
- ► A large cohort allows us to relate health, lifestyle and social factors to mental health outcomes.
- ► A population study design with a high participation rate and a validated endpoint register allows us to relate our findings to a general population.
- ► Self-reported mental health could induce measurement errors because specific cardiovascular outcomes are not easily differentiated from symptoms of mental disease.
- ► The (inverse) causality of CVD and mental health has never been demonstrated and calls for further studies that examine previous life factors and prediagnostic mental health trajectories.

INTRODUCTION

Anxiety and depression are related to both onset and poorer outcomes of cardiovascular disease (CVD) worldwide. Epidemiological data suggest a 28.7% prevalence of depression among participants with myocardial infarction (MI),[1 2] which is far higher than in the general population (17.8%).[3] In addition, participants with atrial fibrillation (AF) have reported a high burden of depressive symptoms.[4] Furthermore, one-third of stroke survivors develop depression,[5] and one-quarter develop anxiety disorders.[6] This study aims to enhance understanding of mental health among individuals with MI, AF and stroke, including an attempt to improve knowledge about mechanisms and factors associated with poor mental health in these participants.

Epidemiological research suggests that depression in patients with coronary artery

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disease is related to increased risk of future cardiac events[7] and higher mortality rates resulting from the disease.[2] This increased risk of mortality is partly explained by depression as an independent risk factor for developing coronary heart disease,[8] but is also thought to affect patients' coping strategies and compliance with treatment plans.[9] Furthermore, clinical depression is a stronger predictor of CVD development in initially healthy individuals compared with individuals who report depressed mood.[8] A meta-analysis concluded that depression serves as a predictor of many CVDs, but the evidence is seemingly related to a high level of heterogeneity between the studies included.[10]

Although the connection between mental health and increased risk of new cardiovascular events or death is well known,[11–14] the inverse association has not been demonstrated. The majority of these studies suffer from methodological weaknesses such as reverse causality and measurement methods. For example, in the meta-analysis by Van der Kooy *et al*[10] an overall relative risk of 2.54 (95% CI: 2.07 to 3.10) for CVD was reported for studies measuring major depressive disorder by structured diagnostic interview, compared with a risk of 1.39 (95% CI: 1.26 to 1.54) for studies that measured depressive symptoms but not disorders. However, most studies only measured depression once, rendering the association between susceptibility to depression and risk of CVD poorly understood.

The Tromsø Study includes a validated endpoint registry that collects data on incident cases of MI, AF and stroke in the participants. It enables us to follow these participants, since they participated in the Tromsø Study between 1994 and 2016. The aim was to assess mental health trajectories before and after MI, AF or stroke. We used the surveys and physical examinations from the Tromsø Study to track individuals for up to 20 years before CVD onset. Our first objective was to assess how health, lifestyle and social factors related to a mental health outcome. The second objective was to link mental health trajectories to the onset of CVD.

METHODS

Study design and sample

The Tromsø Study is an ongoing population-based cohort study conducted in the municipality of Tromsø, Northern Norway, and is the most extensive population study of its kind in Norway.[15] The Tromsø Study started in 1974 to help combat the high mortality of CVD in Northern Norway. However, during the 47 years since the Tromsø Study commenced, increasing emphasis has been placed on other chronic diseases and conditions. It has been a deliberate policy to invite a wide range of health research groups to conduct subprojects in connection with the surveys. The Tromsø Study has conducted seven surveys to date, collecting data on several lifestyle factors and biomarkers.[16] Tromsø4 (1994) was the first wave to include self-reported mental health. A total of 26 992 persons participated in Tromsø4. The response rate was 71.8%. This was followed by Tromsø5 (n=8062, response rate=77.9%), Tromsø6 (n=12 981, response rate=65.7%) and Tromsø7 (n=21 083, response rate=65.0%). All panels included both new participants and reinvited Tromsø4 participants (https://uit.no/research/tromsostudy).

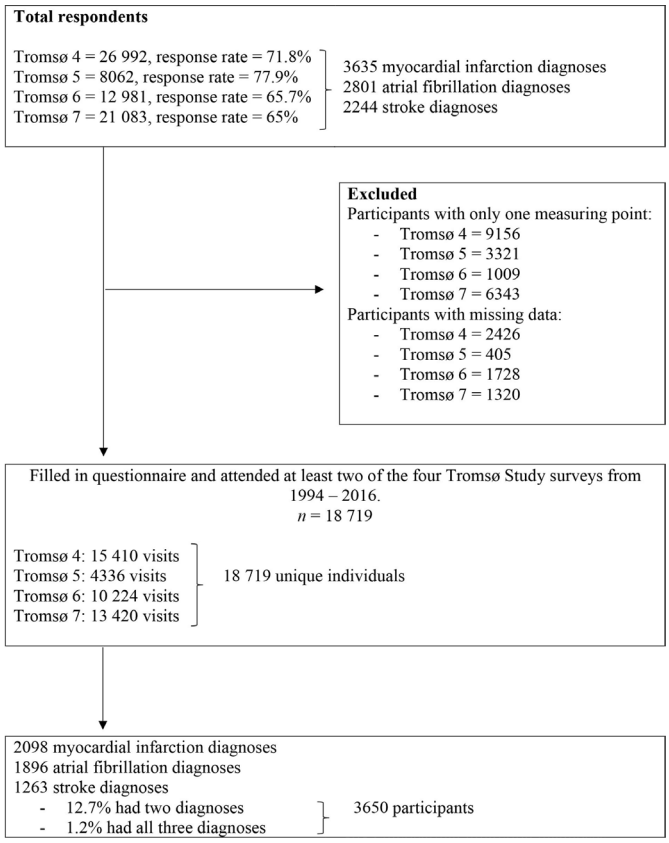

Figure 1 Flow chart of the inclusion of participants in the study.

