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Long-term trajectories of anxiety and depression in patients with stable coronary heart disease and risk of subsequent cardiovascular events

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Abstract

Background: Anxiety and depression seem to be under-recognized in their importance and are often not incorporated in subsequent prevention strategies in routine clinical care of coronary heart disease.

Methods: The KAROLA cohort included coronary heart disease patients participating in an in-patient rehabilitation program (years 1999/2000) and followed after 1, 3, 6, 8, 10, 13, and 15 years. We identified anxiety and depression trajectories based on the hospital anxiety and depression scale subdomains using joint latent class mixture time-to-event models. We included cardiovascular (CV) events and non-CV mortality as competing endpoints.

Results: We included 1,109 patients (15.4% female; mean age, 59.4 (standard deviation [*SD*] = 8.0) years) with baseline covariate data. Over a median follow-up of 14.8 years, participants experienced 324 subsequent CV events. We identified four anxiety and depression trajectory classes, a low-stable class (52.2% and 69.6% of patients for anxiety and depression, respectively), moderate-stable class (37.6% and 23.8%), increasing class (2.3% and 3.3%), and high-stable/high-decreasing class (7.9% and 3.3%). The hazard ratio (HR) for subsequent CV events for the increasing anxiety class was 2.13 (95% confidence interval [CI], 0.61; 7.45) compared with the low-stable class after covariate adjustment. Patients following the high-decreasing anxiety trajectory showed an HR of 1.72 (95% CI, 1.11; 2.68) and patients following the high-stable depression trajectory an HR of 2.47 (95% CI, 1.35; 4.54).

Conclusions: Chronic high anxiety and depression trajectory classes were associated with increased risk of subsequent CV events. Assessments of both symptoms of anxiety and depression during long-term routine medical care are recommended to identify patients who would benefit from appropriate interventions.

KEYWORDS

anxiety, cardiovascular events, coronary artery disease, depression, mortality, trajectories

1 | INTRODUCTION

Anxiety and depression have been recognized as coronary heart disease (CHD) risk factors (Charlson, Stapelberg, Baxter, & Whiteford, 2011; Roest, Martens, de Jonge, & Denollet, 2010). Still, mental health risk factors such as anxiety and depression seem to be under-recognized in their importance and are often not incorporated in subsequent prevention strategies in routine clinical practice. However, there is plenty of evidence that symptoms of anxiety and depression determine the prognosis of patients with CHD (Doering et al., 2010; Kuhlmann et al., 2019; Lespérance, Frasure-Smith, Talajic, & Bourassa, 2002; Melle et al., 2004; Moser et al., 2011; Rugulies, 2002; Watkins et al., 2013), a fact, meanwhile, also reflected in the appropriate guidelines (Lichtman et al., 2008; Piepoli et al., 2016; Smith et al., 2011).

In an earlier study, we reported that patients with normal baseline anxiety and depression levels but an increase during the first year after an index event, are at higher risk for subsequent cardiovascular (CV) events (Rothenbacher et al., 2015). Furthermore, whereas about half of the patients with moderate or severe symptoms of depression at baseline transitioned to no symptoms during 5 years of follow-up, about 6% of patients with no symptoms at baseline transitioned to symptoms of depression within this period (Meyer et al., 2019). For symptoms of anxiety, about 40–50% of the patients with symptoms at baseline transitioned to no symptoms and about 7% of patients with no symptoms to symptoms of anxiety. Although, screening for anxiety and depression symptoms is already recommended (Piepoli et al., 2016; Smith et al., 2011), it might be useful not only at an initial assessment but also during routine follow-up visits.

