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# Community series in psychocardiology: Exploring the brain-heart interface, volume II

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# Community series in psychocardiology: Exploring the brain-heart interface, volume II

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# Editorial: Community series in psychocardiology: exploring the brain-heart interface - Volume II

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Editorial on the Research Topic
Community series in psychocardiology: exploring the brain-heart interface - Volume II

In the intricate web of human health, the connection between mental processes and cardiovascular health is indisputable. A simple Google search of "heart-mind connection research" returns over 400,000 hits, underscoring the breadth and depth of exploration into this nexus. While historical intuition has long hinted at this association, it is only in the past two decades that cardiology, psychiatry, and psychology have begun forging profound and enduring collaborations. Volume I of our discourse (Kahl, Alvarenga & Byrne, 2022, Psychocardiology: Exploring the Brain-Heart Interface, *Frontiers in Psychiatry*, doi. 10 3389/978–2-058–3) laid the groundwork by emphasising the need for further investigation into the brain-heart interface, and thus birthing Volume II of our exploration of this domain.

In Volume 2, Bertele et al. illuminate the significant influence of adverse childhood experiences (ACEs) on adult mental and cardiovascular health, providing evidence that early psychological distress is not confined to the mind but also has the potential to impact onto the body, affecting heart health primarily through lack of exercise and poor dietary choices. They suggest that depression is the mediating factor in the pathway between ACEs and cardiac risk factors, like increased epicardial adipose tissue. This finding carries significant implications for the prevention of heart disease by recognising and addressing mental health issues across the lifespan.

Depression continues to demonstrate its prominence as both a risk factor and a side effect of heart disease, not only amplifying the risk of developing CVD but also worsening its prognosis and complicating its management. Keller-Varady et al.'s work demonstrates the transformative potential of physical exercise in ameliorating both mental and cardiovascular illness. Their six-week intervention program highlights the increased benefit of adding psychological interventions, such as Motivational Interviewing, to promote a physically active lifestyle, as measured by increased physical fitness following

adherence to a physical fitness program. And it would be logical to extrapolate this to an expectation of a positive impact onto cardiovascular health.

In the gerontopsychiatric domain, Schulze-Westhoff et al. investigate the determinants of severe QTc prolongation, which is associated with ventricular dysfunction. The use of antipsychotic drugs in the elderly was linked to QTc prolongation, highlighting the need for tailored approaches in managing psychiatric conditions in elderly individuals. Meanwhile, the management of depression in specific clinical populations, such as cardiac surgery patients, poses unique challenges. Vu and Smith found that depression in cardiac surgery patients seemed to stem from pathophysiological factors such as autonomic nervous system dysregulation, excessive inflammation and disruption of the hypothalamic-pituitary-adrenal axis. Behavioural factors, such as poor diet, insufficient exercise, poor medication compliance and low uptake rates of cardiac rehabilitation also contributed to the development of coronary heart disease in depressed patients. Integrative approaches that combine pharmacotherapy, psychotherapy, and lifestyle interventions hold promise in addressing the complex interplay between depression and cardiovascular health post-surgery.

Posttraumatic stress disorder (PTSD) emerges as another psychological facet intricately linked with heart disease. Using the metacognitive model, Wells et al. examined the prevalence of PTSD in a sample of patients referred to a cardiac rehabilitation program. They found high PTSD in the cardiac rehabilitation sample, and metacognitive beliefs of uncontrollability, worry risk and need to control were linked to both anxiety and depression. The prevalence of post-traumatic stress disorder (PTSD) in patients with coronary heart disease underscores the need for comprehensive screening and intervention strategies, specifically, shedding light on the role of metacognition as a potential intervention for PTSD in this population. Furthermore, by identifying individuals at heightened risk, clinicians can intervene early and mitigate the psychological impact on cardiac illness.

In addition to individual factors, the influence of social determinants, such as relationship status, on the psychological well-being of adults with congenital heart disease cannot be overstated. Social support plays a crucial role, particularly given extensive research linking loneliness to heart disease. Understanding how interpersonal relationships affect mental health is vital for providing comprehensive care to this vulnerable population. Stapel et al. examined the association between relationship status and both anxiety and depression in adults with congenital heart disease, revealing that there are significant impacts. Single individuals exhibited higher depression scores, with single women reporting greater anxiety than single men. This study underscores the advantages of spousal relationships for patients with adult congenital heart disease. Once more, the potential would seem to exist for psychologically based interventions seeking to mitigate the impost of congenital heart disease.

Continuing this theme, Le Grande et al. investigated coping style as a crucial mediator in the relationship between illness knowledge and psychosocial outcomes in women with atrial fibrillation, emphasising the importance of personalised interventions tailored to individual coping mechanisms, and the significant role health care providers need to play in ensuring patients are well versed in the conditions from which they suffer.

Nahlen-Bose undertook a meta-analysis of 67 studies investigating psychosocial interventions in heart failure, revealing the short-term benefit of psychosocial interventions for reducing depression and anxiety and improving quality of life among heart failure patients. Future studies could well focus on the long-term effects of these interventions, not only concerning psychosocial outcomes but also cardiac endpoints.

One of the most promising and innovative approaches to providing psychosocial interventions to cardiac patients involves the use of non-blended web applications as brief metacognitive-based interventions. By leveraging technology, Larionov et al. aimed to deliver accessible and scalable interventions that target cognitive processes underlying emotional distress. Good acceptability and feasibility suggest the potential of these interventions to improving mental well-being and coping strategies in CVD patients, with the expectation of improving cardiac prognosis.

Volume 2 of *Psychocardiology* then, takes up the dominant themes established in Volume 1, providing further evidential weight to an already enticing and persuasive narrative. Those themes, in summary, appear to us to be: first, the prominence of depression in the link between the brain and the heart; second, the importance of considering gender in understanding the brain-heart interface; and third, the enormous potential in translating causal or correlational evidence on the brain-heart interaction into evidence-based interventional strategies addressing both mental and cardiovascular health. And in relation to the last of these themes, the crucial need for intensive and broadly based research into the design, implementation, and evaluation of such intervention strategies. By integrating psychosocial perspectives into cardiovascular care, we can pave the way for improved outcomes and enhanced quality of life for patients facing the dual burden of mental and cardiovascular illness.

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# Behavioral pathway to a broken heart: The link between adverse childhood experiences, depression, physical exercise and cardiovascular health

Sebastian Bertele[1*†], Ivo Heitland[1†], Daniela Fraccarollo[2], Britta Stapel[1], Johann Bauersachs[2], Mechthild Westhoff-Bleck[2] and Kai G. Kahl[1]

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**Background and aim:** Adverse childhood experiences (ACEs) are a major risk factor for unfavorable behavioral, mental and health outcomes later in life. However, the precise pathway *via* which ACEs convey these risks, in particular regarding health outcomes such as cardiovascular disease, remains unknown. Here, we combined psychiatric and cardiac methods to investigate the pathway *via* which childhood adversities may lead to adult adverse cardiovascular health, with a focus on epicardial adipose tissue (EAT) as a risk marker.

**Methods:** 210 adult congenital heart disease outpatients (mean age 35.5 y, 43% female) completed a thorough cardiac and psychiatric evaluation. Psychiatric measurements included an expert interview, the childhood trauma questionnaire (CTQ), Beck's depression inventory II (BDI-II), quality of life and the global scale of functioning, amongst others. All patients completed a full cardiac workup including EAT assessment using echocardiography. We then computed bootstrapping mediation models using ACEs as a predictor, depression and physical activity as mediators and EAT as dependent variable in PROCESS.

**Results:** CTQ scores had a significant indirect effect on EAT *via* a serial mediation of BDI and physical activity [a*b2*d = 0.0260, 95% BCa CI [0.0047, 0.0619]].

**Conclusion:** Using mediation analyses, we show that adverse childhood events are linked to increased depressive symptoms, which are linked to decreased physical activity, which in turn are linked to a higher amount of epicardial adipose tissue. While other pathways most certainly exist and replication is needed, this suggests a meaningful pathway *via* which ACEs lead to adverse cardiovascular health, with several potential targets for health interventions across time.

KEYWORDS

**childhood trauma questionnaire, childhood adversity, childhood maltreatment, cardiovascular disease, depression, physical activity, exercise, epicardial adipose tissue**

# Introduction

Adverse childhood experiences (ACE) are common (1, 2) and pose a high risk for adverse mental health effects (3–5). Emotional or physical abuse and neglect alter what is considered normal psychological development, resulting in limitations of varying degree in mentalization (6), regulation of emotion (7–9), and social interaction (4, 8, 10). All these factors increase a person's likelihood to develop depression or depressive symptoms later in life (2, 10).

ACE such as emotional and physical abuse have long been linked to adverse mental health in adulthood (e.g., major depressive disorder (MDD), post-traumatic stress disorder, anxiety disorder, psychotic disorders) (3, 11, 12) and, more recently, to an earlier decline in cardiovascular health (11, 13) with higher rates of adverse cardiovascular events (e.g., myocardial infarction, coronary artery disease and stroke) (14). Current evidence suggests MDD as an independent risk factor for cardiovascular disease (CVD) (15, 16).

ACE, as described above, are a risk factor for MDD (10). Not only does MDD affect the prevalence of adverse cardiovascular events, it has also been established that depressive symptom have a negative impact on the long-term outcome of those who suffer from CVD (16). A study by Lespérance et al. showed that 5-year mortality after myocardial infarction was higher for those who showed signs of depression (12, 17, 18). Similarly, it has been shown that adult congenital heart disease (ACHD) patients who suffered from MDD showed increased epicardial tissue, a risk marker for the development of CVD (19–21), when compared to those without MDD (22). It therefore stands to reason that there is a link between ACE and cardiac health, potentially through the route of MDD or its psychopathological components.

Moreover, ACE lead to epigenetic (23) changes. They alter the hypothalamus-pituitary-adrenal axis (HPAA) (13), leading to a more pronounced stress reaction in those who have suffered from ACE. Further, increased activation of the sympathetic nervous system and higher activity of the amygdala and limbic system have been described (13). While dysregulation of endocrine and other systems is one possible route to explain the deleterious pathway linking ACE with CVD, other mechanisms may also play a role. Psychological changes (24) concurrent with depressive symptoms like lack of energy or loss of interest may favor an unhealthy lifestyle, which in turn may increase the likelihood of CVD. Behavioral alterations observed with ACE comprises higher rates of tobacco dependence, unhealthy nutritional choices and lack of physical exercise.

One of the generally accepted beneficial behavioral factors to cardiovascular health is physical activity. Regular moderate exercise benefits endothelial function and blood flow (25–27) and reduces general body inflammation (28). Additionally, numerous studies have shown beneficial effects of physical exercise on existing cardiac conditions (26, 27, 29–31). Hence, the absence of physical exercise may be considered a behavioral risk factor for adverse cardiovascular outcomes.

Most current research focuses on the relationship of two variables only–be it the connection between ACE and MDD (24, 32, 33), or the link between physical exercise and CVD (28, 29, 31). Some studies demonstrate links between ACE and CVD (11, 34, 35), and MDD has long been established as an independent risk factor for CVD (15, 16, 36, 37). Research investigating the moderating factors of this connection has thus far been scarce and focused mostly on biochemical and epigenetic changes (34, 38–41). Questions as to what factors mediate the correlation between ACE and CVD, or MDD and CVD remain unclear. The understanding of this pathway may lead to the use of more targeted and effective interventions in patients suffering from both MDD and CVD, and imply useful psychological and behavioral screening measures in the evaluation of cardiovascular risk.

