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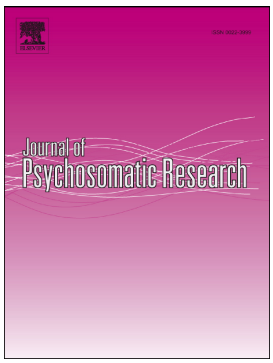

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Eric W. de Heer, Jorge E. Palacios, Herman J. Adèr, Harm W.J. van Marwijk, Andre Tylee, Christina M. van der Feltz-Cornelis

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Chest pain, depression and anxiety in coronary heart disease: consequence or cause? A prospective clinical study in primary care

Eric W de Heer`, PhD[1,2,*+], Jorge E Palacios, PhD[3+], Herman J Adèr, PhD[4], Harm WJ van Marwijk, professor[5], Andre Tylee, professor[3], Christina M van der Feltz-Cornelis, professor[1,2,6]

[1] *Clinical Centre of Excellence for Body, Mind and Health, GGz Breburg, 5042 Tilburg, the Netherlands*
[2] *Tilburg School of Behavioural and Social Sciences, Tranzo Department, Tilburg University, 5073 Tilburg, the Netherlands*
[3] *Institute of Psychiatry, Psychology and Neuroscience, King's College London, SE5 8AF London, UK*
[4] *Johannes van Kessel Advising, 1273 SB Huizen, The Netherlands*
[5] *Division of Primary Care and Public Health, Brighton and Sussex Medical School, University of Brighton, Falmer, BN1 9PX Brighton, UK*
[6] *Mental Health and Addictions Research Group, Department of Health Sciences, University of York, YO10 5DD York, UK*

[*] *Correspondence to: EW de Heer, Clinical Centre of Excellence for Body, Mind and Health, GGz Breburg, Lage Witsiebaan 4, 5042 DA, Tilburg, the Netherlands; e.deheer@ggzbreburg.nl*
[+] Both authors contributed similarly to the article

Key words: chest pain, depression, anxiety, coronary heart disease

ABSTRACT

Objective: To examine if chest pain increases the risk of depression and anxiety, or, on the other hand, depression and anxiety increase the risk of chest pain onset in patients with coronary heart disease (CHD).

Design: Prospective clinical study.

Setting: 16 general practices in the Greater London Primary Care Research Network.

Participants: 803 participants with a confirmed diagnosis of CHD at baseline on the Quality and Outcomes Framework (QOF) CHD registers.

Main outcome measures: Rose Angina Questionnaire, HADS depression and anxiety subscales and PHQ-9 were assessed at seven time points, each 6 months apart. Multi-Level Analysis (MLA) and Structural Equation Modelling (SEM) were applied.

Results: Chest pain predicts both more severe anxiety and depression symptoms at all time points until 30 months after baseline. However, although anxiety predicted chest pain in the short term with a strong association, this association did not last after 18 months. Depression had only a small, negative association with chest pain.

Conclusions: In persons with CHD, chest pain increases the risk of both anxiety and depression to a great extent. However, anxiety and depression have only limited effects on the risk for chest pain. This evidence suggests that anxiety and depression tend to be consequences rather than causes of cardiac chest pain. Intervention studies that support persons with CHD by providing this information should be devised and evaluated, thus deconstructing potentially catastrophic cognitions and strengthening emotional coping.

