BMJ open

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Journal:	*BMJ Open*
Manuscript ID:	bmjopen-2013-003045
Article Type:	Research
Date Submitted by the Author:	12-Apr-2013
Complete List of Authors:	Nielsen, Tine; Section for General Medical Practice, Department of Public Health, Aarhus University Vestergaard, Mogens; Section for General Medical Practice and Research Unit for General Practice, Department of Public Health, Aarhus University Christensen, Bo; Section for General Medical Practice, Department of Public Health, Aarhus University Christensen, Kaj; Research Unit for General Practice, Department of Public Health, Aarhus University Larsen, Karen; Section for General Medical Practice and Research Unit for General Practice, Department of Public Health, Aarhus University
Primary Subject Heading:	Cardiovascular medicine
Secondary Subject Heading:	Mental health, Epidemiology
Keywords:	CARDIOLOGY, Myocardial infarction < CARDIOLOGY, MENTAL HEALTH, Epidemiology < TROPICAL MEDICINE

Mental health status and risk of new cardiovascular events or death in patients with myocardial infarction: a population-based cohort study

Tine Jepsen Nielsen, Mogens Vestergaard, Bo Christensen, Kaj Sparle Christensen, Karen Kjær Larsen

Section for General Medical Practice, Aarhus University, Bartholins Allé 2, 8000 Aarhus C, Denmark
Tine Jepsen Nielsen
Junior research fellow

Section for General Medical Practice and Research Unit for General Practice, Aarhus University, Bartholins Allé 2, 8000 Aarhus C, Denmark
Mogens Vestergaard
Professor

Section for General Medical Practice, Aarhus University, Bartholins Allé 2, 8000 Aarhus C, Denmark
Bo Christensen
Professor

Research Unit for General Practice, Aarhus University, Bartholins Allé 2, 8000 Aarhus C, Denmark
Kaj Sparle Christensen
Senior researcher

Section for General Medical Practice and Research Unit for General Practice, Aarhus University, Bartholins Allé 2, 8000 Aarhus C, Denmark
Karen Kjær Larsen
PhD fellow

Correspondence to: TJ Nielsen. E-mail: tjn@folkesundhed.au.dk

ARTICLE SUMMARY

Article focus

- Myocardial infarction (MI) is often followed by mental health problems such as depression, anxiety, and low mental health status.
- Mounting evidence indicates that depression and anxiety after MI increase the risk of adverse long-term outcome. No previous study has examined the association between mental health status after MI and outcome, independent of depression and anxiety.
- This study examines the association between mental health status after first-time MI and new cardiovascular events or death, when taking into account depression and anxiety as well as clinical, socio-demographic, and behavioural risk factors.

Key messages

- During three years after the MI, patients with the lowest mental health status had a 50% risk of new cardiovascular events or death.
- Low mental health status after MI was a strong predictor of new cardiovascular events or death, independent of depression, anxiety and clinical, socio-demographic, and behavioural risk factors.

Strengths and limitations of this study

- Major strengths of this study are its population-based nature and the homogenous study population. The response rate was high, and information on outcome was collected without loss to follow-up.
- We were able to take into account important mediators such as depression, anxiety, and potential behavioural mediators such as physical activity. However, we cannot rule out the possibility of residual confounding.

Abstract

Objective To examine the association between mental health status after first-time myocardial infarction (MI) and new cardiovascular events or death, taking into account depression and anxiety as well as clinical, socio-demographic, and behavioural risk factors.

Design Population-based cohort study based on questionnaires and nationwide registries. Mental health status was assessed three months after the MI using the Mental Component Summary score from the Short-Form 12 version 2.

Setting Central Denmark Region.

Participants All patients hospitalised with first-time MI from 1 January 2009 through 31 December 2009 (n=880). The participants were categorised in quartiles according to level of mental health status (1st quartile=lowest mental health status).

Main outcome measures Composite endpoint of new cardiovascular events (MI, heart failure, stroke/transient ischaemic attack) and all-cause mortality.

Results During 1,940 person-years of follow-up, 277 persons experienced a new cardiovascular event or died. The cumulative incidence following three years after the MI increased consistently with decreasing mental health status and was 15.0% (95% confidence interval 10.8% to 20.5%) for persons in the fourth quartile 29.1% (23.5% to 35.6%) in the third quartile, 37.0% (30.9% to 43.9%) in the second quartile, and 47.5% (40.9% to 54.5%) in the first quartile. The hazard ratios (HR) were high, even after adjustments for age, socio-demographic characteristics, cardiac disease severity, comorbidity, secondary prophylactic medication, smoking status, physical activity, depression, and anxiety ($HR_{3rd\ quartile}$ 1.90 (95% confidence interval 1.23 to 2.93), $HR_{2nd\ quartile}$ 2.14 (1.37 to 3.33), $HR_{1st\ quartile}$ 2.23 (1.35 to 3.68) when using the fourth quartile as reference).

Conclusions Low mental health status following first-time MI was independently associated with an increased risk of new cardiovascular events or death. Further research is needed to disentangle the pathways that link mental health status following MI to prognosis and to identify interventions that can improve both mental health status and prognosis.

INTRODUCTION

Myocardial infarction (MI) is a severe life event followed by an increased risk of mental health problems such as depression,[1] anxiety,[2] and low mental health status.[3] Several studies have shown that depression[4] and anxiety[2] after MI is associated with a higher risk of cardiovascular events and death, but much less is known about the impact of broader measures of mental health. Mental health status is a generic and broad measure of mental health, which may be useful as a tool to quantify important prognostic aspects of mental health not captured by the more disease-specific measures of depression and anxiety. Four studies[5-8] have investigated the association between mental health status following MI and prognosis. All these have found that low mental health status was significantly associated with increased risk of adverse outcome, independent of clinical risk factors. However, since none of the former studies adjusted for depression or anxiety, it remains unknown whether mental health status in itself adds unique knowledge about the prognosis.

Our aim was to examine the association between mental health status and new cardiovascular events or death in patients with first-time MI when taking into account depression, anxiety, and clinical, socio-demographic, and behavioural risk factors.

METHODS

We conducted a population-based cohort study comprising people in the Central Denmark Region (1,250,000 inhabitants) with a first-time MI based on data from nationwide registers and questionnaires.

Participants

We consecutively invited all patients discharged from hospital with a first-time MI from 1 January 2009 to 31 December 2009. The establishment of the cohort is described in detail elsewhere.[9] Data on patients discharged with MI (in accordance with the International Classification of Diseases (ICD-10) code I21)[10] were received from the Danish National Patient Register on a monthly basis. Patients who had been discharged with MI between 1994 and 2008 were excluded to identify first-time cases. Information on name, address, and vital status was obtained from the Civil Registration System,[11] which also provided the unique personal identification number used to link data between the registers and questionnaires.

Data collection

A pilot-tested hard-copy questionnaire was sent to all participants 12 to 14 weeks after their discharge from hospital, and non-responders received two reminders.[9] The study was approved by the Danish Data Protection Agency (J.nr. 2009-41-3018), the Scientific Research Evaluation Committee of the Danish Academy of General Practitioners (ref. no. 03-2009), and written informed consent was obtained from all participants.

Mental health status

Mental health status was measured using the Mental Component Summary (MCS) score from the validated Danish version of the Short-Form 12 version 2 Health Survey (SF-12).[12-14] The SF-12 consists of 12 items, the MCS score comprises mainly of the six mental items ('Vitality', 'Role-Emotional' (2 items), 'Social Function', and 'Mental Health' (2 items)), but the six physical items are also included in the computation.[12] The SF-12 scores were calculated following the norm-based scoring algorithm[12] using weights derived from confirmatory factor analysis.[15] The MCS score is thus linearly transformed in a way that allows comparison with the mean score (50) and the standard deviation (SD) (10) in the general US population in 1998.[12] The MCS has demonstrated good construct validity.[15] The wording of the mental health status items can be found in the supplemental material (**eFigure 1**).

Depression and anxiety

We assessed depression and anxiety symptoms using the Hospital Anxiety and Depression Scale (HADS).[16] The participants were categorised as having anxiety or depression if they had a score of ≥8 on the HADS-A scale or the HADS-D scale. The HADS was designed to be valid in clinical populations with symptoms of physical disease and hence leaves out items that may be endorsed by physical rather than mental states.[16, 17] The HADS has formerly been validated in MI patients[18, 19] and has proven to have satisfactory reliability (HADS-A and HADS-D Cronbach's $\alpha \approx 0.80$).[18, 20] Among MI patients, a HADS-D≥8 identified possible cases of depression with a sensitivity of 65% and a specificity of 90% (compared with a diagnosis of depression based on a Structured Clinical Interview for DSM-IV).[19] Among acute coronary syndrome patients, a HADS-A≥8 identified possible cases of anxiety with a sensitivity of 91% and a specificity of 61% (compared with a diagnosis of generalised anxiety disorder based on a Structured Clinical Interview for DSM-IV).[21]

Co-morbidity and cardiac disease severity

Information on co-morbidity was retrieved from the Danish National Patient Register, [22] the Danish National Diabetes Register, [23] and the prescription database covering the entire Central Denmark Region. [24] The Danish National Patient Register provided information on stroke (ICD-10: I61, I63, I64), transient cerebral ischemic attack (ICD-10: DG45, DG46), heart failure (ICD-10: I11.0, I13.0, I13.2, I42.0, I42.6, I42.7, I42.9, I50.0, I50.1, I50.9), and revascularization (ICD-10: KFN, KFW) from 1994 to 2008. The Danish National Diabetes Register provided information on diabetes mellitus from 1990 to 2008 according to an algorithm developed on the basis of information from four nationwide registers. [23] The prescription database provided information on all reimbursed drugs according to the Anatomical Therapeutic Chemical Classification System (ATC), dispensing dates, and the total number of tablets dispensed. Participants were categorised with hypertension if they had redeemed prescriptions for at least two classes of antihypertensive drugs (ATC: C02A-D, C02L, C03A-B, C03D-E, C03X, C04, C05, C07, C08, C09) 0 to 180 days before the index MI. Participants were categorised with depression before MI if they had redeemed a prescription for an antidepressant (ATC: N06A) 0 to 180 days before the index MI. Participants were categorised with severe mental disorder if they had redeemed a prescription for antipsychotics (ATC: N05A) 0 to 180 days before the index MI.

Cardiac disease severity was measured by the British Medical Research Council (MRC) dyspnea score, a self-report instrument. [25] A score ≥3 has been shown to provide a simple and valid method for predicting overall mortality. [26]

Health behaviour, health care interventions, and socio-demographics

Data on smoking, alcohol use, physical activity, intake of fruit and vegetables, intake of fish, intake of fish oil supplement, height, and weight (body mass index=weight [kg] per height [m^2]) were self-reported and classified according to the general recommendations from the Danish National Board of Health. [9] To assess physical activity, we asked, "How many days per week are you generally physically active for at least 30 minutes per day? You may include any physical activity at work or in your spare time that makes your pulse rate increase". Response options were from zero days to every day per week. Physical activity was computed as a continuous variable (days/week).

We defined cardiac rehabilitation [27, 28] in the questionnaire and asked whether they had participated in hospital-based phase two cardiac rehabilitation. Those who responded "yes,

and I took part" were classified as 'participants' those who responded "yes, but I didn't take part" or "no" were classified as 'non-participants'.[9]

Drug prescription data were obtained from the prescription database.[24] Data on aspirin (ATC: B01AC06), clopidogrel (ATC: B01AC04), statins (ATC: C10AA), β-blockers (ATC: C07), ACE-inhibitors/angiotensin 2 receptor blockers (ATC: C09), furosemide (ATC: C03C), aldosterone antagonists (ATC: C03D), and antidepressants (ATC: N06A) were collected. We calculated whether the participant had tablets available on the day that we sent the questionnaire (the number of tablets on the last redeemed prescription before the questionnaire was sent ≥ the number of days to the questionnaire was sent) and defined the participant as 'receiving treatment' if tablets were available. We defined the participant as 'receiving secondary prophylactic medication' if the participant was receiving treatment with three or more of the following drugs: aspirin, clopidogrel, statins, and β-blockers. We defined the participant as 'receiving heart failure medication' if the participant was receiving treatment with furosemide or aldosterone antagonists.

Data on age at MI and sex were obtained from the Civil Registration System.[11] Each participant's socio-demographic characteristics (cohabitation status, education, labour market status) from the year before MI (2008) were retrieved from the Danish Integrated Database for Labour Market Research.[29]

Cardiovascular events and death

Outcome events were measured as a composite endpoint comprising new cardiovascular events (MI, heart failure, stroke or transient ischaemic attack) and all-cause mortality. Information on outcomes was collected from baseline (the day we sent the questionnaire) to the last day of follow-up (31 July 2012). The Danish National Patient Register[22] provided information on cardiovascular events. Vital status (dead or alive) was obtained from the Civil Registration System.[11]

Statistical analysis

Neither natural thresholds nor clinically based thresholds are defined for the MCS score, so we divided the participants into quartiles according to their score (1st quartile had the lowest score; 4th quartile had the highest score). This categorisation was done to enhance clinical interpretability and to evaluate a possible dose response relationship.

In order to address the potential risk of selection bias, we used antidepressant consumption as a proxy for depression and calculated hazard ratios (HRs) for the association

between antidepressant consumption and new cardiovascular events or death for both participants and non-participants.

The association between baseline characteristics and MCS score was assessed using $\chi 2$ statistics for categorical variables and analysis of variance for continuous variables, or Kruskal-Wallis tests when the conditions for analysis of variance were not fulfilled.

We calculated the event-free survival time as the time from three months after the MI (baseline evaluation of mental health status) to the first cardiovascular event or death. If no event or death occurred, the participant was censored on 31 July 2012. Two persons emigrated during the time of follow-up, and they were censored on the day of their emigration. Owing to the use of nationwide registers, we had complete follow-up of all participants.

The unadjusted association between mental health status and new cardiovascular events or death was presented graphically with Kaplan-Meier curves. The cumulative incidence three years after the MI was estimated using the cumulative hazards function, and identical incidence was tested using the log-rank test.

The risk of cardiovascular events or death associated with mental health status was compared using Cox proportional hazards regression. The covariates for the multivariate model (age, sex, cohabitation status, education, labour market status, cardiac disease severity, history of stroke, diabetes mellitus, heart failure, secondary prophylactic medication, smoking status, physical activity, depression, and anxiety) were chosen on the basis of previous studies. We evaluated whether the HRs of mental health status following MI varied by subgroups by testing for interaction using Wald test in an age-adjusted model, and the results are presented in a forest plot. Too few outcome events were available to test for interaction in quartiles, so we tested it in a dichotomised (median cut) model. We excluded variables with less than five events in a subgroup.

Finally, we calculated HRs for the association between each of the mental health status items (continuous; per one-point lower item score) and outcome.

No variable had more than 0.3% missing data, except body mass index (for which 2.5% data were missing) and education (for which 3.3% data were missing), and analyses were done on complete data only. $P<0.05$ was considered statistically significant.

RESULTS

Participant characteristics

Among a total of 1,288 eligible patients with first-time MI, 880 (68.3%) completed the SF-12, and the mean MCS score was 44.9 (SD 11.5). Non-participants were more often women, older, had fewer socioeconomic resources, and more comorbid conditions than participants (Web Extra Supplement Table A). The estimates of the association between antidepressant consumption and new cardiovascular events or death in participants, HR 1.55 (95% confidence interval 1.12 to 2.14) and in non-participants, HR 1.46 (1.01 to 2.10), were similar. Compared to participants with higher mental health status, the participants with the lowest mental health status (1st quartile, table 1) were impaired in a range of variables; e.g. symptoms of depression and anxiety, cardiac disease severity, comorbidity, socioeconomic resources, and health behaviour.

Cumulative incidence

A total of 277 outcomes (230 new cardiovascular events and 47 deaths) occurred during 1,940 person years of follow-up (median 2.6 years, SD 1.0). The Kaplan-Meier curves (figure 1) show that the unadjusted risk of a cardiovascular event or death increased with decreasing mental health status. During three years after the MI, the cumulative incidence of the composite endpoint was 47.5% (95% confidence interval 40.9% to 54.5%) for persons in the first, 37.0% (30.9% to 43.9%) in the second, 29.1% (23.5% to 35.6%) in the third, and 15.0% (10.8% to 20.5%) in the fourth quartile, P<0.001.

Association between mental health status and new cardiovascular events or death

The age-adjusted HRs for new cardiovascular events or death in post-MI patients increased with decreasing mental health status ($HR_{3rd\ quartile}$ 2.09 (95% confidence interval 1.36 to 3.19), $HR_{2nd\ quartile}$ 2.67 (1.77 to 4.03), $HR_{1st\ quartile}$ 3.53 (2.36 to 5.27), table 2). Additional adjustment for cardiac disease severity, physical activity, depression, and anxiety attenuated the association. In the fully adjusted model, the MI patients with the lowest mental health status had a more than two-fold higher risk of new cardiovascular events or death compared to the patients with the highest mental health status (table 2).

We found no statistically significant difference in the HRs between any subgroups of MI patients (figure 2).

Exploratory analysis of the six mental health status items

Table 3 outlines the association between mental health status item scores and subsequent cardiovascular events or death. The items were entered as continuous variables and the HRs reflect the risk of new cardiovascular events or death per one point lower item score. The largest HRs were seen for the 'Vitality' item, HR 1.24 (95% confidence interval 1.09 to 1.42), the 'Mental Health' item 1, HR 1.19 (1.04 to 1.35), and the 'Role-Emotional' item 1, HR 1.16 (1.04 to 1.29).

DISCUSSION

In this population-based cohort study, we found that low mental health status after first-time MI predicted an increased risk of new cardiovascular events or death in a dose-response manner. The association was explained partly by cardiac disease severity, physical activity, depression, and anxiety. However, even after adjustments for these variables, patients with the lowest mental health status had a more than two-fold higher risk of new cardiovascular events or death compared to those with the highest mental health status.

Strengths and limitations of the study

Major strengths of this study are its population-based nature and the homogenous study population; we invited all patients with first-time MI during one year in a well-defined area. Our response rate was reasonably high (68.3%), and information on outcome was collected without loss to follow-up. Non-participants tended to have fewer social resources and more comorbid conditions, and they hence resembled the participants with the lowest mental health status. In order to address the potential risk of selection bias, we used antidepressant consumption as a proxy for depressive symptoms similarly to previous studies.[30] The estimates of the association between antidepressant consumption and new cardiovascular events or death in participants were similar. Thus, bias due to selection of study participants seems to be an unlikely explanation for our findings.