This study examines such a possible pathway between ACE and unfavorable cardiovascular outcomes, and hypothesized that there is a direct behavioral pathway where MDD and subsequent lack of physical exercise moderate higher risk for adverse cardiovascular outcomes, particularly epicardial adipose tissue which is an established risk marker for cardiovascular events.

# Materials and methods

## Participants and study design

The data shown here are part of the PSYConHEART study, an ongoing research project investigating the morbidity and mortality factors in cardiovascular disease, and adults with congenital heart disease (ACHD) in particular. Parts of the data and the study protocol have been published earlier (22). All study procedures were approved by the local ethical committee of Hanover medical school. Written informed consent in accordance with the Declaration of Helsinki was provided by all subjects. All patients were recruited from the ACHD outpatient clinic of the Dep. of Cardiology and Angiology at the Hannover Medical School in Hannover, Germany. Inclusion criteria were (1) structural congenital heart disease, (2) ability to read and complete the informed consent form and questionnaires in German, and (3) age of 18 or older. Exclusion criteria were instable cardiac condition and pregnancy. The sample comprised two-hundred fifteen ACHD patients (120 males, 90 females) of whom 21 had to be excluded due to incomplete data. Details of the underlying heart diseases and treatments are given in Table 1 as well as a previous publication (22).

TABLE 1 Sociodemographic and cardiological data of the sample population.

| | Total $N = 194$ |
|---|---|
| Female gender | 85 (43.8%) |
| Age | 35.1 (±11.1) |
| BMI | 25.4 (±4.98) |
| Drinks per week | 1.96 (±3.44) |
| Smoker | 52 (26.8%) |
| In Partnership | 110 (56.7%) |
| **Schoolyears** | |
| Up to 9 years | 31 (16.0%) |
| Up to 11 years | 93 (47.9%) |
| Up to 13 years | 70 (36.1%) |
| Currently Working | 161 (83.0%) |
| **NYHA Class** | |
| I | 149 (76.8%) |
| II | 34 (17.5%) |
| III | 11 (5.7%) |
| IV | 0 (0%) |
| LVEF (in %) | 56.8 (±8.62) |
| EAT | 0.433 (±0.210) |
| **Congenital heart defect** | |
| Simple shunts | 15 (7.7%) |
| Atrioventricular septal defect | 8 (4.1%) |
| Mitral valve disease | 4 (2.1%) |
| Anomalous pulmonary venous connection | 1 (0.5%) |
| Bicuspid aortic valve | 26 (13.4%) |
| Subaortic stenosis | 6 (3.1%) |
| Coarctation | 23 (11.9%) |
| Congenital pulmonary stenosis | 8 (4.1%) |
| Double chambered right ventricle | 2 (1%) |
| Tetralogy of fallot | 29 (14.9%) |
| Ebstein anomaly | 6 (3.1%) |
| Marfan syndrome | 16 (8.2%) |
| D-Transposition: Atrial switch | 24 (12.4%) |
| D-Transposition: Arterial switch | 1 (0.5%) |
| Congenital corrected transposition | 3 (1.5%) |
| Fontan type circulation | 16 (8.2%) |
| Eisenmenger syndrome | 6 (3.1%) |

## Assessment of psychiatric disorders and behavioral factors

The psychiatric diagnosis was based on the Structured Clinical Interview for Diagnostic and Statistical Manual of Mental disorders, 4th edition (SCID) (42). Raters were experienced psychologists or psychiatrists and blinded for all cardiac data obtained from the patients. All participants underwent full SCID workup. Patients were included in analysis regardless of other diagnoses, like e.g., substance-abuse-disorders or psychotic disorders. Depressive symptoms were assessed using the Beck's depression inventory II (BDI-II) (43), depression severity was assessed using the Montgomery-Åsberg Depression Rating Scale (MADRS) (44). Furthermore, participants completed a demographic survey that included educational, marital, employment status, smoking habits (expressed as pack-years), and alcohol drinking behavior (expressed as drinks consumed per week). Physical activity and exercise were assessed using a 6-point Likert scale with descriptors described as "no physical activity or exercise training" (1); "occasional physical activity (such as walking) or exercise training" (2); "light physical activity or exercise training, but <1 × weekly (3); moderate physical activity or exercise: regular physical activity (cycling or walking) or exercise training 1 × weekly (4); often, more than 1 × exercise training weekly, or cycling plus regular walking; and "very often, exercise training more than 3 × weekly"(5) "daily, exercise training" (6) (45).

## Assessment of adverse childhood experiences

The extended German version Childhood Trauma Questionnaire (CTQ) (46, 47) was used to assess ACE. The 32-item self report questionnaire measures a total of seven subscales on a five-point Likert-Scale. The subscales are emotional abuse, emotional neglect, physical abuse, physical neglect, sexual abuse, Inconsistency, and, as part of the extended version of the questionnaire, "playing down" which measures the patients' tendency to downplay extreme experiences as normal.

For analysis in the pathway analysis only the total mean CTQ-Score was used.

## Assessment of cardiac disease

Each patient was thoroughly examined by a cardiologist as described before (22). Functional status was determined according to the New-York Heart Classification (NYHA class) (48). In short, echocardiography was performed in all patients to evaluate cardiac morphology and function. Cardiac defects were categorized as simple, of moderate or of great complexity using the Warns classification (49). Echocardiographic assessment of EAT was derived from two-dimensional standard parasternal long axis/short axis views at end-diastole. EAT thickness was measured on the right free ventricular wall perpendicular to the aortic annulus. The cardiologist performing echocardiographic assessments (M.W.-B.) was blind to all psychiatric data.

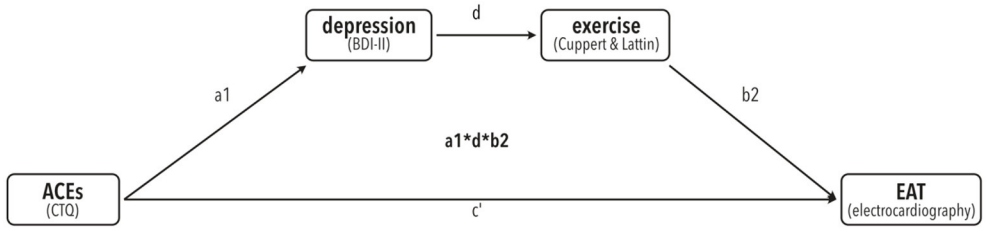


FIGURE 1
A-priori proposed mediation model of the link of ACE's (predictor) with EAT (dependent variable) *via* serial mediators depression (BDI-II) and exercise (Cuppett & Latin scale).

## Statistical analyses

All statistical analyses were conducted with SPSS Statistics version 26.0 (IBM Corp., Amonk, NY, USA) (50) and R "Bird Hippie" V4.1.2 (51). An alpha of 0.05 was used for all statistical tests. Mediation analysis was performed by calculating bias-corrected accelerated (BCa) 95% confidence intervals (CIs) using bootstrapping with 10,000 resamples *via* the PROCESS procedure V3.4 for SPSS (52–54). To test our a-priori hypothesis that ACE's are linked to BDI, which is linked to physical activity, which is linked to EAT, we used a serial mediator model (number 6) with CTQ score as predictor, BDI and physical activity as mediators (in that order), and EAT as dependent variable. For an overview of the model tested here, see Figure 1.

In addition to this bootstrapping-based mediation analysis, following current guidelines (52), we performed regression analyses of all single paths of our mediation model to illustrate single-path links.

# Results

## Sample characteristics

For an overview of demographic and cardiovascular characteristics of the sample, see Table 1. The total sample included in statistical analysis included 194 patients with a mean age at the time of evaluation of 35 years (SD = 11.1 years), of which 85 (43.8%) were female. Less than a third of the patients were smoking at the time and a rough two thirds were in a romantic relationship or married. More than three quarters of the patients were currently working a job.

The sample's mean left ventricular ejection fraction was fairly good at 56.8% (SD = 8.62%) and symptoms of heart failure–especially dyspnoea–were low for most and moderate for some. None of the patients included in the analysis suffered from a NYHA grade IV heart failure.

All results from SCID-diagnostics are presented in Table 2. For characteristics of psychometric properties relevant to this study please refer to Table 3. The mean score from BDI-II was 7.06 (SD = 8.74) and, thus, quite low. However, 40 Patient's scored above the cut-off-level of 14 for a minor depressive Episode (respectively, 8.8% had minor depression, 8.8% moderate depression and 3.1% major depression). This was congruent with results of the semi-structured interview for DSM-IV (55) where 24.2% of the patients could be diagnosed with major depressive episodes and 38.7% patients fulfilled criteria of having suffered from depression within their lifetime. Only 15.6% reported a parent suffering from Depressions. For a more detailed report on the psychiatric characteristics of the sample population, please refer to earlier publications (56).

## Mediation model

To test for significant mediation of the effect of CTQ on EAT *via* the serial mediators BDI and physical exercise (see Figure 1 for our model), we tested presence of a completely standardized indirect effect using bias-corrected bootstrapping with 10,000 resamples and a 95% CI.

There was a significant indirect effect of CTQ on EAT via depression and exercise (a1*d*b2 = 0.0260, se = 0.00148, 95%CI: LL = 0.0047, UL = 0.0619), meaning the effect of CTQ on EAT was mediated *via* the links CTQ -> BDI, BDI -> exercise and exercise -> EAT (Also compare Figure 2).