INTRODUCTION

Background

Coronary heart disease (CHD) is the number one cause of death worldwide.[1] Clinically, it is mainly characterized by chest pain.[2] Chest pain in a patient with known CHD could signify new or unresolved issues with the coronaries. Biopsychosocial issues such as social isolation, adverse life events, chronic health conditions, coping mechanisms, distress, anxiety, or depression may also play a role, as either the consequence or the cause of the chest pain. Several studies have shown that especially comorbid depression and anxiety frequently co-occur with chest pain cross-sectionally.[3-6] It is also clear that this comorbidity has a substantial additional impact on quality of life,[7] even when depression or anxiety are in remission.[4,8]

The relationship may be two-sided. Longitudinal epidemiological research shows overall associations between psychological problems and chest pain. In patients with CHD, chest pain increases the risk of occurrence of a new depression more than 3-fold.[9] Chest pain is also associated with patients exhibiting 3-year chronic symptomatology of distress, as compared to patients with low chest pain symptoms throughout the same period.[10] The finding that patients with a depressive disorder are also at increased risk of developing CHD supports a bidirectional association.[11-13] Furthermore, in a meta-analysis the association between anxiety and risk of CHD in healthy individuals was explored.[14] The results of this study show that anxiety was associated with incident CHD at follow up (ranging from 2 to 20.9 years).

Rationale

Given the possibly bidirectional association between chest pain and depression and anxiety in patients with CHD, so far it remains unknown which factor contributes mostly to onset of the other. The question remains whether chest pain contributes to the onset of depression and anxiety more, or, the other way around, that depression and anxiety contribute to the onset of chest pain in patients with CHD more. A precise understanding of which factor is the strongest predictor in this association would be highly relevant to support decisions in clinical practice as well as in designing public health policies.

Objective

The aim of this longitudinal study is to examine if chest pain increases the risk of depression and/or anxiety, or, on the other hand, if depression and anxiety increase the risk of the onset of chest pain in CHD.

METHODS

Study design and Setting

Details of the cohort study protocol have been reported elsewhere.[15] The sampling frame comprised people on the Quality and Outcomes Framework (QOF) CHD registers kept by participating general practices. The Greater London Primary Care Research Network recruited sixteen General Practices from the inner city and suburban south London. Recruitment and baseline assessments were completed during 2008-2009.

Participants

The cohort was described in more detail elsewhere.[16] The sampling focus of the main study, of which data was used for the present study, was on patients with CHD. General practitioners are remunerated for keeping CHD registers under the QOF. Practices participating in this Framework and based in South London were recruited by the London Primary Care Research Network (PCRN). Recruitment was based on an 'opt-in' procedure. All patients on the CHD registers in participating general practices were firstly invited by the practices themselves to participate in the study. Those agreeing to be contacted were put through to the research team, who gave them further information about the study and provided a consent form. Consenting patients were assessed at baseline and then every six months over a 3-year period. Written informed consent was obtained for all participants before the initial assessment was conducted. Ethical approval was granted through the Bexley and Greenwich Research Ethics Committee (REC reference number: 07/H0809/38).

Measures

Specific to this analysis, the measures of interest were the following:

Rose Angina Questionnaire

A modified version of the Rose Questionnaire[17] was used at baseline and all follow-up assessments to assess the presence and symptoms of chest pain. The modification consisted specifying a time period for the occurrence of chest pain, instead of asking if it "ever"

occurred. At baseline the time period evaluated was one year before baseline. At each follow-up visit, the occurrence of chest pain since the previous visit was assessed. Published in 1962 with the purpose of detecting angina pectoris in field studies,[17] the Rose Questionnaire has been widely used to determine the prevalence of angina and CHD in a large number of epidemiological studies across the world. The short version of the questionnaire was developed as some aspects of the original were deemed possibly redundant. It was established that a quick, three question method could just as efficiently detect the crucial predictive component of mortality: exertional pain.[18] Similar to past studies using the full version to identify patients with 'non-exertional pain' and 'exertional pain',[19] the short version of the Rose Questionnaire allows for this classification with just three questions. For the purposes of the UPBEAT-UK cohort, the chest pain categorical variable comprised three groups: 'no pain', 'exertional pain', and 'non-exertional pain'.[16] Those three categories were also used for the present study. Participants who did not report having chest pain were classified as having 'no chest pain'. Participants who did report having chest pain, but not when hurrying, walking uphill, etc. were classified as having 'non-exertional chest pain'. Participants who reported chest pain that occurred on exertion (i.e. when hurrying, walking uphill, etc.) were classified as having 'exertional chest pain'.