Information on MI was registered prospectively and did not rely on the participants' or the relatives' memory. The MI diagnosis in the Danish National Patient Register was based on the current European Society of Cardiology criteria for MI, coded by the physician in charge of the discharge, and the information is known to have a high sensitivity (90%) and specificity (92%).[10] The specificity was even higher in our study because we confirmed the MI diagnosis by reviewing the discharge summaries,[9] and this reduced the risk of information bias. We also

reduced the risk of information bias by using previously translated and validated scales, pilot testing the questionnaire among MI patients, and using high-quality register data.

We used a new algorithm for the calculation of the MCS score from the SF-12 version 2 using weights constructed by oblique confirmatory factor analysis, which allows the physical and mental component summary score to be correlated. Fleishman et al developed this new scoring algorithm [15] due to controversy regarding the traditional scoring algorithm. [31-33] The traditional scoring algorithm forces mental and physical health to be uncorrelated. Consequently, when physical scores are well below the mean and mental scores somewhat less below the mean, as is often the case in patients with physical illness, this scoring method will result in an artifactual migration of the MCS score towards the mean. [31] In sub-analyses, we estimated HRs based on traditionally computed MCS scores (Web Extra Supplement Table B). As expected, they were smaller compared to the HRs based on MCS scores computed with the new scoring algorithm. We evaluated mental health status three months after MI, allowing mental health to reach a more stable level after this major life event.

A diagnosis of depression or anxiety should ideally be based on a diagnostic interview. Since a previous study has estimated the sensitivity of the HADS-D≥8 for identification of depression to be 65% in MI patients, [19] a substantial number of participants with depression may have been misclassified as not having depression. However, we identified 18.3% with depression in our population (HADS-D≥8), which is in keeping with the prevalence of post-MI depression identified by structured clinical interviews in other studies (19.8%). [1] We found no studies reporting on the sensitivity and specificity of the HADS-A in an MI population. However, among acute coronary syndrome patients, a HADS-A≥8 had a sensitivity of 91%. [21] Accordingly, we most likely identified the majority of patients with anxiety. In a sensitivity analysis, we excluded patients with depression or anxiety (HADS-A/D≥8), and this did not weaken the estimates (Web Extra Supplement Table C).

Schizophrenia and bipolar disorder are known to be associated with a higher risk of mortality, and part of this excess risk is attributable to cardiovascular diseases. [34] We used a prescription of antipsychotics, between MI and 180 days before, as an approximation of severe mental disorder. Thirteen participants had redeemed such a prescription. To examine how much of the association could be explained by these patients, we excluded this group in a sensitivity analysis (not shown), and this did not weaken the estimates.

Lifestyle behaviour was self-reported, and participants with low mental health status may have been more likely underreport adverse lifestyle, including physical inactivity. However, participants with low mental health status did in fact report adverse lifestyle in our study, and

a study on depression [35] found no differences when substituting self-reported physical activity with an objective measure of physical fitness.

Information on a range of participant characteristics and the large sample size allowed us to take into account several potential confounders, such as socio-demographic characteristics, cardiac disease severity, comorbidity, and behavioural factors. In sub-analyses, we adjusted for other potential confounders (body mass index, hypertension, history of depression, antidepressant use, intake of alcohol, fish, and fruit, and participation in phase two cardiac rehabilitation), but this did not change the estimates (≤4%). However, we cannot rule out the possibility of residual confounding.

Comparison with other studies

Four previous studies [5-8] have investigated the association between mental health status after MI and prognosis independent of various clinical risk factors, such as disease severity. They used different measures of mental health status (COOP charts, [6] Quality of Life after MI questionnaire, [8] the World Health Organization Quality of Life Instrument Abbreviated, [7] and SF-12 [5]), and they all found an independent association between low mental health status and higher risk of adverse outcomes. Compared with our study, these studies were conducted in modest-sized cohorts (n=112, [6] 375, [8] 145 [7]), had short follow-up (four to five months, [6] 18 months [8]), mental health status was assessed up to five years or more after MI, [5, 7] included only women [7] or patients who had an ejection fraction <30%. [5] Most importantly, none of these four MI studies took into account important mediators such as depression, anxiety, and potential behavioural mediators such as physical activity.

Our study is the first to explore the association between mental health status after MI and new cardiovascular events or death in subgroups, and we identified no factors that modified the risk. However, the sample size was low in some of the subgroups.

Our study is also the first to explore the association between mental health status and cardiovascular events or death on an item level. We found that the 'Vitality' item, the 'Role-Emotional' item 1, and the 'Mental Health' item 1 were significantly associated with adverse events after adjustments for clinical, socio-demographic, behavioural, and other psychological risk factors, whereas the remaining items were not. Our results indicate that these items are the most important for the association between mental health status (MCS score) and adverse events. Yet, it is important to keep in mind that the items have different weights and that the physical items are also included when computing the MCS score. [12, 15]

Implications for clinicians

In addition to psychological, social, and functional impairment, clinicians should be aware that low mental health status following MI is associated with an increased risk of new cardiovascular events and death. Our results underline the importance of always considering and prioritising mental health issues in post-MI patients. In this study, we identified low mental health status after MI to be a significant risk factor for poor prognosis, independent of clinical, socio-demographic, behavioural, and other psychological risk factors. In other words, mental health status has incremental value in the identification of patients at elevated risk for adverse outcome. Adding mental health status measurement to our present risk factor armamentarium could help clinicians to distinguish between groups of patients with a very low versus a very high risk of adverse outcome, and thereby help identify vulnerable patients in need of optimised care. However, we do not know whether measurement of mental health status and improved knowledge of prognosis will translate into better outcomes for our patients. This is an important focus for future research in this field.

Possible explanations and future research

This study suggests that mental health status may capture prognostic aspects of mental health which are not captured by measures of depression and anxiety. Further research is needed to clarify more specifically what aspects of mental health that are at play.

The underlying explanation for the association between mental health status after MI and new cardiovascular events or death remains unclear. Our study evaluated cardiac disease severity, behavioural factors, and treatment strategies concurrently with mental health status. We therefore cannot determine whether these factors were the cause or the result of the mental health status. We were unable to assess whether the association was explained by biological mechanisms (such as heart rate variability, platelet function, or inflammatory mechanisms) since we had no information on these biological variables. Future studies should incorporate such biological variables. [36]

Further research is also needed to identify interventions that could improve both mental health status and prognosis in MI patients. Murphy et al [37] examined the effectiveness of a complex intervention designed to improve outcomes, including mental health status (measured with SF-12) for patients with coronary heart disease in a cluster randomised controlled trial. The intervention was “tailored care plans for practices (practice based training in prescribing and behaviour change, administrative support, quarterly newsletter), and tailored care plans for patients (motivational interviewing, goal identification, and target

setting for lifestyle change)." [37] They found that admissions to hospital were significantly reduced after an intensive 18-month intervention to improve outcomes for patients with coronary heart disease, but there was no change in mental health status. It was not stated how they computed the MCS score, but they probably used the traditional scoring algorithm as the study were conducted prior to Fleishman's publication. [15] Hence, artifactual migration of the MCS score towards the mean in these physically ill participants may at least in part explain the lack of association.

Conclusion

We found that low mental health status following MI was associated with an increased risk of new cardiovascular events or death. The association was explained partly by cardiac disease severity, physical activity, depression, and anxiety, but low mental health status remained an independent prognostic risk factor. Further research is needed to disentangle the pathways that link mental health status following MI to prognosis and, in continuation hereof, to identify interventions that can improve both mental health status and prognosis.

Contributorship: TJN, and KKL, MV, BC, KSC conceived the study idea and designed the study. KKL collected the data. TJN, and KKL, MV, BC, KSC reviewed the literature. TJN, and KKL, MV, BC, KSC directed the analyses, which were carried out by TJN. All authors participated in the discussion and interpretation of the results. TJN organised the writing and wrote the initial drafts. All authors critically revised the manuscript for intellectual content and approved the final version. TJN is the guarantor.

Funding: The study was supported by the Danish Independent Research Council (grant 12-126032), the Tryg Foundation (grant number 7844-07), the Danish Health Insurance Foundation (grant number 2010B013) and the Lundbeck Foundation. None of the funding sources had a role in the design, conduct, analysis, or reporting of the study.

Competing interests: All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: TJN had financial support from the Danish Independent Research Council for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

Ethical approval: Not needed.

Data sharing: No additional data available.

Table 1 | Baseline characteristics of 880 patients with first-time myocardial infarction in 2009 by quartiles[a] of mental health status (Mental Component Summary score from the Short-Form 12 version 2)

Variable[b]	Baseline MCS Score				P Value
	1st Quartile n=220	2nd Quartile n=220	3rd Quartile n=220	4th Quartile n=220	
Self-reported health[e]					
Mental health status (MCS score)[c], mean (range)	28.8 (11.1-37.2)	42.2 (37.2-47.0)	51.0 (47.0-54.5)	57.7 (54.5-60.8)	<.001
HADS-A/D ≥8, No. (%)	152 (69.7)	79 (36.07)	22 (10.0)	2 (0.91)	<.001
Socio-demographic characteristics					
Age, y, mean (SD)	68.9 (12.4)	68.4 (12.3)	65.6 (11.2)	64.5 (10.0)	<.001
Male sex, No. (%)	120 (54.6)	138 (62.7)	177 (80.5)	173 (78.6)	<.001
Cohabitation status, living alone, No. (%)[d]	94 (42.7)	82 (37.3)	55 (25.0)	47 (21.4)	<.001
Education, No. (%)[d]					
<10 years	114 (53.3)	105 (50.2)	85 (39.7)	76 (35.5)	
10-12 years	76 (35.5)	81 (38.8)	99 (46.3)	101 (47.2)	
>12 years	24 (11.2)	23 (11.0)	30 (14.0)	37 (173)	.004
Labour market status, No. (%)[d]					
Working	50 (22.7)	70 (31.8)	99 (45.0)	103 (46.8)	
Pension	136 (61.8)	123 (55.9)	105 (47.7)	107 (48.6)	
Out of the work force	34 (15.5)	27 (12.3)	16 (7.3)	10 (4.6)	<.001
Health status[e]					
Body mass index, mean (SD)	26.5 (5.1)	26.3 (4.8)	26.8 (4.5)	26.9 (4.5)	.626
Comorbid conditions, No. (%)[f]					
Hypertension[g]	88 (40.0)	75 (34.1)	54 (24.6)	54 (24.6)	<.001
Stroke	21 (9.6)	16 (7.3)	7 (3.2)	5 (2.3)	.002
TCI	12 (5.5)	3 (1.4)	3 (1.4)	10 (4.6)	.021
Revascularization	37 (16.8)	16 (7.3)	12 (5.5)	15 (6.8)	<.001
Heart failure	16 (7.3)	4 (1.8)	4 (1.8)	4 (1.8)	<.001
Diabetes mellitus	51 (23.2)	38 (17.3)	24 (10.9)	21 (9.6)	<.001
Depression[h]	44 (20.0)	21 (9.6)	11 (5.0)	9 (4.1)	<.001
Cardiac disease severity[e]					
MRC dyspnea score ≥3, No. (%)	110 (50.2)	45 (20.5)	21 (9.6)	3 (1.4)	<.001

Medication use, No. (%)[e]					
Aspirin	166 (75.5)	168 (76.4)	173 (78.6)	186 (84.6)	.086
Clopidogrel	159 (72.3)	164 (74.6)	173 (78.6)	184 (83.6)	.025
β-blocker	174 (79.1)	181 (82.3)	178 (80.9)	180 (81.8)	.837
Statin	169 (76.8)	184 (83.6)	190 (86.4)	195 (88.6)	.005
ACE-inhibitors/AT-II-receptor block	111 (50.5)	111 (50.5)	107 (48.6)	100 (45.5)	.689
Furosemide/Aldosterone antagonist	93 (42.3)	64 (29.1)	35 (15.9)	27 (12.3)	<.001
Antidepressants	53 (24.1)	24 (10.9)	9 (4.1)	8 (3.6)	<.001
Secondary prophylactic medication	146 (66.4)	160 (72.7)	162 (73.6)	166 (75.5)	.163
Potential behavioural mediators[e]					
Alcohol consumption >14/21 units/wk, No. (%)	8 (3.6)	12 (5.5)	8 (3.6)	14 (6.4)	.438
Smoking status, No. (%)					
Current	54 (24.8)	49 (22.4)	44 (20.0)	30 (13.6)	
Past	124 (56.9)	122 (55.7)	121 (55.0)	128 (58.2)	
Never	40 (18.4)	48 (21.9)	55 (25.0)	62 (28.2)	.048
Intake of fruit and vegetables ≥3 portions/d, No. (%)	69 (31.4)	75 (34.1)	86 (39.1)	100 (45.5)	.013
Intake of fish ≥3 times/d, No. (%)	61 (27.7)	78 (35.5)	93 (42.5)	96 (43.8)	.001
Intake of fish oil supplement, No. (%)	57 (25.9)	50 (22.7)	75 (34.1)	69 (31.4)	.035
Physical activity, d/wk, mean (SD)	3.6 (2.8)	5.1 (2.3)	5.3 (2.1)	5.7 (1.8)	<.001
Participation in phase two cardiac rehabilitation[e]	110 (50.2)	119 (54.1)	144 (65.5)	142 (64.8)	.001

Abbreviations: MRC, Medical Research Council; ACE, angiotensin converting enzyme; AT, angiotensin; HADS-A/D, Hospital Anxiety and Depression Scale-Anxiety/Depression; MCS, Mental Component Summary.

[a]1st quartile had the lowest MCS score; 4[th] quartile had the highest MCS score.

[b]Totals may not sum to their respective totals due to missing data. No variable had more than 3.3% missing data.

[c]Norm-based scoring (1998 U.S. population) using weights derived from confirmatory factor analysis.

[d]Information collected the year before MI (in 2008). [e]Information collected three months after MI. [f]Information collected at the time of MI.

[g]Redeemed prescription for at least two classes of antihypertensive drugs between MI and 180 days before.

[h]Redeemed prescription for antidepressants between MI and 180 days before.

Figure 1 | Kaplan-Meier curves by quartiles of mental health status (Mental Component Summary score from the Short-Form 12 version 2)

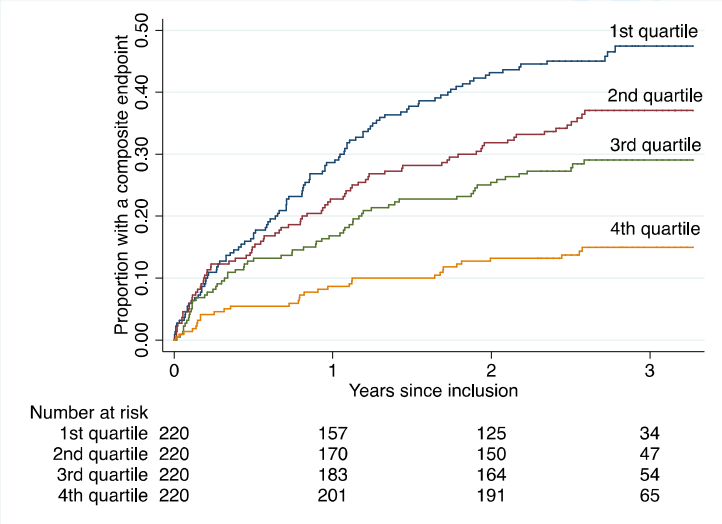


Table 2 | Association between mental health status (Mental Component Summary score from the Short-Form 12 version 2) and subsequent cardiovascular events or death, with sequential adjustment for potential confounders

	Hazard ratio (95% confidence interval)			
Adjusted variables[a]	**1st Quartile MCS (102/220)[b]**	**2nd Quartile MCS (80/220)[b]**	**3rd Quartile MCS (63/220)[b]**	**4th Quartile MCS (32/220)[b]**
Age	3.53 (2.36 to 5.27)	2.67 (1.77 to 4.03)	2.09 (1.36 to 3.19)	1 (reference)
Socio-demographic characteristics[c]	3.56 (2.35 to 5.38)	2.57 (1.69 to 3.92)	2.06 (1.34 to 3.16)	1 (reference)
MRC dyspnea score ≥3	2.74 (1.76 to 4.26)	2.30 (1.50 to 3.53)	1.96 (1.27 to 3.00)	1 (reference)
Comorbidity[d]	2.65 (1.70 to 4.13)	2.29 (1.50 to 3.51)	1.99 (1.29 to 3.05)	1 (reference)
Secondary prophylactic medication	2.77 (1.78 to 4.31)	2.32 (1.51 to 3.56)	1.95 (1.27 to2.99)	1 (reference)
Smoking status	2.76 (1.76 to 4.31)	2.31 (1.51 to 3.56)	1.96 (1.27 to 3.01)	1 (reference)

Physical activity	2.47 (1.56 to 3.91)	2.25 (1.47 to 3.46)	1.89 (1.23 to 2.91)	1 (reference)
HADS-A/D score ≥8	2.26 (1.37 to 3.73)	2.15 (1.38 to 3.35)	1.87 (1.21 to 2.88)	1 (reference)