## Additional regression analyses

Although usage of the mediation procedure developed by Baron and Kenny (57) that employs single regression analyses has been proven invalid and is no longer advised (58, 59), we conducted additional regression analyses to illustrate the relationships between the variables used in our mediation model. All these relationships were significant as described in the following and the same mediation effect was found when using Baron and Kenny criteria (see Figure 3). Please note that presence or absence of such links is neither necessary nor

TABLE 2 Complete results from SCID-Diagnostics as *n* (% of *N*).

| | Total $N = 194$ |
|---|---|
| Current major depression | 47 (24.2%) |
| Lifetime major depression | 75 (38.7%) |
| Chronic depression | 25 (12.9%) |
| Dysthymia | 15 (7.7%) |
| Adjustment disorder | 2 (1%) |
| Hypomania | 3 (1.5%) |
| Delusional disorder | 0 (0%) |
| Schizophrenia | 0 (0%) |
| Substance abuse disorder | 10 (5.2%) |
| Specific phobias | 14 (7.2%) |
| Panic disorder with agoraphobia | 5 (2.6%) |
| Agoraphobia | 7 (3.6%) |
| Panic disorder without agoraphobia | 11 (5.7%) |
| Social phobia | 5 (2.6%) |
| OCD | 3 (1.5%) |
| Bipolar I | 1 (0.5%) |
| Bipolar II | 2 (1%) |
| Generalized anxiety disorder | 14 (7.2%) |
| PTSD | 4 (2.1%) |
| Somatoform disorder | 6 (3.1%) |
| Eating disorders | 6 (3.1%) |
| ADHD | 6 (3.1%) |
| Dyslexia | 15 (7.7%) |
| Avoidant personality disorder | 19 (9.8%) |
| Dependent personality disorder | 11 (5.7%) |
| Anancastic personality disorder | 27 (13.9%) |
| Negativisticpersonality disorder | 0 (0%) |
| Depressive personality disorder | 0 (0%) |
| Paranoid personality disorder | 0 (0%) |
| Schizotypical personality disorder | 1 (0.5%) |
| Schizoid personality disorder | 0 (0%) |
| Histrionic personality disorder | 0 (0%) |
| Narcicistic personality disorder | 3 (1.5%) |
| Borderline personality disorder | 18 (9.3%) |
| Antisocial personality disorder | 1 (0.5%) |

TABLE 3 Data relevant for the pathway-analysis.

| | Total $N = 194$ |
|---|---|
| Sportscore | |
| 1 | 40 (20.6%) |
| 2 | 29 (14.9%) |
| 3 | 33 (17.0%) |
| 4 | 35 (18.0%) |
| 5 | 34 (17.5%) |
| 6 | 23 (11.9%) |
| BDI-2 | 7.60 (±8.74) |
| 0–8 no depression | 122 (62.9%) |
| 9–13 minimal depression | 32 (16.5%) |
| 14–19 minor depression | 17 (8.8%) |
| 20–28 moderate depression | 17 (8.8%) |
| 29–63 severe depression | 6 (3.1%) |
| CTQ | 40.5 (±13.2) |
| Emotional Abuse | 7.42 (±3.53) |
| None to minimal | 144 (74.2%) |
| Low to moderate | 32 (16.5%) |
| Moderate to severe | 7 (3.6%) |
| Severe to extreme | 11 (5.7%) |
| Physical Abuse | 5.89 (±2.50) |
| None to minimal | 173 (89.2%) |
| Low to moderate | 10 (5.2%) |
| Moderate to severe | 4 (2.1%) |
| Severe to extreme | 7 (3.6%) |
| Sexual Abuse | 5.68 (±2.59) |
| None to minimal | 174 (89.7%) |
| Low to moderate | 4 (2.1%) |
| Moderate to severe | 10 (5.2%) |
| Severe to extreme | 6 (3.1%) |
| Emotional Neglect | 8.93 (±3.91) |
| None to minimal | 126 (64.9%) |
| Low to moderate | 50 (25.8%) |
| Moderate to severe | 11 (5.7%) |
| Severe to extreme | 7 (3.6%) |
| Physical Neglect | 6.61 (±2.32) |
| None to minimal | 145 (74.7%) |
| Low to moderate | 32 (16.5%) |
| Moderate to severe | 12 (6.2%) |
| Severe to extreme | 5 (2.6%) |
| Inconsistency | 5.12 (±2.78) |
| Playing down | 0.820 (±1.00) |

Shown as either n (% of N) or Mean (± standard deviation).

meaningful in the analysis of mediation, which can be measured using single bootstrapping techniques (53, 59). Nonetheless, we chose to show these data for an easier understanding of the relationships.

## Discussion and limitations

In this study, we examined the relationship between adverse childhood experiences (ACE) and their link to increased cardiovascular risk in adulthood. The results of the statistical analysis support the hypothesis that ACE path the way to

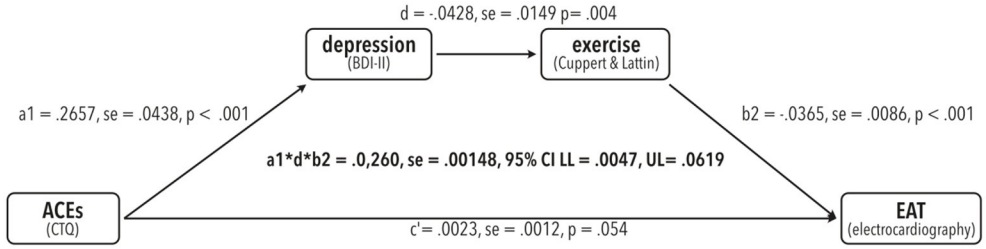


FIGURE 2
Results from the testing the serial mediation model (model number 6) proposed in Figure 1 using bias-corrected bootstrapping with 10,000 resamples in PROCESS for R V4.0.1 with a 95% confidence interval (CI). Unstandardized regression coefficients are shown with the corresponding se (standard error) as well as t-values and *p*-values per path. Indirect effect statistics are shown in the center with completely standardized regression coefficients, se and corresponding lower limits (LL) and upper limits (U).

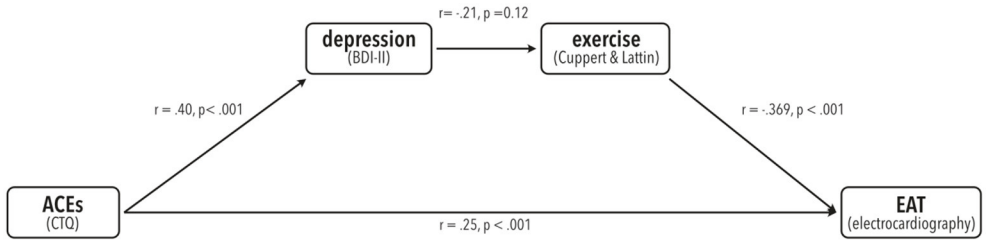


FIGURE 3
Illustration of the results from single linear regression analyses from all paths present in the mediation model. Pearson's r-values and corresponding *p*-values are shown.

the development of depressive symptoms. Loss of energy and anhedonia are important symptoms of depression, therefore one could argue that the reduction of physical activity may be the consequence of depressive psychopathology. The net effect of depression plus physical inactivity may then foster the development of epicardial adipose tissue over time. This temporal sequence is in line with the allostasis model (60, 61), which describes the cumulative effects of experiences in life that involve ordinary events as well as major challenges, resulting in physiological changes and health jeopardizing behaviors (35).

ACE, *via* the pathway of depression and subsequent reduced physical exercise, correlates with an increase in epicardial adipose tissue and, therefore, risk for adverse cardiac outcomes.

This pathway opens room for interventions on all levels of prevention and may be considered within the framework of preventative medicine. Future research may focus on primary prevention of ACE altogether—an intervention which will likely need to happen on a societal level and appears even more important in view of the consequences of ACE for cardiovascular health.

Secondary prevention may focus on avoiding the development of depressive symptoms in those who have suffered from ACE. In this view, secondary prevention may not only improve the quality of life of those who suffered ACE, but also reduce the risk of psychiatric and cardiovascular morbidity in later life.

Once depression has developed, the pathway described above implies that special interest of tertiary prevention may be the increase of physical activity. These patients may profit doubly from approaches focusing on the reduction of loss of energy–once in terms of depression and once in terms of a reduction in cardiovascular risk. Thus, preferred medications may be those which are effective and have a favorable side effect profile, i.e., low risk of gaining weight. Psychotherapeutic interventions that increase activity, such as cognitive behavioral therapy (62), acceptance and commitment treatment (54, 63), or behavioral activation (64, 65), have shown efficacy in the treatment of depression but may also be beneficial for cardiac health although evidence in this regard is currently lacking. Other psychological interventions have also shown effectiveness particularly in patients with underlying ACE, such as the cognitive behavioral analysis system of psychotherapy (CBASP) (66, 67).

Of course, this pathway shows the behavioral level of connection between ACE and EAT and questions as to the biological mechanisms behind it remain mostly unclear. Part of the increased cardiovascular risk after ACE may be explained through HPAA-activation. Former studies from our center

linked ACE to hypercortisolism with a consecutive increase of adrenal gland volume as mediating factors for EAT (68, 69). Further research may however incorporate e.g., epigenetic factors and their link to observable behavior as well to generate a more complete understanding of the mechanisms behind this behavioral pathway.

The results of our study add to the literature in that ACEs have long-term effects on mental and physical health, and on health behavior. Hughes et al. found in their systematic review that multiple ACE pose a major risk for many health conditions, and, especially, for next-generation ACE (35).

Other studies described marked changes in the HPAA both in terms of lowered and elevated cortisol levels. A meta-analysis by Klaassens et al. (38) found that while neither adulthood exposure to trauma nor PTSD changed HPAA-functioning, they significantly augmented cortisol suppression. Khoury et al., in yet another meta-analysis evaluating the association between ACE and hair cortisol levels (39), suggested that there is in fact a hyperactivity of the HPAA that due to neurodepletion forms into a hypoactivity and thereby lowered cortisol levels. These changes in cortisol secretion have hitherto been linked to a marked increase in cardiovascular risk (35, 70). Pilkington et al. found in their meta-analysis that ACE, especially emotional neglect, correlated with maladaptive schemas (24)—which in turn contribute to various psychological problems, including depression (11, 71).

This study's results point toward a definite behavioral pathway that links ACE to CVD-risk by means of depression and consecutive physical inactivity and, thus, provides insight into possible points of intervention.

Previous studies using mediation analysis to examine the pathway linking ACE to cardiovascular risk, support this study's findings. A report of the Whitehall II study cohort by Deschênes et al. found that ACE were associated with a higher risk of diabetes *via* the pathway of depressive symptoms or cardiometabolic dysregulation (34). Slopen et al., complementary to this study, found that positive childhood experiences were connected to cardiovascular health, mediated by depressive status and social support (40). Kraynak et al. found a possible pathway between childhood physical abuse and corticolimbic activity (specifically that between amygdala, ACC and vmPFC) mediated by systemic inflammatory response (IL-6 levels). As there is a connection between long-term IL-6 levels and physical activity (72), the pathway shown in this study may extend the Kraynak's findings. Further research in mediating factors may complete the pathway that links ACE to depressive symptoms, neuroendocrinological dysfunction, systemic inflammatory response and cardiovascular health.

Limitations of this study exist. Firstly, there is the general limitation of a relatively small sample size and the herewith connected question of representation of the studied sample for a more general population. While we aimed to correct this by means of bootstrapping, further studies replicating the findings of this study are needed to confirm the pathway.

Secondly, there is the issue as to the selection of patients studied. The sample included only patients with congenital heart disease and may therefore not be representative for a broader population. Not in the least, because of the major impact that the diagnosis of a congenital heart disease has on the family system, potentially causing an atmosphere of anxiety and insecure attachment and, thus, harboring ACEs. Interestingly, both amount of ACE and their severity as reported by this study's subjects were relatively low (which, duly noted, implies that there, at least, was no over-reporting due to the retrospective collection of data on ACE). No more than 6% of the patients reported ACE corresponding with moderate to severe scores and even on the scale of emotional neglect, only 35.1% answered above the cut-off value. Hence, there is a slim possibility that the mediated effect may be a coincidental result or that a greater effect of ACE remains masked.

Thirdly, the retrospective report of childhood trauma may have lead to recall and other kinds of memory or reporting biases (73, 74). Hence, a prospective longitudinal study that examines the relationship between ACE and later health, especially with a focus on the development of psychiatric morbidity and connected cardiovascular morbidity, may provide further insight into the mechanisms that connect ACE with cardiovascular risk. We do, however, believe that the patient's individual perception of their childhood experiences as traumatic, regardless of whether or not external observers would rate them as such, plays a major role for the effects that ACE have on the patient's later biography. We thus believe it justified to use a retrospective self-report questionnaire.