Hospital Anxiety and Depression Scale (HADS)

Participants completed the 14-item HADS,[20] originally intended to identify symptoms regarding the emotional component of a psychical illness, by distinguishing them from those physical items that may be caused by the physical condition itself. The one-factor scale was then divided into two separate scales of seven items each. The HADS scores the severity of depressive and anxiety symptoms, both subscales ranging from 0 to 21. These subscales of the HADS are well-validated and provide a probable diagnosis of depression (HADS-D) or anxiety (HADS-A) for those scoring above the cut point of 8, established as the optimal cut-off for detecting clinically significant symptoms of depression and anxiety.[21] The cut-off score for severe levels of depression or anxiety is 12. Thus, scores of 8-11 represent a clinically significant, possible diagnosis of depression or anxiety, and scores of 12 and higher represent a clinically significant, probable diagnosis of depression or anxiety. The HADS has been extensively validated[22] and both subscales of the HADS have a good internal consistency (Cronbach's alpha for HADS-D ranges from 0·67 to 0·90; Cronbach's alpha for HADS-A ranges from 0·68-0·93).[21] The HADS has been widely used in people with medical illnesses, and its factor structure was confirmed.[23-25]

Patient Health Questionnaire (PHQ-9)

The PHQ-9 was used to assess the severity of depressive symptoms. The PHQ-9 is a brief, validated instrument, consisting of 9 items, that scores each of the DSM-IV criteria for Major Depressive Disorder.[26] Each item is scored from 0 (not at all) to 3 (nearly every day). The total score thus varies from 0 to 27, with higher scores indicating higher levels of depressive symptoms. Scores of 0-5, 6-10, 11-15, and 16-20 represent mild, moderate, moderately severe, and severe depression, respectively, where a score of 10 is used as a clinical cut-off.[27]

Confounders

Age, gender, ethnicity, relationship status, employment status, and educational level.

Time points

All measures were reported at seven time points, each six months apart, from t0 (baseline) to t6 (36 months). These were recoded to the number of months, for example, t24 = follow up at 24 months after baseline.

Data Analysis

DEMOGRAPHIC AND BASELINE CHARACTERISTICS

First, initial data analysis was performed on the whole data set, to explore demographic variables and baseline characteristics.

Next, the analyses consisted of 3 steps. For step 1 (multilevel analysis), the questionnaires were used as a categorized variable. For steps 2 and 3 (structural equation modelling), the questionnaires were used as a continuous variable.

Step 1: as a first step, multilevel analysis (MLA) was performed to assess the variability at the practice level, to assess interdependence of variables over trajectories of time, and to assess the usefulness of the variables for incorporation in the next phase in which structural equation modelling (SEM) was planned. Three-valued recoded variables (PHQ-9, HADS-A and HADS-D) were only used in the MLA which were aimed at getting a first impression of the one-way relationships with the Rose Questionnaire. Practices, demographic variables, as well as the predictor and dependent variables (Rose Questionnaire, HADS-D, HADS-A and PHQ-

9) were taken into account. The Rose Questionnaire was considered to be ordinal and the transformation suggested by Rasbash et al.[28] was applied to use it as a dependent variable in the multilevel models. For PHQ-9, HADS-A and HADS-D, we used the categorised scores. All three have three ordered categories, and the same transformation as for the Rose Questionnaire was used to be able to use them as dependent variables. The original categorised scores were used when these variables were used as independents in the models. We first used a model with 3-levels (Time point, Patient and Practices). This analysis showed that although there was some variation between the general practices, this variation was not associated with the outcomes. Hence a 2-level MLA model could be run leaving the practice level out of the model and keeping only the time point and patient level. As age, ethnicity, and relationship had no significant association with the Rose Questionnaire, PHQ-9, HADS-D and HADS-A, and gender, employment, and education showed an association, the latter were included in all multilevel models. HADS-D varied insufficiently for the values of the Rose Questionnaire to study the correlation of the latter with all time points. Hence HADS-D was not included in subsequent models. Thus, we only used PHQ-9 to represent depression, and HADS-A to represent anxiety.

