

Psychological mediators related to clinical outcome in cognitive behavioural therapy for coronary heart disease: A sub-analysis from the SUPRIM trial

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Abstract

Background: The Secondary Prevention in Uppsala Primary Healthcare Project (SUPRIM) was a randomized controlled trial of a group-based cognitive behavioural therapy stress management programme for patients with coronary heart disease. The project was successful in reducing the risk of fatal or non-fatal first recurrent cardiovascular events. The aim of this study was to analyse the effect of cognitive behavioural therapy on self-rated stress, somatic anxiety, vital exhaustion and depression and to study the associations of these factors with the reduction in cardiovascular events.

Methods: A total of 362 patients were randomly assigned to intervention or usual care groups. The psychological outcomes were assessed five times during 24 months and analysed using linear mixed models. The mediating roles of the outcomes were analysed using joint modelling of the longitudinal and time to event data.

Results: The intervention had a positive effect on somatic anxiety ($p < 0.05$), reflecting a beneficial development over time compared with the controls. Stress, vital exhaustion and depression did not differ between the groups over time. Mediator analysis suggested that somatic anxiety may have mediated the effect of treatment on cardiovascular events.

Conclusions: The intervention had a small positive effect on somatic anxiety, but did not affect stress, vital exhaustion or depression in patients with coronary heart disease. Somatic anxiety was associated with an increased risk of cardiovascular events and might act as a partial mediator in the treatment effect on cardiovascular events. However, the mechanisms between the intervention and the protective cardiovascular outcome remain to be identified.

Keywords

Stress management, cognitive behavioural therapy, coronary heart disease, depression, anxiety, vital exhaustion

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Introduction

Managing psychosocial risk factors such as stress, depression, vital exhaustion and anxiety are important in the successful prevention of recurrent cardiac events in patients with coronary heart disease (CHD). Psychological interventions for these patients are suggested to promote healthy behaviours and reduce the risk of recurrent cardiac events.¹ Several trials have evaluated psychological interventions targeting stress, anxiety, depression and vital exhaustion, while also attempting to influence cardiac outcomes and mortality in patients with CHD. The results have been inconsistent in that some studies have shown small or no benefit

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on cardiac outcomes, while others have shown positive results. The successful interventions have been characterized by being group-based, behaviourally oriented stress management programmes,²⁻⁶ whereas the less successful interventions were either shorter or mainly individually-based.⁷⁻⁹

The Secondary Prevention in Uppsala Primary Health Care Project (SUPRIM) was a randomized controlled trial (RCT) evaluating whether a one-year stress management programme, in addition to usual care, reduced cardiovascular outcomes compared with usual care only in patients with CHD.³ The main findings were a 41% reduction in fatal or non-fatal first recurrent cardiovascular events in the intervention group compared with the control group and a 45% reduction in recurrent myocardial infarction (MI) during the 94 months of follow-up. The use of antihypertensive or lipid-lowering drugs, antidepressants and smoking habits could not explain the outcome.³ However, treatment effects on the separate psychological risk factors targeted in SUPRIM have not been analysed. The aim of this study was to investigate whether and to what extent stress, somatic anxiety, depression and vital exhaustion were affected by the intervention and whether these possible differences were associated with a reduction in cardiac outcome.

Methods

Participants

Patients were recruited between 1996 and 2002 if they fulfilled the following inclusion criteria: age <76 years; discharged from Uppsala University Hospital after an MI, percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG); living in the hospital primary catchment area; Swedish speaking; healthy enough to be referred back to their general practitioner within 1 year from admission; and willing to participate in the SUPRIM study. Of the 812 patients consecutively screened for eligibility, 362 were included and randomized (192 to the treatment and 170 to the control group), of which 85 (23.5%) were women. Of the 450 patients excluded, 302 did not meet the inclusion criteria (the most common reason was not fulfilling the time criterion of being referred to the general practitioner within a year, mostly due to hospital administrative reasons) and 148 declined to participate. Of the included patients 185 (51.1%) had been admitted after an MI, 122 (33.7%) for CABG and 55 (15.2%) for PCI. There was no difference in medical history or risk factor profile between the two groups at baseline. Seventy-one of the post-MI patients had a PCI during the index admission and three had a CABG. During the follow-up

period (on average 94 months), 146 patients had at least one cardiovascular event, five of whom died from the first cardiovascular event. A further 12 patients died without experiencing a non-fatal cardiovascular event.