In summary, we found an association of ACE to cardiovascular risk (in terms of increased EAT) which was mediated by means of depression and subsequent reduction of physical activity, and have thereby shown a first behavioral pathway that links ACE to cardiovascular health. While there are some limitations mainly due to statistical power (which was corrected by bootstrapping), and potential selection bias (too low CTQ-values, only ACHD patients), these findings are robust–especially in view of the logical soundness of the hypothesis.

## Data availability statement

All data supporting the conclusions of this article will be made available by the authors upon request without undue reservation.

## Ethics statement

The studies involving human participants were reviewed and approved by Ethics Commission of Hanover Medical School.

The patients/participants provided their written informed consent to participate in this study.

## Author contributions

The text was primarily written (in equal shares) by IH and SB. All authors listed contributed substantially to this study's conception, design, and performance. All authors contributed to the article and approved the submitted version.

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## Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

## Publisher's note



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# A meta-review of systematic reviews and meta-analyses on outcomes of psychosocial interventions in heart failure

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**Introduction:** Chronic heart failure is a severe condition that influences not just the physical dimension but also the mental dimension in patients. Comorbidity of depression and anxiety are prevalent and the quality of life is reduced. Despite the psychological impact there are no recommendations in the guidelines for psychosocial interventions for people with heart failure. The aim of this meta-review is to synthesize results of systematic reviews and meta-analyses on the outcomes of psychosocial interventions in heart failure.

**Methods:** Searches were conducted in PubMed, PsychInfo, Cinahl and the Cochrane Library. In total, seven articles were included after screening 259 studies for eligibility.

**Results:** The included reviews had, in total, 67 original studies included. The measured outcomes in the systematic reviews and meta-analyses were; depression, anxiety, quality of life, hospitalization, mortality, self-care and physical capacity. The results are inconsistent but show some short-term benefit of psychosocial interventions for reduced depression and anxiety and improved quality of life. However, the long-term effects were sparsely followed up.

**Discussion:** This meta-review appears to be the first in the field of the efficacy of psychosocial interventions in chronic heart failure. This meta-review identifies gaps in the current available evidence that need to be further explored, such as booster sessions, longer follow-up time for evaluation and incorporating clinical outcomes and measures of stress processes.

KEYWORDS

**anxiety, depression, heart failure, intervention, psychosocial, quality of life, review**

## Introduction

The prognosis of chronic heart failure (CHF) is serious, as the survival rate is comparable with common forms of cancer (1). The prevalence of CHF is estimated to be 1–2 percent of the population but increases sharply with age, where the prevalence in people older than 70 years is >10 percent. Heart failure is a clinical syndrome with symptoms such as breathlessness, fatigue and ankle swelling and may have objective signs such as pulmonary crackles. CHF is caused by functional and/or structural pathology and the outcome may be a reduced cardiac output or increased intracardiac pressure (2). Living with heart failure affects several dimensions of the person's life, not just the physical but also their emotional, social and spiritual dimensions. CHF requires people to adjust to a new life situation and adopt coping strategies (3). The prevalence of depression and anxiety is high (4, 5) and depression is an independent predictor of mortality

in CHF (6). Moreover, the quality of life (QoL) is reduced where depression has been found to correlate with QoL (7). With regard to the psychological impact, patients with CHF may, besides pharmacological and device treatment, need psychosocial interventions. Yet, the latest guidelines for CHF are lacking recommendations for psychosocial interventions (2), most likely because the evidence is not coherent or sufficient. In the guidelines for CHF, level A evidence is data generated from multiple randomized controlled trials or meta-analyses (2). This meta-review aims to synthesize results of systematic reviews and meta-analyses on outcomes of psychosocial interventions in heart failure.

# Methods

## Eligibility criteria

The inclusion criteria were systematic reviews and meta-analyses on psychosocial interventions for persons with heart failure that evaluate psychological outcomes. Psychosocial interventions were defined as interventions that had a psychoeducative component, e.g., cognitive behavioral therapy (CBT) or coping skills training. The studies should have been published within the last 10 years.

Exclusion criteria were: original studies not written in English, comparative reviews or meta-analyses between different treatments for depression, e.g., between pharmacological treatment and psychosocial interventions, reviews or meta-analyses on cardiac rehabilitation or interventions solely focusing on tai-chi, yoga or mindfulness or other interventions that lack a psychoeducative component and reviews with mixed patient populations.

## Search strategy and quality assessment

Searches in the following databases were performed in September 2022: PubMed, PsychInfo, Cinahl and Cochrane library. Reference lists in the articles, that were read in full text, were also screened for eligible studies. The search string was "(((heart failure AND (intervention OR therapy)) AND (psycho* OR coping)) AND (review OR meta-analys*)." The filter was set to article-type: Meta-analysis, Review, Systematic review in PubMed and Literature review, Systematic review, Meta-analysis in PsychInfo.

AMSTAR-2 was used as a guide for the quality assessment of the systematic reviews and meta-analyses (8). The AMSTAR-2 tool consists of 16 quality appraisal items. Based on the evaluation a recommended level of critically low to high quality was suggested. The tool does not generate a quality score. Seven of the items are considered critical, for example, risk-of-bias assessment in the individual studies. If the study did not fulfill one critical item, the recommended level is low quality and if two critical items are not fulfilled the study is assessed as critically low quality.

## Data extraction and analysis

Data from the articles concerning type of review, numbers and types of studies included, total number of participants, intervention, comparator, outcomes and effect size were extracted to an article matrix. Furthermore, all original studies included in the systematic reviews and meta-analyses were charted in a table to investigate how many times the individual original studies were included in the systematic reviews and meta-analyses.

The results of the studies were grouped based on the outcome measures and described in a narrative form.

# Results

## Study selection and characteristics of included studies

Initially, 259 titles were screened after duplicates had been removed. After abstracts were screened, 16 articles were read in full text. Eleven of those articles did not meet the eligibility criteria and the reasons for exclusions of each article can be found in Supplementary material 1. An additional two articles were found to meet the eligibility criteria through reference screening of the full text articles, hence seven articles were included in the study (9–15) (Figure 1).

The characteristics of the included studies are shown in Table 1. Of the seven studies, four included only randomized controlled trials and three included a mixture of both randomized controlled trials and non-randomized controlled trials. Six of the studies had performed meta-analyses. Two of the studies focused solely on CBT and the rest had a mixture of CBT and other forms of psychosocial interventions like coping skills training. The main comparator was usual care solely or usual care and/or heart failure education. In total, 67 individual original studies were included in the systematic reviews and meta-analyses, where 19 of the original studies were included in several (between 2 and 7) of the systematic reviews and meta-analyses (Supplementary material 2). Possible explanations for the variability of the how many times an original study was included in the reviews could be the intervention type or sample size, e.g., if it was a pilot study or a full-scale study. The different outcome measures in the systematic reviews and meta-analyses were depression, anxiety, quality of life (QoL), hospitalization, mortality, self-care and physical capacity. The most frequent measured outcomes were depression and QoL, that all reviews had included as outcomes. The other outcomes were included on average in two to three of the reviews.

The quality appraisal with AMSTAR-2 yielded five studies to have moderate quality (9–13), one study to have low quality (14) and one to be of critically low quality (15). The article with critically low quality had, for instance, not performed a risk-of-bias assessment of the individual articles which is consider a critical item in AMSTAR-2.

## Depression

All seven reviews had depression as an outcome measure post-intervention, where two of the reviews also reported longer-term assessments (10, 12). Two of the reviews included patients with CHF and comorbid depression or depressive symptoms (11, 12). In the five meta-analyses post-intervention, four meta-analyses reported statistically significant reduction in depression with a small to moderate effect size (0.27–0.41) (9, 10, 12, 14).

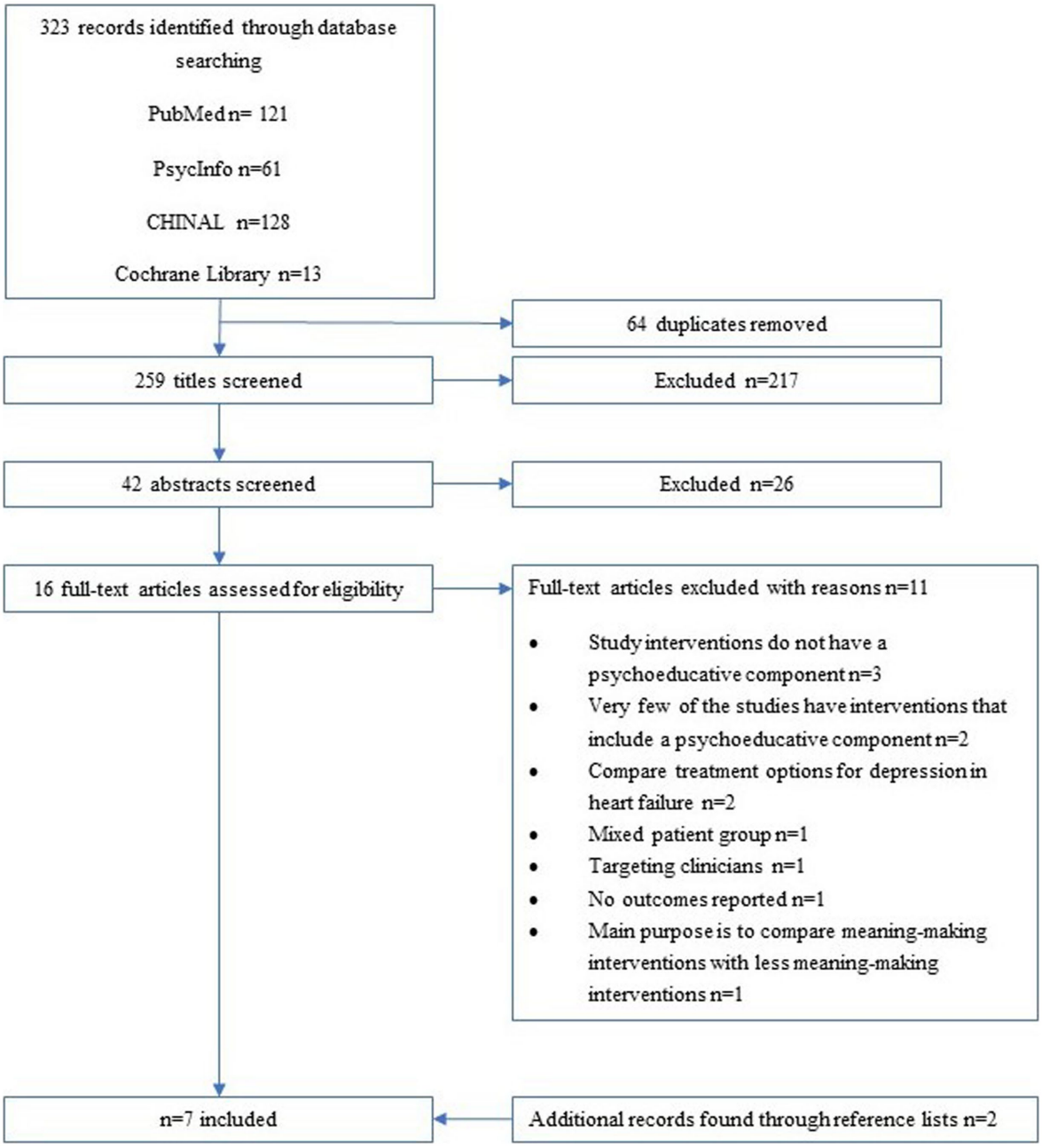


FIGURE 1
Flowchart of identification, screening and inclusion process.