Step 2: at step 2 structural equation modelling (SEM) was performed, for which the questionnaires were used as a continuous variable (in contrast to the use of the questionnaires as categorized variables in the MLA in step 1). For structural equation models, it is essential that respondents have data at all time points. We used the cross-validation approach described in Adèr & Mellenbergh[29] to be able to assess the stability of our models. We started by randomly dividing the data into two datasets, A and B. Next, a three-step procedure was followed:

First, modelling was done on dataset A. Only full cases were used, that is, respondents from whom data was collected at all seven time points. This provided two models: (a) One in which the Rose Questionnaire is used to predict HADS-A and depression as measured with the PHQ-9 at later time points and, (b) a model in which both PHQ-9 and HADS-A predict the Rose Questionnaire at later time points. As a sensitivity analysis, once these models were established, in a second step, they were verified using dataset B. This procedure was followed to be able to check the stability and validity of the resulting models.

Step 3: as a third step, the estimates in the final SEMs were refined using data of respondents of which data were not collected at later time points.

For this step, the following procedure was followed, for the models in which anxiety (HADS-A) and depression (PHQ-9) were explored:

1. We started from the model fitted on the second half of the dataset of subjects who were present at all measurement points (baseline to 36 months).
2. We did a series of analyses, adding respondents that had all measurements up to month 30, month 24, month 18, month 12, month 6, and baseline (in that order). Note that the respondents present in later analyses were always present in analyses with fewer time points (Thus, patients present in the 36-month analysis were present in all analyses).
3. Of each analysis, we used the estimates of arrows to and from the last time point to enhance the 36-months analysis. For the model exploring the association between chest pain and anxiety and depression, all time points were used.
4. As a fourth step, estimates for the time point corresponding to 36 months were left out as they were inconsistent between the analyses in the first modelling phase and the verification phase. The final models thus used the usual coding for PHQ-9 and HADS-A and have 30 months as their last time point.

As this is a longitudinal study, not a clinical trial, there are no events between time points that were planned in the design of the study. Therefore, it was sufficient to consider the predictive power of the Rose Questionnaire, HADS-A, and PHQ-9 at the first time point. Consequently, the term 'lost-to-follow-up' is not applicable here. In fact, in this study, data of cases with missing observations at later time points were used to improve the estimates after baseline as described above.

RESULTS

The sample is extensively described elsewhere.[9] Eight hundred three people participated (figure 3). Of this sample, 95.9% had a diagnosis of coronary artery disease (42.2% had a documented history of myocardial infarction and 53.7% a diagnosis of ischaemic heart disease or angina). The remaining 4.1% on the CHD register had a primary diagnosis of arrhythmia, heart failure, or not-specified. Of the total sample, 18.5% (149/803) met the criteria for an ICD-10 defined diagnosis of a depressive or an anxiety disorder; 6.7% (54/803) met criteria for depressive disorder and 3.2% (26/803) for anxiety disorder. Demographic variables and baseline characteristics are given in Table 1. Most participant were male (69.9%), mean age was 71.1. The association between individual levels of the Rose questionnaire and the anxiety and depression measurements turns out to be comparable for all levels, including No Pain (results not shown).