Mechanisms that link depression to increased CV risk include an unhealthy lifestyle (e.g., smoking, unhealthy food choices, and less physical activity) and low adherence to behavior change recommendations or CV medication regimes (Katzmann, Mahfoud, Böhm, Schulz, & Laufs, 2018; Khawaja, Westermeyer, Gajwani, & Feinstein, 2009). Depression is associated with alterations in autonomic function, changes in the hypothalamic–pituitary axis and in other endocrine markers, which affect hemostatic and inflammatory processes, endothelial function, and myocardial perfusion (Dantzer, O'Connor, Freund, Johnson, & Kelley, 2008; Khawaja et al., 2009). In addition, depression has been linked to an unfavorable lipid profile including higher very-low-density lipoprotein cholesterol, higher triglyceride, and lower high-density lipoprotein cholesterol levels (Bot et al., 2019). A recent Mendelian randomization study suggests that higher levels of triglycerides and C-reactive protein are causally related to depression (Khandaker et al., 2019).

Chronic anxiety is linked to reduced heart rate variability (Chalmers, Quintana, Abbott, & Kemp, 2014), hypertension (Pan et al., 2015), and inflammation (Khandaker, Zammit, Lewis, & Jones, 2016; Pitsavos et al., 2006; Tayefi et al., 2017).

Trajectories of symptoms of anxiety and depression symptom severity over many years have not been well characterized in individuals with CHD and their associations with long-term prognostic outcomes and other competing risks have rarely been studied. However, understanding depression and anxiety symptom trajectories and factors associated with these trajectories are essential for further development of secondary prevention strategies, to improve quality of life, as well as long-term prognosis in patients with CHD. The aim of this study, therefore, was to describe the long-term trajectories of symptoms of anxiety and depression, describe the association with potential pathogenic factors during follow-up (demographic characteristics, markers of lipid metabolism, inflammation, and cardiac function), and finally quantify the risk for subsequent CV disease events after adjustment for covariates and considering competing risks in a cohort of patients with stable CHD at study entry.

2 | METHODS

2.1 | Study population and study design

The prospective KAROLA cohort study included participants with CHD (International Classification of Diseases [ICD], 9th Rev. pos. 410–414) aged 30–70 years participating in an in-patient rehabilitation program between January 1999 and May 2000 in one of two rehabilitation clinics in Germany (Schwabenland-Klinik, Isny, and Klinik am Südpark, Bad Nauheim), as previously described (Rothenbacher, Hahmann, Wüsten, Koenig, & Brenner, 2007). In Germany, all patients discharged from an acute care hospital after an acute coronary syndrome or coronary artery bypass grafting are offered a comprehensive in-hospital rehabilitation program.

KAROLA only included participants who were admitted to rehabilitation within 3 months after their first acute event or coronary artery bypass grafting. Of all eligible participants admitted to the in-patient rehabilitation clinic during the recruitment period, 58% agreed to participate (n = 1,206). All subjects gave written informed consent. The study was approved by the Ethics Boards of the Universities of Ulm (No. 186/98) and Heidelberg and the Physicians' chambers of the States of Baden-Württemberg and Hessen.

2.2 | Data collection

At the beginning of the in-patient rehabilitation program, all participants filled out a standardized questionnaire containing sociodemographic information and medical history. Participants were followed after 1, 3, 6, 8, 10, 13, and 15 years. Information was obtained from the patient via a mailed standardized questionnaire. The German Hospital Anxiety and Depression Scale (HADS) version (Herrmann, 1997) was included in all questionnaires but those at the 10- and 13-year follow-up. HADS is a standardized, self-administered questionnaire containing 14 questions to quantify generalized anxiety and depression (seven items each) in medical patients (Zigmond & Snaith, 1983) and performs well in patients with cardiac diseases. All items are scored on a four-point Likert scale (0–3 points). A summary score is calculated for both the anxiety subscale and depression subscale, each ranging from 0 to 21. For both

HADS subscales, a cut point of ≥8 is suggested to detect symptoms for anxiety disorders and depression (Zigmond & Snaith, 1983).

2.3 | Follow-up and evaluation of CV disease events

Up to the 15-year follow-up (ending May 2015), primary care physicians completed standardized questionnaires regarding nonfatal subsequent CV disease events since discharge from the in-patient rehabilitation clinic. The vital status during follow-up was assessed via the residents' registration office. In case of death, the exact date and location of death were obtained. Death certificates were obtained from the local public health departments and the main cause of death was coded according to the International Classification of Diseases (ICD-9 pos. 390–459; ICD-10 pos. I0–I99, and R57.0). A subsequent CV event was defined as CV disease as the main cause of death or a primary care physician reporting a diagnosis of nonfatal myocardial infarction or stroke.

