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ORIGINAL RESEARCH

Association of anxiety and recurrent cardiovascular events: investigating different aspects of anxiety

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Aims While elevated levels of anxiety are associated with worse prognosis of cardiovascular disease (CVD), this association may vary between different aspects of anxiety. The aim of this study was to analyse self-reported behavioural, physiological, affective, and cognitive aspects of anxiety and their relation to the risk of recurrent CV events.

Methods and results This prospective cohort study utilized data from the U-CARE Heart trial. Participants ($N = 935$, post myocardial infarction) answered the Hospital Anxiety and Depression Scale (HADS: Anxiety subscale) and the Cardiac Anxiety Questionnaire (CAQ: Fear, Avoidance & Attention subscales). HADS Anxiety reflected physiological aspects, CAQ Fear reflected cognitive and affective aspects, CAQ Avoidance reflected behavioural aspects, and CAQ Attention reflected cognitive aspects of anxiety. Cox regression was used to estimate the risk between anxiety and recurrent major adverse cardiac event (MACE). During the follow-up period (mean 2.9 years), 124 individuals (13%) experienced a specified MACE endpoint. HADS Anxiety and CAQ Total were both associated with increased risk of MACE [hazard ratio (HR) = 1.52, 95% confidence interval (CI): 1.15–2.02 and HR = 1.30, 95% CI: 1.04–1.64, respectively]. Among the CAQ subscales, there was support for an association between Avoidance and risk of MACE (HR = 1.37, 95% CI 1.15–1.64), but not for Attention and Fear.

Conclusion The results support that anxiety is associated with an increased risk of recurrent MACE in post-myocardial infarction patients. The association between anxiety and risk was strong for the aspects of anxiety relating to behaviour and physiology, while the support for an association with cognitive and affective aspects was lacking.

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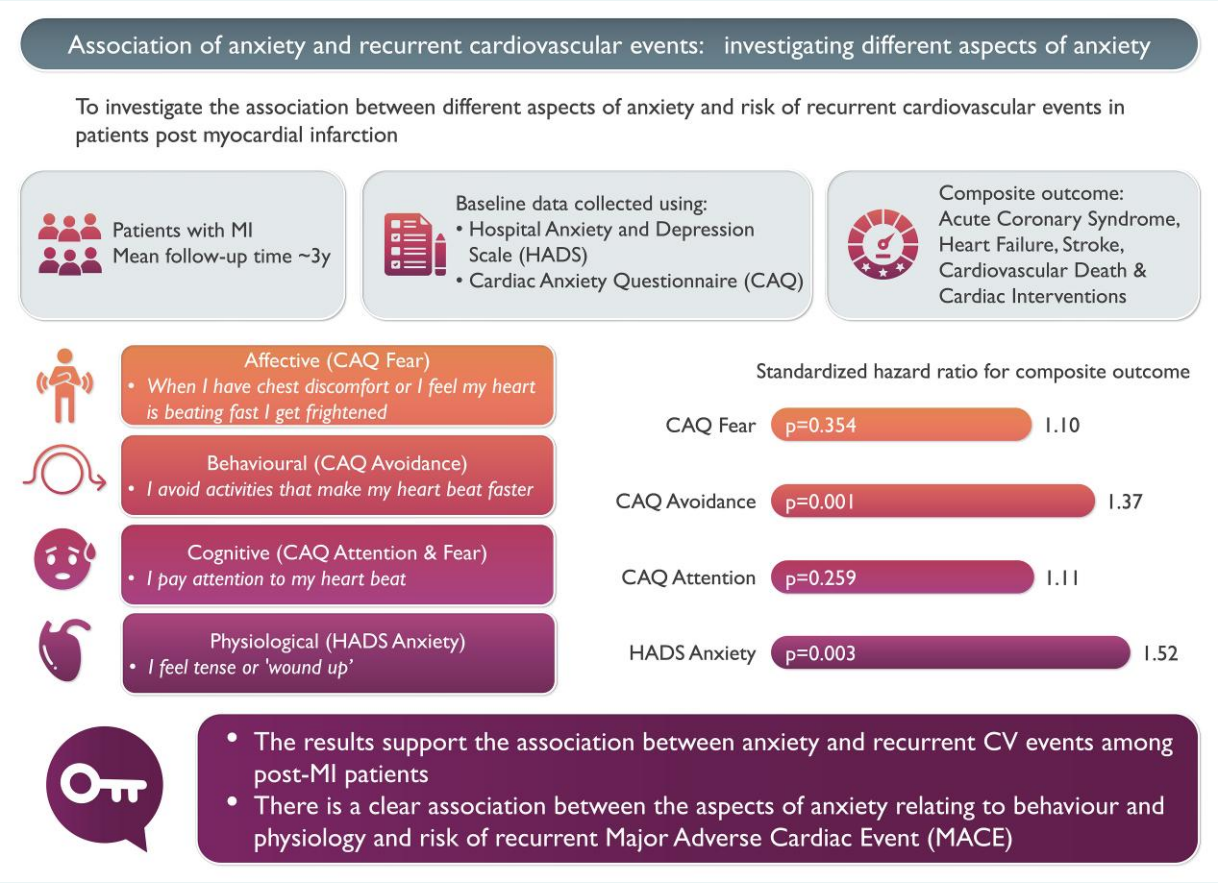
Graphical Abstract