Table 1: Baseline characteristics of the total sample (N=803)

Demographic variables[a]		
Gender, n (%)	Male	561 (69.9)
	Female	242 (30.1)
Age, mean (SD)		71·1 (10.9)
Education, n (%)	< 2 years	376 (46.8)
	> 2 years	415 (51.7)
Employment, n (%)	Unemployed	30 (3.7)
	Paid work	148 (18.4)
	Retired	619 (77.1)
Outcome variables[a]		
ROSE questionnaire, n (%)	No chest pain	299 (37.2)
	Exertional chest pain	94 (11.7)
	Non-exertional chest pain	143 (17.8)
PHQ-9, n (%)	None or mild depressive symptoms	510 (63.5)
	Moderate depressive symptoms	155 (19.3)
	Severe depressive symptoms	136 (16.9)
HADS anxiety score, n (%)	<8 No clinically significant anxiety symptoms	650 (80.9)
	8-11 Clinically significant, possible diagnosis of anxiety	79 (9.8)
	>11 Clinically significant, probable diagnosis of anxiety	71 (8.8)

Abbreviations: SD = standard deviation; PHQ-9 = patient health questionnaire; HADS = hospital anxiety and depression scale
[a]N differs due to missing data
Numbers are based on the correction of variables in the preliminary analysis.

Results of the SEM analysis are shown in Figures 1 and 2. As mentioned before, we used a cross-validation approach to assess the stability of the models. Figures 1 and 2 show the models found in the verification step of the SEM analysis. Only the structural model is shown. Coefficients in the Figures are standardized scores and in most cases coefficients < 0.1 have been left out. Figure 1 shows the prediction of anxiety and depressive symptoms by chest pain: chest pain predicts both clinically significant, more severe symptoms of anxiety and

depressive at all time points. The associations in the model obtained in the verification step of the modelling process (using data set B) correspond to those obtained in the first step in which dataset A was used. The observed associations are high, ranging from 0.89 to 0.95.

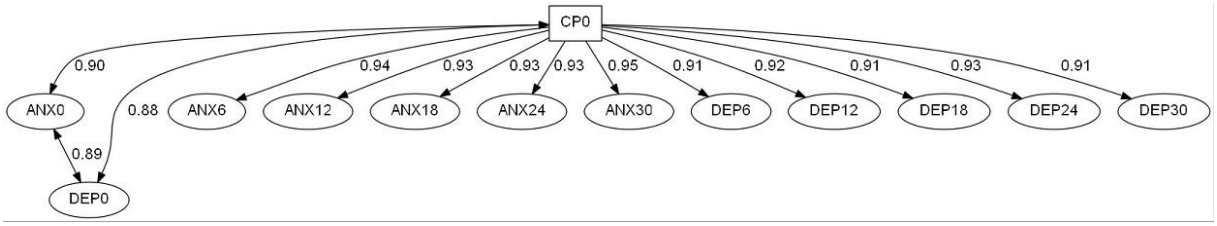

Figure 1: Chest pain estimated by Rose predicting Anxiety estimated by HADS Anxiety and Depression estimated by PHQ9 (coefficients are standardized sores). **Legend:** CP0: Chest pain at time point zero; ANXi: Anxiety at time point i; DEPi: Depression at time point i.

Figure 2 gives the prediction of chest pain by anxiety and depressive symptoms. Although more severe symptoms of anxiety were associated with chest pain in the first few timepoints (up to 18 months), this association did not last. More severe symptoms of depression had a strong negative association with chest pain at baseline (-0.81) and at six months (-0.415), and only a small, negative association (-0.143) with chest pain after 24 months. Several links in the model obtained in the first step of the modelling process (using dataset A) had to be left out during the verification step (using data set B) since associations did not correspond. In particular, all links to the last time point (36 months) were left out.