2.4 | Laboratory methods

Baseline fasting blood samples were obtained at the end of the rehabilitation. Serum samples underwent centrifugation within 2 hr. Samples were stored for up to 1 month at −20°C and then transferred to a −80°C freezer until analysis. Serum was collected from 1- and 3-year follow-up by the primary care physicians and sent after centrifugation to the study center. Obtained aliquots were stored at −80°C until analysis. Blood lipids and high-sensitivity C-reactive protein at baseline were determined by routine methods in a central laboratory. Cystatin C was measured by immunonephelometry on a Behring Nephelometer II (Dade-Behring). N-terminal pro-B-natriuretic peptide (NT-proBNP) was measured by electrochemiluminescence on an Elecsys 170 (Roche Diagnostics). High-sensitivity cardiac troponin T measurements were performed with a high-sensitivity assay (Roche Diagnostics) on an Elecsys 2010 platform. In parallel, high-sensitivity cardiac troponin I was determined on an Abbott ARCHITECT i1000 platform. Midregional pro-A-type natriuretic peptide (MR-proANP) concentrations were measured with an automated sandwich chemiluminescence immunoassay on a KRYPTOR System (BRAHMS AG, Hennigsdorf/Berlin, Germany).

2.5 | Statistical analysis

Participant characteristics were described as means and standard deviations (*SD*s) and frequencies and percentages, where appropriate. We identified linear anxiety and depression trajectory classes using joint latent class mixture time-to-event models (Proust-Lima, Philipps, & Liquet, 2017). Models for anxiety score and depression score were fit separately. The longitudinal submodel included time after hospital admission as fixed, random, and mixture effects and anxiety or depression score as the dependent variable.

The time-to-event submodel included CV events as endpoints and non-CV mortality as a competing event. Time at risk started at discharge from the in-patient rehabilitation clinic (left truncation) and ended when reaching one of the endpoints. Time at risk was censored when the patient was lost to follow-up or at the last (15-year) follow-up assessment. Based on prognostic factors reported in the literature, sex (female vs. male), age, education (<10 vs. ≥10 years), smoking (former/current vs. never smoker), body mass index (BMI), physical activity (≥3 hr vs. <3 hr per week), history of myocardial infarction (yes vs. no), history of type 2 diabetes (yes vs. no), and the number of affected vessels (2 or 3 vs. 0 or 1) identified in the angiographic evaluation were included as covariates. Missing information on physical activity (2.5%) and an unknown number of affected vessels (5.0%) were treated as extra categories in the analyses. The time-to-event submodel was set up as a parametric proportional hazard model. The submodels were joined by time after hospital admission as the shared component. The appropriate number of trajectory classes was determined by increasing it from one to five and subsequently staying with the number of classes leading to the smallest Bayesian information criterion (Pickles & Croudace, 2010). After identification of trajectory classes, the most common class was chosen as reference.

Associations of demographic and clinical characteristics, as well as associations of selected biomarkers with the probability of class memberships, were investigated in an exploratory manner using log-binomial models on an extended data set including one row per individual and class (Beyersmann, Allignol, & Schumacher, 2012, pp. 108–109). The probability of class membership, as estimated by the joint latent class mixture time-to-event model, served as the dependent variable. The model concerning demographic and clinical characteristics was mutually adjusted. The biomarker models included sex and age, and one biomarker at a time. Biomarkers with skewed distributions were log-transformed in advance. The results are reported as the relative probability of class membership, compared with the reference trajectory class, per one *SD* of the respective biomarker (either on natural or on log-scale). We performed all analyses with R (R Foundation for Statistical Computing, Vienna, Austria) version 3.5.1. Joint latent class mixture time-to-event model was estimated using the R package lcmm version 1.1.8.