One meta-analysis reported a non-significant result, however, the authors mentioned results that showed a trend for reduction in depression in the intervention group (15). One meta-analyses also divided the meta-analyses for CBT and stress management intervention where both showed significant reductions in depression (CBT −0.37, 95% CI −0.70 to −0.05, $p = 0.024$, Stress management −0.51, 95% CI −0.83 to −0.19, $p = 0.002$) (9). Follow-up assessments showed inconsistent results where one meta-analysis had sustained reductions in depression after 3 months with a moderate effect size (12) and one meta-analysis could not show a sustained effect at last follow-up assessment (21.86 weeks ±14.65, range = 12–52 weeks) (10).

Two studies had not performed a meta-analysis due to high heterogeneity (11, 13) and presented the result in a narrative form. In the systematic review by Jiang et al. (13) 10 studies evaluated depression, and four reported significant reduction in depression. Helal et al. (11) divided the synthesis for depression in three groups: (1) CBT: Two of five studies reported statistically significant reduction in depression in the intervention group. The other three studies reported non-significant reductions in depression for the intervention group. (2) Combined CBT and exercise: One study showed statistically significant reduction in depression for the intervention group. The other study did not show significant between-group differences. (3) Other psychological interventions: Three studies

TABLE 1 Article matrix.

| First author and year published | Type of review | Number of studies included and design of studies included | Total number of participants | Intervention | Comparator | Outcomes | Effect size, SMD (95% CI) |
|---|---|---|---|---|---|---|---|
| Chernoff et al., 2022 | Systematic review and meta-analysis | 23 RCTs except 1 that had an incomplete randomization (15 included in the meta-analysis) | 1,370 included in the meta-analyses | Psychosocial interventions – two groups: CBT and stress management | Mostly usual care and/or heart failure education | Depression<br>Anxiety<br>QoL<br>Hospitalization<br>Mortality | Post-intervention (all studies CBT + stress management)<br>Depression −0.41 (−0.66 to −0.17) $p = 0.001$, $k = 15$<br>Anxiety −0.33 (0,51 to −0.15) $p < 0.001$, $k = 8$<br>QoL 0.14 (−0.002 to 0.29) $p = 0.053$, $k = 8$ |
| Gathright et al., 2021 | Systematic review and meta-analysis | 23 RCTs | 2,294 | Stress management interventions defined as approaches to strengthen an individual's skills to identify, understand, and cope with psychological and physical stress. | Mostly usual care and/or heart failure education | Depression<br>Anxiety<br>QoL<br>Exercise capacity | *First post-intervention assessment:*<br>Depression 0.39 (0.03–0.75), $k = 13$<br>Anxiety 0.49 (0.09–0.89), $k = 10$<br>QoL 0.82 (0.40–1.24), $k = 16$<br>Exercise capacity 0.57 (0.20–0.95), $k = 14$<br>The last assessment post-intervention did not show any significant differences between intervention and control groups |
| Helal et al., 2020 | Systematic review | 9, 5 RCTs and 4 NRSI | 757 | Psychological interventions. Mainly CBT and coping skills training | Mostly usual care and/or heart failure education | Depression<br>QoL<br>Hospitalization<br>Mortality | N/A |
| Jeyanantham et al., 2017 | Systematic review and meta-analysis | 6, 5 RCTs and 1 NRSI (observational) | 320 | CBT | Mostly usual care | Depression<br>QoL<br>Hospitalization<br>Mortality | *Post-intervention*<br>Depression −0.34 (−0.60 to −0.08) $p = 0.01$, $k = 5$<br>*3 months FU*<br>−0.32 (−0.59 to −0.04) $p = 0.03$, $k = 5$<br>*Post intervention*<br>QoL −0.31 (−0.58 to −0.05) $p = 0.02$, $k = 5$<br>No difference in QoL after 3 months.<br>No differences in hospitalization or mortality |
| Jiang et al., 2018 | Systematic review and meta-analysis | 25 RCTs (in 29 articles) | 3,837 | Psychological interventions defined as interventions based on psychological principles, such as CBT, motivational interviewing, nondirective counseling, and supportive therapy | Usual care | Self-care<br>QoL<br>Physical function | No effect size on self-care as high heterogeneity recommended not to combine results.<br>Anxiety (short-term FU) −0.07 (−0.59 to 0.45), $k = 4$<br>(mid-term FU) −0.69 (−1.69 to 0.31), $k = 4$<br>(long-term FU) 0.04 (−0.45 to 1.25), $k = 2$<br>QoL (3-months FU) combined MD −7.53 (−12.83 to −2.23), $k = 3$<br>Not significant at 5–6 months FU.<br>Physical function (6-months FU) combined MD 30.17 (−13.85 to 74.19) $p = 0.18$, $k = 3$ |

*(Continued)*

TABLE 1 (Continued)

| First author and year published | Type of review | Number of studies included and design of studies included | Total number of participants | Intervention | Comparator | Outcomes | Effect size, SMD (95% CI) |
|---|---|---|---|---|---|---|---|
| Peng et al., 2019 | Systematic review and meta-analysis | 8 RCTs | 480 | CBT | Mostly usual care and /or heart failure education | Depression<br>QoL<br>Self-care<br>6-min walk test distance | Depression −0.27 (−0.47 to −0.06) $p = 0.01$, $k = 5$<br>QoL 0.21 (−0.01 to 0.42) $p = 0.06$, $k = 5$<br>Self-care 0.12 (−0.18 to 0.42) $p = 0.44$, $k = 2$<br>6-min walking test 0 (−0.28 to 0.28) $p = 0.99$, $k = 3$ |
| Samartzis et al., 2013 | Meta-analysis | 16 RCTs | 1,074 | Psychosocial interventions defined as a structured nonpharmacologic intervention conducted by health professionals that is focused on improving the psychologic and/or social aspects of a patient's health | Usual care | QoL<br>Depression | QoL 0.46 (0.19–0.72) $p < 0.001$, $k = 16$<br>Depression 0.98 (0.01–1.94), $k = 3$ |

RCT, Randomized Controlled Trial; NRSI, non-randomized studies of interventions; CBT, Cognitive behavioral therapy; QoL, Quality of Life; SMD, Standardized Mean Difference; CI, Confidence Interval; FU, Follow-up; MD, Mean Difference; *k* denotes number of studies included in the meta-analysis.

(coping skills training, mindfulness-based psychoeducation, and innovative holistic meditation) showed statistically significant reduction in depression in favor for intervention group.

## Anxiety

Three of the reviews reported anxiety as an outcome measure (9, 10, 13). Two meta-analyses showed statistically significant improvements in anxiety with a moderate effect size (0.33 and 0.49) (9, 10). In one meta-analysis no significant improvements were found (13). Meta-analyses on follow-up assessments between 3 and 12 months could not find any significant effect on anxiety (10, 13).

## Quality of life

All seven reviews had quality of life as an outcome measure. Six of the reviews performed meta-analyses where four reviews found statistically significant improvements in quality of life with a moderate to high effect size (pooled standardized difference 0.31–0.82) (10, 12, 15) and combined mean difference of −7.53 on the Minnesota Living with heart failure questionnaire (13). The effect was not sustained after 3–6 months follow-up (10, 12, 13). In one of the meta-analyses that did not find a statistically significant effect for all the included studies, divided the studies into CBT and stress management and then found a significant improvement for CBT, with a small effect size (0.20), but not for stress management interventions (9). In the systematic review where no meta-analyses had been performed four (two RCTs, one prospective cohort study and one pilot study) out of seven studies reported statistically significant improvement in HRQoL (11). Furthermore, one meta-analysis found that face-to-face was more effective than telephone interventions (15).

## Clinical outcomes

Three reviews reported clinical outcomes on hospitalizations and mortality (9, 11, 12). In each of the systematic reviews and meta-analyses there were between 1/3 and 2/3 of the included original studies that had data on clinical outcomes. One meta-analysis found no significant effect on mortality or rehospitalizations (12). The two other studies presented the result in a narrative form and the results were inconsistent (9, 11). Three out of five original studies reported less cardiac events in favor of the intervention group in one of the reviews (9). In the other review one out of three original studies reported significant reduction in mortality for the intervention group and all RCTs reported statistically significant reduction in hospitalization rates favoring the intervention group (11).

## Self-care

Two reviews had self-care as an outcome measure (13, 14). One of them had performed a meta-analysis that could not find any significant improvements in self-care (14). The other review did not perform a meta-analysis due to high heterogeneity. Of the nine original studies that evaluated the effectiveness of psychological interventions on self-care, six of the studies reported a positive short-term (at 1–3 months post intervention) effect of psychological intervention on a patient's self-care behaviors in patients without clinical depression (13).

## Physical capacity

Three reviews had physical capacity as an outcome measure (10, 13, 14). The physical capacity was mainly measured by a 6-min walking test. The findings are inconsistent, where one meta-analysis found significant improvement in physical capacity (10) whereas another meta-analysis did not find significant improvements (14). Longer-term evaluations could not find a significant effect at 3–6 months follow-up (10, 13).

## Moderators

Three of the reviews also performed meta-regression analyses to check for potential moderators of change in the outcome measures (9, 10, 15). The different moderators were; severity of heart failure as measured by New York Heart Association (NYHA) class, mean age, sex, length of study, intervention type, mean ejection fraction (EF) at baseline, proportion using beta-blockers and delivery modality (individual vs. group format, presence of home practice). Female sex was associated with a reduction in depression (9) and anxiety were more successfully reduced when the sample had a higher proportion of females (10). NYHA class I and II were associated with reduction in depression (9) and the effect size of QoL was less when the sample consisted of more patients in NYHA class III and IV (10). With regard to intervention type one review found a difference in QoL where CBT was associated with reduction in QoL whereas stress management interventions were not (9). There was no moderating effect on the other outcomes. One review did not find any significant moderating effect of the variables NYHA class, mean age, sex and length of study on the effect size for QoL (15).