Keywords Anxiety • Aspects • Cardiovascular disease • Morbidity • Myocardial infarction • Recurrent MACE

Novelty

- Considering all phenomenological aspects of anxiety: affective, cognitive, behavioural, and physiological, gives a wider and more comprehensive picture.
- Building on previous research of cardiac anxiety and risk of recurrent cardiovascular (CV) events, with larger sample size, more events and controlling for more CV risk factors, strengthens the evidence base.
- Rigorous consideration of confounding, illustrated with a causal diagram, and complemented by several supplementary analyses, gives transparency and improves clinical utility and replicability.

Introduction

Cardiovascular disease (CVD) is the main cause of mortality worldwide.[1] Among patients with CVD, it is common to observe a higher prevalence of psychological distress, such as anxiety and depression, acting bidirectionally as both risk factors and consequences of CVD.[2] Anxiety as a risk factor has become increasingly investigated, but research has revealed somewhat inconsistent results.[3] Generally, meta-analyses indicate that high levels of anxiety are associated with worse CVD prognosis.[4–9] However, some individual studies indicate no association—or even a reversed relation—between anxiety and morbidity in various cardiac patients.[10–18]

A reason for this may be that anxiety can be defined in various ways. For example, it may refer to either psychiatric disorders or symptom levels, be reported as trait or state anxiety or refer to any of several symptom dimensions. Sometimes, it is defined by the stimulus evoking anxiety, typically different forms of phobias.[19] One such example is cardiac anxiety (CA),[20] which is common among patients both with and without CVD.[21] Cardiac anxiety is not a psychiatric diagnosis but is assessed based on symptom levels on the CA Questionnaire (CAQ), which has three subscales: Fear (CAQ-F), Avoidance (CAQ-Av), and Attention (CAQ-Att).[20,22] The subscales of the CAQ relate to a common way of categorizing anxiety based on phenomenological attributes. For example, in cognitive behaviour therapy, symptoms of anxiety are

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classified in affective, physiological, cognitive, and behavioural subsystems.[23] Regarding the CAQ, the subscale Fear would relate to affective and cognitive symptoms, Avoidance to behavioural symptoms and attention to cognitive symptoms, while no subscale of the CAQ relates to physiological symptoms of anxiety. Assessing physiological symptoms of anxiety (e.g. tightness in the chest, rapid heartbeat, or nausea) in patients with CVD may prove challenging, due to symptom overlap between the conditions.[24] The Hospital Anxiety and Depression Scale (HADS) was designed with this in mind and can be used to assess symptoms of anxiety and depression in the presence of somatic disease.[25] Furthermore, as six out of the seven items on the anxiety scale (HADS-A) contain a component of arousal, reflecting the experience of physiological tension and unease, it would seem adequate in assessing the physiological aspect.

There is both empirical and theoretical support of the notion that different aspects of anxiety relate differently to prognosis of CVD. The theorized pathways between anxiety and CVD are behavioural and physiological.[3] Most risk factors for CVD that also have been associated with anxiety belong to these two categories (e.g. sedentary behaviour, substance abuse, inflammation, dysregulated ANS, etc.).[3,26] Empirically, one study investigated the association between CAQ subscales and risk of recurrent major adverse cardiac events (MACE) after myocardial infarction (MI).[27] They only found evidence for an association between CAQ-Av and recurrent MACE.[27] However, the sample was quite small ($n = 193$), which may have caused associations between risk and other subscales to go undetected.[28] Additionally, this study adjusted for age, gender, previous MI, left ventricular ejection fraction (LVEF), and depressive symptoms in the analyses. There are other known risk factors for CVD that also may be anxiolytic, for example disease markers like hypertension and diabetes,[29–31] sociodemographic factors like education and country of birth[32,33] and social support.[34,35]

While behavioural and physiological pathways are thought to contribute negatively, cognitive aspects of anxiety could possibly be protective against recurrent cardiovascular (CV) events. For example, one study found that CAQ-Att was associated with less smoking, more frequent physical activity and better adherence to cardiac rehabilitation.[21] Still, direct evidence of a protective association between CAQ-Att and risk of MACE is lacking,[27] and more research is needed. Understanding the nuanced connections between anxiety and recurrent CV events is crucial for developing targeted interventions, improving patient quality of life, and refining healthcare practices in CV care.