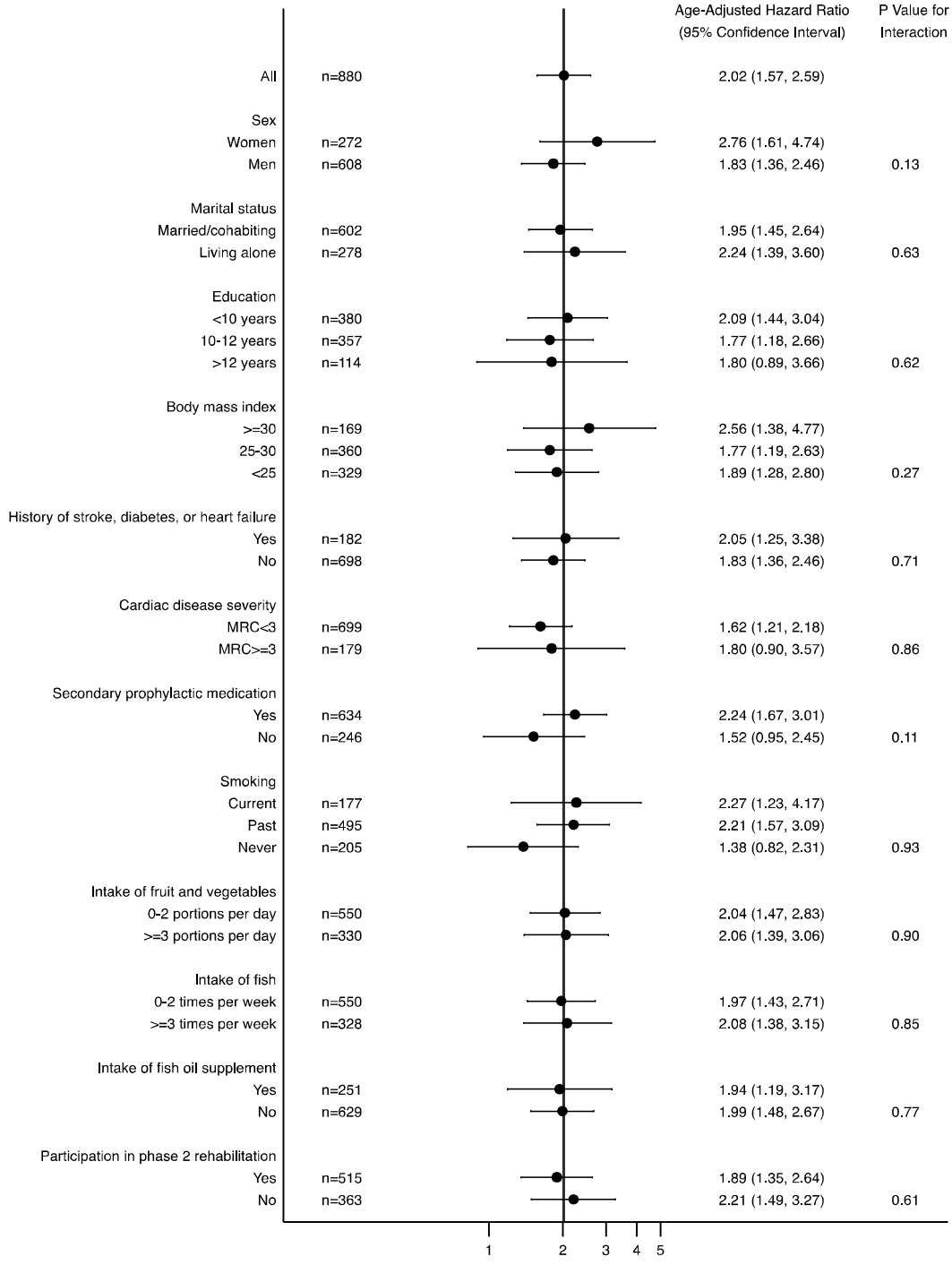
Abbreviations: MCS, Mental Component Summary; HADS-A/D, Hospital Anxiety and Depression Scale-Anxiety/Depression; MRC, Medical Research Council.
[a] Each model includes the variables from the preceding row so that the final model includes all the variables listed in this table.
[b] No. of outcomes/no. of persons in quartile.
[c] Sex, cohabitation status, education, labour market status. [d] History of stroke, diabetes mellitus, or heart failure.

Table 3 | Association between mental health status item scores (continuous; per one point lower item score) and subsequent cardiovascular events or death, with sequential adjustment for potential confounders and mediators

Adjusted variables[a]	Hazard ratio (95% confidence interval)					
	Vitality	Role-Emotional 1	Role-Emotional 2	Social Functioning	Mental Health 1	Mental Health 2
Age	1.41 (1.27 to 1.56)	1.29 (1.18 to 1.41)	1.26 (1.15 to 1.37)	1.23 (1.12 to 1.35)	1.31 (1.18 to 1.46)	1.21 (1.09 to 1.35)
Socio-demographic characteristics[b]	1.41 (1.26 to 1.57)	1.31 (1.19 to 1.43)	1.28 (1.17 to 1.41)	1.21 (1.10 to 1.34)	1.33 (1.19 to 1.48)	1.21 (1.08 to1.36)
MRC dyspnea score ≥3	1.30 (1.16 to 1.47)	1.21 (1.10 to 1.34)	1.18 (1.07 to 1.31)	1.12 (1.01 to 1.24)	1.24 (1.11 to 1.40)	1.11 (0.98 to 1.25)
Comorbidity[c]	1.28 (1.14 to 1.44)	1.21 (1.09 to 1.33)	1.16 (1.05 to 1.28)	1.10 (0.99 to 1.22)	1.25 (1.11 to 1.40)	1.11 (0.98 to 1.25)
Secondary prophylactic medication	1.31 (1.17 to 1.48)	1.22 (1.11 to 1.35)	1.18 (1.07 to 1.31)	1.12 (1.01 to 1.24)	1.24 (1.11 to 1.40)	1.11 (0.98 to 1.25)
Smoking status	1.31 (1.17 to 1.48)	1.22 (1.10 to 1.34)	1.18 (1.06 to 1.30)	1.12 (1.00 to 1.24)	1.25 (1.11 to 1.41)	1.11 (0.98 to 1.25)
Physical activity	1.27 (1.13 to 1.44)	1.18 (1.07 to 1.31)	1.14 (1.03 to 1.27)	1.08 (0.97 to 1.21)	1.22 (1.09 to 1.38)	1.07 (0.95 to 1.21)
HADS-A/D score ≥8	1.24 (1.09 to 1.42)	1.16 (1.04 to 1.29)	1.11 (0.99 to 1.24)	1.03 (0.91 to 1.16)	1.19 (1.04 to 1.35)	1.00 (0.87 to 1.16)

Abbreviations: HADS-A/D, Hospital Anxiety and Depression Scale-Anxiety/Depression. MRC, Medical Research Council.
[a] Each model includes the variables from the preceding row so that the final model includes all the variables listed in this table.
[b] Sex, cohabitation status, education, labour market status. [c] History of stroke, diabetes mellitus, or heart failure.

Figure 2 | Association between baseline mental health status (median cut) and subsequent cardiovascular events or death for patients with myocardial infarction and specific characteristics



WEB EXTRA SUPPLEMENT

Table A | Comparison of participants and non-participants

Variable	Participants (n=880)	Non-participants (n=408)	P Value
Socio-demographic characteristics			
Age, y, mean (SD)	66.8 (11.7)	72.1 (14.7)	<.001
Male sex, No. (%)	608 (69.1)	226 (55.4)	<.001
Cohabitation status, living alone, No. (%)[a]	278 (31.6)	230 (56.4)	<.001
Education, No. (%)[a]			
<10 years	380 (44.7)	206 (58.2)	
10-12 years	357 (42.0)	112 (31.6)	
>12 years	114 (13.4)	36 (10.2)	<.001
Labour market status, No. (%)[a]			
Working	322 (36.6)	75 (18.4)	
Pension	471 (53.5)	283 (69.4)	
Out of the work force	87 (9.9)	50 (12.3)	<.001
Comorbid conditions, No. (%)[b]			
Stroke	49 (5.6)	45 (11.0)	<.001
Revascularization	80 (9.1)	35 (8.6)	.764
Congestive heart failure	28 (3.2)	45 (11.0)	<.001
Diabetes mellitus	134 (15.2)	101 (24.8)	<.001
Depression[c]	85 (9.7)	93 (22.8)	<.001

[a]Information collected the year before MI (in 2008).
[b]Information collected at the time of MI.

Table B | Association between mental health status (Mental Component Summary score from the Short-Form 12 version 2; traditional scoring method) and subsequent cardiovascular events or death, with sequential adjustment for potential confounders

Adjusted variables[a]	Hazard ratio (95% confidence interval)			
	1st quartile MCS (96/220)[b]	2nd quartile MCS (70/220)[b]	3rd quartile MCS (64/225)[b]	4th quartile MCS (47/215)[b]
Age	2.40 (1.69 to 3.40)	1.60 (1.10 to 2.31)	1.40 (0.96 to 2.04)	1 (reference)
Socio-demographic characteristics[c]	2.50 (1.74 to 3.61)	1.62 (1.10 to 2.37)	1.43 (0.97 to 2.11)	1 (reference)
MRC dyspnea score ≥3	1.94 (1.32 to 2.85)	1.49 (1.01 to 2.19)	1.33 (0.90 to 1.97)	1 (reference)
Comorbidity[d]	1.92 (1.30 to 2.83)	1.52 (1.03 to 2.23)	1.40 (0.95 to 2.07)	1 (reference)
Secondary prophylactic medication	1.94 (1.32 to 2.86)	1.49 (1.01 to 2.19)	1.34 (0.91 to 1.98)	1 (reference)
Smoking status	1.93 (1.31 to 2.84)	1.45 (0.99 to 2.14)	1.34 (0.90 to 1.98)	1 (reference)
Physical activity	1.76 (1.19 to 2.62)	1.41 (0.96 to 2.08)	1.32 (0.89 to 1.95)	1 (reference)
HADS-A/D score ≥8	1.57 (1.01 to 2.45)	1.33 (0.89 to 1.99)	1.30 (0.88 to 1.93)	1 (reference)

Abbreviations: MCS, Mental Component Summary; HADS-A/D, Hospital Anxiety and Depression Scale-Anxiety/Depression. MRC, Medical Research Council.
[a] Each model includes the variables from the preceding row so that the final model includes all the variables listed in this table.
[b] No. of outcomes/no. of persons in quartile.
[c] Sex, cohabitation status, education, labour market status. [d] History of stroke, diabetes mellitus, or heart failure.

Table C | Stratified analysis for those without depression and anxiety, n=622. Association between mental health status (Mental Component Summary score from the Short-Form 12 version 2) and subsequent cardiovascular events or death, with sequential adjustment for potential confounders and mediators

Adjusted variables[a]	Hazard ratio (95% confidence interval)			
	1st quartile MCS (63/155)[b]	2nd quartile MCS (48/156)[b]	3rd quartile MCS (38/154)[b]	4th quartile MCS (19/157)[b]
Age	3.39 (2.01 to 5.73)	2.63 (1.55 to 4.49)	2.20 (1.27 to 3.81)	1 (reference)
Socio-demographic characteristics[c]	3.49 (2.04 to 5.98)	2.59 (1.51 to 4.44)	2.05 (1.17 to 3.56)	1 (reference)
MRC dyspnea score ≥3	3.15 (1.81 to 5.48)	2.45 (1.42 to 4.22)	2.00 (1.15 to 3.48)	1 (reference)
Comorbidity[d]	3.03 (1.74 to 5.29)	2.44 (1.42 to 4.19)	1.91 (1.10 to 3.34)	1 (reference)
Secondary prophylactic medication	3.22 (1.85 to 5.59)	2.44 (1.42 to 4.20)	2.02 (1.16 to 3.52)	1 (reference)
Smoking status	3.13 (1.79 to 5.46)	2.52 (1.46 to 4.33)	1.99 (1.14 to 3.46)	1 (reference)
Physical activity	3.03 (1.72 to 5.34)	2.49 (1.44 to 4.29)	1.97 (1.13 to 3.43)	1 (reference)

Abbreviations: MCS, Mental Component Summary; MRC, Medical Research Council.
[a] Each model includes the variables from the preceding row so that the final model includes all the variables listed in this table.
[b] No. of outcomes/no. of persons in quartile.
[c] Sex, cohabitation status, education, labour market status. [d] History of stroke, diabetes mellitus, or heart failure.

eFigure 1 | The 6 mental health status items from the Short-Form 12 version 2

4. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?
a. Accomplished less than you would like.
b. Did work or other activities less carefully than usual.

6. These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the past 4 weeks…
a. Have you felt calm and peaceful?
b. Did you have a lot of energy?
c. Have you felt downhearted and depressed?

7. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting friends, relatives, etc.)?

The options for all of the items are:
All of the time, most of the time, some of the time, a little of the time, none of the time.

4a: Role-Emotional item 1.
4b: Role-Emotional item 2.
6a: Mental Health item 1.
6b: Vitality.
6c: Mental Health item 2.
7: Social Functioning.

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STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3
Objectives	3	State specific objectives, including any prespecified hypotheses	3
Methods			
Study design	4	Present key elements of study design early in the paper	3-4
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	3-4, 6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	3-4, 6
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	-
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	3-6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	3-6
Bias	9	Describe any efforts to address potential sources of bias	6-7, 9-11
Study size	10	Explain how the study size was arrived at	3
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	4-7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	6-7
		(*b*) Describe any methods used to examine subgroups and interactions	7
		(*c*) Explain how missing data were addressed	7
		(*d*) If applicable, explain how loss to follow-up was addressed	-
		(*e*) Describe any sensitivity analyses	6-7, 10-11
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	3, 8
		(b) Give reasons for non-participation at each stage	3
		(c) Consider use of a flow diagram	3
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	8, 14
		(b) Indicate number of participants with missing data for each variable of interest	7
		(c) Summarise follow-up time (eg, average and total amount)	8
Outcome data	15*	Report numbers of outcome events or summary measures over time	8, 15
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	7-9, 15
		(*b*) Report category boundaries when continuous variables were categorized	14
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	8, 15
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	8, 10-11
Discussion			
Key results	18	Summarise key results with reference to study objectives	9-13
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	9-13
Generalisability	21	Discuss the generalisability (external validity) of the study results	9
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	13

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ open

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Journal:	*BMJ Open*
Manuscript ID:	bmjopen-2013-003045.R1
Article Type:	Research
Date Submitted by the Author:	03-Jul-2013
Complete List of Authors:	Nielsen, Tine; Section for General Medical Practice, Department of Public Health, Aarhus University Vestergaard, Mogens; Section for General Medical Practice and Research Unit for General Practice, Department of Public Health, Aarhus University Christensen, Bo; Section for General Medical Practice, Department of Public Health, Aarhus University Christensen, Kaj; Research Unit for General Practice, Department of Public Health, Aarhus University Larsen, Karen; Section for General Medical Practice and Research Unit for General Practice, Department of Public Health, Aarhus University
Primary Subject Heading:	Cardiovascular medicine
Secondary Subject Heading:	Mental health, Epidemiology
Keywords:	CARDIOLOGY, Myocardial infarction < CARDIOLOGY, MENTAL HEALTH, EPIDEMIOLOGY, Cardiac Epidemiology < CARDIOLOGY, Ischaemic heart disease < CARDIOLOGY

Mental health status and risk of new cardiovascular events or death in patients with myocardial infarction: a population-based cohort study

Tine Jepsen Nielsen, Mogens Vestergaard, Bo Christensen, Kaj Sparle Christensen, Karen Kjær Larsen

Section for General Medical Practice, Aarhus University, Bartholins Allé 2, 8000 Aarhus C, Denmark
Tine Jepsen Nielsen
Junior research fellow

Section for General Medical Practice and Research Unit for General Practice, Aarhus University, Bartholins Allé 2, 8000 Aarhus C, Denmark
Mogens Vestergaard
Professor

Section for General Medical Practice, Aarhus University, Bartholins Allé 2, 8000 Aarhus C, Denmark
Bo Christensen
Professor

Research Unit for General Practice, Aarhus University, Bartholins Allé 2, 8000 Aarhus C, Denmark
Kaj Sparle Christensen
Senior researcher

Section for General Medical Practice and Research Unit for General Practice, Aarhus University, Bartholins Allé 2, 8000 Aarhus C, Denmark
Karen Kjær Larsen
PhD fellow

Correspondence to: TJ Nielsen. E-mail: tjn@folkesundhed.au.dk

ARTICLE SUMMARY

Article focus

- Myocardial infarction (MI) is often followed by mental health problems such as depression, anxiety, and low mental health status.
- Mounting evidence indicates that depression and anxiety after MI increase the risk of adverse long-term outcome. No previous studies have examined the association between mental health status after MI and outcome, independent of depression and anxiety.
- This study examines the association between mental health status after first-time MI and new cardiovascular events or death, when taking into account depression and anxiety as well as clinical, socio-demographic, and behavioural risk factors.

Key messages

- During three years after the MI, patients with the lowest mental health status had an almost 50% risk of new cardiovascular events or death.
- Low mental health status after MI was a strong predictor of new cardiovascular events or death, independent of depression, anxiety and clinical, socio-demographic, and behavioural risk factors.

Strengths and limitations of this study

- Major strengths of this study are its population-based nature and the homogenous study population. The response rate was reasonably high, and information on outcome was collected without loss to follow-up.
- We were able to take into account important mediators such as depression, anxiety, and potential behavioural mediators such as physical activity. However, we cannot rule out the possibility of residual confounding.

Abstract

Objective To examine the association between mental health status after first-time myocardial infarction (MI) and new cardiovascular events or death, taking into account depression and anxiety as well as clinical, socio-demographic, and behavioural risk factors.

Design Population-based cohort study based on questionnaires and nationwide registries. Mental health status was assessed three months after the MI using the Mental Component Summary score from the Short-Form 12 version 2.

Setting Central Denmark Region.

Participants All patients hospitalised with first-time MI from 1 January 2009 through 31 December 2009 (n=880). The participants were categorised in quartiles according to level of mental health status (1st quartile=lowest mental health status).

Main outcome measures Composite endpoint of new cardiovascular events (MI, heart failure, stroke/transient ischaemic attack) and all-cause mortality.

Results During 1,940 person-years of follow-up, 277 persons experienced a new cardiovascular event or died. The cumulative incidence following three years after the MI increased consistently with decreasing mental health status and was 15.0% (95% confidence interval 10.8% to 20.5%) for persons in the fourth quartile 29.1% (23.5% to 35.6%) in the third quartile, 37.0% (30.9% to 43.9%) in the second quartile, and 47.5% (40.9% to 54.5%) in the first quartile. The hazard ratios (HR) were high, even after adjustments for age, socio-demographic characteristics, cardiac disease severity, comorbidity, secondary prophylactic medication, smoking status, physical activity, depression, and anxiety ($HR_{3rd\ quartile}$ 1.90 (95% confidence interval 1.23 to 2.93), $HR_{2nd\ quartile}$ 2.14 (1.37 to 3.33), $HR_{1st\ quartile}$ 2.23 (1.35 to 3.68) when using the fourth quartile as reference).

Conclusions Low mental health status following first-time MI was independently associated with an increased risk of new cardiovascular events or death. Further research is needed to disentangle the pathways that link mental health status following MI to prognosis and to identify interventions that can improve both mental health status and prognosis.

INTRODUCTION

Myocardial infarction (MI) is a severe life event followed by an increased risk of mental health problems such as depression,[1] anxiety,[2] and low mental health status.[3] Several studies have shown that depression[4] and anxiety[2] after MI is associated with a higher risk of cardiovascular events and death, but much less is known about the impact of broader measures of mental health. Mental health status is a generic and broad measure of mental health, which may be useful as a tool to quantify important prognostic aspects of mental health not captured by the more disease-specific measures of depression and anxiety. Four studies[5-8] have investigated the association between mental health status following MI and prognosis. All these have found that low mental health status was significantly associated with increased risk of adverse outcome, independent of clinical risk factors. However, since none of the former studies adjusted for depression or anxiety, it remains unknown whether mental health status in itself adds unique knowledge about the prognosis.