A total of 3650 participants with a validated MI, AF or stroke diagnosis were included in our study: 960 were recorded as having two of the diagnoses, while 260 had all three diagnoses.

We used an accelerated longitudinal design for our study. It includes multiple single trajectories, each starting at a different time relative to the MI, AF or stroke event. The main advantage of an accelerated longitudinal design is its ability to span a longer time range over a shorter follow-up period than would be possible with a single-cohort longitudinal design.[17] The method enables the utilisation of repeated measurements to estimate change over time. We used repeated measurements based on comprehensive questionnaires, biological samples and clinical examinations from Tromsø4 (1994–1995), Tromsø5 (2001), Tromsø6 (2007–2008) and Tromsø7 (2015–2016). The follow-up period was from 1994 to 2016. The flow diagram (figure 1) shows how the participants were included in the study. Each participant was tracked for two or more measuring points for this analysis. Thus, the participants can enter the study at different time points, and their first measuring point is regarded

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as the baseline. The study sample includes 15 410 participants from Tromsø4, 4336 from Tromsø5, 10 224 from Tromsø6 and 13 420 from Tromsø7, adding up to 18 719 unique persons. In this study, the first recordings of MI, AF or stroke were from 1968 and the last from 2018.

We used the Strengthening the Reporting of Observational Studies in Epidemiology cohort reporting guidelines.[18]

Measurements

Mental health symptoms

Symptoms of anxiety and depression were measured using well-validated instruments for self-reported symptoms. For Tromsø4, the Conor Mental Health Index (CONOR-MHI) was used, while the subsequent surveys of Tromsø5–Tromsø7 used the Hopkins Symptom Checklist-10 (HSCL-10). HSCL-10 measures anxiety symptoms with four items and depression with six items during the previous 7 days.[19] CONOR-MHI is a partly modified instrument from the HSCL-10 and is highly correlated with HSCL-10 (r=0.8). It is therefore possible to track symptoms of anxiety and depression in the Tromsø Study from 1994 until 2016. In stage 3 of the analysis, the purpose was to examine the development of mental health symptom levels of clinical significance before and after an MI, AF or stroke diagnosis. We thus used the recommended cut-off level of 2.15 for significant symptoms, which is equivalent to the 1.85 level in HSCL-10[20] and the subthreshold was HSCL ≥1.40, <1.85; and CONOR-MHI ≥1.60,<2.15. In stage 4, we examined the development of symptoms of anxiety and depression along a continuum. We standardised the continuous variable for better longitudinal comparison and could thus use symptom levels as continuous measurements.

Myocardial infarction, atrial fibrillation and stroke

The Tromsø Study collected data on incident cases of MI, AF and stroke by linkage to the discharge diagnosis registry with a search for relevant diagnoses at the University Hospital of North Norway (including outpatients) for the participants by using the unique national identification number. The systematic registration of CVD events started in 1974 and ended in 2014 for MI and stroke, and in 2016 for AF. The incident cases of MI, AF and stroke subtypes were identified retrospectively and determined by an endpoint committee using medical records and medical notes. This process is described in detail elsewhere.[21 22] Stroke subtypes were recoded into one variable representing all types of stroke. All validated events were included since the purpose was to examine the mental health trajectory and not to estimate CVD incidence.

Covariates

The analyses included covariates regarding demographic and social factors (eg, sex and age,[23] civil status,[24] having support from family[25]), health and lifestyle factors (eg, body mass index (BMI)),[26] systolic blood pressure,[27] physical activity,[28] smoking and use of alcohol[29]) and psychological health factors (eg, use of therapy and antidepressants[30]). All covariates were included in all surveys represented in this study.

Demographic and social factors

The participants' age and sex were included as possible confounders in the analyses. Information about the marital/partnership status was also included, and the variable was grouped individually: married or in a registered partnership, widow or widower and separated or single. Data on whether the participants lived alone or with someone were added to the model as a covariate. In addition, information on the highest attained level of education was added in the analysis, categorised into 'primary/secondary school', 'high school' and 'college/university'.

Health and lifestyle factors

The questionnaire collected data on the Health Impact Index (HII), which classifies participants with one or more comorbid diseases according to their impact on self-reported health by assigning them weight, and HII score is the total of the weighted scores of every weighted condition the participant has.[31] A dichotomous variable assessed daily smoking in Tromsø4, but it was possible to define former smokers from another variable measuring time since quitting. An alternative, 'former smoker', was added in the later versions of an ordinal variable about smoking in Tromsø5–Tromsø7. The number of alcoholic drinks (beer, wine and spirits) typically consumed during 2 weeks was reported, and the numbers were categorised into 'none', '2–4 units' and '≥5'. Leisure-time physical activity was reported, estimating weekly physical activity during leisure time (ie, walking, swimming or exercise/sport). The responses were categorised into inactive (0 to less than once weekly average) and active (≥1 times weekly average).

At the screening site, trained personnel performed physiological measurements; weight and height were measured and used to calculate BMI by kg/m^2. Blood pressure was measured three times, with 1 min intervals after 2 min' seated rest. The mean of the two latter systolic blood pressure measurements is included as a covariate in the analyses. Non-fasting blood samples were drawn to measure serum total cholesterol concentration and glycated haemoglobin.

Psychological healthcare factors

Use of psychotherapy (not in therapy/currently in therapy) and self-reported use of antidepressants (not using/using) were added to the model as covariates as these can influence the relationship between mental health symptoms and MI, AF and stroke.