The aim of this study was to evaluate the association between specific anxiety subscales and the risk of recurrent MACE in post-MI patients. It was hypothesized that symptoms of avoidance and physiological arousal would have a more pronounced relation to the risk of a recurrent MACE than cognitive or affective symptoms.

Methods

Study design and participants

This study is a prospective cohort study, utilizing data from the U-CARE Heart trial. The U-CARE Heart trial was a Swedish multi-centre randomized controlled trial (RCT) evaluating the effect of internet-delivered cognitive behavioural therapy (iCBT) in patients who had a recent MI. All participants of the U-CARE Heart trial had provided informed consent. For further details regarding study design and results, we refer to previous reports.[36,37] Ethical approval was signed by the regional Ethics Committee in Uppsala (2011/217). The choice of a prospective cohort design enabled the longitudinal evaluation of anxiety's impact on cardiovascular events over a span of over 5 years.

Procedure

The current study included 935 participants that were screened for eligibility for the RCT. All screened participants were <75 years of age, had an acute MI within 8–10 weeks before screening, had no language difficulties and were willing to participate online. Participants were recruited during routine follow-up visits in 25 Swedish cardiac clinics from September 2013 to December 2016. Consenting participants were sent an email with a password to a secure internet-based portal where they completed the screening assessment in the time-period of 8–10 weeks after hospital discharge. The screening assessment included a compilation of self-report questionnaires and was conducted before the randomization procedure.[37] Patients who scored >7 on either the depression or anxiety subscale of the HADS were randomized. In total, 239 fulfilled this criterion, and 117 were randomized to treatment. Very weak to no evidence of effectiveness for the treatment was found,[36,37] and treatment adherence was low (7/117 completed more than 1 treatment module).[38]

Measures

Outcome

Mean follow-up time was 2.87 years [standard deviation (SD) ± 1.12] and the longest follow-up period was 5.27 years. Data on CV events and mortality during follow-up were obtained from the Patient Registry and the Cause of Death Registry of the National Board of Health and Welfare in Sweden.[39] This is a high quality registry covering 100% of all deaths that occur in Sweden,[40] except those who may have emigrated. ICD-10 diagnostic codes were used.[41] A composite MACE outcome was created comprising time from the date of the screening assessment to the first occurrence of any of the following diagnoses: CV death (ICD cause of death code I), acute coronary syndrome (ACS) (ICD codes I20, I21, and I22), heart failure (HF) (ICD codes I50 and I11.0), stroke (ICD codes I61, I62, I63, and I64), and coronary revascularization (intervention codes FNG00, FNG02, FNG05, FNG10, and FNC).

Cardiac anxiety questionnaire

The CAQ is a measure of CA.[20] It consists of 18 items rated on a 5-point Likert scale with scores ranging from 0 (never) to 4 (always), where a high score indicates more symptoms. The authors of the questionnaire recommend dividing the score by the number of items,[20] making the total (CAQ-T) and subscale scores range between 0 and 4. Factor analysis has shown it is best supported by a 3-factor structure, with the subscales Fear, Avoidance, and Attention.[22] In our sample, the internal consistency ranged from $\alpha = 0.88$–0.92 for the total score and the subscales Avoidance and Fear, while the subscale Attention had $\alpha = 0.76$.

Hospital anxiety and depression scale

The HADS is used to assess symptoms of anxiety and depression in the presence of comorbid somatic disease.[25] It comprises 14 items (seven for symptoms of anxiety and seven for symptoms of depression). The items are rated on a 4-point Likert scale (range 0–3), with a total score range from 0 to 42 (max 21 on each subscale). A high score indicates more symptoms and a clinical cut-off has been established at >7 on either subscale.[42] The HADS has shown good internal consistency, and around 0.80 sensitivity and specificity rates for anxiety and mood disorders.[42] In our sample, the internal consistency ranged from $\alpha = 0.90$–0.94 for the total score and the subscales.