The SUPRIM study was approved by the regional research ethics board with registration numbers 2007/026, UPS 9658 and UPS03305; trial registration at clinicaltrials.gov, identifier NCT00888485.

Design and procedure

Both groups of patients received usual care with standard risk factor optimization according to current guidelines. Psychological outcomes were assessed five times, i.e. once every six months, for 24 months. The participants were informed about the group allocation after the baseline assessments. The earliest inclusion was three months after discharge from hospital and the latest was one year according to inclusion criteria. Intervention started between 0 and 11 months (median 26 days) after randomization; for further details, see Gulliksson et al.³

Intervention

The stress management programme was based on cognitive behavioural therapy and consisted of five key components (education, self-monitoring, skills training, cognitive restructuring and spiritual development) and focused on reducing daily experiences of stress, such as time urgency, hostility and excessive worrying. The one-year programme of 20 two-hour group sessions (five to nine participants in each group) followed a structured treatment manual. Women and men attended separate sex-specific groups led by psychologists, nurses and a lay welfare worker, who were all specially trained for this programme. The therapists were supervised by the psychologist who designed the intervention (GB, co-author of this paper). The programme has been described in detail elsewhere¹⁰ and has been used in other trials.^{4,11,12}

Psychological mediators

Stress was assessed with The Everyday Life Stress Scale (ELSS) consisting of 20 items about time urgency and hostility in daily life ranked on a four-degree scale. The internal consistency was high ($\alpha=0.90$).¹³ The ELSS has been used in previous studies regarding stress management among women with CHD.^{11,12}

Anxiety was assessed with the Somatic Anxiety Scale consisting of 21 items and developed for this study. Bodily reactions to anxiety, such as sweating, hyperventilation and bodily sensations, were rated on 100 mm

visual analogue scales ranging from never to very often. Internal consistency was high in this population at baseline ($\alpha=0.93$).

Vital exhaustion was assessed by the Maastricht Vital Exhaustion Questionnaire consisting of 19 items on a three-point scale (0–2), with higher scores indicating a higher degree of vital exhaustion.¹⁴ The internal consistency was high ($\alpha=0.93$) in this population at baseline. The instrument has been used in other studies with MI patients.^{14,15}

Depression was assessed with The Depressive Mood Scale, which consists of 20 items on four-point scales. The instrument was developed from the Hamilton Depression Scale and the Beck Depression Inventory. It has been validated in a study with MI patients and correlated well with the Montgomery–Åsberg Depression Rating Scale (Spearman's $\rho=0.79$, $p\leq 0.001$).¹⁶ The internal consistency was high ($\alpha=0.87$).

Exploratory outcome measures

Social support was assessed by the AVAT subscale from The Social Support Scale, which was later shortened and validated¹⁷ focusing on the availability of attachment. Physical activity was assessed by a question about the amount and intensity of physical activity during the previous year.

Clinical outcomes

Hospital admission data were obtained from the National Hospital Discharge Registry and mortality data were obtained from the National Cause of Death Registry. The mean follow-up time was 94 months post-randomization. The variables used were date and cause of death. All deaths, irrespective of their cause, the first cardiovascular event (fatal or non-fatal) and the first MI (fatal or non-fatal) after baseline were identified according to the International Classification of Diseases revision 8-10; for further details see Gulliksson et al.³

Statistical analyses

All results were analysed using an intention-to-treat approach. The effect of the intervention on the primary outcomes was evaluated by the fixed effect interaction term between groups and time. Linear mixed models (LMM) with (restricted) maximum likelihood were used to estimate the parameters. Maximum likelihood is efficient because it uses all the available observations and is independent of the drop-out rate under the missing at random assumption.¹⁸ To improve efficiency we included sex, age, education and previous MI in an adjusted regression model. Residual analyses and a

check for outliers were performed to assess model adequacy. Transformations were carried out accordingly and, as a result, the square-root of somatic anxiety was used in all analyses. Effect size was calculated for the observed untransformed mean differences of the groups in the pre-post design with unequal sample sizes according to Klauer.¹⁹

To study whether the psychological outcomes mediated the effect of the intervention on cardiovascular events, an approach similar to that of Baron and Kenny²⁰ was used. A psychological outcome was considered to be a mediator between the intervention and cardiovascular events if the following criteria were met: (a) the intervention had an effect on cardiovascular events; (b) the intervention was associated with the psychological outcome; (c) the psychological outcome was associated with cardiovascular events while controlling for the intervention; and (d) after inclusion of the psychological outcome, the hazards ratio (HR) of the intervention was smaller than the HR in (a).