3 | RESULTS

Overall, 1,109 patients with stable CHD at baseline were included in this analysis. Patients had a mean age of 59.4 years at baseline and 15.4% were female. Further characteristics are displayed in Table 1. Over a median follow-up of 14.8 years, the participants provided 4,780 HADS assessments, 324 participants experienced a subsequent (fatal or nonfatal) CV event (27.4 events per 1,000 person-years), and 147 participants died due to other causes (12.4 deaths per 1,000 person-years).

We identified four anxiety trajectory classes based on the anxiety subdomain of the HADS, as well as four depression trajectory classes based on the depression subdomain of the HADS. The number and form

TABLE 1 Characteristics of the study population

	N	
Age (years), mean (*SD*)	1,109	59.4 (8.0)
Female sex, *n* (%)	1,109	171 (15.4)
Education <10 years, *n* (%)	1,109	663 (59.8)
Former/current smoker, *n* (%)	1,109	759 (68.4)
Body mass index, mean (*SD*)	1,109	26.9 (3.3)
Physical activity, *n* (%)		
Up to 3 hr per week	1,109	512 (46.2)
More than 3 hr per week	1,109	569 (51.3)
Not answered	1,109	28 (2.5)
History of myocardial infarction, *n* (%)	1,109	650 (58.6)
History of type 2 diabetes, *n* (%)	1,109	195 (17.6)
Clinical score (angiographic evaluation), *n* (%)		
0- or 1-vessel disease	1,109	287 (25.9)
2-vessel disease	1,109	291 (26.2)
3-vessel disease	1,109	476 (42.9)
Unknown	1,109	55 (5.0)
Anxiety score, mean (*SD*)		
Baseline (median 22 days after hospitalization)	1,093	4.9 (3.8)
1-year follow-up	975	5.3 (3.7)
3-year follow-up	809	5.3 (3.8)
6-year follow-up	784	5.0 (3.6)
8-year follow-up	711	4.9 (3.7)
15-year follow-up	408	4.6 (3.4)
Depression score, mean (*SD*)		
Baseline	1,093	4.4 (3.5)
1-year follow-up	975	4.7 (3.8)
3-year follow-up	809	4.7 (3.7)
6-year follow-up	784	4.3 (3.7)
8-year follow-up	711	4.4 (3.7)
15-year follow-up	408	4.6 (3.6)
Follow-up for CV events/non-CV mortality		
Follow-up time (years), median (Q1; Q3)[a]	1,109	14.8 (13.3; 14.9)
CV events, n (%)	1,109	324 (29.2)
Non-CV mortality, n (%)	1,109	147 (13.3)
Lost before last follow-up, n (%)	1,109	232 (20.9)

Abbreviations: CV, cardiovascular; *SD*, standard deviation.
[a]Calculated using the reverse Kaplan–Meier method.

of trajectory classes were similar for depression and anxiety models (Figure 1). Both models identified a low-stable class (Class 1), a moderate-stable class (Class 2), an increasing class (Class 3), and high-decreasing class (for anxiety), and a high-stable class (for depression), respectively (Class 4). The low-stable class was the most frequent class for symptoms of anxiety (52.2% of patients) and depression (69.6% of patients), followed by the moderate-stable classes (37.6% and 23.8% of patients, respectively; Table 2). The remaining patients were distributed across the increasing (2.3% and 3.3%) and high-stable/high-decreasing (7.9% and 3.3%) trajectory classes. While the identified trajectories were similar for symptoms of anxiety and depression, patients did not necessarily fall into the same class for both domains; concordance was found for 67% of patients (Cohen's $\kappa = 0.35$; Table S1).

As shown in Figure 1 (middle panels), the cumulative 15-year CV event incidence varied between 29% and 54% depending on the anxiety and depression trajectory classes, while the competing cumulative 15-year incidence for non-CV mortality varied between 11% and 42% (Figure 1, right panels).