Statistical analyses

We performed the statistical analyses in four stages using Stata V.16.1.[32] See online supplemental material for the full analysis plan.

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Stage 1: descriptive characteristics

Calculations of means, SD and percentages of the variables stratified by severity of self-reported anxiety and depression symptoms at baseline were conducted, in addition to the frequency of observations for each diagnosis of MI, AF or stroke for each period.

Stage 2: development of sample characteristics over time relative to CVD diagnosis

We used cross-tabulation to describe the number of participants with significant mental health symptoms in different periods relative to the CVD event. Participants were grouped relative to the first MI, AF and stroke diagnosis at >10, 10–5, 4.9–1 and <1 year before the event and 1 and >1 year after the event.

Stage 3: mixed-effects model

We wanted to assess how health, lifestyle and social factors related to a mental health outcome. We fitted two-level logistic models for ordered responses[33] with mental health scores as the dependent variable. We fitted separate models for each condition, MI, AF and stroke, to estimate the effect of having increased symptom levels on the ordinal response variable (no symptoms/subthreshold/significant symptoms) for all independent variables.

Stage 4: fixed-effects model

We wanted to assess the relationship between mental health trajectories and the onset of CVD. We fitted separate models for each CVD diagnosis before and after the event. We did this to improve the model's fit, given that changes in mental health symptoms increased before the event and tended to remain high or decline after the event. This two-stage trend can be seen in figure 2, showing descriptive statistics and plots for the mental health symptom trajectories.

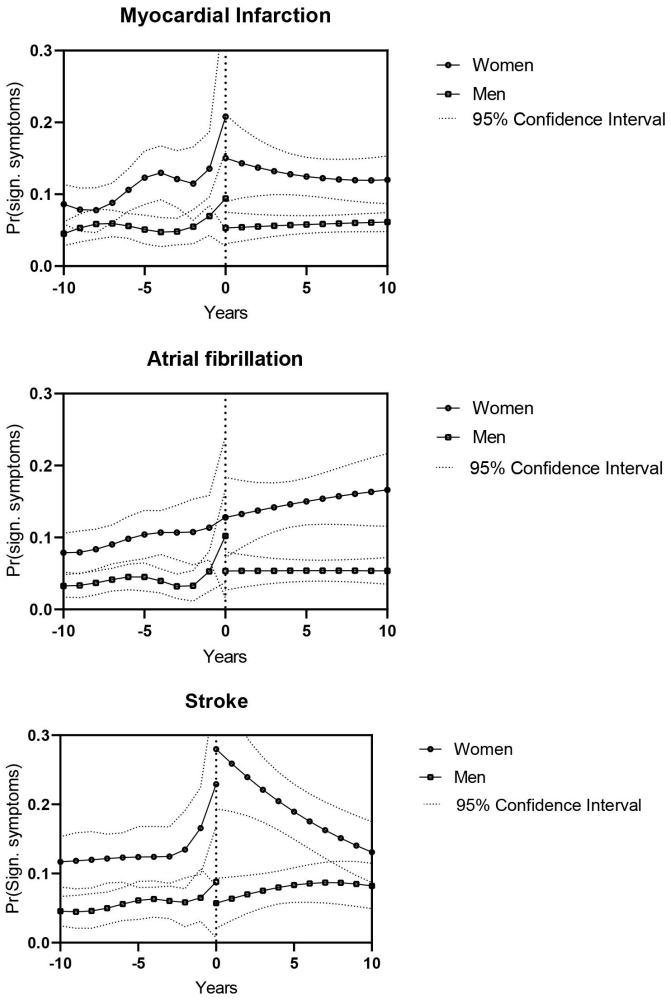

Figure 2 Cubic marginal plots for levels of mental health symptoms before and after myocardial infarction, atrial fibrillation and stroke diagnoses showing proportion with significant symptoms.

Controlling for attrition

Fixed-effects models require that we censor all participants that attended only once; hence 34.5% of the participants are lost. A loss of >20% could represent a significant selection bias. Conditional exchangeability assumes no unaccounted for sources of confounding and selection bias due to this loss of follow-up. The primary reason for attrition was that most Tromsø4 participants were not reinvited until Tromsø7. Tromsø5 and Tromsø6 were mainly follow-up studies that invited a random selection of Tromsø4 participants; however, the Tromsø5 and Tromsø6 invitations were selected to avoid selection bias.[34] Hence, we do not regard this as a significant source of bias.

All-cause death needs to be followed up since mortality is related to both heart disease and mental health. Time of death was retrieved from the Norwegian Cause of Death Registry. We found that 7285 persons had died since baseline. We used inverse probability weighting (IPW) with pooled logistic regression to assess survival bias for all diagnoses. IPW can be used to create the pseudopopulation that would have been observed, if losses to follow-up had occurred but been random in terms of measured determinants of loss to follow-up.[35] For valid estimation, the assumptions of exchangeability, positivity and correct model specification in the outcome and weight model must hold.[36] The probabilities were obtained by modelling the observed loss to follow-up as a function of survival. Weights from the IPW model ranged from 1.51 to 2.96, with a mean of 2.00. This concurs with positivity that requires a non-zero probability of not being lost to follow-up each time that losses occur within every combination of observed, measured variables that contribute to the selection bias. The assumptions of the logistic regression model (ie, sample size, multicollinearity and no significant outliers) were also met. The IPW model thus met the required assumptions.