Criterion (a) was tested using Cox proportional hazards regression. Criterion (b) was tested using LMM. To test criterion (c), we used joint modelling of the longitudinal responses and time to event data.²¹ The joint modelling approach allows for event-dependent drop-outs in a longitudinal analysis, while the longitudinal outcomes were modelled according to the previously specified LMMs. To account for death from causes other than a cardiovascular event, the time to event data were modelled using a competing risks model with a spline-approximated baseline risk function. Criterion (d), about the magnitude of the mediation, was presented on a descriptive basis and calculated as (HR for intervention in (a) – HR for intervention in (c))/(HR for intervention in (a) – 1).^{22,23} It should be mentioned that although the intervention was randomized, the mediator was not randomized and confounders must therefore be included in all steps (a)–(c). The results from the mediation analysis are presented as descriptive because it is unclear how to calculate standard errors in this particular setting.

All analyses were performed in R 3.1.1²⁴ using the packages *nmle*,²⁵ *survival*,²⁶ *JM*²⁷ and *ggplot2*.²⁸

Results

The two study groups were well balanced in terms of baseline characteristics (Table 1). The control group reported more symptoms of somatic anxiety over time, whereas the intervention group did not change their ratings (Figure 1). The effect size for somatic anxiety was small ($d_{\text{corr}}=0.15$). No treatment effect was found for stress, vital exhaustion or depression. However, a decrease over time was observed in both groups for stress. Adding age, sex, education and

Table 1. Baseline characteristics of the study population.

	Intervention group (n = 192)	Control group (n = 170)
Age at baseline (years)	62.0 ± 7.94	61.0 ± 8.28
Female sex	43 (22.4)	42 (24.7)
Married	150 (78.1)	132 (77.6)
<i>Highest educational level</i>	(n = 189)	(n = 161)
Compulsory education	67 (35.4)	62 (38.5)
Vocational training	62 (32.8)	57 (35.4)
High school	22 (11.6)	10 (6.2)
University education	38 (20.1)	32 (19.9)
Disability pensioner	33 (17.2)	15 (8.8)
Old-age pensioner	96 (50.0)	76 (44.7)
<i>Psychological assessments</i>		
Everyday life stress scale	18.2 ± 8.4	19.0 ± 8.8
Somatic anxiety	505 ± 323	538 ± 366
Vital exhaustion	13.3 ± 8.4	13.4 ± 8.0
Depression	17.9 ± 10.2	18.0 ± 10.6

Data presented as mean ± SD values or no. (%).

previous MI did not change these results. The adjusted regression models showed that the women reported higher levels of somatic anxiety, vital exhaustion and depression. Participants with a university education reported less somatic anxiety and older participants reported less stress (Table 2).

Exploratory analyses showed that the estimated interactions of intervention and time on social support and physical activity were -0.07 (95% confidence interval (CI) -0.23 to 0.09) and 0.07 (95% CI -0.53 to 0.69), respectively, suggesting no effect of the treatment on these outcomes.

Sensitivity analyses were performed using the time since the start of the intervention instead of the time since randomization; missing data were replaced by multiple imputation instead of LMM. Neither of these analyses changed the results (data not shown).

Somatic anxiety, depression and vital exhaustion, but not daily stress, were associated with the nine-year risk of a fatal or non-fatal cardiovascular event, independent of participation in the intervention. No association with death due to other causes was found.