As displayed in Table 2, patients belonging to the moderate-stable anxiety class did not show an increased risk of CV events or non-CV mortality compared with patients following the low-stable anxiety trajectory. The risk for patients on the increasing anxiety trajectory was associated with a hazard ratio (HR) of 2.13 (95% CI, 0.61; 7.45) for CV events and an HR of 6.00 (95% CI, 0.90; 40.1) for non-CV mortality compared with patients on the low-stable trajectory class. However, the low-class share has to be considered and both CI included the null. Patients following the high-decreasing anxiety class had an HR of 1.72 (95% CI, 1.11; 2.68) for CV events and an HR of 1.77 (95% CI, 0.87; 3.59) for non-CV mortality.

The risk for patients on the moderate-stable depression trajectory was associated with an HR of 1.18 (95% CI, 0.34; 4.07) for CV events and an HR of 1.94 (95% CI, 0.21; 17.5) for non-CV mortality. The increasing depression trajectory was associated with an HR of 1.65 (95% CI, 0.44; 6.15) for CV events and an HR of 2.76 (95% CI, 0.31; 27.7) for non-CV mortality compared with patients on the low-stable trajectory class, with both 95% CI including the null. Patients following the high-stable depression class had an HR of 2.47 (95% CI, 1.35; 4.54) for CV events and an HR of 2.26 (95% CI, 0.77; 6.65) for non-CV mortality.

When looking at the demographic and clinical characteristics of the probability of class membership in an exploratory manner, we found that female sex at baseline is associated with a higher probability of belonging to the moderate-stable or the high-decreasing anxiety trajectory classes and lower age to be associated with high-decreasing class when compared with low-stable Class 2 (Table S2). We also found a higher BMI to be associated with an increased probability of belonging to the high-decreasing anxiety trajectory class. Concerning depression, higher age was associated with a higher relative probability of belonging to the increasing class when compared with low-stable class (relative probability, 1.51 [95% CI, 1.05; 2.17]).

In addition, we assessed 989 biomarker samples at baseline, 860 at 1-year follow-up, and 646 at the 3-year follow-up and Table S3 shows numbers and mean values by the included biomarkers. As displayed in Table S4, we did not find consistent associations of blood lipids with the probability of trajectory class membership in these exploratory analyses. Higher C-reactive protein (assessed at two time-points only), cystatin C, and cardiac troponins, were notably associated with a higher probability of belonging to the increasing or high-stable depression trajectory class. Associations of selected biomarkers with other anxiety or depression classes were inconsistent.