# Discussion

To the author's knowledge, this is the first meta-review on the outcomes of psychosocial interventions in CHF. The results were somewhat inconsistent where both positive and negative results were found in mental health, QoL, self-care, clinical outcomes and physical capacity. Figure 2 gives a graphical overview of the results at the first post-intervention measurement point. Four out of five meta-analyses reported a significant reduction in depression with a small to moderate effect size (9, 10, 12, 14). The study that reported a non-significant result, although a trend toward reduction, did not have depression as the primary outcome and included only three original studies in the meta-analysis for depression (15). Anxiety was also reported to be reduced significantly in two of three meta-analyses with a moderate effect size (9, 10). The long-term follow-up assessment for depression and anxiety showed some support for a long-term effect of reduced depression at 3 months but no sustained effect for reduced anxiety (10, 12, 13). The results are somewhat consistent with findings from a meta-analysis on psychosocial interventions in patients with cardiovascular diseases where short-term effects on anxiety and depression was found but was not sustained at follow-up assessments (16). However, there were few studies that had long-term follow-ups which was also the case in the current meta-review. Notably, the meta-analysis that found a sustained effect of reduced depression had a highly selective sample consisting of mostly male with a mean age ranging from 55 to 66 years (12), in contrast to CHF being most prevalent in people over 70 years (2). Furthermore, one meta-analysis in the current meta-review points out that the studies favoring the intervention group had a longer medium durability of the interventions in comparison to studies favoring control (9). This meta-review gives some support to that psychosocial interventions can have a short-term effect on QoL as several of the studies reported significant results (10, 12, 13, 15) and, in a subgroup analysis, for CBT interventions solely (9). The effect was, however, not sustained at follow-up (10, 12, 13). Discussions are raised in several of the included systematic reviews and meta-analysis as to whether booster sessions could promote a long-term effect on the outcome measurements. There could be some support for this suggestion and worthwhile to explore as one meta-analysis that particularly investigated the effect of booster sessions in CBT, albeit with a different patient population, found that interventions with booster sessions were more effective and the effect was more sustainable (17).

Clinical outcomes, as measured by hospitalizations and mortality, were sparsely evaluated and, when it was performed, showed inconsistent results. Besides psychological outcomes and QoL, clinical outcomes are also important factors to consider when evaluating a psychosocial intervention, although it is usually not the primary outcome. Clinical outcomes provide objective measures and could be useful when assessing cost-effectiveness and deciding whether the intervention should be implemented in clinical practice. Sparsely evaluated was also self-care behavior and physical capacity with contradictory results. While self-care behavior is measured by self-assessment, physical capacity is an objective measure. The meta-analysis that found an improvement in physical capacity had also partly included studies with a combination of stress-management and a physical movement component (10).

Although this meta-review identified several included outcome measures for psychosocial interventions, one of the included systematic review and meta-analysis raises the lack of measuring critical stress processes like perceived stress and coping strategies in the original studies (10). Coping strategies have, for instance, been associated with different levels of depression depending on whether adaptive or maladaptive coping was used as a strategy in patients with CHF (18) and therefore could be useful to address and measure.

Another aspect to take into consideration is the format of how the psychosocial intervention is delivered. Patients with CHF might

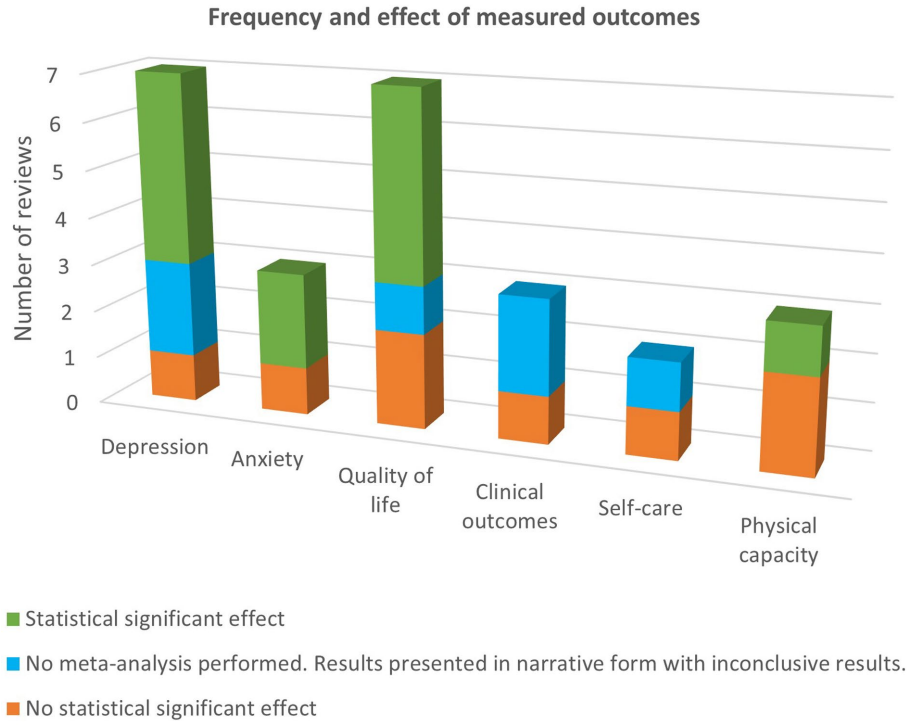


FIGURE 2
Frequency and effect of measured outcomes at the first post-intervention measurement point.

find it straining to go on several visits for reasons such as fatigue. Tele-rehabilitation could be an alternative format of delivery in order to reach more patients who otherwise would decline participation. Tele-rehabilitation interventions in CHF have shown some positive effect on quality of life, physical capacity and mental health (19). Home-based treatment based on self-help is another possible option. Home-based meta-cognitive therapy for cardiac patients have been found to be a feasible approach (20).

## Limitations

This meta-review has some limitations. Firstly, there is no definite consensus on what constitutes a psychosocial intervention. The original studies in the included reviews had different kinds of interventions and it cannot be guaranteed that all of them had a psychoeducative component which was an inclusion criterion in this study. The study cannot conclude which type of psychosocial intervention is favorable for an intended effect. Secondly, there was heterogeneity in the reviews and the original studies often had small sample sizes hence the results should be interpreted with caution. Thirdly, since some of the original studies were included in several of the systematic reviews and meta-analyses, there could have been an overlap in the results. Fourth, the quality according to AMSTAR-2 did not assess any of the articles to be of high quality which might impact the accuracy of the results. Notably, none of the included articles where a Cochrane review. Fifth, this meta-review, although approached in a systematic manner, might not have covered all available data. Finally, this meta-review was performed by one researcher hence there is a risk of bias.

## Conclusion and future direction for research

This appears to be the first meta-review in the field of psychosocial interventions in CHF. The meta-review found that psychosocial interventions in CHF may reduce depression, anxiety and improve quality of life but the results are inconsistent and the support for long-term effects, when measured, were few. Some points are raised to take into consideration for future studies. Interventions should be evaluated with long-term follow-ups and explore whether booster sessions could provide a sustained effect and whether the durability of the intervention has on impact on effect and sustainability. Studies should strive to have adequate sample sizes and include clinical outcomes and measures of stress and coping strategies. Furthermore, large-scale, high-quality studies that compare different types of psychosocial interventions could be useful.

## Data availability statement

The original contributions presented in the study are included in the article/Supplementary material, further inquiries can be directed to the corresponding author.

## Author contributions

The author has contributed to the conception and design of the study, acquisition of data, analysis and interpretation of data, drafting the article and revising it critically for important intellectual content.

## Conflict of interest

The author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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## Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2023.1095665/full#supplementary-material

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# Determinants of severe $QT_c$ prolongation in a real-world gerontopsychiatric setting

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**Introduction:** $QT_c$ prolongation carries the risk of ventricular tachyarrhythmia (Torsades de Pointes) and sudden cardiac death. Psychotropic drugs can affect ventricular repolarization and thus prolong the $QT_c$ interval. The present study sought to investigate the risk factors (pharmacological and non-pharmacological) of severe $QT_c$ prolongation in gerontopsychiatric patients.

**Methods:** Electrocardiograms of patients on a gerontopsychiatric ward were screened for $QT_c$ prolongation. Medication lists were examined utilizing the AzCERT classification. Potential drug interactions were identified with the electronic drug interaction program mediQ.

**Results:** The overall prevalence of $QT_c$ prolongation was 13.6%, with 1.9% displaying severe $QT_c$ prolongation (≥500 ms). No statistically significant differences between patients with moderate and severe $QT_c$ prolongation were identified; however, patients with severe $QT_c$ prolongation tended to take more drugs ($p$=0.063). 92.7% of patients with $QT_c$ prolongation took at least one AzCERT-listed drug, most frequently risperidone and pantoprazole. Risperidone and pantoprazole, along with pipamperone, were also most frequently involved in potential drug interactions. All patients displayed additional risk factors for $QT_c$ prolongation, particularly cardiac diseases.

**Conclusion:** In addition to the use of potentially $QT_c$-prolonging drugs, other risk factors, especially cardiac diseases, appear to be relevant for the development of $QT_c$ prolongation in gerontopsychiatric patients. Pantoprazole was frequently involved in potential drug interactions and should generally not be used for more than 8 weeks in geriatric populations. As clinical consequences of $QT_c$ prolongation were rare, potentially $QT_c$-prolonging drugs should not be used overcautiously; their therapeutic benefit should be considered as well. It is paramount to perform diligent benefit–risk analyses prior to the initiation of potentially $QT_c$-prolonging drugs and to closely monitor their clinical (side) effects.

KEYWORDS

**$QT_c$ prolongation, geriatrics, geriatric psychiatry, drug safety, AzCERT classification, elderly**

# Introduction

The QT interval in the electrocardiogram (ECG) comprises the time from the beginning of the QRS complex to the end of the T wave and reflects ventricular repolarization (1). The QT interval depends on the heart rate; therefore, various formulas (e.g., according to Bazett, Hegglin, Fridericia, and Framingham) have been developed to calculate the rate-corrected QT ($QT_c$) interval (2). A prolonged $QT_c$ interval in the ECG indicates impaired ventricular repolarization and is associated with the occurrence of certain ventricular tachyarrhythmias, so-called torsades de pointes (TdP), and sudden cardiac death (SCD) (3). A prolonged $QT_c$ interval is considered to start at 450 ms in men and 470 ms in women (4). Above 500 ms, the probability of occurrence of TdP and SCD is significantly increased across genders (3, 4). Pathophysiologically, a prolonged $QT_c$ interval is elicited by a dysfunction of certain cardiac sodium or potassium channels, either congenital (due to specific gene mutations) or acquired. Acquired forms of $QT_c$ prolongation occur more frequently than congenital forms (5). A common reason for acquired $QT_c$ prolongation is the intake of certain drugs that interact with cardiac ion channels and may thus lead to disturbances in ventricular repolarization (6). Paradoxically, this applies in particular to the class of antiarrhythmic drugs, but also to certain antibiotics (e.g., macrolide antibiotics) and many psychotropic drugs (6, 7). However, there exist numerous other risk factors for prolongation of the $QT_c$ interval, such as cardiac diseases, thyroid dysfunction, electrolyte disturbances (e.g., hypokalemia, hyponatremia), or age > 65 years (8, 9).

The investigation of at-risk populations for $QT_c$ prolongation is of paramount importance (10, 11). Gerontopsychiatric patients represent a high-risk population due to their age, presence of somatic comorbidities, and frequent use of psychotropic drugs that potentially extend the $QT_c$ interval (10, 12). Due to altered pharmacodynamic and pharmacokinetic properties, along with frequent polypharmacy, the probability of occurrence of adverse drug reactions (ADRs) is significantly increased in geriatric patients (13, 14). In clinical practice, prolongations of the $QT_c$ interval are often suspected to be caused by psychotropic drugs without considering the presence of other risk factors (15). This, in turn, can lead to potential drug prescribing omissions (PPOs), if clinically indicated drugs are withheld due to fears of $QT_c$ prolongation. PPOs carry the risk of worsening psychopathology (16, 17).