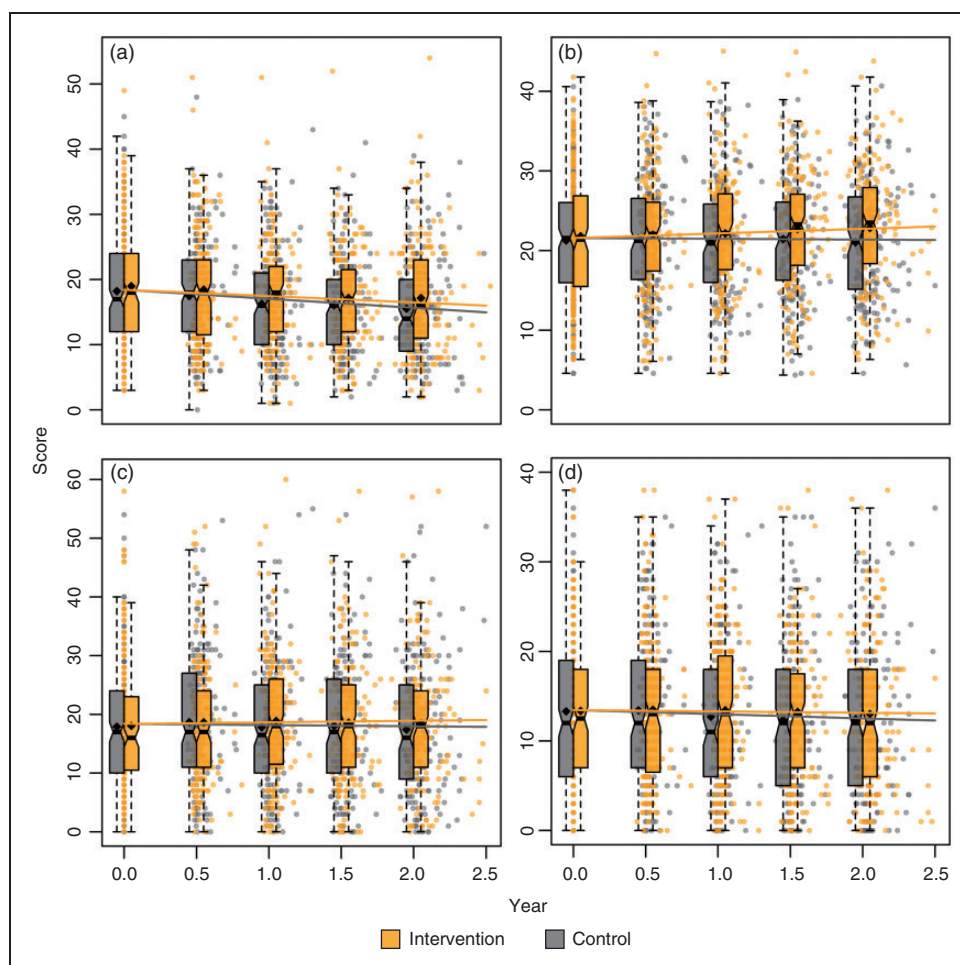


Figure 1. Change over time of the four psychological outcomes for the study groups. The change is shown with boxplots and estimated group means (closed circles), together with fitted lines from the crude linear mixed models: (a) Everyday life stress scale, (b) Somatic Anxiety scale, (c) Depressive mood scale and (d) Maastricht vital exhaustion questionnaire.

Table 2. Estimated fixed effects in psychological outcomes, crude and adjusted models.

	Everyday Life Stress Scale		Somatic Anxiety Scale		Depressive Mood Scale		Maastricht Vital Exhaustion Questionnaire	
	Crude (95% CI)	Adjusted (95% CI)	Crude (95% CI)	Adjusted (95% CI)	Crude (95% CI)	Adjusted (95% CI)	Crude (95% CI)	Adjusted (95% CI)
Time (years)	-0.97 (-1.37 to -0.56) ^{***}	-0.97 (-1.38 to -0.56) ^{***}	0.58 (0.16 to 0.99) ^{**}	0.56 (0.15 to 0.97) ^{**}	0.27 (-0.30 to 0.84)	0.26 (-0.30 to 0.83)	-0.16 (-0.62 to 0.31)	-0.16 (-0.63 to 0.30)
Age (years)	-0.10 (-0.20 to -0.002) [*]	-0.10 (-0.20 to -0.002) [*]		-0.07 (-0.15 to 0.02)		-0.01 (-0.14 to 0.12)		-0.01 (-0.10 to 0.09)
Sex (reference female)	0.66 (-1.19 to 2.51)	0.66 (-1.19 to 2.51)		-1.70 (-3.29 to -0.10) [*]		-4.75 (-7.16 to -2.34) ^{***}		-4.72 (-6.57 to -2.88) ^{***}
Education (reference no university)	0.38 (-1.58 to 2.34)	0.38 (-1.58 to 2.34)		-3.48 (-5.17 to -1.79) ^{***}		-1.32 (-3.87 to 1.23)		-1.04 (-2.99 to 0.91)
PMI (reference no PMI)	-0.38 (-1.36 to 0.60)	-0.38 (-1.36 to 0.60)		0.26 (-0.58 to 1.11)		-0.34 (-1.62 to 0.94)		0.04 (-0.94 to 1.01)
Intervention * Time	-0.42 (-0.94 to 0.11)	-0.41 (-0.94 to 0.12)	-0.68 (-1.21 to -0.14) [*]	-0.65 (-1.18 to -0.11) [*]	-0.47 (-1.23 to 0.29)	-0.46 (-1.22 to 0.30)	-0.31 (-0.93 to 0.30)	-0.30 (-0.91 to 0.31)
Constant	18.43 (17.58 to 19.28) ^{***}	24.19 (17.70 to 30.67) ^{***}	21.58 (20.84 to 22.32) ^{***}	27.63 (22.03 to 33.23) ^{***}	18.39 (17.33 to 19.44) ^{***}	23.15 (14.72 to 31.59) ^{***}	13.46 (12.62 to 14.30) ^{***}	17.59 (11.13 to 24.05) ^{***}
Observations (individuals)	1648 (355)	1649 (355)	1649 (355)	1649 (355)	1649 (355)	1649 (355)	1648 (355)	1648 (355)