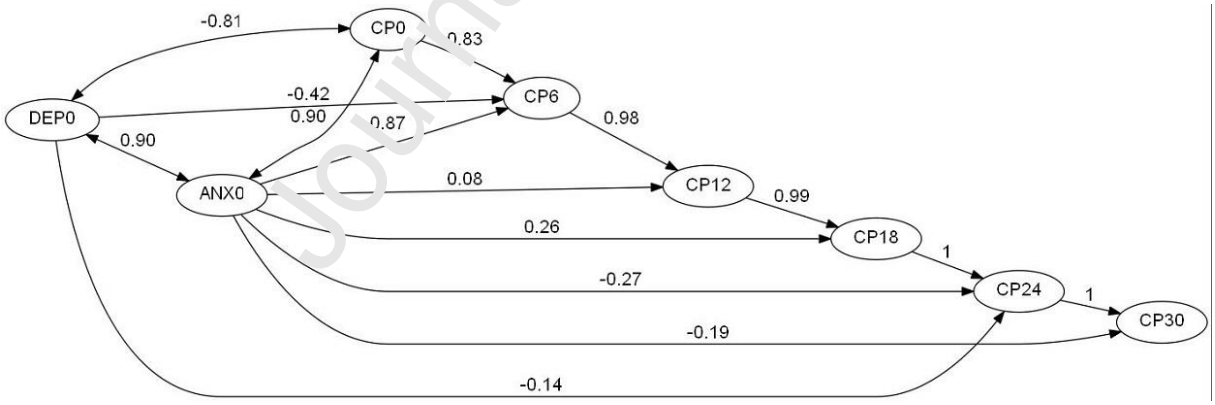

Figure 2: Depression estimated by PHQ9 and Anxiety estimated by HADS Anxiety predicting the occurrence of Chest pain estimated by Rose (coefficients are standardized scores). **Legend:** CP0, DEP0, ANX0: Chest pain, Depression and Anxiety at time point zero; CPi: Chest pain at time point i.

DISCUSSION

Our study shows that in patients with CHD, chest pain at baseline contributes to the onset of clinically significant, more severe symptoms of depression and anxiety more, with

coefficients around 0.9, than the other way around. Depression and anxiety at baseline have only limited effects on the risk for onset of chest pain. Regarding the direction of the relationship between chest pain and depression or anxiety, our results suggests that clinically significant more severe symptoms of depression and anxiety tend to be consequences of the pain rather than causes of it.

Anxiety only has a short-term effect on chest pain, and depression seems to have a small protective effect against chest pain. One interpretation for this finding might be that medication could play a role in this. Beta blockers are frequently used in case of chest pain in CHD, in which fatigue is a common adverse effect; this might play a role in the level of physical activity, and hence the amount of experienced chest pain. Unfortunately, the level of physical activity was not available in this sample, so this possibility could not be explored. Also, research indicates that beta-blockers are associated with less depressive symptoms in patients with cardiac disorders.[30,31] This might explain the slight 'protective' effect on chest pain that was found in case of depression. Unfortunately, the use of medication in this sample was not available for analysis, so this possibility could not be further explored and this should be a topic for further research.

Generalisability

All the patients in this study were recruited from primary care CHD registers in the South London region. If patients were only at risk for CHD and not diagnosed as such, they were not in the register. Patients with any chest pain in this study still had CHD, probably somewhat under control due perhaps to a previous intervention, such as coronary artery bypass graft. Most patients were long-term CHD patients, who had had the usual treatments and medications. Hence, these study results apply to an urban population with CHD and more or less chest pain, which is primarily treated by their general practitioner.

Limitations of the study

The HADS-D subscale turned out to be unstable to such an extent in the preliminary MLA that it could not be used for analysis. This may be in line with the findings of a systematic review, which established that the ability of the HADS to differentiate between anxiety and depression is unclear.[32] The validity of the HADS to discern depression and anxiety from each other by its subscales has been subject to extensive debate in the literature[33] and our finding that the PHQ9 performed better is in line with such earlier findings. Fortunately, in our study the PHQ-9 was available for establishing levels of depression and the cross-

validation enabled us to develop a stable structural model. The PHQ-9 includes items such as fatigue and sleeping too much, which might refer to the somatic component of depression but also to regular symptoms of CHD or as a side effect of medication. Hence we do not expect a particular bias in any direction.