IPW showed that loss to follow-up did not significantly change the result, which supports the claim that MI, AF and stroke drive the later decline in mental health. IPW was also used to check for bias due to comorbidity (432 persons were registered with MI and stroke, 823 with MI and AF, 434 with AF and stroke). We also excluded persons with more than one CVD diagnosis from the

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models. Neither method changed the results. All models were tested with IPW. The results reported in this paper are non-weighted.

Patient and public involvement

The Tromsø Study is led by a working committee and a scientific council. We would like to thank the participants from the national patient organisation for heart and lung disease in Norway for valuable input to our study. We collaborate with the National Association for Heart and Lung Diseases in Norway (lhl.no). The patient representatives endorsed research on mental health issues for heart patients, and they helped us to inform our objectives by including patients' priorities, experience and preferences. The results will be disseminated through the Tromsø Study research blog, and local and national media.

RESULTS

Sample characteristics

A total of 18 719 participants (52.3% women) were included, and of these, 2098 (32.9% women) were diagnosed with MI, 1896 (41.9% women) with AF and 1263 (43.9% women) with stroke in the Tromsø Study.

Table 1 shows baseline characteristics of participants with and without self-reported significant symptoms of anxiety and depression. We found no significant difference in symptom severity for those who entered the study with no CVD but contracted MI, AF or stroke during the follow-up (ie, participants with past events were omitted). Among participants with a CVD diagnosis at baseline, 6.1% of those with MI, 9.4% of those with AF and 6.8% of those with a stroke diagnosis had mental health symptoms. Symptoms of anxiety and depression were found in 7.7% of women compared with 4.6% of men. Of participants who lived alone, 9.0% reported mental health symptoms compared with 5.6% of those living with others. Participants with a lower level of education, comorbid diseases, daily smoking and inactivity reported higher symptom levels than the reference group. Unsurprisingly, 36.2% of those in therapy reported higher or subthreshold mental health symptoms, and 39.7% of the participants who used antidepressant drug treatment were classified similarly.

Association between mental health and MI, AF or stroke over time

We found that most (69.3%, n=638) of the individuals with CVD that reported significant mental health symptoms *after* the event had already reported significant mental health symptoms before the CVD event. Figure 2 shows that the development of *significant* mental health symptoms started at least 2–3 years before the event and ~7 years for women before MI. Table 2 shows cross-tabulation of the characteristics over time relative to the onset of MI, AF and stroke characteristics. We observe that mental health symptom levels were highest the year before and after the diagnoses. Figures for MI were 10.7% the year before and 8.0% the year after. Participants with AF reported 8.7% the year before and 11.6% the year after. As for persons with stroke, we found 10.6% the year before and 20.0% the year after the stroke. Cubic splines were used to examine whether the trajectories showed evidence of specific turning points.

Table 2 also shows variances in serum total cholesterol before and after an MI, AF or stroke diagnosis. The pairwise comparison shows that systolic blood pressure was lower the year after MI and AF but not stroke. Furthermore, BMI levels were stable, but there were fewer daily smokers after MI, AF and stroke. The proportion of individuals doing hard exercise every week shows no significant changes except that in individuals with stroke, the proportion was lowest 1–5 years before the stroke event. We also see that the use of therapy and antidepressants was lowest at the onset of an MI, AF or stroke diagnosis, but there are too few observations to compare.

Factors associated with mental health symptoms

Table 3 shows the results for the mixed-effects models. This model uses the ordinal outcome and thus estimates the probability of having increased symptom levels. For the beneficial factors, we found that 10 years increase in age was associated with a 14%–27% reduced risk of significant mental health symptoms before CVD but was only a significant protective factor for MI after the event. Physical activity was associated with lower symptoms both before an event (OR 0.64–68) and after (OR 0.39–0.57). Living with others was beneficial before MI and stroke but not after CVD events for the social variables. Drinking 2–4 units of alcohol every 2 weeks was associated with lower symptom levels before AF, but we found no other association between alcohol and mental health.

We found that women had a higher risk than men. Having one or more comorbid diseases is another overall negative factor. This was associated with increased symptom levels both before and after the CVD event. Furthermore, the number and seriousness of the comorbid diseases showed a cumulative effect. Daily smoking was associated with 25%–32% higher symptom levels before an MI or a stroke event, but not after. Several physical factors were associated with mental health. Hypertension was associated with an increased risk of mental health symptoms before MI. Diabetes was associated with a higher risk before MI and after MI and stroke. Hyperlipidaemia was not associated with mental health symptoms. Finally, educational level was not associated with mental health.

Table 4 shows the results from the fixed-effects models. The analytical goal was to examine time as a risk factor. The separate model estimates the within-subject change before the CVD event and in the years after the event. We estimated the standardised symptom scores for every other year to show the non-linear trends. There was a significant linear association between time in years relative to diagnoses of stroke and mental health symptom score (in SD units) from 0.011 ten years before the diagnosis to 0.082 at the time of the event. After the event we

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Table 1 Baseline characteristics for the study population stratified by severity of self-reported anxiety and depression symptoms