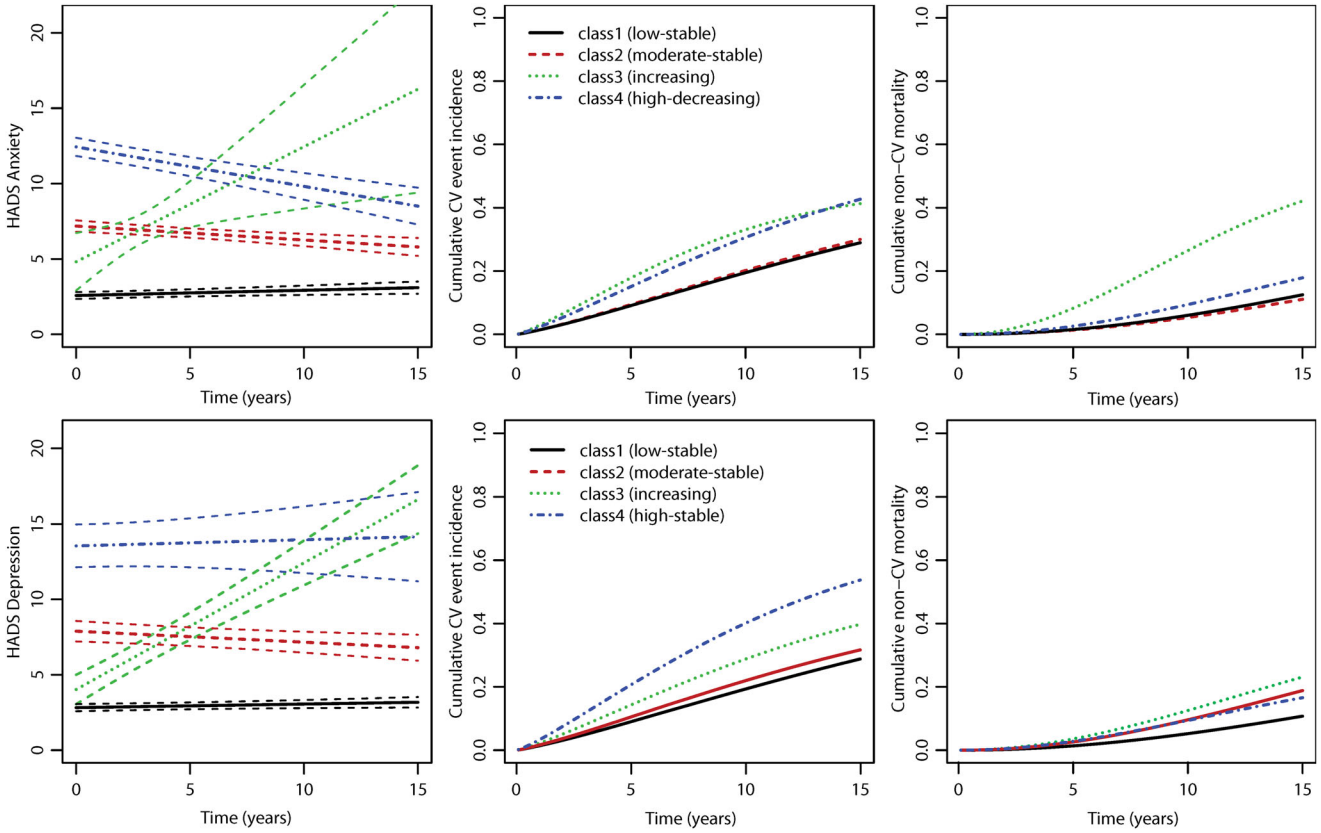

FIGURE 1 Identified anxiety and depression trajectories and event incidence. Left panels: identified anxiety and depression trajectory classes (means with corresponding 95% confidence bands); middle panels: cumulative CV event incidence by follow-up time for mean covariate levels; right panels: cumulative non-CV mortality for mean covariate levels. CV, cardiovascular; HADS, Hospital Anxiety and Depression Scale

4 | DISCUSSION

In this cohort study, including 1,109 patients with stable CHD at baseline, we identified four trajectory classes for both anxiety and depression over long-term follow-up based on the subdomains of the HADS. The high-decreasing class of anxiety symptoms and the high-stable trajectory class of depression symptoms were significantly associated with an increased risk of subsequent CV events, independent

TABLE 2 Risk of subsequent CV events and non-CV mortality by trajectory class (n = 1,109)

		CV events		Non-CV mortality	
Trajectory	Class share in %	Cumulative 15-year incidence[a]	HR (95% CI)[a]	Cumulative 15-year mortality[a]	HR (95% CI)[a]
Anxiety					
Class 1 (low-stable)	52.2	28.9%	(Ref.) 1.00	12.5%	(Ref.) 1.00
Class 2 (moderate-stable)	37.6	30.0%	1.04 (0.43; 2.50)	11.1%	0.89 (0.21; 3.80)
Class 3 (increasing)	2.3	41.3%	2.13 (0.61; 7.45)	42.1%	6.00 (0.90; 40.1)
Class 4 (high-decreasing)	7.9	42.7%	1.72 (1.11; 2.68)	17.9%	1.77 (0.87; 3.59)
Depression					
Class 1 (low-stable)	69.6	28.8%	(Ref.) 1.00	10.7%	(Ref.) 1.00
Class 2 (moderate-stable)	23.8	31.7%	1.18 (0.34; 4.07)	18.8%	1.94 (0.21; 17.5)
Class 3 (increasing)	3.3	39.7%	1.65 (0.44; 6.15)	23.1%	2.76 (0.31; 24.7)
Class 4 (high-stable)	3.3	53.7%	2.47 (1.35; 4.54)	16.6%	2.26 (0.77; 6.65)

Abbreviations: CI, confidence interval; CV, cardiovascular; HR, hazard ratio.