Another limitation is that this study is based on longitudinal cohort data that do not allow for controlling all theoretically possible factors that might play a role in causality, as it is not possible to randomize for such factors in a cohort study. No data were collected of pharmacotherapy or comorbid conditions, among others, which may have had an impact on the level of pain or psychological wellbeing of the patient. Moreover, in a qualitative study in a small sub-sample (n=30) of the UPBEAT study, patients reported a variety of themes which might impact the association between chest pain and depression and anxiety, such as social isolation, medical illness and disability, adverse life events, and coping mechanisms,[34] which might influence the association between chest pain and depression and anxiety. However, this is the first study that allows assuming a direction of causality, taking this limitation into account. The lack of data on physical activity is another limitation of this study. Anxiety and depression have its effect on physical exertion. For example, persons who are anxious about their cardiovascular symptoms, are more likely to avoid physical exertion. Furthermore, persons with a depression are more likely to be less active. In both cases, these persons are protected from exertional chest pain. Future research needs to take this into account. Furthermore, most participants in this study did not have a clinically diagnosed depressive or anxiety disorder at baseline. As a consequence, we were unable to test whether a possible relationship exists of chest pain with severity (measured with the HADS) of diagnosed depression and anxiety.

Clinical implications

This is a finding of high clinical relevance. Patients with CHD fearing that worries might lead to increased symptomatology and thus worsening of the experience of their condition, can be assured that there is an insufficient ground for such fears. That may be a relief for patients fearing cardiac deterioration because of depressive or anxiety symptoms. Cardiologists and general practitioners can play an important role in assuring their patients. The core idea would be to help people deal with their chest pain symptoms and fatigue. To help them discern which chest pain would be a reason to visit the doctors for further investigation and how to tease these physical and psychological symptoms apart. Counselling patients and providing this information, deconstructing catastrophic cognitions, and strengthening emotional coping

may be an adequate approach given these findings. In a qualitative study in the UPBEAT sample, most participants found talking therapies and interventions providing the opportunity for social interaction, support and exercise, such as Cardiac Rehabilitation, to be helpful whereas anti-depressants were not favoured.[34] Also, how to become or remain active and not give in to possibly paralysing feelings of demoralisation, and, last but not least, help patients alleviating possible feelings of guilt would be helpful. Such treatments could be delivered by trained general practice nurses or psychotherapists providing this in the context of Cognitive and Behavioural Therapy,[35] Acceptance and Commitment Therapy[36] or metacognitive therapy.[37] Hence, the findings of this study pertain to multiple professional audiences.

Research implications

Now that this study established that chest pain seems to primarily pose a risk for developing anxiety and depression and not the other way around, intervention studies should be devised and evaluated that support patients with CHD in coping with their chest pain at a psychological level. A qualitative study in the context of this study revealed that patients had issues with sexual problems, employment problems, and financial problems, besides their health problems.[38] Coming to terms not only with dealing with the chest pain in a de-catastrophizing way but also with these problems, may be required as the focus of new interventions. Further research is also needed to explore the role of other, biopsychosocial, factors (e.g. cardiac medication, physical activity, coping strategies, attachment style) in the interface of chest pain and anxiety and depression in CHD.

Conclusion

Psychological problems are the consequence rather than the cause of chest pain in primary care patients with stable CHD.

CONTRIBUTORS

CFC designed the analyses together with HA, HvM, AT, JP, and EdH. JP and EdH prepared the analyses. HA performed the analyses. EdH, JP, HA, and CFC wrote the manuscript and HvM and AT commented on it. AT got funding for and oversaw the principal project leading to the data used for this article. CFC funded and facilitated data analyses and writing of this article. All authors approved the final version of this article. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

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COMPETING INTERESTS

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: CFC reports grants from 'The Education and Innovation Fund (O&O)', grants from 'The Netherlands Organisation for Health Research and Development (ZonMw)', grants from Innovatiefonds zorgverzekeraars', grants from 'Netherlands Organisation for Scientific Research (NWO)', outside the submitted work. AT has given advice on a panel for Lundbeck about NICE depression 2018. All other authors have no support from any organization for the submitted work; no financial relationships with any organizations 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

Ethical approval was granted through the Bexley and Greenwich Research Ethics Committee (REC reference number: 07/H0809/38). Written, informed consent was obtained for all participants before the initial assessment was conducted.