ENRICHD Social Support Instrument

The ENRICHD Social Support Instrument (ESSI) was developed to measure social support among patients post-MI, and with other chronic illnesses.[43] The questionnaire comprises seven items, where six are scored on a 5-point Likert scale, ranging from 1 (none of the time) to 5 (all the time). Item 7 (living with spouse) is binary and scored 4 for 'yes' and 2 for 'no'. Thus, total score range is 8–34, where a high score indicates more social support.

Sociodemographic characteristics and cardiac risk factors

Self-reported data on sex, age, physical activity, current smoking (yes/no), education level, and country of birth (born in Sweden or not) were collected in a customized questionnaire. Education was reported by four levels (Elementary school, High school, <3 years University, and >3 years University). Being sedentary or at most engaging in light physical activity

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(e.g. yoga or slow walks) during leisure time defined as low physical activity. Data on height, weight, hypertension, diabetes, infarct type (STEMI/NSTEMI), LVEF (≥50%/<50%), and diagnosis of an MI prior to the one qualifying for inclusion to the study were collected from the SWEDEHEART register.[44] Body mass index (BMI) was calculated based on height and weight (kg/m^2), and obesity was defined as a BMI equal to or higher than 30.

Statistical analyses

Stata Software Package (version 18.0) was used to perform most statistical analyses, R (version 4.1.2) was used for the calculation of absolute risk (AR). Group comparisons in descriptive data were analysed with Pearson's χ^2 test. There was between 0.5% and 4% missing data for the CAQ, diabetes, previous MI, hypertension, and infarct type. The variable for LVEF had ∼11.5% missing data. The missing data were determined to be missing at random and multiple imputation was applied, utilizing chained equations with predictive mean matching.[45]

Main analysis

Multivariate Cox regression models were used to estimate the continuous association between anxiety scores and the composite endpoint event. Violations of the proportional hazards assumption were examined by assessing the slopes in the scaled Schoenfeld residuals. Each anxiety scale and subscale was fitted in a separate regression model, together with potentially confounding variables. Variables were determined as confounding if they were hypothesized to have a causal effect on exposure and outcome, and not to be a mediating variable (see supplementary material online, *Figure S1*). These were sociodemographic characteristics (age, sex, education, and country of birth), clinical characteristics (history of MI, hypertension, LVEF, infarct type, and diabetes), and self-reported social support and depressive symptoms. Education was modelled as a categorical variable with four levels: sex, country of birth and clinical characteristics were modelled as binary variables, and social support (ESSI) as a continuous scale variable. We also drew plots of the survival function of each of the anxiety scales and subscales, with survival function of the lines at the 25th, 50th, and 75th percentiles of the respective scale.

For easier comparison of hazard ratios (HR) between the different anxiety measures, the scores of each scale and subscale were converted to a standardized value, where one unit represents 1 SD. Additionally, for facilitation of clinical interpretation of the results, AR was calculated.[46] The AR was calculated based on the cox models by predicting risk at different set values of the anxiety scales (−1SD, mean, +1SD, and +2SD), set at 3 years follow-up time. The covariates were standardized and allowed the same distributions as they have in the dataset.

Sensitivity analyses

Several sensitivity analyses were conducted. First, the main analysis was repeated without multiple imputations. Second, the main analysis was repeated for each individual endpoint, as well as a composite endpoint containing all-cause death. These analyses included all first events of the specific endpoint, regardless if other endpoints had occurred before. Although these analyses have too few events per variable to be sufficiently powered,[47] they provide insight to the contribution of different endpoints. Third, the main analysis was repeated, excluding those who received iCBT ($n = 117$) to provide transparency regarding the potential impact of misclassification of anxiety levels. If other variables than the HADS-A score was affected, it was likely due to treatment interference.

Supplementary analyses

Additional supplementary analyses were conducted to illustrate the following: (i) the unadjusted associations between each covariate and MACE, (ii) correlations between all scales and subscales, and (iii) internal consistency of all scales and subscales, represented with Cronbach's α.

Results

Sample

Data were collected from a total of 935 participants (76% males; mean age 62.2 years). Further baseline characteristics are presented in *Table 1*. In total, 124 patients experienced at least one MACE during the follow-up time. The 124 first events were: CV death = 3 (0.3%), stroke = 8 (0.9%), HF = 31 (3.3%), ACS = 58 (6.2%), and revascularization = 27 (2.9%). Three individuals were diagnosed with HF and ACS as first events on the same day and were only counted once. An additional 4 (<0.01%) individuals died from non-CVD causes.