Our aim was to examine the association between mental health status and new cardiovascular events or death in patients with first-time MI when taking into account depression, anxiety, and clinical, socio-demographic, and behavioural risk factors.

METHODS

We conducted a population-based cohort study comprising people in the Central Denmark Region (1,250,000 inhabitants) with a first-time MI based on data from nationwide registers and questionnaires.

Participants

We consecutively invited all patients discharged from hospital with a first-time MI from 1 January 2009 to 31 December 2009. The establishment of the cohort is described in detail elsewhere.[9] Data on patients discharged with MI (in accordance with the International Classification of Diseases (ICD-10) code I21)[10] were received from the Danish National Patient Register on a monthly basis. Patients who had been discharged with MI between 1994 and 2008 were excluded to identify first-time cases. Information on name, address, and vital status was obtained from the Civil Registration System,[11] which also provided the unique personal identification number used to link data between the registers and questionnaires.

Data collection

A pilot-tested hard-copy questionnaire was sent to all participants 12 to 14 weeks after their discharge from hospital, and non-responders received two reminders.[9] The study was approved by the Danish Data Protection Agency (J.nr. 2009-41-3018), the Scientific Research Evaluation Committee of the Danish Academy of General Practitioners (ref. no. 03-2009), and written informed consent was obtained from all participants.

Mental health status

Mental health status was measured using the Mental Component Summary (MCS) score from the validated Danish version of the Short-Form 12 version 2 Health Survey (SF-12).[12-14] The SF-12 consists of 12 items, the MCS score comprises mainly of the six mental items ('Vitality', 'Role-Emotional' (2 items), 'Social Function', and 'Mental Health' (2 items)), but the six physical items are also included in the computation.[12] The SF-12 scores were calculated following the norm-based scoring algorithm[12] using weights derived from confirmatory factor analysis.[15] The MCS score is thus linearly transformed in a way that allows comparison with the mean score (50) and the standard deviation (SD) (10) in the general US population in 1998.[12] The MCS has demonstrated good construct validity.[15] The wording of the mental health status items can be found in the supplemental material (**eFigure 1**).

Depression and anxiety

We assessed depression and anxiety symptoms using the Hospital Anxiety and Depression Scale (HADS).[16] The participants were categorised as having anxiety or depression if they had a score of ≥8 on the HADS-A scale or the HADS-D scale. The HADS was designed to be valid in clinical populations with symptoms of physical disease and hence leaves out items that may be endorsed by physical rather than mental states.[16, 17] The HADS has formerly been validated in MI patients[18, 19] and has proven to have satisfactory reliability (HADS-A and HADS-D Cronbach's $\alpha \approx 0.80$).[18, 20] Among MI patients, a HADS-D≥8 identified possible cases of depression with a sensitivity of 65% and a specificity of 90% (compared with a diagnosis of depression based on a Structured Clinical Interview for DSM-IV).[19] Among acute coronary syndrome patients, a HADS-A≥8 identified possible cases of anxiety with a sensitivity of 91% and a specificity of 61% (compared with a diagnosis of generalised anxiety disorder based on a Structured Clinical Interview for DSM-IV).[21]

Co-morbidity and cardiac disease severity

Information on co-morbidity was retrieved from the Danish National Patient Register, [22] the Danish National Diabetes Register, [23] and the prescription database covering the entire Central Denmark Region. [24] The Danish National Patient Register provided information on stroke (ICD-10: I61, I63, I64), transient cerebral ischemic attack (ICD-10: DG45, DG46), heart failure (ICD-10: I11.0, I13.0, I13.2, I42.0, I42.6, I42.7, I42.9, I50.0, I50.1, I50.9), and revascularization (ICD-10: KFN, KFW) from 1994 to 2008. The Danish National Diabetes Register provided information on diabetes mellitus from 1990 to 2008 according to an algorithm developed on the basis of information from four nationwide registers. [23] The prescription database provided information on all reimbursed drugs according to the Anatomical Therapeutic Chemical Classification System (ATC), dispensing dates, and the total number of tablets dispensed. Participants were categorised with hypertension if they had redeemed prescriptions for at least two classes of antihypertensive drugs (ATC: C02A-D, C02L, C03A-B, C03D-E, C03X, C04, C05, C07, C08, C09) 0 to 180 days before the index MI. Participants were categorised with depression before MI if they had redeemed a prescription for an antidepressant (ATC: N06A) 0 to 180 days before the index MI. Participants were categorised with severe mental disorder if they had redeemed a prescription for antipsychotics (ATC: N05A) 0 to 180 days before the index MI.

Cardiac disease severity was measured by the British Medical Research Council (MRC) dyspnea score, a self-report instrument. [25] A score ≥3 has been shown to provide a simple and valid method for predicting overall mortality.[26]

Health behaviour, health care interventions, and socio-demographics

Data on smoking, alcohol use, physical activity, intake of fruit and vegetables, intake of fish, intake of fish oil supplement, height, and weight (body mass index=weight [kg] per height [m^2]) were self-reported and classified according to the general recommendations from the Danish National Board of Health. [9] To assess physical activity, we asked, "How many days per week are you generally physically active for at least 30 minutes per day? You may include any physical activity at work or in your spare time that makes your pulse rate increase". Response options were from zero days to every day per week. Physical activity was computed as a continuous variable (days/week).

We defined cardiac rehabilitation[27, 28] in the questionnaire and asked whether they had participated in hospital-based phase two cardiac rehabilitation. Those who responded "yes,

and I took part" were classified as 'participants' those who responded "yes, but I didn't take part" or "no" were classified as 'non-participants'. [9]

Drug prescription data were obtained from the prescription database. [24] Data on aspirin (ATC: B01AC06), clopidogrel (ATC: B01AC04), statins (ATC: C10AA), β-blockers (ATC: C07), ACE-inhibitors/angiotensin 2 receptor blockers (ATC: C09), furosemide (ATC: C03C), aldosterone antagonists (ATC: C03D), and antidepressants (ATC: N06A) were collected. We calculated whether the participant had tablets available on the day that we sent the questionnaire (the number of tablets on the last redeemed prescription before the questionnaire was sent ≥ the number of days to the questionnaire was sent) and defined the participant as 'receiving treatment' if tablets were available. We defined the participant as 'receiving secondary prophylactic medication' if the participant was receiving treatment with three or more of the following drugs: aspirin, clopidogrel, statins, and β-blockers. We defined the participant as 'receiving heart failure medication' if the participant was receiving treatment with furosemide or aldosterone antagonists.

Data on age at MI and sex were obtained from the Civil Registration System. [11] Each participant's socio-demographic characteristics (cohabitation status, education, labour market status) from the year before MI (2008) were retrieved from the Danish Integrated Database for Labour Market Research.[29]

Cardiovascular events and death

Outcome events were measured as a composite endpoint comprising new cardiovascular events (MI, heart failure, stroke or transient ischaemic attack) and all-cause mortality. Information on outcomes was collected from baseline (the day we sent the questionnaire) to the last day of follow-up (31 July 2012). The Danish National Patient Register[22] provided information on cardiovascular events. Vital status (dead or alive) was obtained from the Civil Registration System.[11]

Statistical analysis

Neither natural thresholds nor clinically based thresholds are defined for the MCS score, so we divided the participants into quartiles according to their score (1st quartile had the lowest score; 4th quartile had the highest score). This categorisation was done to enhance clinical interpretability and to evaluate a possible dose response relationship.

In order to address the potential risk of selection bias, we used antidepressant consumption as a proxy for depression and calculated hazard ratios (HRs) for the association

between antidepressant consumption and new cardiovascular events or death for both participants and non-participants.

The association between baseline characteristics and MCS score was assessed using $\chi 2$ statistics for categorical variables and analysis of variance for continuous variables, or Kruskal-Wallis tests when the conditions for analysis of variance were not fulfilled.

We calculated the event-free survival time as the time from three months after the MI (baseline evaluation of mental health status) to the first cardiovascular event or death. If no event or death occurred, the participant was censored on 31 July 2012. Two persons emigrated during the time of follow-up, and they were censored on the day of their emigration. Owing to the use of nationwide registers, we had complete follow-up of all participants.

The unadjusted association between mental health status and new cardiovascular events or death was presented graphically with Kaplan-Meier curves. The cumulative incidence three years after the MI was estimated using the cumulative hazards function, and identical incidence was tested using the log-rank test.

The risk of cardiovascular events or death associated with mental health status was compared using Cox proportional hazards regression. The covariates for the multivariate model (age, sex, cohabitation status, education, labour market status, cardiac disease severity, history of stroke, diabetes mellitus, heart failure, secondary prophylactic medication, smoking status, physical activity, depression, and anxiety) were chosen on the basis of previous studies. To check for multicollinearity between depression/anxiety symptoms and mental health status we calculated the variance inflation factor which was 1.5. Values above 10 indicate multicollinearity.[30] We evaluated whether the HRs of mental health status following MI varied by subgroups by testing for interaction using Wald test in an age-adjusted model, and the results are presented in a forest plot. Too few outcome events were available to test for interaction in quartiles, so we tested it in a dichotomised (median cut) model. We excluded variables with less than five events in a subgroup.

Finally, we calculated HRs for the association between each of the mental health status items (continuous; per one-point lower item score) and outcome.

No variable had more than 0.3% missing data, except body mass index (for which 2.5% data were missing) and education (for which 3.3% data were missing), and analyses were done on complete data only. $P<0.05$ was considered statistically significant.

RESULTS

Participant characteristics

Among a total of 1,288 eligible patients with first-time MI, 880 (68.3%) completed the SF-12, and the mean MCS score was 44.9 (SD 11.5). Non-participants were more often women, older, had fewer socioeconomic resources, and more comorbid conditions than participants (Web Extra Supplement Table A). The estimates of the association between antidepressant consumption and new cardiovascular events or death in participants, HR 1.55 (95% confidence interval 1.12 to 2.14) and in non-participants, HR 1.46 (1.01 to 2.10), were similar. Compared to participants with higher mental health status, the participants with the lowest mental health status (1st quartile, table 1) were impaired in a range of variables; e.g. symptoms of depression and anxiety, cardiac disease severity, comorbidity, socioeconomic resources, and health behaviour.

Cumulative incidence

A total of 277 outcomes (230 new cardiovascular events and 47 deaths) occurred during 1,940 person years of follow-up (median 2.6 years, SD 1.0). The Kaplan-Meier curves (figure 1) show that the unadjusted risk of a cardiovascular event or death increased with decreasing mental health status. During three years after the MI, the cumulative incidence of the composite endpoint was 47.5% (95% confidence interval 40.9% to 54.5%) for persons in the first, 37.0% (30.9% to 43.9%) in the second, 29.1% (23.5% to 35.6%) in the third, and 15.0% (10.8% to 20.5%) in the fourth quartile, P<0.001.

Association between mental health status and new cardiovascular events or death

The age-adjusted HRs for new cardiovascular events or death in post-MI patients increased with decreasing mental health status ($HR_{3rd\ quartile}$ 2.09 (95% confidence interval 1.36 to 3.19), $HR_{2nd\ quartile}$ 2.67 (1.77 to 4.03), $HR_{1st\ quartile}$ 3.53 (2.36 to 5.27), table 2). Additional adjustment for cardiac disease severity, physical activity, depression, and anxiety attenuated the association. In the fully adjusted model, the MI patients with the lowest mental health status had a more than two-fold higher risk of new cardiovascular events or death compared to the patients with the highest mental health status (table 2).

We found no statistically significant difference in the HRs between any subgroups of MI patients (figure 2).

Exploratory analysis of the six mental health status items

Table 3 outlines the association between mental health status item scores and subsequent cardiovascular events or death. The items were entered as continuous variables and the HRs reflect the risk of new cardiovascular events or death per one point lower item score. The largest HRs were seen for the 'Vitality' item, HR 1.24 (95% confidence interval 1.09 to 1.42), the 'Mental Health' item 1, HR 1.19 (1.04 to 1.35), and the 'Role-Emotional' item 1, HR 1.16 (1.04 to 1.29).

DISCUSSION

In this population-based cohort study, we found that low mental health status after first-time MI predicted an increased risk of new cardiovascular events or death in a dose-response manner. The association was explained partly by cardiac disease severity, physical activity, depression, and anxiety. However, even after adjustments for these variables, patients with the lowest mental health status had a more than two-fold higher risk of new cardiovascular events or death compared to those with the highest mental health status.

Strengths and limitations of the study

Major strengths of this study are its population-based nature and the homogenous study population; we invited all patients with first-time MI during one year in a well-defined area. Our response rate was reasonably high (68.3%), and information on outcome was collected without loss to follow-up. Non-participants tended to have fewer social resources and more comorbid conditions, and they hence resembled the participants with the lowest mental health status. In order to address the potential risk of selection bias, we used antidepressant consumption as a proxy for depressive symptoms similarly to previous studies.[31] The estimates of the association between antidepressant consumption and new cardiovascular events or death in participants and non-participants were similar. Thus, bias due to selection of study participants seems to be an unlikely explanation for our findings.

Information on MI was registered prospectively and did not rely on the participants' or the relatives' memory. The MI diagnosis in the Danish National Patient Register was based on the current European Society of Cardiology criteria for MI, coded by the physician in charge of the discharge, and the information is known to have a high sensitivity (90%) and specificity (92%).[10] The specificity was even higher in our study because we confirmed the MI diagnosis by reviewing the discharge summaries,[9] and this reduced the risk of information bias. We also

reduced the risk of information bias by using previously translated and validated scales, pilot testing the questionnaire among MI patients, and using high-quality register data.

We used a new algorithm for the calculation of the MCS score from the SF-12 version 2 using weights constructed by oblique confirmatory factor analysis, which allows the physical and mental component summary score to be correlated. Fleishman et al developed this new scoring algorithm[15] due to controversy regarding the traditional scoring algorithm.[32-34] The traditional scoring algorithm forces mental and physical health to be uncorrelated. Consequently, when physical scores are well below the mean and mental scores somewhat less below the mean, as is often the case in patients with physical illness, this scoring method will result in an artifactual migration of the MCS score towards the mean.[32] In sub-analyses, we estimated HRs based on traditionally computed MCS scores (Web Extra Supplement Table B). As expected, they were smaller compared to the HRs based on MCS scores computed with the new scoring algorithm. We evaluated mental health status three months after MI, allowing mental health to reach a more stable level after this major life event.

A diagnosis of depression or anxiety should ideally be based on a diagnostic interview. Since a previous study has estimated the sensitivity of the HADS-D≥8 for identification of depression to be 65% in MI patients,[19] a substantial number of participants with depression may have been misclassified as not having depression. However, we identified 18.3% with depression in our population (HADS-D≥8), which is in keeping with the prevalence of post-MI depression identified by structured clinical interviews in other studies (19.8%).[1] We found no studies reporting on the sensitivity and specificity of the HADS-A in an MI population. However, among acute coronary syndrome patients, a HADS-A≥8 had a sensitivity of 91%.[21] Accordingly, we most likely identified the majority of patients with anxiety. In a sensitivity analysis, we excluded patients with depression or anxiety (HADS-A/D≥8), and this did not weaken the estimates (Web Extra Supplement Table C).

Schizophrenia and bipolar disorder are known to be associated with a higher risk of mortality, and part of this excess risk is attributable to cardiovascular diseases.[35] We used a prescription of antipsychotics, between MI and 180 days before, as an approximation of severe mental disorder. Thirteen participants had redeemed such a prescription. To examine how much of the association could be explained by these patients, we excluded this group in a sensitivity analysis (not shown), and this did not weaken the estimates.

Lifestyle behaviour was self-reported, and participants with low mental health status may have been more likely to underreport adverse lifestyle, including physical inactivity. However, participants with low mental health status did in fact report adverse lifestyle in our study, and

a study on depression[36] found no differences when substituting self-reported physical activity with an objective measure of physical fitness.

Information on a range of participant characteristics and the large sample size allowed us to take into account several potential confounders, such as socio-demographic characteristics, cardiac disease severity, comorbidity, and behavioural factors. In sub-analyses, we adjusted for other potential confounders (body mass index, hypertension, history of depression, antidepressant use, intake of alcohol, fish, and fruit, and participation in phase two cardiac rehabilitation), but this did not change the estimates (≤4%). However, we cannot rule out the possibility of residual confounding.

Comparison with other studies

Four previous studies[5-8] have investigated the association between mental health status after MI and prognosis independent of various clinical risk factors, such as disease severity. They used different measures of mental health status (COOP charts,[6] Quality of Life after MI questionnaire,[8] the World Health Organization Quality of Life Instrument Abbreviated,[7] and SF-12[5]), and they all found an independent association between low mental health status and higher risk of adverse outcomes. Compared with our study, these studies were conducted in modest-sized cohorts (n=112,[6] 375,[8] 145[7]), had short follow-up (four to five months,[6] 18 months[8]), mental health status was assessed up to five years or more after MI,[5, 7] included only women[7] or patients who had an ejection fraction <30%.[5] Most importantly, none of these four MI studies took into account important mediators such as depression, anxiety, and potential behavioural mediators such as physical activity.

Our study is the first to explore the association between mental health status after MI and new cardiovascular events or death in subgroups, and we identified no factors that modified the risk. However, the sample size was low in some of the subgroups.

Our study is also the first to explore the association between mental health status and cardiovascular events or death on an item level. We found that the 'Vitality' item, the 'Role-Emotional' item 1, and the 'Mental Health' item 1 were significantly associated with adverse events after adjustments for clinical, socio-demographic, behavioural, and other psychological risk factors, whereas the remaining items were not. Our results indicate that these items are the most important for the association between mental health status (MCS score) and adverse events. Yet, it is important to keep in mind that the items have different weights and that the physical items are also included when computing the MCS score.[12, 15]

Implications for clinicians

In addition to psychological, social, and functional impairment, clinicians should be aware that low mental health status following MI is associated with an increased risk of new cardiovascular events and death. Our results underline the importance of always considering and prioritising mental health issues in post-MI patients. In this study, we identified low mental health status after MI to be a significant risk factor for poor prognosis, independent of clinical, socio-demographic, behavioural, and other psychological risk factors. In other words, mental health status has incremental value in the identification of patients at elevated risk for adverse outcome. Adding mental health status measurement to our present risk factor armamentarium could help clinicians to distinguish between groups of patients with a very low versus a very high risk of adverse outcome, and thereby help identify vulnerable patients in need of optimised care. However, we do not know whether measurement of mental health status and improved knowledge of prognosis will translate into better outcomes for our patients. This is an important focus for future research in this field.