DATA SHARING

Data used for this manuscript was made available by a third party, the Up-Beat UK study, and is therefore not publicly available.

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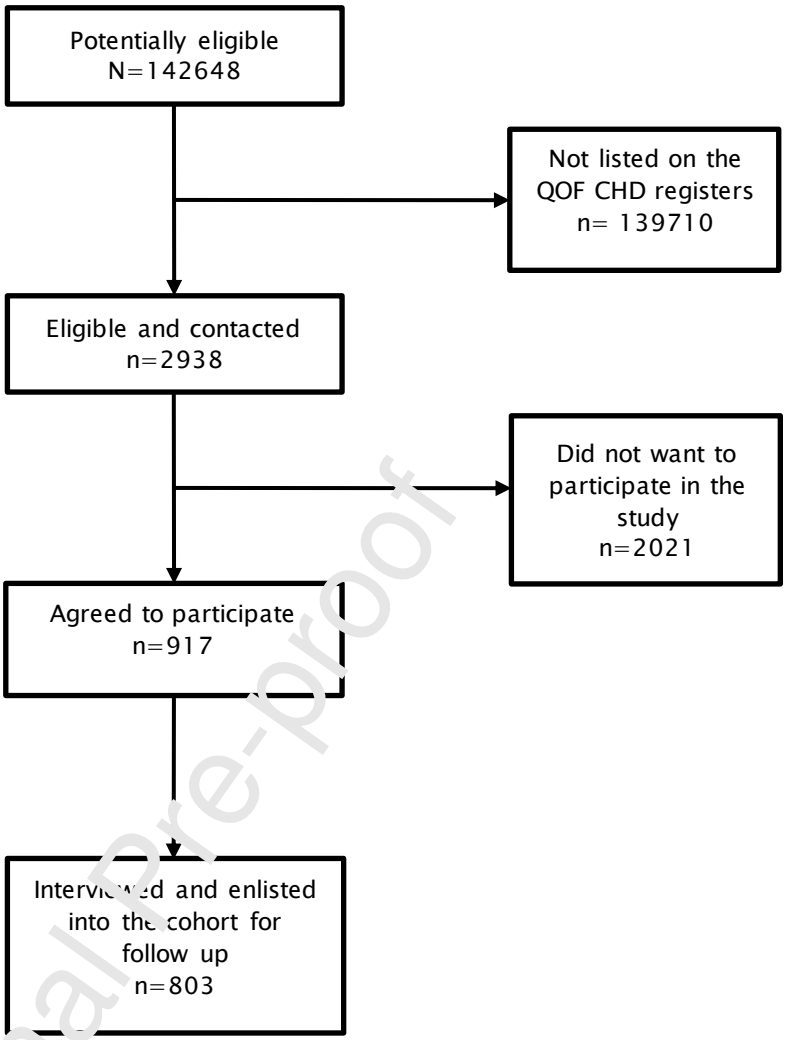

Figure 3: Flowchart of inclusion procedure UPBEAT study

Highlights of:

Chest pain, depression and anxiety in coronary heart disease: consequence or cause? A prospective clinical study in primary care

- 803 primary care patients with CHD were followed-up every 6 months for 3 years.
- Chest pain predicts symptoms of anxiety and depression in the long term.
- Symptoms of anxiety predict chest pain only in the short term.
- Symptoms of depression might be a protective factor for chest pain.
- Anxiety and depression tend to be consequences of pain rather than causes of it.