The aim of our study was to investigate the determinants and risk factors of severe compared to moderate $QT_c$ prolongation in gerontopsychiatric patients. For this purpose, the ECGs of patients on a gerontopsychiatric ward of a large university hospital in Germany were screened for prolonged $QT_c$ intervals. Using the Arizona Center for Education and Research on Therapeutics (AzCERT) classification of potentially $QT_c$-prolonging drugs, patients' medication lists were analyzed (18). In addition, drug interactions with potential impact on ventricular repolarization were explored.

# Methods

## Ethics approval

This study was approved by the Ethics Committee of Hannover Medical School (No. 10595_BO_K_2022) and adheres to the Declaration of Helsinki (1964) and its later amendments (current version from 2013).

## Eligibility criteria

Patients were enrolled in the study (i) if they were ≥ 65 years of age, (ii) if they were treated on the gerontopsychiatric ward of the Department of Psychiatry, Social Psychiatry and Psychotherapy of Hannover Medical School between 01 January 2014 and 31 December 2021, (iii) if they or their legal representative had provided written informed consent that patient-related data be used for clinical research, and (iv) if they exhibited a $QT_c$ prolongation in the ECG (for definition see next paragraph), which was confirmed by manual ECG re-evaluation.

Hannover Medical School is a large university hospital and tertiary care referral center in northern Germany. The gerontopsychiatric ward is a 27-bed facility specialized on the treatment and care of elderly psychiatric inpatients.

## Categorization of QTc prolongation

The length of the $QT_c$ interval was calculated with Bazett's formula. According to the criteria of the European Medicines Agency (EMA), $QT_c$ intervals ≥ 450 ms in men and ≥ 470 ms in women were categorized as prolonged (19). Moderate $QT_c$ prolongation was defined as a prolonged $QT_c$ interval < 500 ms. Severe $QT_c$ prolongation was defined as a $QT_c$ interval ≥ 500 ms (19). 12-lead ECG machines were used in our study, whereby ECGs were scanned into.pdf formats. In a first step, all patients with a prolonged $QT_c$ interval in the automatic electronic calculation of ECG parameters were identified. In the next step, the ECGs of these patients were manually re-evaluated. To this end, manual calipers were used and the tangent method was applied to determine the end of the T wave. The length of the $QT_c$ interval was determined in lead II. RR and $QT_c$ intervals were averaged across several beats. U waves as correlates of late repolarization were assessed in leads $V_2$ and $V_3$, and—if present—were not included in the calculation of $QT_c$ intervals. In patients with a heart rate > 100 beats per minute (bpm), the $QT_c$ interval was calculated with Fridericia's formula (1). In the presence of right and/or left bundle branch blocks, Bogossian's formula was used to calculate the $QT_c$ interval (1, 20). ECGs with numerous artifacts and flat T waves were excluded.

## Medication chart reviews, drug interaction checks, risk factors for $QT_c$ prolongation, and demographic characteristics

Medication charts of enrolled patients were analyzed by an interdisciplinary team of experts in psychiatry, internal medicine, and clinical pharmacology. Regularly taken drugs were assessed with the aid of the AzCERT classification (9, 18).

AzCERT is part of the Critical Path Institute established by the United States Food and Drug Administration (FDA) and is one of 14 centers dedicated to improving drug development processes (18). AzCERT maintains CredibleMeds, an online database which categorizes the risk of individual drugs to prolong the $QT_c$ interval and/or to elicit TdP (18). Three main categories are differentiated:

1. Drugs that, under normal clinical conditions, significantly increase the risk for $QT_c$ prolongation/TdP ("known risk").

2. Drugs with known capacity to prolong the $QT_c$ interval but with lacking evidence regarding the development of TdP ("possible risk").
3. Drugs with a conditional risk for $QT_c$ prolongation/TdP when given in excessive dosages or in the presence of other risk conditions ("conditional risk").

Drug interaction checks were performed with mediQ (Psychiatrische Dienste Aargau AG, mediQ Kompetenzzentrum für Medikamentensicherheit, Windisch, Switzerland), an electronic drug interaction program specialized on psychopharmaceuticals. mediQ categorizes the clinical severity of drug interactions as "low," "average," or "high." For the purpose of our study, drug interactions with an association to possible $QT_c$ prolongation were considered. Thus, for each patient case, potential interaction pairs and the AzCERT categories of the involved drugs were recorded.

Demographic characteristics—i.e., age, sex, and International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10) diagnoses—were retrieved from patient records. We used the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula to calculate estimated glomerular filtration rates (eGFR). Hospital discharge letters were used to identify cases in which an acute cardiac event occurred during the hospital stay and cases in which the medication was changed due to $QT_c$ prolongation.

## Statistical analysis

All statistical analyses were conducted with IBM SPSS Statistics for Windows, version 28 (Armonk, New York, NY, United States). Descriptive statistical methods were used to summarize the data. Quantitative variables were tested for normal distribution with the Shapiro–Wilk test and by inspection of the histogram and Q–Q plot. Due to skewed distribution, quantitative variables are depicted as medians with interquartile ranges (IQRs). For quantitative variables, differences between patients with moderate and patients with severe $QT_c$ prolongation were analyzed with the Mann–Whitney *U* test for independent samples. Categorical variables are displayed as absolute and relative frequencies. For categorical variables, differences between patients with moderate and patients with severe $QT_c$ prolongation were analyzed with Pearson's chi-squared test or Fisher's exact test. Fisher's exact test was preferred if any of the four cells of a $2 \times 2$ table had less than five observations. $p$ values $< 0.05$ were considered statistically significant. Due to the exploratory nature of our investigation, no adjustments for multiple testing were made.

# Results

## Study population

One hundred and twenty-two of 899 screened patients (13.6%) fulfilled the eligibility criteria and were enrolled in the study (Figure 1). The median age of the study population ($n = 122$) was 77 years (IQR 70–83 years; minimum 65 years; maximum 99 years) and 38.5% (47/122) of the patients were female (Table 1). The median $QT_c$ interval duration in the study population was 477 ms (IQR 466–490 ms; minimum 451 ms; maximum 525 ms). 86.1% (105/122) of the patients displayed a moderate $QT_c$ prolongation, while 13.9% (17/122) exhibited a severe $QT_c$ prolongation. The median eGFR in the study population was 67 ml/min (IQR 49–81.25 ml/min; minimum 15 ml/min; maximum 103 ml/min). The patients took a median of 7.5 drugs (IQR 4–9 drugs; minimum 0 drugs; maximum 18 drugs), with a median of 2 AzCERT-listed drugs (IQR 1–3 AzCERT-listed drugs; minimum 0 AzCERT-listed drugs; maximum 6 AzCERT-listed drugs). Dementia was the most frequent psychiatric diagnosis in the study population (40.2%; 49/122). The most prevalent somatic disorder was arterial hypertension, which affected 77.9% (95/122) of the patients. Other frequent risk factors for $QT_c$ prolongation in our study population were chronic heart failure (41.0%; 50/122) and coronary heart disease (32.8%; 40/122).

## Treatment modifications and cardiac events

The medication was changed in 10.7% (13/122) of patients as a consequence of $QT_c$ prolongation. In 23.1% (3/13) of treatment modifications, antidepressants were discontinued, while in 69.2% (9/13) antipsychotic medications were stopped; one case regarded a discontinuation of pantoprazole. Four patients experienced a cardiac event during their hospital stay (myocardial infarction, $n = 2$; malign cardiac arrhythmia, $n = 2$). In one of these cases (one case of malign cardiac arrhythmia), a causal involvement of $QT_c$ prolongation was suspected. The respective patient developed a TdP tachyarrhythmia, and also had a severely prolonged $QT_c$ interval, as well as various risk factors for TdP (arterial hypertension, chronic heart failure, hyponatremia, and hypokalemia). In the remaining three cases (two cases of myocardial infarction, one case of malign cardiac arrhythmia), a causal involvement of $QT_c$ prolongation could not be ruled out. Three of these patients died, one patient recovered with sequelae.

## Comparison between patients with moderate and severe $QT_c$ prolongation

There were no statistically significant differences between patients with moderate and patients with severe $QT_c$ prolongation regarding renal function or presence of comorbidities previously characterized as risk factors for $QT_c$ prolongation (Table 2). We observed non-significant trends towards a higher proportion of females among patients with severe $QT_c$ prolongation compared to patients with moderate $QT_c$ prolongation [58.8% (10/17) vs. 35.2% (37/105); $p = 0.064$] and towards a higher number of drugs taken [9 drugs (IQR 6–11 drugs) vs. 7 drugs (IQR 4–9 drugs); $p = 0.063$].

## Characteristics of drug prescriptions and categorization according to the AzCERT classification

In total, 857 medications were prescribed in the study population. The most frequently prescribed drugs were ramipril (4.8%; 41/857)

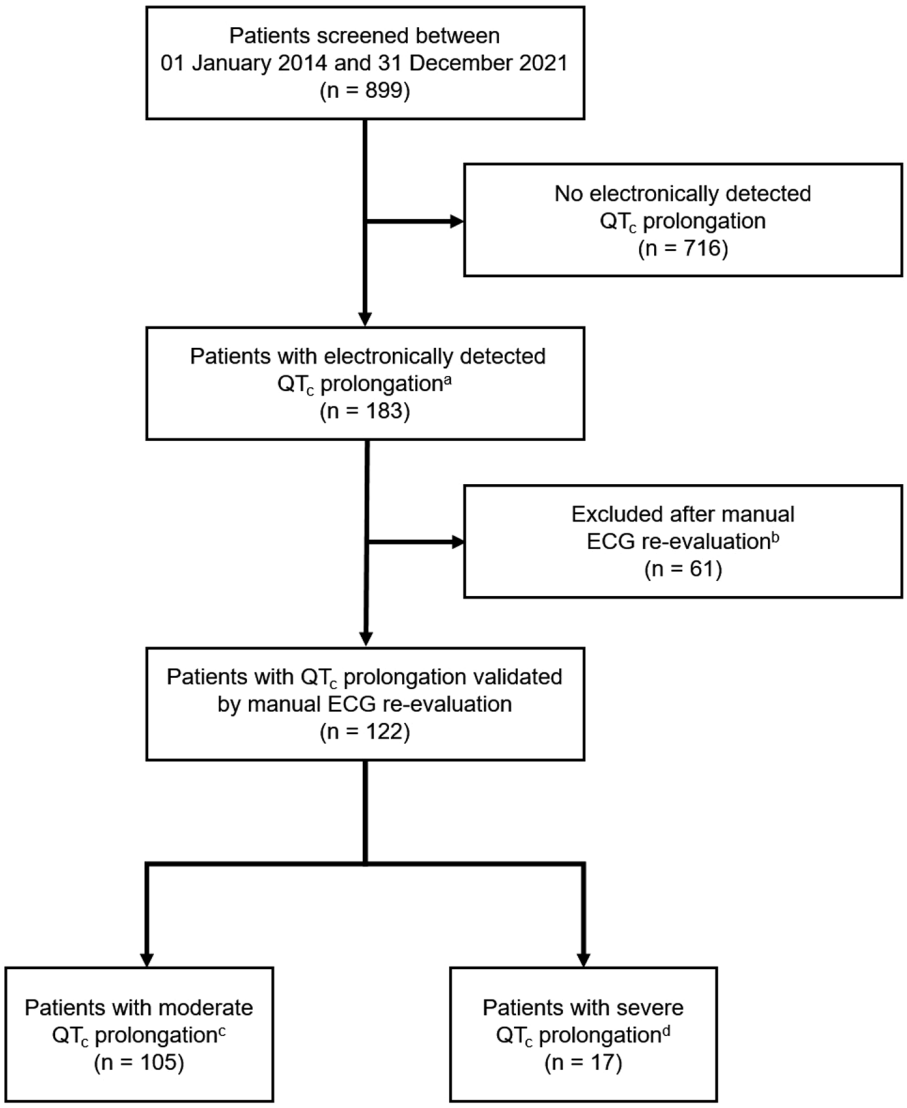


FIGURE 1
Flow of patients. [a]QTc intervals ≥450ms in men/≥470ms in women were considered prolonged. [b]E.g., due to artifacts. [c]Moderate QTc prolongation was defined as a prolonged QTc interval <500ms. [d]Severe QTc prolongation was defined as a QTc interval ≥500ms (irrespective of gender). ECG, electrocardiogram; $QT_c$, rate-corrected QT.