CI: confidence interval; PMI: previous myocardial infarction.

p* < 0.05; *p* < 0.01; ****p* < 0.001.

A unit increase in somatic anxiety and vital exhaustion corresponded to a 1.04-fold increase in the risk of a fatal or non-fatal cardiovascular event (95% CI 1.01–1.06 and 1.02–1.06, respectively) and for depression a 1.02-fold increase (95% CI 1.01–1.04). In the mediation analysis of the four psychological outcomes according to Baron and Kenny,²⁰ the first criterion was met in that the intervention had an effect on cardiovascular events (Table 3). The second criterion was met only for somatic anxiety (Table 2), whereas the third and fourth criteria were met by all but one outcome (Table 3). Thus only somatic anxiety met all four criteria for being a mediator, although we only considered the fourth criterion descriptively. The magnitude of mediation (i.e. the fourth criterion) for somatic anxiety was $(0.64 - 0.68)/(0.64 - 1) = 0.165$, i.e. about a 16% decrease in the HR of the intervention on cardiovascular events.

Discussion

Stress management had a small protective effect on somatic anxiety; however, stress, vital exhaustion and depression did not differ between the groups over time. There was an association between somatic anxiety, depression and vital exhaustion and the risk of fatal or non-fatal cardiovascular events. Somatic anxiety was found to be a mediator between the intervention and cardiovascular events.

It is unknown what the assessed somatic anxiety represents, with items that tap bodily sensation and muscle tension, but it might be both a reaction to the CHD, such as cardiac anxiety, or symptoms of stress originating from time urgency or hostility. The intervention's stabilizing impact on somatic anxiety, in contrast with the increasing levels in the control group, could be due to better coping abilities promoted by the intervention.

The ENRICHD study found that somatic, but not cognitive, symptoms of depression at 12 months following MI predicted subsequent mortality, whereas depressive symptoms measured close to the acute event were not related to the post-MI prognosis. Thus if psychological symptoms persist or worsen over a longer period of time, then they may be more hazardous. In the SUPRIM study, the control patients showed more somatic anxiety symptoms at later follow-ups. In parallel with the ENRICHD findings, this may indicate that patients who do not develop coping strategies for psychological symptoms, particularly somatic reactions, have a worse prognosis in the long term.²⁹

The lack of effect on three out of four psychological outcomes, which were the main theoretical targets of the intervention, was unexpected based on the positive results reported from other studies with similar group interventions and psychological outcomes.^{5,11,30}

Table 3. Mediation analyses with estimates from Cox proportional hazards model for fatal or non-fatal cardiovascular events.

	HR [†] (95% CI) adjusted for:				
	HR (95% CI)	Everyday Life Stress Scale	Somatic Anxiety Scale	Depressive Mood Scale	Maastricht Vital Exhaustion Questionnaire
Effect of intervention on cardiovascular event	(a) 0.64 (0.46–0.89) ^{***}	(d) 0.63 (0.45–0.88) ^{***}	(d) 0.70 (0.50–0.98) [*]	(d) 0.68 (0.49–0.94) [*]	(d) 0.66 (0.47–0.91) [*]
Association between psychological outcome and cardiovascular event		(c) 1.00 (0.98–1.02)	(c) 1.04 (1.01–1.06) [*]	(c) 1.02 (1.01–1.04) [*]	(c) 1.04 (1.02–1.06) ^{***}

CI: confidence interval; CV: cardiovascular; HR: hazards ratio.