Possible explanations and future research

This study suggests that mental health status may capture prognostic aspects of mental health which are not captured by measures of depression and anxiety. Further research is needed to clarify more specifically what aspects of mental health that are at play.

The underlying explanation for the association between mental health status after MI and new cardiovascular events or death remains unclear. Our study evaluated cardiac disease severity, behavioural factors, and treatment strategies concurrently with mental health status. We therefore cannot determine whether these factors were the cause or the result of the mental health status. We were unable to assess whether the association was explained by biological mechanisms (such as heart rate variability, platelet function, or inflammatory mechanisms) since we had no information on these biological variables. Future studies should incorporate such biological variables.[37]

Further research is also needed to identify interventions that can improve both mental health status and prognosis in MI patients. Murphy et al[38] examined the effectiveness of a complex intervention designed to improve outcomes, including mental health status (measured with SF-12) for patients with coronary heart disease in a cluster randomised controlled trial. The intervention was "tailored care plans for practices (practice based training in prescribing and behaviour change, administrative support, quarterly newsletter), and tailored care plans for patients (motivational interviewing, goal identification, and target

setting for lifestyle change)." [38] They found that admissions to hospital were significantly reduced after an intensive 18-month intervention to improve outcomes for patients with coronary heart disease, but there was no change in mental health status. It was not stated how they computed the MCS score, but they probably used the traditional scoring algorithm as the study were conducted prior to Fleishman's publication. [15] Hence, artifactual migration of the MCS score towards the mean in these physically ill participants may at least in part explain the lack of association.

Conclusion

We found that low mental health status following MI was associated with an increased risk of new cardiovascular events or death. The association was explained partly by cardiac disease severity, physical activity, depression, and anxiety, but low mental health status remained an independent prognostic risk factor. Further research is needed to disentangle the pathways that link mental health status following MI to prognosis and, in continuation hereof, to identify interventions that can improve both mental health status and prognosis.

Contributorship: TJN, and KKL, MV, BC, KSC conceived the study idea and designed the study. KKL collected the data. TJN, and KKL, MV, BC, KSC reviewed the literature. TJN, and KKL, MV, BC, KSC directed the analyses, which were carried out by TJN. All authors participated in the discussion and interpretation of the results. TJN organised the writing and wrote the initial drafts. All authors critically revised the manuscript for intellectual content and approved the final version. TJN is the guarantor.

Funding: The study was supported by the Danish Independent Research Council (grant 12-126032), the Tryg Foundation (grant number 7844-07), the Danish Health Insurance Foundation (grant number 2010B013) and the Lundbeck Foundation. None of the funding sources had a role in the design, conduct, analysis, or reporting of the study.

Competing interests: All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: TJN had financial support from the Danish Independent Research Council for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

Ethical approval: Not needed.

Data sharing: No additional data available.

Table 1 | Baseline characteristics of 880 patients with first-time myocardial infarction in 2009 by quartiles[a] of mental health status (Mental Component Summary score from the Short-Form 12 version 2)

Variable[b]	Baseline MCS Score				P Value
	1st Quartile n=220	2nd Quartile n=220	3rd Quartile n=220	4th Quartile n=220	
Self-reported health[e]					
Mental health status (MCS score)[c], mean (range)	28.8 (11.1-37.2)	42.2 (37.2-47.0)	51.0 (47.0-54.5)	57.7 (54.5-60.8)	<.001
HADS-A/D ≥8, No. (%)	152 (69.7)	79 (36.07)	22 (10.0)	2 (0.91)	<.001
Socio-demographic characteristics					
Age, y, mean (SD)	68.9 (12.4)	68.4 (12.3)	65.6 (11.2)	64.5 (10.0)	<.001
Male sex, No. (%)	120 (54.6)	138 (62.7)	177 (80.5)	173 (78.6)	<.001
Cohabitation status, living alone, No. (%)[d]	94 (42.7)	82 (37.3)	55 (25.0)	47 (21.4)	<.001
Education, No. (%)[d]					
<10 years	114 (53.3)	105 (50.2)	85 (39.7)	76 (35.5)	
10-12 years	76 (35.5)	81 (38.8)	99 (46.3)	101 (47.2)	
>12 years	24 (11.2)	23 (11.0)	30 (14.0)	37 (173)	.004
Labour market status, No. (%)[d]					
Working	50 (22.7)	70 (31.8)	99 (45.0)	103 (46.8)	
Pension	136 (61.8)	123 (55.9)	105 (47.7)	107 (48.6)	
Out of the work force	34 (15.5)	27 (12.3)	16 (7.3)	10 (4.6)	<.001
Health status[e]					
Body mass index, mean (SD)	26.5 (5.1)	26.3 (4.8)	26.8 (4.5)	26.9 (4.5)	.626
Comorbid conditions, No. (%)[f]					
Hypertension[g]	88 (40.0)	75 (34.1)	54 (24.6)	54 (24.6)	<.001
Stroke	21 (9.6)	16 (7.3)	7 (3.2)	5 (2.3)	.002
TCI	12 (5.5)	3 (1.4)	3 (1.4)	10 (4.6)	.021
Revascularization	37 (16.8)	16 (7.3)	12 (5.5)	15 (6.8)	<.001
Heart failure	16 (7.3)	4 (1.8)	4 (1.8)	4 (1.8)	<.001
Diabetes mellitus	51 (23.2)	38 (17.3)	24 (10.9)	21 (9.6)	<.001
Depression[h]	44 (20.0)	21 (9.6)	11 (5.0)	9 (4.1)	<.001
Cardiac disease severity[e]					
MRC dyspnea score ≥3, No. (%)	110 (50.2)	45 (20.5)	21 (9.6)	3 (1.4)	<.001
Medication use, No. (%)[e]					
Aspirin	166 (75.5)	168 (76.4)	173 (78.6)	186 (84.6)	.086
Clopidogrel	159 (72.3)	164 (74.6)	173 (78.6)	184 (83.6)	.025
β-blocker	174 (79.1)	181 (82.3)	178 (80.9)	180 (81.8)	.837
Statin	169 (76.8)	184 (83.6)	190 (86.4)	195 (88.6)	.005
ACE-inhibitors/AT-II-receptor block	111 (50.5)	111 (50.5)	107 (48.6)	100 (45.5)	.689
Furosemide/Aldosterone antagonist	93 (42.3)	64 (29.1)	35 (15.9)	27 (12.3)	<.001
Antidepressants	53 (24.1)	24 (10.9)	9 (4.1)	8 (3.6)	<.001
Secondary prophylactic medication	146 (66.4)	160 (72.7)	162 (73.6)	166 (75.5)	.163
Potential behavioural mediators[e]					
Alcohol consumption >14/21 units/wk, No. (%)	8 (3.6)	12 (5.5)	8 (3.6)	14 (6.4)	.438
Smoking status, No. (%)					
Current	54 (24.8)	49 (22.4)	44 (20.0)	30 (13.6)	
Past	124 (56.9)	122 (55.7)	121 (55.0)	128 (58.2)	
Never	40 (18.4)	48 (21.9)	55 (25.0)	62 (28.2)	.048
Intake of fruit and vegetables ≥3 portions/d, No. (%)	69 (31.4)	75 (34.1)	86 (39.1)	100 (45.5)	.013
Intake of fish ≥3 times/d, No. (%)	61 (27.7)	78 (35.5)	93 (42.5)	96 (43.8)	.001
Intake of fish oil supplement, No. (%)	57 (25.9)	50 (22.7)	75 (34.1)	69 (31.4)	.035
Physical activity, d/wk, mean (SD)	3.6 (2.8)	5.1 (2.3)	5.3 (2.1)	5.7 (1.8)	<.001
Participation in phase two cardiac rehabilitation[e]	110 (50.2)	119 (54.1)	144 (65.5)	142 (64.8)	.001

Abbreviations: MRC, Medical Research Council; ACE, angiotensin converting enzyme; AT, angiotensin; HADS-A/D, Hospital Anxiety and Depression Scale-Anxiety/Depression; MCS, Mental Component Summary.

[a]1st quartile had the lowest MCS score; 4th quartile had the highest MCS score.

[b]Totals may not sum to their respective totals due to missing data. No variable had more than 3.3% missing data.

[c]Norm-based scoring (1998 U.S. population) using weights derived from confirmatory factor analysis.

[d]Information collected the year before MI (in 2008). [e]Information collected three months after MI. [f]Information collected at the time of MI.

[g]Redeemed prescription for at least two classes of antihypertensive drugs between MI and 180 days before.

[h]Redeemed prescription for antidepressants between MI and 180 days before.

Figure 1 | Kaplan-Meier curves by quartiles of mental health status (Mental Component Summary score from the Short-Form 12 version 2)

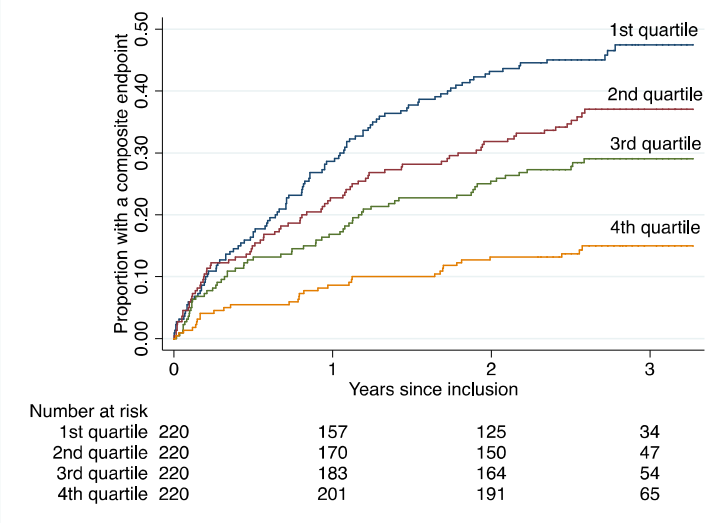


Table 2 | Association between mental health status (Mental Component Summary score from the Short-Form 12 version 2) and subsequent cardiovascular events or death, with sequential adjustment for potential confounders

Adjusted variables[a]	Hazard ratio (95% confidence interval)			
	1st Quartile MCS (102/220)[b]	2nd Quartile MCS (80/220)[b]	3rd Quartile MCS (63/220)[b]	4th Quartile MCS (32/220)[b]
Age	3.53 (2.36 to 5.27)	2.67 (1.77 to 4.03)	2.09 (1.36 to 3.19)	1 (reference)
Socio-demographic characteristics[c]	3.56 (2.35 to 5.38)	2.57 (1.69 to 3.92)	2.06 (1.34 to 3.16)	1 (reference)
MRC dyspnea score ≥3	2.74 (1.76 to 4.26)	2.30 (1.50 to 3.53)	1.96 (1.27 to 3.00)	1 (reference)
Comorbidity[d]	2.65 (1.70 to 4.13)	2.29 (1.50 to 3.51)	1.99 (1.29 to 3.05)	1 (reference)
Secondary prophylactic medication	2.77 (1.78 to 4.31)	2.32 (1.51 to 3.56)	1.95 (1.27 to2.99)	1 (reference)
Smoking status	2.76 (1.76 to 4.31)	2.31 (1.51 to 3.56)	1.96 (1.27 to 3.01)	1 (reference)
Physical activity	2.47 (1.56 to 3.91)	2.25 (1.47 to 3.46)	1.89 (1.23 to 2.91)	1 (reference)
HADS-A/D score ≥8	2.26 (1.37 to 3.73)	2.15 (1.38 to 3.35)	1.87 (1.21 to 2.88)	1 (reference)

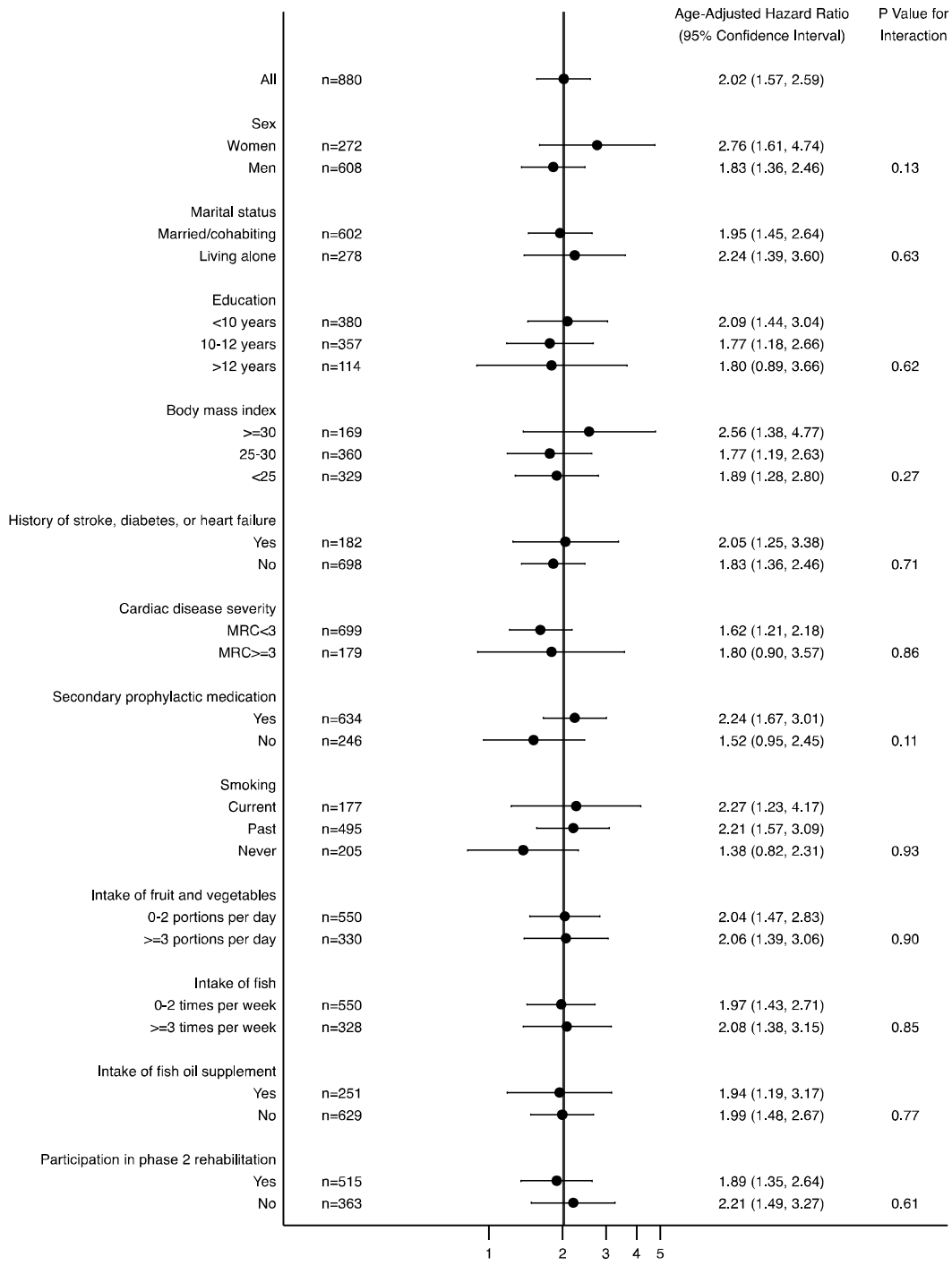
Abbreviations: MCS, Mental Component Summary; HADS-A/D, Hospital Anxiety and Depression Scale-Anxiety/Depression; MRC, Medical Research Council.
[a] Each model includes the variables from the preceding row so that the final model includes all the variables listed in this table.
[b] No. of outcomes/no. of persons in quartile.
[c] Sex, cohabitation status, education, labour market status. [d] History of stroke, diabetes mellitus, or heart failure.

Table 3 | Association between mental health status item scores (continuous; per one point lower item score) and subsequent cardiovascular events or death, with sequential adjustment for potential confounders and mediators

Adjusted variables[a]	Hazard ratio (95% confidence interval)					
	Vitality	Role-Emotional 1	Role-Emotional 2	Social Functioning	Mental Health 1	Mental Health 2
Age	1.41 (1.27 to 1.56)	1.29 (1.18 to 1.41)	1.26 (1.15 to 1.37)	1.23 (1.12 to 1.35)	1.31 (1.18 to 1.46)	1.21 (1.09 to 1.35)
Socio-demographic characteristics[b]	1.41 (1.26 to 1.57)	1.31 (1.19 to 1.43)	1.28 (1.17 to 1.41)	1.21 (1.10 to 1.34)	1.33 (1.19 to 1.48)	1.21 (1.08 to1.36)
MRC dyspnea score ≥3	1.30 (1.16 to 1.47)	1.21 (1.10 to 1.34)	1.18 (1.07 to 1.31)	1.12 (1.01 to 1.24)	1.24 (1.11 to 1.40)	1.11 (0.98 to 1.25)
Comorbidity[c]	1.28 (1.14 to 1.44)	1.21 (1.09 to 1.33)	1.16 (1.05 to 1.28)	1.10 (0.99 to 1.22)	1.25 (1.11 to 1.40)	1.11 (0.98 to 1.25)
Secondary prophylactic medication	1.31 (1.17 to 1.48)	1.22 (1.11 to 1.35)	1.18 (1.07 to 1.31)	1.12 (1.01 to 1.24)	1.24 (1.11 to 1.40)	1.11 (0.98 to 1.25)
Smoking status	1.31 (1.17 to 1.48)	1.22 (1.10 to 1.34)	1.18 (1.06 to 1.30)	1.12 (1.00 to 1.24)	1.25 (1.11 to 1.41)	1.11 (0.98 to 1.25)
Physical activity	1.27 (1.13 to 1.44)	1.18 (1.07 to 1.31)	1.14 (1.03 to 1.27)	1.08 (0.97 to 1.21)	1.22 (1.09 to 1.38)	1.07 (0.95 to 1.21)
HADS-A/D score ≥8	1.24 (1.09 to 1.42)	1.16 (1.04 to 1.29)	1.11 (0.99 to 1.24)	1.03 (0.91 to 1.16)	1.19 (1.04 to 1.35)	1.00 (0.87 to 1.16)

Abbreviations: HADS-A/D, Hospital Anxiety and Depression Scale-Anxiety/Depression. MRC, Medical Research Council.
[a] Each model includes the variables from the preceding row so that the final model includes all the variables listed in this table.
[b] Sex, cohabitation status, education, labour market status. [c] History of stroke, diabetes mellitus, or heart failure.