	Participants in database	Participants with no symptoms	Participants with subthreshold symptoms	Participants with significant symptoms
Overall (n, %)	19 851	14 698 (73.81)	3912 (19.65)	1241 (6.23)
Mental health symptoms at baseline*				
No diagnosis (reference group) (n, %)	15 984	11 862 (74.2)	3146 (19.7)	976 (6.1)
Myocardial infarction events during study (n, %)	362	253 (69.9)	87 (24.0)	22 (6.1)
Atrial fibrillation events during study (n, %)	127	90 (70.9)	25 (19.7)	12 (9.4)
Stroke events during study (n, %)	132	89 (67.4)	34 (25.8)	9 (6.8)
Psychological health factors				
Use of therapy				
Not in therapy (n, %)	18 588	14 016 (75.4)	3575 (19.2)	997 (5.4)
Currently in therapy (n, %)	505	170 (33.7)	152 (30.1)	183 (36.2)
Use of antidepressant medication				
Not using (n, %)	19 176	14 393 (75.1)	3721 (19.4)	1062 (5.5)
Using (n, %)	375	118 (31.5)	108 (28.8)	149 (39.7)
Demographic factors				
Age, years (mean, SD)	45.60 (12.53)	45.53 (12.50)	45.44 (12.55)	46.01 (12.32)
Women (n, %)	10 601	7482 (70.6)	2308 (21.8)	811 (7.7)
Men (n, %)	9250	7216 (78.0)	1604 (17.3)	430 (4.6)
Social factors				
Married or in a registered partnership (n, %)	11 613	8899 (76.6)	2114 (18.2)	600 (5.2)
Separated/single (n, %)	8238	5799 (70.4)	1798 (21.8)	641 (7.8)
Highest level of education				
Primary/secondary school (n, %)	5797	4169 (71.9)	1183 (20.4)	445 (7.7)
High school (n, %)	6619	4980 (75.2)	1288 (19.5)	351 (5.3)
College/university (n, %)	5307	4049 (76.3)	1002 (18.9)	256 (4.8)
Household				
Living with others (n, %)	15 832	11 991 (75.7)	2962 (18.7)	879 (5.6)
Living alone (n, %)	4019	2707 (67.4)	950 (23.6)	362 (9.0)
Health and lifestyle factors				
Comorbidity† (mean/SD)	0.42 (0.90)	0.37 (0.84)	0.54 (1.02)	0.65 (1.12)
Body mass index				
<18.5 kg/m^2 (n, %)	197	127 (64.5)	49 (24.9)	21 (10.7)
18.5–24.9 kg/m^2 (n, %)	10 030	7361 (73.4)	2016 (20.1)	653 (6.5)
25–29.9 kg/m^2 (n, %)	7488	5681 (75.9)	1391 (18.6)	416 (5.6)
≥30 kg/m^2 (n, %)	2131	1527 (71.7)	454 (21.3)	150 (7.0)
Systolic blood pressure (mm Hg) (mean, SD)	131.97 (18.80)	132.26 (18.62)	131.02 (18.91)	130.77 (19.66)
Total cholesterol (mmol/L) (mean, SD)	5.98 (1.27)	5.98 (1.27)	5.96 (1.27)	5.96 (1.28)
Glycated haemoglobin (%) (mean, SD)	5.56 (0.64)	5.55 (0.62)	5.58 (0.69)	5.57 (0.66)
Usual alcohol intake (2 weeks)				
None (n, %)	7604	5499 (72.3)	1578 (20.8)	527 (6.9)
2–4 units (n, %)	11 391	8613 (75.6)	2148 (18.9)	630 (5.5)
≥5 (n, %)	445	312 (70.1)	90 (20.2)	43 (9.7)
Smoking habits				
Daily smoking (n, %)	6642	4621 (69.6)	1449 (21.8)	572 (8.6)
No smoking (n, %)	747	524 (70.1)	161 (21.6)	62 (8.3)

Continued

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Table 1 Continued

	Participants in database	Participants with no symptoms	Participants with subthreshold symptoms	Participants with significant symptoms
Physical activity leisure time				
Inactive (n, %)	8121	5885 (71.7)	1741 (21.2)	586 (7.1)
Physical activity ≥1–2 times per week (n, %)	11 639	8813 (75.7)	2171 (18.7)	655 (5.6)

*X^2 for cross-tabulation of symptom levels. MI: Pearson X^2=0.9310 p=0.628, AF: Pearson X^2=2.8847 p=0.236, Pearson X^2=4.8435, Pr=0.089. Participants with pre-existing diagnosis before study entry were excluded.
†Comorbidity measured by Health Impact Index.

see a significant decrease in symptoms from 0.218 at the time of the diagnosis to 0.064 ten years after the stroke. There was a significant monotonous non-linear association between time in years relative to diagnoses of MI and mental health symptom score (in SD units) from −0.107 ten years before the diagnosis to 0.025 at the time of the event. After the diagnosis we see a decrease from 0.145 to −0.075 ten years after the event. Atrial fibrillation was not associated with any overall change relative to the event, except among women before the diagnosis (see online supplemental tables 1 and 2).

We used random-effects models to examine whether group differences between the sexes were significant. We found that all sex differences were significant (p<0.001). However, there was no significant interaction between sex and time.

DISCUSSION

We assessed how health, lifestyle and social factors relate to a mental health outcome. We found that the risk of developing mental health symptoms before and after CVDs was significantly higher for women, younger persons and persons with comorbid diseases. Furthermore, modifiable lifestyle factors such as physical activity and daily smoking were related to mental health status. Biological factors such as hypertension were related to mental health before MI, and diabetes was a significant factor before MI, and after MI and stroke.

We wanted to link mental health trajectories to the onset of CVD. The trajectories declined but remained high after the events. Our study also shows that mental health symptoms increased considerably in the years before MI, stroke and AF (women only). We have little evidence that this prediagnostic association can be explained as a sign of underlying heart disease or misinterpreted physical symptoms:

First, we compared the reported symptom levels between individuals with and without CVD (see online supplemental table 3). Although dizziness was associated with CVD, fear and feeling useless were more critical. Thus, we found little support that an underlying CVD condition could explain the observed increase in symptoms before the event.