[a]Adjusted for baseline sex, age, education, smoking status, body mass index, physical activity, history of myocardial infarction, history of type 2 diabetes, and angiographic evaluation.

of considered demographic and clinical characteristics. In 67%, concordance of symptoms of anxiety and depression classes was found, but a considerable proportion of patients fell into different trajectory classes concerning symptoms of anxiety and depression.

4.1 | Prevalence, determinants, and trajectories of symptoms of anxiety and depression in patients with CHD

Symptoms of anxiety and depression are widespread in patients with CHD. In the EUROASPIRE III study, a study from 22 countries including 8,580 patients with CHD recruited consecutively 6 months after the acute CHD event, the prevalence of depression (HADS score ≥8) was 21.2% for males and 26.6% for females (Pająk et al., 2013). Symptoms of depression are negatively associated with favorable lifestyle changes. Smoking, poor health behavior, and lack of physical activity seem to play a major role (Elderon & Whooley, 2013). Notably, the persistence of these symptoms is the single biggest driver of health care costs in this patient population (Palacios, Khondoker, Mann, Tylee, & Hotopf, 2018). As shown by Ladwig et al. (2018) in the case of depression after stroke and myocardial infarction, only a minority of patients are treated despite the considerable burden of symptoms, although safe and effective treatment strategies exist.

Exercise and increased physical activity may be used as a powerful add-on therapy to psycho- as well as pharmacotherapy in primary as well as secondary prevention. However, many barriers exist in implementation. In a study of general practitioners, barriers included a lack of knowledge and skills of physicians, patient's opinions and behaviors, a lack of information about treatments provided by mental health professionals, together with long waiting lists for treatment appointments (Sinnema et al., 2013). An improved implementation of guideline-formulated knowledge in routine clinical care is therefore necessary.

Our exploratory analysis suggested that physical activity may be inversely associated with high anxiety or depression trajectories. This is in line with previous analyses of the present study population showing that those being less physically active after 1 year had a higher probability of worse depression and anxiety symptom severity and of CV events after 5 and 10 years regardless of their anxiety or depression status at baseline (Meyer et al., 2019). Interventions aiming at increasing physical activity in CHD patients who additionally suffer from anxiety or depression might be especially beneficial for these patients.

4.2 | Possible pathogenic mechanism of anxiety and depression and biomarker analyses

In our exploratory analyses, higher cystatin C and markers of cardiac function (NT-proBNP, MR-proANP) and cardiac damage (troponins) were associated with the increasing high-stable depression trajectory. Although the details of the underlying mechanisms linking symptoms of anxiety and depression to CV disease need to be clarified, several possible mechanisms have been proposed (for details see also the review of Headrick et al. (2017)). However, all the described factors only account for a small fraction of the associated risk (Carney & Freedland, 2017). It is still unclear whether specific interventions to improve symptoms of anxiety or depression result in lower mortality from specific causes (Machado et al., 2018), although it has been shown in a meta-analysis that psychological treatments reduce the odds for all-cause mortality (Linden, Phillips, & Leclerc, 2007).

The sympathetic nervous system seems to be an important determinant of disease progression. Patients with depression seem to have increased autonomic nervous system activity and associated CV adverse effects including vasoconstriction, heart rate, and heart rate variability (Dhar & Barton, 2016). In an animal model, depression induced exaggerated apoptotic signaling, death, and tissue remodeling after a myocardial infarction (Shi et al., 2014; Wang et al., 2013). However, the findings await corroboration in human patients. Like depression, chronic anxiety is linked to reduced heart rate variability (Chalmers et al., 2014) and inflammation (Khandaker et al., 2016; Pitsavos et al., 2006). In addition, anxiety-associated hypertension may increase CV risk (Pan et al., 2015).