Figure 2 | Association between baseline mental health status (median cut) and subsequent cardiovascular events or death for patients with myocardial infarction and specific characteristics



WEB EXTRA SUPPLEMENT

Table A | Comparison of participants and non-participants

Variable	Participants (n=880)	Non-participants (n=408)	P Value
Socio-demographic characteristics			
Age, y, mean (SD)	66.8 (11.7)	72.1 (14.7)	<.001
Male sex, No. (%)	608 (69.1)	226 (55.4)	<.001
Cohabitation status, living alone, No. (%)[a]	278 (31.6)	230 (56.4)	<.001
Education, No. (%)[a]			
<10 years	380 (44.7)	206 (58.2)	
10-12 years	357 (42.0)	112 (31.6)	
>12 years	114 (13.4)	36 (10.2)	<.001
Labour market status, No. (%)[a]			
Working	322 (36.6)	75 (18.4)	
Pension	471 (53.5)	283 (69.4)	
Out of the work force	87 (9.9)	50 (12.3)	<.001
Comorbid conditions, No. (%)[b]			
Stroke	49 (5.6)	45 (11.0)	<.001
Revascularization	80 (9.1)	35 (8.6)	.764
Congestive heart failure	28 (3.2)	45 (11.0)	<.001
Diabetes mellitus	134 (15.2)	101 (24.8)	<.001
Depression[c]	85 (9.7)	93 (22.8)	<.001

[a]Information collected the year before MI (in 2008).
[b]Information collected at the time of MI.

Table B | Association between mental health status (Mental Component Summary score from the Short-Form 12 version 2; traditional scoring method) and subsequent cardiovascular events or death, with sequential adjustment for potential confounders

Adjusted variables[a]	Hazard ratio (95% confidence interval)			
	1st quartile MCS (96/220)[b]	2nd quartile MCS (70/220)[b]	3rd quartile MCS (64/225)[b]	4th quartile MCS (47/215)[b]
Age	2.40 (1.69 to 3.40)	1.60 (1.10 to 2.31)	1.40 (0.96 to 2.04)	1 (reference)
Socio-demographic characteristics[c]	2.50 (1.74 to 3.61)	1.62 (1.10 to 2.37)	1.43 (0.97 to 2.11)	1 (reference)
MRC dyspnea score ≥3	1.94 (1.32 to 2.85)	1.49 (1.01 to 2.19)	1.33 (0.90 to 1.97)	1 (reference)
Comorbidity[d]	1.92 (1.30 to 2.83)	1.52 (1.03 to 2.23)	1.40 (0.95 to 2.07)	1 (reference)
Secondary prophylactic medication	1.94 (1.32 to 2.86)	1.49 (1.01 to 2.19)	1.34 (0.91 to 1.98)	1 (reference)
Smoking status	1.93 (1.31 to 2.84)	1.45 (0.99 to 2.14)	1.34 (0.90 to 1.98)	1 (reference)
Physical activity	1.76 (1.19 to 2.62)	1.41 (0.96 to 2.08)	1.32 (0.89 to 1.95)	1 (reference)
HADS-A/D score ≥8	1.57 (1.01 to 2.45)	1.33 (0.89 to 1.99)	1.30 (0.88 to 1.93)	1 (reference)

Abbreviations: MCS, Mental Component Summary; HADS-A/D, Hospital Anxiety and Depression Scale-Anxiety/Depression. MRC, Medical Research Council.
[a] Each model includes the variables from the preceding row so that the final model includes all the variables listed in this table.
[b] No. of outcomes/no. of persons in quartile.
[c] Sex, cohabitation status, education, labour market status. [d] History of stroke, diabetes mellitus, or heart failure.

Table C | Stratified analysis for those without depression and anxiety, n=622. Association between mental health status (Mental Component Summary score from the Short-Form 12 version 2) and subsequent cardiovascular events or death, with sequential adjustment for potential confounders and mediators

Adjusted variables[a]	Hazard ratio (95% confidence interval)			
	1st quartile MCS (63/155)[b]	2nd quartile MCS (48/156)[b]	3rd quartile MCS (38/154)[b]	4th quartile MCS (19/157)[b]
Age	3.39 (2.01 to 5.73)	2.63 (1.55 to 4.49)	2.20 (1.27 to 3.81)	1 (reference)
Socio-demographic characteristics[c]	3.49 (2.04 to 5.98)	2.59 (1.51 to 4.44)	2.05 (1.17 to 3.56)	1 (reference)
MRC dyspnea score ≥3	3.15 (1.81 to 5.48)	2.45 (1.42 to 4.22)	2.00 (1.15 to 3.48)	1 (reference)
Comorbidity[d]	3.03 (1.74 to 5.29)	2.44 (1.42 to 4.19)	1.91 (1.10 to 3.34)	1 (reference)
Secondary prophylactic medication	3.22 (1.85 to 5.59)	2.44 (1.42 to 4.20)	2.02 (1.16 to 3.52)	1 (reference)
Smoking status	3.13 (1.79 to 5.46)	2.52 (1.46 to 4.33)	1.99 (1.14 to 3.46)	1 (reference)
Physical activity	3.03 (1.72 to 5.34)	2.49 (1.44 to 4.29)	1.97 (1.13 to 3.43)	1 (reference)

Abbreviations: MCS, Mental Component Summary; MRC, Medical Research Council.
[a] Each model includes the variables from the preceding row so that the final model includes all the variables listed in this table.
[b] No. of outcomes/no. of persons in quartile.
[c] Sex, cohabitation status, education, labour market status. [d] History of stroke, diabetes mellitus, or heart failure.

eFigure 1 | The 6 mental health status items from the Short-Form 12 version 2

4. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?
a. Accomplished less than you would like.
b. Did work or other activities less carefully than usual.

6. These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the past 4 weeks…
a. Have you felt calm and peaceful?
b. Did you have a lot of energy?
c. Have you felt downhearted and depressed?

7. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting friends, relatives, etc.)?

The options for all of the items are:
All of the time, most of the time, some of the time, a little of the time, none of the time.

4a: Role-Emotional item 1.
4b: Role-Emotional item 2.
6a: Mental Health item 1.
6b: Vitality.
6c: Mental Health item 2.
7: Social Functioning.

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Mental health status and risk of new cardiovascular events or death in patients with myocardial infarction: a population-based cohort study

Tine Jepsen Nielsen, Mogens Vestergaard, Bo Christensen, Kaj Sparle Christensen, Karen Kjær Larsen

Section for General Medical Practice, Aarhus University, Bartholins Allé 2, 8000 Aarhus C, Denmark
Tine Jepsen Nielsen
Junior research fellow

Section for General Medical Practice and Research Unit for General Practice, Aarhus University, Bartholins Allé 2, 8000 Aarhus C, Denmark
Mogens Vestergaard
Professor

Section for General Medical Practice, Aarhus University, Bartholins Allé 2, 8000 Aarhus C, Denmark
Bo Christensen
Professor

Research Unit for General Practice, Aarhus University, Bartholins Allé 2, 8000 Aarhus C, Denmark
Kaj Sparle Christensen
Senior researcher

Section for General Medical Practice and Research Unit for General Practice, Aarhus University, Bartholins Allé 2, 8000 Aarhus C, Denmark
Karen Kjær Larsen
PhD fellow

Correspondence to: TJ Nielsen. E-mail: tjn@folkesundhed.au.dk

ARTICLE SUMMARY

Article focus

- Myocardial infarction (MI) is often followed by mental health problems such as depression, anxiety, and low mental health status.
- Mounting evidence indicates that depression and anxiety after MI increase the risk of adverse long-term outcome. No previous studies have examined the association between mental health status after MI and outcome, independent of depression and anxiety.
- This study examines the association between mental health status after first-time MI and new cardiovascular events or death, when taking into account depression and anxiety as well as clinical, socio-demographic, and behavioural risk factors.

Key messages

- During three years after the MI, patients with the lowest mental health status had an almost 50% risk of new cardiovascular events or death.
- Low mental health status after MI was a strong predictor of new cardiovascular events or death, independent of depression, anxiety and clinical, socio-demographic, and behavioural risk factors.

Strengths and limitations of this study

- Major strengths of this study are its population-based nature and the homogenous study population. The response rate was reasonably high, and information on outcome was collected without loss to follow-up.
- We were able to take into account important mediators such as depression, anxiety, and potential behavioural mediators such as physical activity. However, we cannot rule out the possibility of residual confounding.

Abstract

Objective To examine the association between mental health status after first-time myocardial infarction (MI) and new cardiovascular events or death, taking into account depression and anxiety as well as clinical, socio-demographic, and behavioural risk factors.

Design Population-based cohort study based on questionnaires and nationwide registries. Mental health status was assessed three months after the MI using the Mental Component Summary score from the Short-Form 12 version 2.

Setting Central Denmark Region.

Participants All patients hospitalised with first-time MI from 1 January 2009 through 31 December 2009 (n=880). The participants were categorised in quartiles according to level of mental health status (1st quartile=lowest mental health status).

Main outcome measures Composite endpoint of new cardiovascular events (MI, heart failure, stroke/transient ischaemic attack) and all-cause mortality.

Results During 1,940 person-years of follow-up, 277 persons experienced a new cardiovascular event or died. The cumulative incidence following three years after the MI increased consistently with decreasing mental health status and was 15.0% (95% confidence interval 10.8% to 20.5%) for persons in the fourth quartile 29.1% (23.5% to 35.6%) in the third quartile, 37.0% (30.9% to 43.9%) in the second quartile, and 47.5% (40.9% to 54.5%) in the first quartile. The hazard ratios (HR) were high, even after adjustments for age, socio-demographic characteristics, cardiac disease severity, comorbidity, secondary prophylactic medication, smoking status, physical activity, depression, and anxiety ($HR_{3rd\ quartile}$ 1.90 (95% confidence interval 1.23 to 2.93), $HR_{2nd\ quartile}$ 2.14 (1.37 to 3.33), $HR_{1st\ quartile}$ 2.23 (1.35 to 3.68) when using the fourth quartile as reference).

Conclusions Low mental health status following first-time MI was independently associated with an increased risk of new cardiovascular events or death. Further research is needed to disentangle the pathways that link mental health status following MI to prognosis and to identify interventions that can improve both mental health status and prognosis.

INTRODUCTION

Myocardial infarction (MI) is a severe life event followed by an increased risk of mental health problems such as depression,[1] anxiety,[2] and low mental health status.[3] Several studies have shown that depression[4] and anxiety[2] after MI is associated with a higher risk of cardiovascular events and death, but much less is known about the impact of broader measures of mental health. Mental health status is a generic and broad measure of mental health, which may be useful as a tool to quantify important prognostic aspects of mental health not captured by the more disease-specific measures of depression and anxiety. Four studies[5-8] have investigated the association between mental health status following MI and prognosis. All these have found that low mental health status was significantly associated with increased risk of adverse outcome, independent of clinical risk factors. However, since none of the former studies adjusted for depression or anxiety, it remains unknown whether mental health status in itself adds unique knowledge about the prognosis.

Our aim was to examine the association between mental health status and new cardiovascular events or death in patients with first-time MI when taking into account depression, anxiety, and clinical, socio-demographic, and behavioural risk factors.

METHODS

We conducted a population-based cohort study comprising people in the Central Denmark Region (1,250,000 inhabitants) with a first-time MI based on data from nationwide registers and questionnaires.

Participants

We consecutively invited all patients discharged from hospital with a first-time MI from 1 January 2009 to 31 December 2009. The establishment of the cohort is described in detail elsewhere.[9] Data on patients discharged with MI (in accordance with the International Classification of Diseases (ICD-10) code I21)[10] were received from the Danish National Patient Register on a monthly basis. Patients who had been discharged with MI between 1994 and 2008 were excluded to identify first-time cases. Information on name, address, and vital status was obtained from the Civil Registration System,[11] which also provided the unique personal identification number used to link data between the registers and questionnaires.

Data collection

A pilot-tested hard-copy questionnaire was sent to all participants 12 to 14 weeks after their discharge from hospital, and non-responders received two reminders.[9] The study was approved by the Danish Data Protection Agency (J.nr. 2009-41-3018), the Scientific Research Evaluation Committee of the Danish Academy of General Practitioners (ref. no. 03-2009), and written informed consent was obtained from all participants.

Mental health status

Mental health status was measured using the Mental Component Summary (MCS) score from the validated Danish version of the Short-Form 12 version 2 Health Survey (SF-12).[12-14] The SF-12 consists of 12 items, the MCS score comprises mainly of the six mental items ('Vitality', 'Role-Emotional' (2 items), 'Social Function', and 'Mental Health' (2 items)), but the six physical items are also included in the computation.[12] The SF-12 scores were calculated following the norm-based scoring algorithm[12] using weights derived from confirmatory factor analysis.[15] The MCS score is thus linearly transformed in a way that allows comparison with the mean score (50) and the standard deviation (SD) (10) in the general US population in 1998.[12] The MCS has demonstrated good construct validity.[15] The wording of the mental health status items can be found in the supplemental material (**eFigure 1**).

Depression and anxiety

We assessed depression and anxiety symptoms using the Hospital Anxiety and Depression Scale (HADS).[16] The participants were categorised as having anxiety or depression if they had a score of ≥8 on the HADS-A scale or the HADS-D scale. The HADS was designed to be valid in clinical populations with symptoms of physical disease and hence leaves out items that may be endorsed by physical rather than mental states.[16, 17] The HADS has formerly been validated in MI patients[18, 19] and has proven to have satisfactory reliability (HADS-A and HADS-D Cronbach's $\alpha \approx 0.80$).[18, 20] Among MI patients, a HADS-D≥8 identified possible cases of depression with a sensitivity of 65% and a specificity of 90% (compared with a diagnosis of depression based on a Structured Clinical Interview for DSM-IV).[19] Among acute coronary syndrome patients, a HADS-A≥8 identified possible cases of anxiety with a sensitivity of 91% and a specificity of 61% (compared with a diagnosis of generalised anxiety disorder based on a Structured Clinical Interview for DSM-IV).[21]

Co-morbidity and cardiac disease severity

Information on co-morbidity was retrieved from the Danish National Patient Register, [22] the Danish National Diabetes Register, [23] and the prescription database covering the entire Central Denmark Region. [24] The Danish National Patient Register provided information on stroke (ICD-10: I61, I63, I64), transient cerebral ischemic attack (ICD-10: DG45, DG46), heart failure (ICD-10: I11.0, I13.0, I13.2, I42.0, I42.6, I42.7, I42.9, I50.0, I50.1, I50.9), and revascularization (ICD-10: KFN, KFW) from 1994 to 2008. The Danish National Diabetes Register provided information on diabetes mellitus from 1990 to 2008 according to an algorithm developed on the basis of information from four nationwide registers. [23] The prescription database provided information on all reimbursed drugs according to the Anatomical Therapeutic Chemical Classification System (ATC), dispensing dates, and the total number of tablets dispensed. Participants were categorised with hypertension if they had redeemed prescriptions for at least two classes of antihypertensive drugs (ATC: C02A-D, C02L, C03A-B, C03D-E, C03X, C04, C05, C07, C08, C09) 0 to 180 days before the index MI. Participants were categorised with depression before MI if they had redeemed a prescription for an antidepressant (ATC: N06A) 0 to 180 days before the index MI. Participants were categorised with severe mental disorder if they had redeemed a prescription for antipsychotics (ATC: N05A) 0 to 180 days before the index MI.

Cardiac disease severity was measured by the British Medical Research Council (MRC) dyspnea score, a self-report instrument. [25] A score ≥3 has been shown to provide a simple and valid method for predicting overall mortality.[26]

Health behaviour, health care interventions, and socio-demographics

Data on smoking, alcohol use, physical activity, intake of fruit and vegetables, intake of fish, intake of fish oil supplement, height, and weight (body mass index=weight [kg] per height [m^2]) were self-reported and classified according to the general recommendations from the Danish National Board of Health. [9] To assess physical activity, we asked, "How many days per week are you generally physically active for at least 30 minutes per day? You may include any physical activity at work or in your spare time that makes your pulse rate increase". Response options were from zero days to every day per week. Physical activity was computed as a continuous variable (days/week).

We defined cardiac rehabilitation[27, 28] in the questionnaire and asked whether they had participated in hospital-based phase two cardiac rehabilitation. Those who responded "yes,

and I took part" were classified as 'participants' those who responded "yes, but I didn't take part" or "no" were classified as 'non-participants'. [9]

Drug prescription data were obtained from the prescription database. [24] Data on aspirin (ATC: B01AC06), clopidogrel (ATC: B01AC04), statins (ATC: C10AA), β-blockers (ATC: C07), ACE-inhibitors/angiotensin 2 receptor blockers (ATC: C09), furosemide (ATC: C03C), aldosterone antagonists (ATC: C03D), and antidepressants (ATC: N06A) were collected. We calculated whether the participant had tablets available on the day that we sent the questionnaire (the number of tablets on the last redeemed prescription before the questionnaire was sent ≥ the number of days to the questionnaire was sent) and defined the participant as 'receiving treatment' if tablets were available. We defined the participant as 'receiving secondary prophylactic medication' if the participant was receiving treatment with three or more of the following drugs: aspirin, clopidogrel, statins, and β-blockers. We defined the participant as 'receiving heart failure medication' if the participant was receiving treatment with furosemide or aldosterone antagonists.

Data on age at MI and sex were obtained from the Civil Registration System. [11] Each participant's socio-demographic characteristics (cohabitation status, education, labour market status) from the year before MI (2008) were retrieved from the Danish Integrated Database for Labour Market Research.[29]

Cardiovascular events and death

Outcome events were measured as a composite endpoint comprising new cardiovascular events (MI, heart failure, stroke or transient ischaemic attack) and all-cause mortality. Information on outcomes was collected from baseline (the day we sent the questionnaire) to the last day of follow-up (31 July 2012). The Danish National Patient Register[22] provided information on cardiovascular events. Vital status (dead or alive) was obtained from the Civil Registration System.[11]

Statistical analysis

Neither natural thresholds nor clinically based thresholds are defined for the MCS score, so we divided the participants into quartiles according to their score (1st quartile had the lowest score; 4th quartile had the highest score). This categorisation was done to enhance clinical interpretability and to evaluate a possible dose response relationship.