Main analysis

Unadjusted and adjusted analyses are reported in *Table 2*. When adjusting for the predetermined set of covariates, the estimated HR for the composite CV endpoint was 1.52 [95% confidence interval (CI) 1.15–2.02; $P = 0.003$] for HADS-A, and 1.30 (95% CI 1.04–1.64; $P = 0.021$) for CAQ-T. Among the three CAQ subscales, the estimated HR for the composite CV endpoint was 1.37 (95% CI 1.15–1.64; $P = 0.001$) for CAQ-Av. No evidence for an association was found for the other two subscales ($P = 0.354$ and $P = 0.259$).

The AR for each anxiety scale and subscale is reported in *Table 3*. The risk differences between the mean value and +1 SD were 5.7%-points (%-pt.) for HADS-A, 3.3%-pt. for CAQ-T, 1.3%-pt. for CAQ-F, 4.2%-pt. for CAQ-Av, and 1.1%-pt. for CAQ-Att (for all means and SDs of anxiety scales, see *Table 1*).

Plots of survival functions for each anxiety scale and subscale are presented in *Figure 1*.

Sensitivity analyses

Running the main analysis without multiple imputation led to slight reductions in power, but yielded essentially identical results. Results of analyses of individual endpoint events showed a variation where HF was related to CAQ-Av but not HADS-A, while the opposite was true for ACS (see supplementary material online, *Table S1*). Excluding the treatment group did not change the support for other associations than HADS-A for which the association with MACE was no longer supported (*Table 4*).

Supplementary analyses

See supplementary material online, *Table S2* for crude associations between all covariates and the composite endpoint event. The strongest correlation was found between HADS-A and HADS-D ($\rho = 0.77$) (see supplementary material online, *Table S3*).

Discussion

This prospective cohort study found that self-reported anxiety was associated with increased risk of recurrent MACE in a post-MI population. Investigating anxiety scales separately gave results indicating strong support for the association between the aspects of anxiety assessed with HADS-A and CAQ-Av, and no support for the association between the aspects of anxiety assessed with CAQ-F and CAQ-Att.

To facilitate the interpretation of clinical relevance of the findings, the AR of each anxiety scale and subscale was calculated and presented. As with the HR's, the largest risk differences could be seen for HADS-A and CAQ-Av. Using HADS-A as an example (in this sample: mean = 5, SD = 4.2), the risk for recurrent MACE of an individual with a score of ∼1 point on the HADS-A scale would be 8.8%, while the risk for an individual with a score of ∼13 points would be 26.3%. For reference, 13 points on the HADS-A scale indicates clinical levels of anxiety but is below the threshold for severe anxiety which is >15.[48] With life-time prevalence rates of anxiety disorders being reported at ∼30% in the adult population,[49] screening for these symptoms would both seem reasonable and clinically valuable.

These findings corroborate the results of the previous study by Van Beek *et al.*[27] that CAQ-Av is clearly associated with increased risk of recurrent MACE. Although we adjusted for five additional CVD risk

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Table 1 Background characteristics of subjects

Variable *n* (%)	Total 935 (100)	No MACE 811 (87)	MACE 124 (13)	*P*-value
Age, mean ± SD	62.2 ± 8.1	62.0 ± 8.2	63.8 ± 7.0	0.018
Women, *n* (%)	220 (24)	192 (24)	28 (23)	0.79
Randomized to iCBT, *n* (%)	117 (13)	92 (11)	25 (20)	0.006
Education, *n* (%)				0.54
Elementary school	190 (20)	162 (20)	28 (23)	
High school	349 (37)	308 (38)	41 (33)	
<3 years university	41 (33)	156 (19)	29 (23)	
>3 years university	211 (23)	185 (23)	26 (21)	
Born in Sweden, *n* (%)	846 (90)	736 (91)	110 (89)	0.47
STEMI[f], *n* (%)	393 (42)	343 (42)	50 (40)	0.58
LVEF < 50%[h], *n* (%)	258 (25)	206 (25)	52 (42)	<0.001
Low physical activity[a], *n* (%)	229 (25)	180 (22)	49 (40)	<0.001
Obesity[g], *n* (%)	211 (24)	177 (23)	34 (28)	0.26
Smoking[b], *n* (%)	218 (23)	184 (23)	34 (28)	0.23
Diabetes[d], *n* (%)	142 (16)	111 (14)	31 (25)	0.002
Hypertension[e], *n* (%)	390 (43)	324 (42)	66 (54)	0.012
Previous myocardial infarction[d], *n* (%)	104 (12)	68 (9)	36 (29)	<0.001
Questionnaires, mean ± SD				
HADS anxiety	5.0 ± 4.2	4.9 ± 4.1	6.1 ± 4.6	0.003
HADS depression	3.9 ± 3.7	3.8 ± 3.7	4.5 ± 3.8	0.037
CAQ total[c]	0.9 ± 0.6	0.9 ± 0.6	1.1 ± 0.7	<0.001
CAQ fear[c]	0.9 ± 0.8	0.9 ± 0.8	1.1 ± 0.8	0.034
CAQ avoidance[b]	1.0 ± 0.8	0.9 ± 0.8	1.3 ± 0.9	<0.001
CAQ attention[a]	0.8 ± 0.6	0.7 ± 0.6	0.9 ± 0.7	0.028
ESSI	21.7 ± 4.3	21.7 ± 4.2	21.6 ± 4.9	0.85