Second, we found no relationship between CVD risk factors and mental health before the event except for hypertension before MI and smoking in general. Rutledge *et al*[37] also found that diabetes and smoking status were more strongly associated with cardiovascular outcomes among women with lower depression scores, whereas waist–hip ratio values predicted outcomes only among those with higher depressive symptoms. It means that the degree to which modifiable CVD risk factors are associated with CVD outcomes may depend on depression status.

Finally, our findings could indicate that we were observing mental health trajectories that resulted in a CVD. Most participants with significant symptoms post-diagnosis also had a prediagnostic history of significant symptoms. Many participants had a history of increased morbidity (eg, angina pectoris) before the first 'hard' CVD, and we found a significant association for comorbid diseases in general. The high levels of mental health symptoms could thus be explained by the increase of physical symptoms leading up to a diagnosis. Angina often precedes MI, and it is also associated with mental health symptoms.[38] Thus, the high levels of mental health symptoms before MI could have been caused by the increase of angina in the period leading up to the MI, and the observed lower levels of mental health symptoms after MI could be because of the absence of chest pain.[39] In the post-hoc analysis, we examined angina separately and found an association leading up to AF, but surprisingly we found no significant change related to MI or stroke.

The idea of mental health issues as reacting to a CVD concurs with our observation of a peak year after stroke, but we observed more persons with significant symptoms before the event for MI. Kendler *et al*[40] found that the onset of CVD more strongly predicts the risk of major depression than the other way around. Furthermore, they found the effect of major depression on CVD to be primarily acute. There was a modest increase in the risk of CVDs after the onset of major depression, but this increased risk was strongly related to severity and recurrence in major depression. Depression and anxiety were associated with cognitive and emotional consequences following stroke,[41] especially the first 12 months, which could explain our study results. The potentially devastating consequences of

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Table 2 Characteristics of participants over time relative to the onset of myocardial infarction (MI), atrial fibrillation (AF) and stroke

	Time before MI				Time after MI		Time before AF				Time after AF		Time before stroke				Time after stroke	
	<10 years	10–5 years	4.9–1 years	<1 year	First year	>1 year	<10 years	10–5 years	4.9–1 years	<1 year	First year	>1 year	<10 years	10–5 years	4.9–1 years	<1 year	First year	>1 year
Number of observations*	948	865	697	168	125	1326	1147	914	736	172	103	949	668	544	450	113	75	596
Mental health problems (%)	5.8	5.9	6.5	10.7	8.0	6.9	5.8	6.1	5.4	8.7	11.7	7.7	7.3	8.8	7.1	10.6	20.0	8.3
Health services																		
Use of therapy (%)	1.1	2.3	1.5	0.0	1.1	1.7	1.8	1.2	1.2	0.0	2.6	1.5	1.4	1.8	2.3	1.3	6.0	1.1
Use of antidepressant medication (%)	1.6	1.8	2.7	0.7	1.9	3.1	1.2	2.9	3.2	4.0	5.6	3.6	2.4	4.4	3.9	4.5	7.0	5.1
Any general practitioner visits (%)	74.1	78.8	84.8	86.8	94.2	91.1	77.2	84.1	88.2	88.7	96.0	94.2	78.8	84.8	84.9	89.8	97.2	91.9
Hospitalisation (%)	12.1	13.8	16.3	21.7	95.0	25.3	14.1	15.5	18.0	20.1	71.1	27.8	13.3	18.8	16.0	25.0	83.8	23.6
Physiotherapist visits (%)	19.1	17.8	17.9	18.2	18.0	19.9	19.8	18.5	21.2	20.0	31.5	25.2	19.2	21.9	22.7	12.7	50.8	27.7
CAM†/healer/traditional medicine (%)	3.5	4.2	3.0	2.3	4.3	3.3	3.5	4.1	3.3	6.4	0.0	6.3	2.4	3.5	6.1	6.9	16.7	4.6
Demographic and social factors																		
Married or in a registered partnership (%)	65.1	66.6	64.4	68.9	63.9	69.6	69.8	66.1	67.4	67.5	54.3	66.2	64.5	64.2	61.5	59.4	68.8	63.7
Living with others (%)	73.9	73.5	72.3	72.6	78.4	75.7	76.2	72.9	73.6	71.5	67.0	71.7	71.7	69.5	69.8	68.1	77.3	70.2
Health and lifestyle factors																		
Comorbidity (mean)	0.84	1.19	1.44	1.42	1.56	1.37	1.04	1.51	1.73	1.67	1.55	1.01	1.04	1.51	1.73	1.67	1.55	1.01
Body mass index (kg/m^2) (mean)	26.55	26.90	27.02	27.21	26.32	27.44	26.43	26.81	26.74	26.60	26.79	26.35	26.43	26.81	26.74	26.60	26.79	26.35
Systolic blood pressure (mm Hg) (mean)	146.4	150.1	151.8	150.2	150.6	139.6	145.6	152.2	153.7	155.1	154.8	149.1	145.6	152.2	153.7	155.1	154.8	149.1
Total cholesterol (mmol/L) (mean)	6.72	6.72	6.55	6.63	6.22	5.54	6.59	6.48	6.31	6.13	6.15	5.87	6.59	6.48	6.31	6.13	6.15	5.87
Glycated haemoglobin (%) (mean)	5.60	5.67	5.83	5.82	5.83	6.11	5.51	5.69	5.84	5.70	5.79	5.82	5.51	5.69	5.84	5.70	5.79	5.82
Daily smoking (%)	36.6	35.0	30.1	34.5	16.8	17.8	27.9	21.7	17.3	17.4	15.5	10.7	31.3	30.3	30.0	28.3	25.3	18.7
Alcohol intake (≥5 units) (%)	2.9	3.2	2.6	4.8	7.3	4.9	4.6	6.2	6.1	7.9	6.8	8.4	4.5	4.8	5.9	3.1	12.3	6.5
Hard exercise ≥1–2 times per week (%)	29.9	31.0	31.6	24.4	27.2	30.3	30.9	33.9	30.7	29.7	32.0	28.6	27.5	30.0	34.2	29.2	25.3	30.7

*The observations of MI, AF and stroke are not independent of each other, %=proportion of total sample for MI, AF and stroke, respectively.
†CAM, complementary and alternative medicines.