In order to address the potential risk of selection bias, we used antidepressant consumption as a proxy for depression and calculated hazard ratios (HRs) for the association

between antidepressant consumption and new cardiovascular events or death for both participants and non-participants.

The association between baseline characteristics and MCS score was assessed using $\chi 2$ statistics for categorical variables and analysis of variance for continuous variables, or Kruskal-Wallis tests when the conditions for analysis of variance were not fulfilled.

We calculated the event-free survival time as the time from three months after the MI (baseline evaluation of mental health status) to the first cardiovascular event or death. If no event or death occurred, the participant was censored on 31 July 2012. Two persons emigrated during the time of follow-up, and they were censored on the day of their emigration. Owing to the use of nationwide registers, we had complete follow-up of all participants.

The unadjusted association between mental health status and new cardiovascular events or death was presented graphically with Kaplan-Meier curves. The cumulative incidence three years after the MI was estimated using the cumulative hazards function, and identical incidence was tested using the log-rank test.

The risk of cardiovascular events or death associated with mental health status was compared using Cox proportional hazards regression. The covariates for the multivariate model (age, sex, cohabitation status, education, labour market status, cardiac disease severity, history of stroke, diabetes mellitus, heart failure, secondary prophylactic medication, smoking status, physical activity, depression, and anxiety) were chosen on the basis of previous studies. To check for multicollinearity between depression/anxiety symptoms and mental health status we calculated the variance inflation factor which was 1.5. Values above 10 indicate multicollinearity.[30] We evaluated whether the HRs of mental health status following MI varied by subgroups by testing for interaction using Wald test in an age-adjusted model, and the results are presented in a forest plot. Too few outcome events were available to test for interaction in quartiles, so we tested it in a dichotomised (median cut) model. We excluded variables with less than five events in a subgroup.

Finally, we calculated HRs for the association between each of the mental health status items (continuous; per one-point lower item score) and outcome.

No variable had more than 0.3% missing data, except body mass index (for which 2.5% data were missing) and education (for which 3.3% data were missing), and analyses were done on complete data only. $P<0.05$ was considered statistically significant.

RESULTS

Participant characteristics

Among a total of 1,288 eligible patients with first-time MI, 880 (68.3%) completed the SF-12, and the mean MCS score was 44.9 (SD 11.5). Non-participants were more often women, older, had fewer socioeconomic resources, and more comorbid conditions than participants (Web Extra Supplement Table A). The estimates of the association between antidepressant consumption and new cardiovascular events or death in participants, HR 1.55 (95% confidence interval 1.12 to 2.14) and in non-participants, HR 1.46 (1.01 to 2.10), were similar. Compared to participants with higher mental health status, the participants with the lowest mental health status (1st quartile, table 1) were impaired in a range of variables; e.g. symptoms of depression and anxiety, cardiac disease severity, comorbidity, socioeconomic resources, and health behaviour.

Cumulative incidence

A total of 277 outcomes (230 new cardiovascular events and 47 deaths) occurred during 1,940 person years of follow-up (median 2.6 years, SD 1.0). The Kaplan-Meier curves (figure 1) show that the unadjusted risk of a cardiovascular event or death increased with decreasing mental health status. During three years after the MI, the cumulative incidence of the composite endpoint was 47.5% (95% confidence interval 40.9% to 54.5%) for persons in the first, 37.0% (30.9% to 43.9%) in the second, 29.1% (23.5% to 35.6%) in the third, and 15.0% (10.8% to 20.5%) in the fourth quartile, P<0.001.

Association between mental health status and new cardiovascular events or death

The age-adjusted HRs for new cardiovascular events or death in post-MI patients increased with decreasing mental health status ($HR_{3rd\ quartile}$ 2.09 (95% confidence interval 1.36 to 3.19), $HR_{2nd\ quartile}$ 2.67 (1.77 to 4.03), $HR_{1st\ quartile}$ 3.53 (2.36 to 5.27), table 2). Additional adjustment for cardiac disease severity, physical activity, depression, and anxiety attenuated the association. In the fully adjusted model, the MI patients with the lowest mental health status had a more than two-fold higher risk of new cardiovascular events or death compared to the patients with the highest mental health status (table 2).

We found no statistically significant difference in the HRs between any subgroups of MI patients (figure 2).

Exploratory analysis of the six mental health status items

Table 3 outlines the association between mental health status item scores and subsequent cardiovascular events or death. The items were entered as continuous variables and the HRs reflect the risk of new cardiovascular events or death per one point lower item score. The largest HRs were seen for the 'Vitality' item, HR 1.24 (95% confidence interval 1.09 to 1.42), the 'Mental Health' item 1, HR 1.19 (1.04 to 1.35), and the 'Role-Emotional' item 1, HR 1.16 (1.04 to 1.29).

DISCUSSION

In this population-based cohort study, we found that low mental health status after first-time MI predicted an increased risk of new cardiovascular events or death in a dose-response manner. The association was explained partly by cardiac disease severity, physical activity, depression, and anxiety. However, even after adjustments for these variables, patients with the lowest mental health status had a more than two-fold higher risk of new cardiovascular events or death compared to those with the highest mental health status.

Strengths and limitations of the study

Major strengths of this study are its population-based nature and the homogenous study population; we invited all patients with first-time MI during one year in a well-defined area. Our response rate was reasonably high (68.3%), and information on outcome was collected without loss to follow-up. Non-participants tended to have fewer social resources and more comorbid conditions, and they hence resembled the participants with the lowest mental health status. In order to address the potential risk of selection bias, we used antidepressant consumption as a proxy for depressive symptoms similarly to previous studies.[31] The estimates of the association between antidepressant consumption and new cardiovascular events or death in participants and non-participants were similar. Thus, bias due to selection of study participants seems to be an unlikely explanation for our findings.

Information on MI was registered prospectively and did not rely on the participants' or the relatives' memory. The MI diagnosis in the Danish National Patient Register was based on the current European Society of Cardiology criteria for MI, coded by the physician in charge of the discharge, and the information is known to have a high sensitivity (90%) and specificity (92%).[10] The specificity was even higher in our study because we confirmed the MI diagnosis by reviewing the discharge summaries,[9] and this reduced the risk of information bias. We also

reduced the risk of information bias by using previously translated and validated scales, pilot testing the questionnaire among MI patients, and using high-quality register data.

We used a new algorithm for the calculation of the MCS score from the SF-12 version 2 using weights constructed by oblique confirmatory factor analysis, which allows the physical and mental component summary score to be correlated. Fleishman et al developed this new scoring algorithm[15] due to controversy regarding the traditional scoring algorithm.[32-34] The traditional scoring algorithm forces mental and physical health to be uncorrelated. Consequently, when physical scores are well below the mean and mental scores somewhat less below the mean, as is often the case in patients with physical illness, this scoring method will result in an artifactual migration of the MCS score towards the mean.[32] In sub-analyses, we estimated HRs based on traditionally computed MCS scores (Web Extra Supplement Table B). As expected, they were smaller compared to the HRs based on MCS scores computed with the new scoring algorithm. We evaluated mental health status three months after MI, allowing mental health to reach a more stable level after this major life event.

A diagnosis of depression or anxiety should ideally be based on a diagnostic interview. Since a previous study has estimated the sensitivity of the HADS-D≥8 for identification of depression to be 65% in MI patients,[19] a substantial number of participants with depression may have been misclassified as not having depression. However, we identified 18.3% with depression in our population (HADS-D≥8), which is in keeping with the prevalence of post-MI depression identified by structured clinical interviews in other studies (19.8%).[1] We found no studies reporting on the sensitivity and specificity of the HADS-A in an MI population. However, among acute coronary syndrome patients, a HADS-A≥8 had a sensitivity of 91%.[21] Accordingly, we most likely identified the majority of patients with anxiety. In a sensitivity analysis, we excluded patients with depression or anxiety (HADS-A/D≥8), and this did not weaken the estimates (Web Extra Supplement Table C).

Schizophrenia and bipolar disorder are known to be associated with a higher risk of mortality, and part of this excess risk is attributable to cardiovascular diseases.[35] We used a prescription of antipsychotics, between MI and 180 days before, as an approximation of severe mental disorder. Thirteen participants had redeemed such a prescription. To examine how much of the association could be explained by these patients, we excluded this group in a sensitivity analysis (not shown), and this did not weaken the estimates.

Lifestyle behaviour was self-reported, and participants with low mental health status may have been more likely to underreport adverse lifestyle, including physical inactivity. However, participants with low mental health status did in fact report adverse lifestyle in our study, and

a study on depression[36] found no differences when substituting self-reported physical activity with an objective measure of physical fitness.

Information on a range of participant characteristics and the large sample size allowed us to take into account several potential confounders, such as socio-demographic characteristics, cardiac disease severity, comorbidity, and behavioural factors. In sub-analyses, we adjusted for other potential confounders (body mass index, hypertension, history of depression, antidepressant use, intake of alcohol, fish, and fruit, and participation in phase two cardiac rehabilitation), but this did not change the estimates (≤4%). However, we cannot rule out the possibility of residual confounding.

Comparison with other studies

Four previous studies[5-8] have investigated the association between mental health status after MI and prognosis independent of various clinical risk factors, such as disease severity. They used different measures of mental health status (COOP charts,[6] Quality of Life after MI questionnaire,[8] the World Health Organization Quality of Life Instrument Abbreviated,[7] and SF-12[5]), and they all found an independent association between low mental health status and higher risk of adverse outcomes. Compared with our study, these studies were conducted in modest-sized cohorts (n=112,[6] 375,[8] 145[7]), had short follow-up (four to five months,[6] 18 months[8]), mental health status was assessed up to five years or more after MI,[5, 7] included only women[7] or patients who had an ejection fraction <30%.[5] Most importantly, none of these four MI studies took into account important mediators such as depression, anxiety, and potential behavioural mediators such as physical activity.

Our study is the first to explore the association between mental health status after MI and new cardiovascular events or death in subgroups, and we identified no factors that modified the risk. However, the sample size was low in some of the subgroups.

Our study is also the first to explore the association between mental health status and cardiovascular events or death on an item level. We found that the 'Vitality' item, the 'Role-Emotional' item 1, and the 'Mental Health' item 1 were significantly associated with adverse events after adjustments for clinical, socio-demographic, behavioural, and other psychological risk factors, whereas the remaining items were not. Our results indicate that these items are the most important for the association between mental health status (MCS score) and adverse events. Yet, it is important to keep in mind that the items have different weights and that the physical items are also included when computing the MCS score.[12, 15]

Implications for clinicians

In addition to psychological, social, and functional impairment, clinicians should be aware that low mental health status following MI is associated with an increased risk of new cardiovascular events and death. Our results underline the importance of always considering and prioritising mental health issues in post-MI patients. In this study, we identified low mental health status after MI to be a significant risk factor for poor prognosis, independent of clinical, socio-demographic, behavioural, and other psychological risk factors. In other words, mental health status has incremental value in the identification of patients at elevated risk for adverse outcome. Adding mental health status measurement to our present risk factor armamentarium could help clinicians to distinguish between groups of patients with a very low versus a very high risk of adverse outcome, and thereby help identify vulnerable patients in need of optimised care. However, we do not know whether measurement of mental health status and improved knowledge of prognosis will translate into better outcomes for our patients. This is an important focus for future research in this field.

Possible explanations and future research

This study suggests that mental health status may capture prognostic aspects of mental health which are not captured by measures of depression and anxiety. Further research is needed to clarify more specifically what aspects of mental health that are at play.

The underlying explanation for the association between mental health status after MI and new cardiovascular events or death remains unclear. Our study evaluated cardiac disease severity, behavioural factors, and treatment strategies concurrently with mental health status. We therefore cannot determine whether these factors were the cause or the result of the mental health status. We were unable to assess whether the association was explained by biological mechanisms (such as heart rate variability, platelet function, or inflammatory mechanisms) since we had no information on these biological variables. Future studies should incorporate such biological variables.[37]

Further research is also needed to identify interventions that can improve both mental health status and prognosis in MI patients. Murphy et al[38] examined the effectiveness of a complex intervention designed to improve outcomes, including mental health status (measured with SF-12) for patients with coronary heart disease in a cluster randomised controlled trial. The intervention was "tailored care plans for practices (practice based training in prescribing and behaviour change, administrative support, quarterly newsletter), and tailored care plans for patients (motivational interviewing, goal identification, and target

setting for lifestyle change)." [38] They found that admissions to hospital were significantly reduced after an intensive 18-month intervention to improve outcomes for patients with coronary heart disease, but there was no change in mental health status. It was not stated how they computed the MCS score, but they probably used the traditional scoring algorithm as the study were conducted prior to Fleishman's publication. [15] Hence, artifactual migration of the MCS score towards the mean in these physically ill participants may at least in part explain the lack of association.

Conclusion

We found that low mental health status following MI was associated with an increased risk of new cardiovascular events or death. The association was explained partly by cardiac disease severity, physical activity, depression, and anxiety, but low mental health status remained an independent prognostic risk factor. Further research is needed to disentangle the pathways that link mental health status following MI to prognosis and, in continuation hereof, to identify interventions that can improve both mental health status and prognosis.

Contributorship: TJN, and KKL, MV, BC, KSC conceived the study idea and designed the study. KKL collected the data. TJN, and KKL, MV, BC, KSC reviewed the literature. TJN, and KKL, MV, BC, KSC directed the analyses, which were carried out by TJN. All authors participated in the discussion and interpretation of the results. TJN organised the writing and wrote the initial drafts. All authors critically revised the manuscript for intellectual content and approved the final version. TJN is the guarantor.

Funding: The study was supported by the Danish Independent Research Council (grant 12-126032), the Tryg Foundation (grant number 7844-07), the Danish Health Insurance Foundation (grant number 2010B013) and the Lundbeck Foundation. None of the funding sources had a role in the design, conduct, analysis, or reporting of the study.

Competing interests: All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: TJN had financial support from the Danish Independent Research Council for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

Ethical approval: Not needed.

Data sharing: No additional data available.

Table 1 | Baseline characteristics of 880 patients with first-time myocardial infarction in 2009 by quartiles[a] of mental health status (Mental Component Summary score from the Short-Form 12 version 2)

Variable[b]	Baseline MCS Score				P Value
	1st Quartile n=220	2nd Quartile n=220	3rd Quartile n=220	4th Quartile n=220	
Self-reported health[e]					
Mental health status (MCS score)[c], mean (range)	28.8 (11.1-37.2)	42.2 (37.2-47.0)	51.0 (47.0-54.5)	57.7 (54.5-60.8)	<.001
HADS-A/D ≥8, No. (%)	152 (69.7)	79 (36.07)	22 (10.0)	2 (0.91)	<.001
Socio-demographic characteristics					
Age, y, mean (SD)	68.9 (12.4)	68.4 (12.3)	65.6 (11.2)	64.5 (10.0)	<.001
Male sex, No. (%)	120 (54.6)	138 (62.7)	177 (80.5)	173 (78.6)	<.001
Cohabitation status, living alone, No. (%)[d]	94 (42.7)	82 (37.3)	55 (25.0)	47 (21.4)	<.001
Education, No. (%)[d]					
<10 years	114 (53.3)	105 (50.2)	85 (39.7)	76 (35.5)	
10-12 years	76 (35.5)	81 (38.8)	99 (46.3)	101 (47.2)	
>12 years	24 (11.2)	23 (11.0)	30 (14.0)	37 (173)	.004
Labour market status, No. (%)[d]					
Working	50 (22.7)	70 (31.8)	99 (45.0)	103 (46.8)	
Pension	136 (61.8)	123 (55.9)	105 (47.7)	107 (48.6)	
Out of the work force	34 (15.5)	27 (12.3)	16 (7.3)	10 (4.6)	<.001
Health status[e]					
Body mass index, mean (SD)	26.5 (5.1)	26.3 (4.8)	26.8 (4.5)	26.9 (4.5)	.626
Comorbid conditions, No. (%)[f]					
Hypertension[g]	88 (40.0)	75 (34.1)	54 (24.6)	54 (24.6)	<.001
Stroke	21 (9.6)	16 (7.3)	7 (3.2)	5 (2.3)	.002
TCI	12 (5.5)	3 (1.4)	3 (1.4)	10 (4.6)	.021
Revascularization	37 (16.8)	16 (7.3)	12 (5.5)	15 (6.8)	<.001
Heart failure	16 (7.3)	4 (1.8)	4 (1.8)	4 (1.8)	<.001
Diabetes mellitus	51 (23.2)	38 (17.3)	24 (10.9)	21 (9.6)	<.001
Depression[h]	44 (20.0)	21 (9.6)	11 (5.0)	9 (4.1)	<.001
Cardiac disease severity[e]					
MRC dyspnea score ≥3, No. (%)	110 (50.2)	45 (20.5)	21 (9.6)	3 (1.4)	<.001
Medication use, No. (%)[e]					
Aspirin	166 (75.5)	168 (76.4)	173 (78.6)	186 (84.6)	.086
Clopidogrel	159 (72.3)	164 (74.6)	173 (78.6)	184 (83.6)	.025
β-blocker	174 (79.1)	181 (82.3)	178 (80.9)	180 (81.8)	.837
Statin	169 (76.8)	184 (83.6)	190 (86.4)	195 (88.6)	.005
ACE-inhibitors/AT-II-receptor block	111 (50.5)	111 (50.5)	107 (48.6)	100 (45.5)	.689
Furosemide/Aldosterone antagonist	93 (42.3)	64 (29.1)	35 (15.9)	27 (12.3)	<.001
Antidepressants	53 (24.1)	24 (10.9)	9 (4.1)	8 (3.6)	<.001
Secondary prophylactic medication	146 (66.4)	160 (72.7)	162 (73.6)	166 (75.5)	.163
Potential behavioural mediators[e]					
Alcohol consumption >14/21 units/wk, No. (%)	8 (3.6)	12 (5.5)	8 (3.6)	14 (6.4)	.438
Smoking status, No. (%)					
Current	54 (24.8)	49 (22.4)	44 (20.0)	30 (13.6)	
Past	124 (56.9)	122 (55.7)	121 (55.0)	128 (58.2)	
Never	40 (18.4)	48 (21.9)	55 (25.0)	62 (28.2)	.048
Intake of fruit and vegetables ≥3 portions/d, No. (%)	69 (31.4)	75 (34.1)	86 (39.1)	100 (45.5)	.013
Intake of fish ≥3 times/d, No. (%)	61 (27.7)	78 (35.5)	93 (42.5)	96 (43.8)	.001
Intake of fish oil supplement, No. (%)	57 (25.9)	50 (22.7)	75 (34.1)	69 (31.4)	.035
Physical activity, d/wk, mean (SD)	3.6 (2.8)	5.1 (2.3)	5.3 (2.1)	5.7 (1.8)	<.001
Participation in phase two cardiac rehabilitation[e]	110 (50.2)	119 (54.1)	144 (65.5)	142 (64.8)	.001

Abbreviations: MRC, Medical Research Council; ACE, angiotensin converting enzyme; AT, angiotensin; HADS-A/D, Hospital Anxiety and Depression Scale-Anxiety/Depression; MCS, Mental Component Summary.