MACE or no MACE refers to the endpoint data, i.e. recurrent MACE after hospital admission.
STEMI, ST-elevated myocardial infarction; LVEF, left ventricular ejection fraction; HADS, Hospital Anxiety and Depression Scale; CAQ, Cardiac Anxiety Questionnaire; HADS-A, anxiety subscale; CAQ-T, total score; CAQ-F, fear subscale; CAQ-Av, avoidance subscale; CAQ-Att, attention subscale; ESSI, ENRICHD Social Support Instrument.
[a]1 missing data point.
[b]2 missing data points.
[c]5 missing data points.
[d]31 missing data points.
[e]33 missing data points.
[f]35 missing data points.
[g]49 missing data points.
[h]109 missing data points.

Table 2 Cox regression for composite endpoint

	Crude HR (95% CI)	*P*-value	Adj. HR (95% CI)	*P*-value
HADS anxiety	1.28 (1.09–1.50)	0.003	1.52 (1.15–2.02)	0.003
CAQ total	1.35 (1.16–1.61)	0.002	1.30 (1.04–1.64)	0.021
CAQ fear	1.19 (1.01–1.40)	0.037	1.10 (0.90–1.35)	0.354
CAQ avoidance	1.51 (1.30–1.75)	<0.001	1.37 (1.15–1.64)	0.001
CAQ attention	1.19 (1.01–1.40)	0.033	1.11 (0.92–1.34)	0.259

Each measure of anxiety is adjusted for by age, sex, country of birth, education, social support, depressive symptoms, previous myocardial infarction, infarct type, left ventricular ejection fraction, diabetes, and hypertension. The c-statistic represents each individual model and includes adjusted variables.
HADS, Hospital Anxiety and Depression Scale; CAQ, Cardiac Anxiety Questionnaire; HADS-A, anxiety subscale; CAQ-T, total score; CAQ-F, fear subscale; CAQ-Av, avoidance subscale; CAQ-Att, attention subscale.

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Table 3 Main analysis, absolute risk at 3 years

	−1 SD (%)	Mean (%)	+1 SD (%)	+2 SD (%)
HADS-A	8.8	12.9	18.6	26.3
CAQ-T	10.0	12.6	15.9	19.8
CAQ-F	11.8	12.9	14.2	15.5
CAQ-Av	9.0	12.2	16.3	21.6
CAQ-Att	11.9	13.0	14.1	15.3

Absolute risks are predicted from set values on anxiety scales at 3 years follow-up based on Cox models, covariates age, sex, country of birth, education, social support, depressive symptoms, previous myocardial infarction, infarct type, left ventricular ejection fraction, diabetes, and hypertension.
HADS, Hospital Anxiety and Depression Scale; CAQ, Cardiac Anxiety Questionnaire; HADS-A, anxiety subscale; CAQ-T, total score; CAQ-F, fear subscale; CAQ-Av, avoidance subscale; CAQ-Att, attention subscale.

factors (hypertension, diabetes, education, country of birth, and perceived social support), the association with CAQ-Av remained strong. This association could be seen as support to the theory of behaviour mediating the relationship between anxiety and CVD.[3,26] Having said that, with physical activity being one of the major predictors for CVD risk,[29] and interventions to increase physical activity having shown effective in improving CVD prognosis,[50] far from all individuals engage in physical exercise programmes.[51] Perhaps offering extra support to individuals with anxious avoidance may aid in the engagement of physical activity and improve their mental and physical well-being.