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Table 3 ORs for developing mental health symptoms relative to time for incident myocardial infarction (MI), atrial fibrillation (AF) and stroke

	Symptom levels					
	Before the first diagnosis			After the first diagnosis		
	MI	AF	Stroke	MI	AF	Stroke
Sex						
Male sex associated with the lower OR	0.63*** (0.51 to 0.78)	0.47*** (0.38 to 0.59)	0.52*** (0.40 to 0.68)	0.31*** (0.21 to 0.46)	0.32*** (0.20 to 0.51)	0.40** (0.23 to 0.69)
Age (10 years)	0.81*** (0.75 to 0.89)	0.73*** (0.66 to 0.81)	0.86** (0.77 to 0.96)	0.68*** (0.58 to 0.81)	0.81 (0.64 to 1.01)	0.83 (0.65 to 1.06)
Body weight						
<18.5 kg/m^2	1.46 (0.61 to 3.49)	2.12 (0.70 to 6.42)	0.78 (0.18 to 3.34)	1.81 (0.24 to 13.85)	1.25 (0.02 to 65.56)	10.31* (1.09 to 97.33)
18.5–24.9 kg/m^2	1 Reference	1 Reference	1 Reference	1 Reference	1 Reference	1 Reference
25–29.9 kg/m^2	0.82* (0.67 to 1.00)	0.83 (0.67 to 1.03)	1.01 (0.79 to 1.31)	0.9 (0.64 to 1.26)	1.03 (0.64 to 1.64)	0.76 (0.44 to 1.29)
≥30 kg/m^2	0.81 (0.62 to 1.06)	0.81 (0.62 to 1.07)	0.82 (0.58 to 1.17)	0.88 (0.58 to 1.32)	0.91 (0.52 to 1.57)	1.14 (0.59 to 2.18)
Comorbid diseases	1.23*** (1.16 to 1.32)	1.22*** (1.14 to 1.30)	1.30*** (1.20 to 1.41)	1.27*** (1.17 to 1.38)	1.29*** (1.15 to 1.44)	1.30*** (1.12 to 1.50)
Hypertension	1.29** (1.07 to 1.56)	1.13 (0.92 to 1.39)	1.16 (0.91 to 1.49)	0.97 (0.72 to 1.31)	1.11 (0.74 to 1.67)	1.43 (0.84 to 2.46)
Hyperlipidaemia	1.13 (0.80 to 1.60)	1.02 (0.74 to 1.39)	0.99 (0.67 to 1.45)	1.13 (0.62 to 2.09)	0.92 (0.54 to 1.56)	0.81 (0.41 to 1.62)
Diabetes	1.23* (1.03 to 1.48)	1.16 (0.95 to 1.43)	1.22 (0.96 to 1.56)	1.99*** (1.44 to 2.76)	1.22 (0.79 to 1.91)	1.82* (1.09 to 3.07)
Daily smoker	1.27* (1.04 to 1.54)	1.24 (0.99 to 1.55)	1.46** (1.13 to 1.89)	1.32 (0.93 to 1.88)	1.27 (0.75 to 2.15)	1.22 (0.71 to 2.08)
Alcohol habits						
None	1 Reference	1 Reference	1 Reference	1 Reference	1 Reference	1 Reference
Moderate	0.97 (0.81 to 1.17)	0.72** (0.59 to 0.89)	0.8 (0.63 to 1.02)	0.92 (0.68 to 1.23)	1.15 (0.77 to 1.73)	0.9 (0.56 to 1.43)
High	1.19 (0.71 to 2.00)	1.06 (0.68 to 1.63)	1.03 (0.60 to 1.79)	1.36 (0.71 to 2.61)	0.81 (0.35 to 1.85)	0.88 (0.32 to 2.42)
Physically active	0.65*** (0.55 to 0.78)	0.64*** (0.54 to 0.78)	0.68*** (0.55 to 0.85)	0.57*** (0.43 to 0.76)	0.54** (0.36 to 0.80)	0.39*** (0.24 to 0.62)
Married/partner	0.84 (0.67 to 1.06)	0.88 (0.67 to 1.16)	1.16 (0.85 to 1.59)	0.97 (0.63 to 1.48)	0.83 (0.46 to 1.51)	0.64 (0.32 to 1.26)
Living with others	0.74* (0.58 to 0.95)	0.82 (0.61 to 1.10)	0.61** (0.44 to 0.85)	0.83 (0.53 to 1.31)	0.95 (0.51 to 1.79)	1.49 (0.73 to 3.03)
Highest level of education						
Primary/secondary	1 Reference	1 Reference	1 Reference	1 Reference	1 Reference	1 Reference
High school	0.86 (0.70 to 1.05)	0.84 (0.68 to 1.05)	0.83 (0.64 to 1.08)	0.75 (0.55 to 1.03)	0.56* (0.36 to 0.88)	0.69 (0.40 to 1.17)

Continued

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Table 3 Continued

	Symptom levels					
	Before the first diagnosis			After the first diagnosis		
	MI	AF	Stroke	MI	AF	Stroke
College/university	1.04	0.91	1.19	0.76	0.62	0.76
	(0.80 to 1.35)	(0.70 to 1.20)	(0.86 to 1.66)	(0.50 to 1.15)	(0.37 to 1.04)	(0.40 to 1.45)
Participants (N)	1695	1374	1735	1007	1102	642

95% CIs in brackets, *p<0.05, **p<0.01, ***p<0.001.

stroke can explain the high post-diagnostic mental health symptoms as it causes cell death affecting both the brain and bodily function. These individuals may need rehabilitation and are often prescribed antidepressant medication to follow rehabilitation with a focus on psychosocial coping.