Furthermore, the involved biological networks are complex, and comorbidity and personal lifestyle habits have to be considered. An earlier analysis of our data suggested that well-established risk factors like higher BMI or low-grade chronic inflammation might be associated with categories of depression symptoms, and physical activity may be a moderator, acting bidirectionally (Rothenbacher et al., 2015). The latter association between physical activity and symptoms of anxiety and depression have also been described in the British Whitehall II study, indicating that symptoms of depression and anxiety may also lead to lower physical activity (Azevedo Da Silva et al., 2012).

4.3 | Strengths and limitations

As the study population is predominantly male, we cannot be sure that all findings equally apply to women. Furthermore, the study population was recruited about 3 weeks after the initial acute event and only included patients referred and willing to participate in an inpatient cardiac rehabilitation. Although cardiac rehabilitation is the standard treatment for CHD in Germany, not all patients participate in the program and this could lead to underrepresentation of severely ill patients. However, in Germany, in general, over 80% of patients participated in cardiac rehabilitation after myocardial infarction at the time of baseline recruitment of this study (Grande, Leppin, Romppel, Altenhöner, & Mannebach, 2002). In addition, a recent U.S. claims data analysis, including patients with ischemic heart disease, showed that the presence of comorbid depression was associated with greater participation in cardiac rehabilitation (Krishnamurthi, Schopfer, Shen, & Whooley, 2019). History of myocardial infarction and type 2 diabetes has been assessed via patient

self-report only. Also, no other (noncardiac) somatic comorbidities were included. The observed associations of depression and anxiety trajectories and non-CV mortality may be affected by reverse causality to some extent.

Due to the small class size of identified trajectories, some of the estimates of the investigated associations were imprecise as indicated by wide confidence intervals. In contrast, the chosen approach allowed us to identify interesting small classes that could not be found when relying on standard methods for analysis (e.g., using a single baseline measurement or using predefined classes of change). For example, we found a small increasing depression class which was associated with higher age; this was a rather unexpected finding as most previous studies found younger patients to be at higher risk for depression (Doering et al., 2010; Gottlieb et al., 2004; Moser et al., 2011).

Unfortunately, the sample with baseline biomarkers was smaller than the complete study sample due to a lack of biomaterial for some participants. However, sensitivity analysis indicated a similar distribution of demographics and clinical characteristics in those with and without baseline biomarker data (Table S5). Nonetheless, especially with regard to the biomarker associations, the consistency of the estimates over three assessments suggest that these findings are not purely due to chance.

Furthermore, using a joint model approach, we could include study participants with a varying number of HADS assessments (as low as one assessment only and up to six assessments over 15 years). This economical use of data included all available HADS assessments while at the same time using the complete follow-up period for outcome registration. This way, we minimized potential survivorship bias by not conditioning on those surviving until a follow-up assessment.

When generalizing our results, it should be kept in mind that the reported prevalences of anxiety and depression are quite different throughout studies, which is partly accounted for by differences in the measurement or assessment of symptoms or diagnoses.

5 | CONCLUSIONS

In patients with CHD, chronic high anxiety and depression trajectory classes were associated with an increased risk of subsequent CV events. Although 67% of patients had concordance of symptoms of anxiety and depression classes, a considerable proportion of patients fell into different symptom trajectories classes. Thus, assessments of both anxiety and depression symptoms during long-term routine medical care have the potential to identify patients who would benefit from appropriate interventions.

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CONFLICT OF INTERESTS

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AUTHOR CONTRIBUTIONS

R. S. P., D. R., and H. B. conceived the study. D. R. and W. K. organized and coordinated the laboratory biomarker measurements. F. K. advised on the statistical analysis. R. S. P. performed the statistical analysis. U. M., B. S., R. S., W. K., and H. B. participated in the design and conduct, and coordination of the study. R. S. P., M. L. M., U. M., F. K., B. S., R. S., W. K., H. B., and D. R. have been involved in drafting the manuscript or revising it critically for important intellectual content. All authors read and approved the final manuscript.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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