As we found a strong association between HADS-A and risk for recurrent MACE, this could contribute support to the theory of physiological mechanisms mediating the effect of anxiety on CVD.[3] While this study has not directly assessed physiological reactions, self-reported anxiety and objective measures of physiological arousal have previously been found to correlate well.[52] As such, the results can at least be seen as an indication of the theorized association between physiological arousal and CVD.

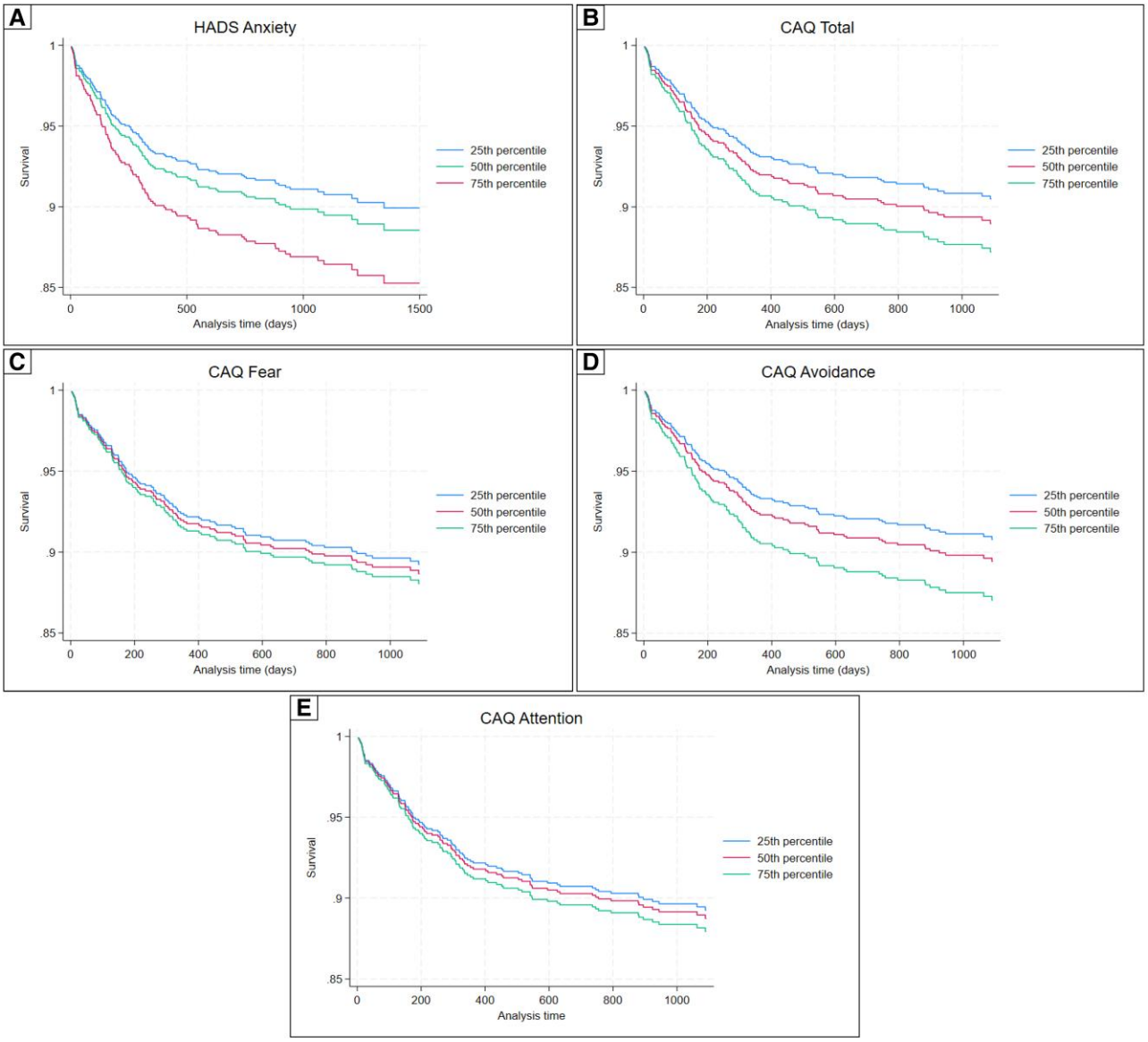

Figure 1 Plot of survival function from main analysis of each anxiety measure. Lines represent survival function at the 25th, 50th, and 75th percentiles of respective anxiety measure. *A*: HADS Anxiety, *B*: CAQ Total, *C*: CAQ Fear, *D*: CAQ Avoidance, *E*: CAQ Attention.