[a]1st quartile had the lowest MCS score; 4th quartile had the highest MCS score.

[b]Totals may not sum to their respective totals due to missing data. No variable had more than 3.3% missing data.

[c]Norm-based scoring (1998 U.S. population) using weights derived from confirmatory factor analysis.

[d]Information collected the year before MI (in 2008). [e]Information collected three months after MI. [f]Information collected at the time of MI.

[g]Redeemed prescription for at least two classes of antihypertensive drugs between MI and 180 days before.

[h]Redeemed prescription for antidepressants between MI and 180 days before.

Figure 1 | Kaplan-Meier curves by quartiles of mental health status (Mental Component Summary score from the Short-Form 12 version 2)

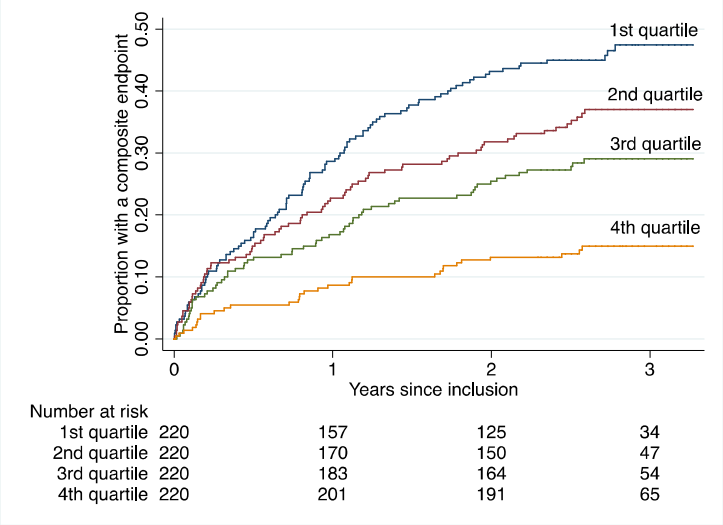


Table 2 | Association between mental health status (Mental Component Summary score from the Short-Form 12 version 2) and subsequent cardiovascular events or death, with sequential adjustment for potential confounders

Adjusted variables[a]	Hazard ratio (95% confidence interval)			
	1st Quartile MCS (102/220)[b]	2nd Quartile MCS (80/220)[b]	3rd Quartile MCS (63/220)[b]	4th Quartile MCS (32/220)[b]
Age	3.53 (2.36 to 5.27)	2.67 (1.77 to 4.03)	2.09 (1.36 to 3.19)	1 (reference)
Socio-demographic characteristics[c]	3.56 (2.35 to 5.38)	2.57 (1.69 to 3.92)	2.06 (1.34 to 3.16)	1 (reference)
MRC dyspnea score ≥3	2.74 (1.76 to 4.26)	2.30 (1.50 to 3.53)	1.96 (1.27 to 3.00)	1 (reference)
Comorbidity[d]	2.65 (1.70 to 4.13)	2.29 (1.50 to 3.51)	1.99 (1.29 to 3.05)	1 (reference)
Secondary prophylactic medication	2.77 (1.78 to 4.31)	2.32 (1.51 to 3.56)	1.95 (1.27 to2.99)	1 (reference)
Smoking status	2.76 (1.76 to 4.31)	2.31 (1.51 to 3.56)	1.96 (1.27 to 3.01)	1 (reference)
Physical activity	2.47 (1.56 to 3.91)	2.25 (1.47 to 3.46)	1.89 (1.23 to 2.91)	1 (reference)
HADS-A/D score ≥8	2.26 (1.37 to 3.73)	2.15 (1.38 to 3.35)	1.87 (1.21 to 2.88)	1 (reference)

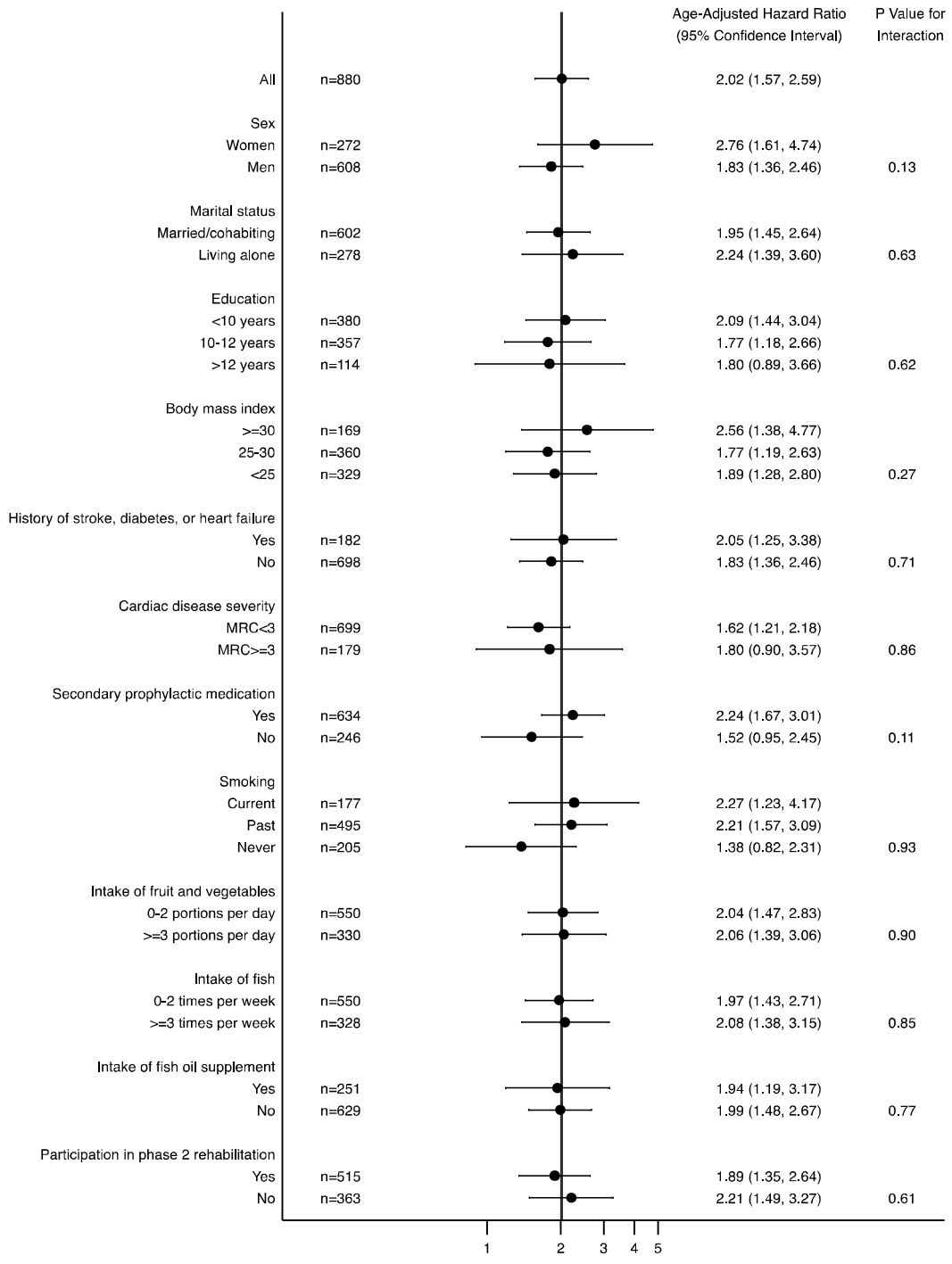
Abbreviations: MCS, Mental Component Summary; HADS-A/D, Hospital Anxiety and Depression Scale-Anxiety/Depression; MRC, Medical Research Council.
[a] Each model includes the variables from the preceding row so that the final model includes all the variables listed in this table.
[b] No. of outcomes/no. of persons in quartile.
[c] Sex, cohabitation status, education, labour market status. [d] History of stroke, diabetes mellitus, or heart failure.

Table 3 | Association between mental health status item scores (continuous; per one point lower item score) and subsequent cardiovascular events or death, with sequential adjustment for potential confounders and mediators

Adjusted variables[a]	Hazard ratio (95% confidence interval)					
	Vitality	Role-Emotional 1	Role-Emotional 2	Social Functioning	Mental Health 1	Mental Health 2
Age	1.41 (1.27 to 1.56)	1.29 (1.18 to 1.41)	1.26 (1.15 to 1.37)	1.23 (1.12 to 1.35)	1.31 (1.18 to 1.46)	1.21 (1.09 to 1.35)
Socio-demographic characteristics[b]	1.41 (1.26 to 1.57)	1.31 (1.19 to 1.43)	1.28 (1.17 to 1.41)	1.21 (1.10 to 1.34)	1.33 (1.19 to 1.48)	1.21 (1.08 to1.36)
MRC dyspnea score ≥3	1.30 (1.16 to 1.47)	1.21 (1.10 to 1.34)	1.18 (1.07 to 1.31)	1.12 (1.01 to 1.24)	1.24 (1.11 to 1.40)	1.11 (0.98 to 1.25)
Comorbidity[c]	1.28 (1.14 to 1.44)	1.21 (1.09 to 1.33)	1.16 (1.05 to 1.28)	1.10 (0.99 to 1.22)	1.25 (1.11 to 1.40)	1.11 (0.98 to 1.25)
Secondary prophylactic medication	1.31 (1.17 to 1.48)	1.22 (1.11 to 1.35)	1.18 (1.07 to 1.31)	1.12 (1.01 to 1.24)	1.24 (1.11 to 1.40)	1.11 (0.98 to 1.25)
Smoking status	1.31 (1.17 to 1.48)	1.22 (1.10 to 1.34)	1.18 (1.06 to 1.30)	1.12 (1.00 to 1.24)	1.25 (1.11 to 1.41)	1.11 (0.98 to 1.25)
Physical activity	1.27 (1.13 to 1.44)	1.18 (1.07 to 1.31)	1.14 (1.03 to 1.27)	1.08 (0.97 to 1.21)	1.22 (1.09 to 1.38)	1.07 (0.95 to 1.21)
HADS-A/D score ≥8	1.24 (1.09 to 1.42)	1.16 (1.04 to 1.29)	1.11 (0.99 to 1.24)	1.03 (0.91 to 1.16)	1.19 (1.04 to 1.35)	1.00 (0.87 to 1.16)

Abbreviations: HADS-A/D, Hospital Anxiety and Depression Scale-Anxiety/Depression. MRC, Medical Research Council.
[a] Each model includes the variables from the preceding row so that the final model includes all the variables listed in this table.
[b] Sex, cohabitation status, education, labour market status. [c] History of stroke, diabetes mellitus, or heart failure.

Figure 2 | Association between baseline mental health status (median cut) and subsequent cardiovascular events or death for patients with myocardial infarction and specific characteristics



WEB EXTRA SUPPLEMENT

Table A | Comparison of participants and non-participants

Variable	Participants (n=880)	Non-participants (n=408)	P Value
Socio-demographic characteristics			
Age, y, mean (SD)	66.8 (11.7)	72.1 (14.7)	<.001
Male sex, No. (%)	608 (69.1)	226 (55.4)	<.001
Cohabitation status, living alone, No. (%)[a]	278 (31.6)	230 (56.4)	<.001
Education, No. (%)[a]			
<10 years	380 (44.7)	206 (58.2)	
10-12 years	357 (42.0)	112 (31.6)	
>12 years	114 (13.4)	36 (10.2)	<.001
Labour market status, No. (%)[a]			
Working	322 (36.6)	75 (18.4)	
Pension	471 (53.5)	283 (69.4)	
Out of the work force	87 (9.9)	50 (12.3)	<.001
Comorbid conditions, No. (%)[b]			
Stroke	49 (5.6)	45 (11.0)	<.001
Revascularization	80 (9.1)	35 (8.6)	.764
Congestive heart failure	28 (3.2)	45 (11.0)	<.001
Diabetes mellitus	134 (15.2)	101 (24.8)	<.001
Depression[c]	85 (9.7)	93 (22.8)	<.001

[a]Information collected the year before MI (in 2008).
[b]Information collected at the time of MI.

Table B | Association between mental health status (Mental Component Summary score from the Short-Form 12 version 2; traditional scoring method) and subsequent cardiovascular events or death, with sequential adjustment for potential confounders

Adjusted variables[a]	Hazard ratio (95% confidence interval)			
	1st quartile MCS (96/220)[b]	2nd quartile MCS (70/220)[b]	3rd quartile MCS (64/225)[b]	4th quartile MCS (47/215)[b]
Age	2.40 (1.69 to 3.40)	1.60 (1.10 to 2.31)	1.40 (0.96 to 2.04)	1 (reference)
Socio-demographic characteristics[c]	2.50 (1.74 to 3.61)	1.62 (1.10 to 2.37)	1.43 (0.97 to 2.11)	1 (reference)
MRC dyspnea score ≥3	1.94 (1.32 to 2.85)	1.49 (1.01 to 2.19)	1.33 (0.90 to 1.97)	1 (reference)
Comorbidity[d]	1.92 (1.30 to 2.83)	1.52 (1.03 to 2.23)	1.40 (0.95 to 2.07)	1 (reference)
Secondary prophylactic medication	1.94 (1.32 to 2.86)	1.49 (1.01 to 2.19)	1.34 (0.91 to 1.98)	1 (reference)
Smoking status	1.93 (1.31 to 2.84)	1.45 (0.99 to 2.14)	1.34 (0.90 to 1.98)	1 (reference)
Physical activity	1.76 (1.19 to 2.62)	1.41 (0.96 to 2.08)	1.32 (0.89 to 1.95)	1 (reference)
HADS-A/D score ≥8	1.57 (1.01 to 2.45)	1.33 (0.89 to 1.99)	1.30 (0.88 to 1.93)	1 (reference)

Abbreviations: MCS, Mental Component Summary; HADS-A/D, Hospital Anxiety and Depression Scale-Anxiety/Depression. MRC, Medical Research Council.
[a] Each model includes the variables from the preceding row so that the final model includes all the variables listed in this table.
[b] No. of outcomes/no. of persons in quartile.
[c] Sex, cohabitation status, education, labour market status. [d] History of stroke, diabetes mellitus, or heart failure.

Table C | Stratified analysis for those without depression and anxiety, n=622. Association between mental health status (Mental Component Summary score from the Short-Form 12 version 2) and subsequent cardiovascular events or death, with sequential adjustment for potential confounders and mediators

Adjusted variables[a]	Hazard ratio (95% confidence interval)			
	1st quartile MCS (63/155)[b]	2nd quartile MCS (48/156)[b]	3rd quartile MCS (38/154)[b]	4th quartile MCS (19/157)[b]
Age	3.39 (2.01 to 5.73)	2.63 (1.55 to 4.49)	2.20 (1.27 to 3.81)	1 (reference)
Socio-demographic characteristics[c]	3.49 (2.04 to 5.98)	2.59 (1.51 to 4.44)	2.05 (1.17 to 3.56)	1 (reference)
MRC dyspnea score ≥3	3.15 (1.81 to 5.48)	2.45 (1.42 to 4.22)	2.00 (1.15 to 3.48)	1 (reference)
Comorbidity[d]	3.03 (1.74 to 5.29)	2.44 (1.42 to 4.19)	1.91 (1.10 to 3.34)	1 (reference)
Secondary prophylactic medication	3.22 (1.85 to 5.59)	2.44 (1.42 to 4.20)	2.02 (1.16 to 3.52)	1 (reference)
Smoking status	3.13 (1.79 to 5.46)	2.52 (1.46 to 4.33)	1.99 (1.14 to 3.46)	1 (reference)
Physical activity	3.03 (1.72 to 5.34)	2.49 (1.44 to 4.29)	1.97 (1.13 to 3.43)	1 (reference)

Abbreviations: MCS, Mental Component Summary; MRC, Medical Research Council.
[a] Each model includes the variables from the preceding row so that the final model includes all the variables listed in this table.
[b] No. of outcomes/no. of persons in quartile.
[c] Sex, cohabitation status, education, labour market status. [d] History of stroke, diabetes mellitus, or heart failure.

eFigure 1 | The 6 mental health status items from the Short-Form 12 version 2

4. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?
a. Accomplished less than you would like.
b. Did work or other activities less carefully than usual.

6. These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the past 4 weeks…
a. Have you felt calm and peaceful?
b. Did you have a lot of energy?
c. Have you felt downhearted and depressed?

7. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting friends, relatives, etc.)?

The options for all of the items are:
All of the time, most of the time, some of the time, a little of the time, none of the time.

4a: Role-Emotional item 1.
4b: Role-Emotional item 2.
6a: Mental Health item 1.
6b: Vitality.
6c: Mental Health item 2.
7: Social Functioning.

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STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3
Objectives	3	State specific objectives, including any prespecified hypotheses	3
Methods			
Study design	4	Present key elements of study design early in the paper	3-4
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	3-4, 6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	3-4, 6
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	-
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	3-6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	3-6
Bias	9	Describe any efforts to address potential sources of bias	6-7, 9-11
Study size	10	Explain how the study size was arrived at	3
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	4-7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	6-7
		(*b*) Describe any methods used to examine subgroups and interactions	7
		(*c*) Explain how missing data were addressed	7
		(*d*) If applicable, explain how loss to follow-up was addressed	-
		(*e*) Describe any sensitivity analyses	6-7, 10-11
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	3, 8
		(b) Give reasons for non-participation at each stage	3
		(c) Consider use of a flow diagram	3
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	8, 14
		(b) Indicate number of participants with missing data for each variable of interest	7
		(c) Summarise follow-up time (eg, average and total amount)	8
Outcome data	15*	Report numbers of outcome events or summary measures over time	8, 15
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	7-9, 15
		(*b*) Report category boundaries when continuous variables were categorized	14
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	8, 15
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	8, 10-11
Discussion			
Key results	18	Summarise key results with reference to study objectives	9-13
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	9-13
Generalisability	21	Discuss the generalisability (external validity) of the study results	9
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	13

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.