(a), (c) and (d) corresponds to the first, third and fourth mediator criterion according to Baron and Kenny²⁰: (a) the intervention has an effect on CV events; (c) psychological outcome is associated with CV events while controlling for the intervention; (d) after inclusion of the psychological outcome, the HR of the intervention was smaller than the HR in (a).

All models were adjusted for age, sex, education and previous myocardial infarction. HRs for death due to other causes are not shown. ^{*} $p < 0.05$; ^{**} $p < 0.01$; ^{***} $p < 0.001$.

The estimates from the linear mixed model for the psychological outcomes are essentially the same as in Table 2 and are therefore not shown.

However, the large and well-designed RCCP study, which found reductions in stress as well as cardiovascular events, recruited patients younger than 65 years who presented type A stress behaviour.⁵ This provided better preconditions to detect an effect on stress and of a behavioural intervention because there was more room for improvement and the study assumed more resourceful participants. Some of the positive effects of other studies may also be due to differences in the characteristics of the patient population, the trial designs and statistical analyses. Claesson et al.¹¹ were only able to perform per-protocol analyses, which may have amplified their effect and, according to the SWITCHD investigators, their results may have been biased due to regression towards the mean.³⁰

Women generally exhibit more psychological suffering than men³¹ and studies that included only women reported higher baseline levels than the SUPRIM study, in which only 23.5% of the participants were women.^{11,12,30} Women might also be more responsive to this kind of treatment. Unfortunately, this study was underpowered for stratified sex analyses. In addition to recruiting both sexes, SUPRIM also recruited participants consecutively and without applying a lowest threshold of symptom level. This resulted in low levels of baseline symptoms with little room for improvement. In fact, participants in the SUPRIM trial did not differ from a matched non-patient population regarding stress, depression, anxiety or vital exhaustion.¹³

The suggested mediating effect of somatic anxiety is in line with previous research on the importance of anxiety as an independent predictor for CHD risk and prognosis in both healthy populations and in post-MI patients.^{32,33} Somatic aspects of anxiety, in contrast with cognitive anxiety symptoms, may be particularly important because they are associated with recurrent MI and mortality in post-MI patients.³⁴ The mediating effect was, however, small and even though it may be directly related to the reduction in cardiovascular outcome, it is unlikely to be the only explanation for the success of the intervention in reducing cardiovascular events. We cannot tell from our results whether somatic anxiety represents a strain that mediates the risk for later cardiovascular events, or whether somatic anxiety merely represents early symptoms of the cardiovascular-related illness. Several other risk factors, such as physical activity, blood pressure and the use of medication were unaffected by the treatment and are therefore unlikely to explain the reduction in cardiovascular events.³

Social support is known to be related to prognosis in patients with CHD^{35,36} and group treatments for patients with CHD seem to be more successful than Individual treatments. The intervention lasted an

entire year and it was observed that the participants often bonded strongly with each other. More social support as a result of this programme could be a possible mediator, but might not have been assessed sensitively enough because the study focused on support in daily life and not on perceived support from the group. The male patients reported better daily support at baseline than a control group from the general population, again leaving little room for improvement.¹³

There were a few methodological limitations. The psychological assessments were timed with the inclusion into the study and not with the onset of treatment, which was sometimes delayed for up to a year after the first assessment. However, a sensitivity analysis taking timing into account did not alter the results. It is possible that important mechanisms were not captured adequately. The two groups did not differ in prescribed medication, but actual compliance was not assessed and the measures of physical activity and social support were perhaps too blunt. Although the study was an RCT, the allocation was not blinded to the patients and this could affect the self-reported psychological outcomes. The Somatic Anxiety Scale is not thoroughly validated, which is a weakness in this study.

Stress management for patients with CHD led to slightly more positive levels of somatic anxiety in the intervention group compared with the control group. Somatic anxiety was found to be associated with fatal and non-fatal cardiovascular events and was found to have a small mediating role between treatment and cardiovascular outcome. It is possible that small changes in a number of variables could work synergistically to affect cardiovascular events, but this could not be shown in the present study. Thus the mechanisms between the intervention and the protective cardiovascular outcome remain to be identified.

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Author contribution

KS, MG and GB contributed to the conception or design of the work. FN, EO, RP, HC, KS, MG and GB contributed to the acquisition, analysis, or interpretation of data for the work. RP carried out the analyses and provided statistical expertise. FN, EO and GB drafted the manuscript. FN, EO, RP, HC, KS, MG and GB critically revised the manuscript. All gave final approval and agreed to be accountable for all aspects of work ensuring integrity and accuracy.

Declaration of conflicting interests

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