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Table 4 Sensitivity analysis, excluding treatment group

	Adj. HR (95% CI)	*P*-value
HADS-A	1.20 (0.85–1.70)	0.291
CAQ-T	1.28 (0.96–1.63)	0.104
CAQ-F	1.04 (0.81–1.32)	0.765
CAQ-Av	1.35 (1.10–1.65)	0.004
CAQ-Att	1.10 (0.88–1.37)	0.159

Analysis excluding those randomized to iCBT in RCT ($n = 117$). Each measure of anxiety is adjusted for by age, sex, country of birth, education, social support, depressive symptoms, previous myocardial infarction, infarct type, left ventricular ejection fraction, diabetes and hypertension. The c-statistic represents each individual model and includes adjusted variables.
HADS, Hospital Anxiety and Depression Scale; CAQ, Cardiac Anxiety Questionnaire; HADS-A, anxiety subscale; CAQ-T, total score, CAQ-F, fear subscale; CAQ-Av, avoidance subscale; CAQ-Att, attention subscale.

The results regarding CAQ-F and CAQ-Att is also in line with the findings from the previous study of the CAQ and risk of recurrent MACE.[27] Although increasing study power with more participants and CV events, no support for an association could be found with risk of recurrent MACE. Hypothetically, some degree of cognitive anxiety could have a protective effect on CV prognosis, by increasing positive health behaviours.[13,21] While our results cannot support that, it is possible that anxiety assessed through CAQ-Att still in some part acts protectively against recurrent MACE, but the close relation to other aspects of anxiety is cancelling out this effect.

Our study also found that anxiety was a strong predictor of risk, even when controlling for depression. While it has been found that controlling for depression can reduce the risk association between anxiety and MACE,[7] it has often been found that anxiety is a better predictor of CVD prognosis than depression.[53–57] Our study adds to this body of research, highlighting the unique contribution of anxiety to risk of MACE.

Strengths and limitations

We cannot exclude the risk of differential misclassification of exposure status for the patients that received iCBT in the RCT. An effective treatment would lead to an overestimation of exposed individuals and bias the results towards the null. However, the treatment had very poor evidence of effectiveness and very low adherence,[36,37] minimizing the risk of this bias. Furthermore, when excluding treatment group from the analysis, only the HR of HADS-A was notably affected. As all in the treatment group had scored above the clinical cut-off (>7) on one of the HADS subscales, and the strong correlation ($\rho = 0.77$) between the two subscales, this would be expected. Excluding them from the analysis also removes half of the patients with clinical levels of anxiety and/or depression from the study sample.

Although we have made an argument for using HADS-A to represent symptoms of physiological arousal, the scale was not designed for this purpose. It was developed on the basis of Generalized Anxiety Disorder and was not considered in terms of phenomenological aspects.[25] However, that may not be a concern in this context, given the face validity of the HADS-A items as indices of physiological arousal. As has been previously stated, the main concern when choosing an assessment tool is that the content of the items captures the content of interest.[58] Yet, our conclusions are not definitive and more research is needed to further assess the association between arousal and CV events.

Making causal inference from observational studies is difficult. However, based on Hill's criteria of causality, there is reasonable indication that anxiety has an effect on CVD risk and prognosis.[9] Building on this point, psychological treatment for CV health is showing limited efficacy in clinical trials.[59] Tailoring complex interventions, based on specific aspects of anxiety may be more effective in improving patient health. Additionally, regardless of causality, these results indicate that the CAQ and HADS-A could be used to improve detection of high-risk individuals.

Finally, there is still a wide array of expressions and divisions of anxiety and triggering situations that are not covered in this study. It would be interesting for future studies to consider the aspects studied here in relation to a wider context, adding more pieces to the puzzle.

Conclusion

This study adds further argument that self-reported anxiety, independent of self-reported depression, is associated with the risk of recurrent MACE in post-MI patients. In addition, examining various anxiety measures, support was found for an association to risk and the scales assessing avoidance and arousal. No support was found for an association between measures assessing fear, worry, or attention and increased risk of recurrent MACE. These findings may be utilized in clinical practice to identify high-risk individuals more efficiently and may potentially assist in optimizing healthcare strategies.

Supplementary material

Supplementary material is available at *European Journal of Cardiovascular Nursing* online.

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Conflict of interest: None declared.

Data availability

The data underlying this article cannot be shared publicly due to the General Data Protection Regulation (2016/679). The data will be shared on reasonable request to the corresponding author.

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