Methodological considerations

We are not aware of any other studies investigating the trajectory of mental health symptoms over several years before and after a diagnosis. A major strength of this study is repeated measurements within the same population and a high participation rate. The endpoint register provides validated information about the participants' first MI, AF or stroke diagnosis but does not include data on recurrent events. The coupling to the Tromsø Study database makes it possible to follow the participants and explore the development of symptoms of anxiety and depression before and after the first MI, AF or stroke diagnosis, as well as to follow how a change in the risk factors relative to the event and symptoms influenced mental health.

Since the statistical methods require multiple measurements, attrition was a concern. There was a significant difference in the mortality rate between the total population and the sample population. This may indicate survival bias in the study. We used inverse probability weighting to control for selection bias, but it did not change the main results of this study. It also indicates that mental health symptoms may be associated with mortality rates for participants with CVD. Follow-up studies should explore the effect of mental health symptoms on mortality for people with MI, AF or stroke.

Regarding methodological weaknesses, several of the variables were self-reported by the participants, potentially introducing bias. The instrument measuring mental health symptoms in Tromsø4 (CONOR-MHI) has been validated against HSCL-10 but with different cut-offs. It is suboptimal to use it with a categorical outcome due to

Table 4 Standardised mental health symptoms score for the time before and after myocardial infarction, atrial fibrillation and stroke

	Myocardial infarction	Atrial fibrillation	Stroke
Mental health change			
Years before the CVD event	n=1695	n=1735	n=1102
−10	−0.107 (−0.149 to −0.064)	−0.050 (−0.072 to −0.028)	0.011 (−0.021 to 0.043)
−8	−0.098 (−0.138 to −0.058)	−0.041 (−0.063 to −0.018)	0.025 (−0.007 to 0.058)
−6	−0.081 (−0.118 to −0.044)	−0.031 (−0.058 to −0.005)	0.040 (0.001 to 0.078)
−4	−0.055 (−0.094 to −0.015)	−0.022 (−0.055 to 0.012)	0.054 (0.005 to 0.103)
−2	−0.020 (−0.077 to 0.038)	−0.012 (−0.054 to 0.029)	0.068 (0.007 to 0.129)
0	0.025 (−0.066 to 0.115)	−0.003 (−0.053 to 0.047)	0.082 (0.008 to 0.156)
Years after the CVD event	n=1374	n=1007	n=642
0	0.145 (0.064 to 0.225)	0.052 (−0.019 to 0.123)	0.218 (0.119 to 0.316)
2	0.091 (0.034 to 0.149)	0.044 (−0.011 to 0.100)	0.187 (0.107 to 0.267)
4	0.042 (0.001 to 0.084)	0.037 (−0.005 to 0.079)	0.156 (0.093 to 0.220)
6	−0.002 (−0.035 to 0.032)	0.029 (−0.004 to 0.062)	0.126 (0.076 to 0.176)
8	−0.041 (−0.075 to −0.007)	0.022 (−0.012 to 0.055)	0.095 (0.052 to 0.138)
10	−0.075 (−0.114 to −0.036)	0.014 (−0.028 to 0.056)	0.064 (0.019 to 0.110)

Estimates with 95% CIs in brackets for the 10 years before and after the cardiovascular event.
CVD, cardiovascular disease.

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the loss of statistical power, but the method allows us to use the largest wave of the Tromsø Study as the baseline. Significant symptom levels imply that a person in clinical assessment is likely to be diagnosed with a mental health disorder. However, it is not possible to draw this conclusion directly from the instrument.

This study has a relatively small sample of cases as it follows participants in a general population. A patient population would potentially be beneficial to investigate relevant factors but would be limited to post-diagnostic follow-up. Our results indicate a significant change in mental health symptoms before an MI, AF or stroke event, and several modifiable factors influence this relationship. The clinical relevance is that we show potentially undercommunicated mental health problems before CVDs, requiring more attention and adequate treatment, especially for women and younger persons. More research is necessary to examine the mechanisms of the risk factors.

Most clinical studies use patient samples, while our sample is from a general population. Our study has fewer post-diagnostic measurement points, and there are about 7 years between the measurements. We are thus unable to draw any conclusion about the trajectories the first year after CVD. Nevertheless, the results suggest that comorbid mental health problems may not disappear over time without treatment. We also point out that comorbid diseases are associated with mental health trajectories. Several disorders such as psychological trauma, obstructive sleep and diabetes could increase mental health risk and CVD risk. Further studies are required to improve understanding of the heart and mind connection.

CONCLUSION

The study shows a significant increase in symptoms that may be related to mental health problems in the years before MI, AF and stroke. For CVD survivors, the symptom levels seem to remain high, especially in women. Furthermore, the study indicates that mental health problems may have developed several years before the event. It suggests that successful heart rehabilitation may need to consider prior life factors. Finally, future research is recommended to examine whether health promotion measures in a general population also create mental health resilience after a CVD.

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Patient consent for publication Consent obtained directly from patient(s).

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