and pantoprazole (4.6%; 39/857), followed by risperidone and lorazepam (each 4.2%; 36/857; Supplementary Table 1). 33.8% (290/857) of the prescribed drugs were indexed on the AzCERT list. 23.0% (28/122) of the patients received one AzCERT-listed drug, while 69.7% took more than one AzCERT-listed drug. 2.3% (20/857) of all prescribed drugs had a known risk of $QT_c$ prolongation according to the AzCERT classification, 20.7% (177/857) had a possible risk, and 9.9% (85/857) had a conditional risk. Haloperidol (0.9%; 8/857) and citalopram (0.5%; 4/857) were the most frequently prescribed drugs with a known risk of $QT_c$ prolongation. Pipamperone (3.4%; 29/857) and mirtazapine (2.0%; 17/857) were the leading drugs with a possible risk of $QT_c$ prolongation, whereas pantoprazole (4.6%; 39/857) and risperidone (4.2%; 36/857) were the most frequently prescribed drugs with a conditional risk of $QT_c$ prolongation.

## Drug interaction checks

The drug interactions (266) with an association to possible $QT_c$ prolongation were detected in the study population. Overall, potentially $QT_c$-prolonging drug interactions were present in 64.8% (79/122) of patients. The most frequent interaction pairs were pipamperone + risperidone (3.8%; 10/266), risperidone + torasemide (3.8%; 10/266), and pantoprazole + risperidone (3.4%; 9/266; Supplementary Table 2). The interaction potential of the two pairs risperidone + citalopram and amiodarone + tramadol (0.8%; 2/266) was categorized as "high" by mediQ. 45.1% (120/266) of the interaction pairs were considered to have an "average" interaction potential, while 54.1% (144/266) exhibited a "low" interaction potential. In the case of the interaction pair chlorprothixene + haloperidol, both involved drugs had a known risk of $QT_c$ prolongation according to the AzCERT

TABLE 1 Characteristics of the study population ($n$=122).

| Variables | *n* | % |
|---|---|---|
| *Sex* | | |
| Female | 47 | 38.5 |
| Male | 75 | 61.5 |
| *Psychiatric diagnoses*[a] | | |
| Depression[b] | 27 | 22.1 |
| Bipolar affective disorder[c] | 12 | 9.8 |
| Schizophrenia or schizophreniform disorder[d] | 22 | 18.0 |
| Mental and behavioral disorder due to use of alcohol, tobacco, or sedatives or hypnotics[e] | 28 | 23.0 |
| Dementia[f] | 49 | 40.2 |
| Delirium[g] | 27 | 22.1 |
| Other psychiatric disorder(s) | 15 | 12.3 |
| *Somatic diagnoses*[a] | | |
| Arterial hypertension | 95 | 77.9 |
| Coronary heart disease | 40 | 32.8 |
| Chronic heart failure | 50 | 41.0 |
| Atrial fibrillation | 23 | 18.9 |
| Cardiac arrhythmia other than atrial fibrillation | 40 | 32.8 |
| Status post stroke | 20 | 16.4 |
| Dyslipidemia | 33 | 27.0 |
| Type-2 diabetes mellitus | 24 | 19.7 |
| Chronic obstructive pulmonary disease | 9 | 7.4 |
| Thyroid dysfunction | 34 | 27.9 |
| Urinary tract infection | 19 | 15.6 |
| Hypokalemia | 26 | 21.3 |
| Hyponatremia | 13 | 10.7 |
| Hypocalcemia | 8 | 6.6 |
| Other somatic disorder(s) | 120 | 98.4 |

[a]Patients could have more than one diagnosis;
[b]ICD-10 F32, F33;
[c]ICD-10 F31;
[d]ICD-10 F06.2, F2X;
[e]ICD-10 F10, F13, F17;
[f]ICD-10 F00, F01, F02, F03;
[g]ICD-10 F05.
The median age of the study population was 77 years (interquartile range 70–83 years).
ICD-10, International Statistical Classification of Diseases and Related Health Problems 10th Revision.

classification. Risperidone (25.2%; 67/266), pipamperone (19.5%; 52/266), pantoprazole (15.4%; 41/266), and quetiapine (15.4%; 41/266) were most frequently involved in drug interactions. 10.9% (29/266) and 89.1% (237/266) of the interactions were characterized as primarily pharmacokinetic and primarily pharmacodynamic, respectively. The most frequent pharmacokinetic interaction pair was melperone + risperidone (2.6%; 7/266; increased plasma concentration of risperidone due to inhibition of CYP2D6 by melperone).

## Discussion

The present study investigated the frequency and risk determinants of severe compared to moderate $QT_c$ prolongation in a gerontopsychiatric patient population in the setting of a large university hospital in Germany. Emphasis was put on investigating prescription characteristics of drugs with potential $QT_c$-prolonging effects according to the AzCERT classification (18). Furthermore, the number and severity of drug interactions with association to potential $QT_c$ prolongation were analyzed.

In psychiatric patients, the frequency of $QT_c$ prolongation was investigated in several studies, with heterogeneous results (21–23). The prevalence of an at least moderate $QT_c$ prolongation ranged from 1 to 10% of patients (21–23), while the proportion of patients with severe $QT_c$ prolongation (> 500 ms) varied between 0.2 and 3% (21, 24, 25). Different study designs, enrollment of both inpatients and outpatients, as well as different age profiles of the participants may serve as explanations for these discrepancies. To date, three studies investigated the characteristics of $QT_c$ prolongation in geriatric psychiatry (26–28). Dumontet et al. (28) found that in a sample of 88 inpatients, 29.4% of men and 21.4% of women displayed $QT_c$ prolongation. In a more recent study from India by Das et al. (26), the prevalence of $QT_c$ prolongation was reported to be 29.4%, with 1.8% of all study participants exhibiting a $QT_c$ interval of > 500 ms. These data referred to patients in gerontopsychiatric outpatient care (26). A previous study by Das et al. (27) with a smaller sample size estimated the prevalence of $QT_c$ prolongation to be 19.2% in men and 10.3% in women. In our study, the prevalence of $QT_c$ prolongation tended to be lower (13.6%); however, the proportion of severe $QT_c$ prolongation (1.9%) was comparable to the recent Das et al. (26) study.

The higher prevalence of $QT_c$ prolongation in gerontopsychiatric patients compared with general psychiatric settings can be explained by the advanced age of patients and age-associated multimorbidity. The markedly lower proportion of $QT_c$ prolongation in our study, in turn, may be due to more narrowly defined inclusion criteria. For example, we did not solely rely on automatic calculations of ECG parameters. Instead, all ECGs suspicious of $QT_c$ prolongation were re-examined manually, taking influences of heart rate and bundle branch blocks into consideration. This led to the exclusion of one-third (61/183) of automatically detected $QT_c$ prolongations.

The most common psychiatric diagnoses in our study population were dementia, substance use disorders, depression, and delirium, which is comparable to other studies (26, 29, 30). Previous studies examined the frequency and significance of risk factors for $QT_c$ prolongation in psychiatric patients (21, 23, 24, 31). In this regard, the influence of potentially $QT_c$-prolonging drugs has been emphasized (26, 32). A study from Pakistan found that 91.6% of psychiatric inpatients were taking potentially $QT_c$-prolonging drugs, which was the most common risk factor (32). These and other results have led to a sometimes overcautious prescription of potentially $QT_c$-prolonging drugs in clinical practice, which may represent a PPO under certain circumstances (15, 17). In fact, studies on the effect of medication on $QT_c$ prolongation in the psychiatric context had varying results (22, 33). Results were also heterogeneous in gerontopsychiatric patient groups (26, 28). Whereas in the Das et al. study all patients with $QT_c$ prolongation received potentially $QT_c$-prolonging drugs, Dumontet et al. (26, 28) found that 57.9% of patients with $QT_c$ prolongation were

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TABLE 2 Comparison of patients with moderate and severe $QT_c$ prolongation.

| Characteristic and category | Total | Patients with moderate $QT_c$ prolongation | Patients with severe $QT_c$ prolongation | *p* value |
|---|---|---|---|---|
| | (*n* =122) | (*n* =105; 86.1%) | (*n* =17; 13.9%) | |
| Median age (IQR)—years | 77 (70–83) | 77 (70–82.5) | 78 (69–84.5) | 0.915[a] |
| Age > 80 years—% (no.) | 23.8 (29) | 22.9 (24) | 29.4 (5) | 0.559[b] |
| Female sex—% (no.) | 38.5 (47) | 35.2 (37) | 58.8 (10) | 0.064[b] |
| Median number of drugs (IQR) | 7.5 (4–9) | 7 (4–9) | 9 (6–11) | 0.063[a] |
| Median number of AzCERT-listed drugs (IQR) | 2 (1–3) | 2 (1–3) | 2 (2–3.5) | 0.241[a] |
| Median eGFR (IQR)—ml/min | 67 (49–81.25) | 67 (52–80.5) | 54 (42–86) | 0.464[a] |
| Arterial hypertension—% (no.) | 77.9 (95) | 77.1 (81) | 82.4 (14) | 0.761[c] |
| Coronary heart disease—% (no.) | 32.8 (40) | 32.4 (34) | 35.3 (6) | 0.812[b] |
| Chronic heart failure—% (no.) | 41.0 (50) | 39.0 (41) | 52.9 (9) | 0.280[b] |
| Type-2 diabetes mellitus—% (no.) | 19.7 (24) | 20.0 (21) | 17.6 (3) | 1.000[c] |
| Dyslipidemia—% (no.) | 27.0 (33) | 25.7 (27) | 35.3 (6) | 0.394[c] |
| Atrial fibrillation—% (no.) | 18.9 (23) | 19.0 (20) | 17.6 (3) | 1.000[c] |
| Cardiac arrhythmia other than atrial fibrillation—% (no.) | 32.8 (40) | 30.5 (32) | 47.1 (8) | 0.177[b] |
| Thyroid dysfunction—% (no.) | 27.9 (34) | 27.6 (29) | 29.4 (5) | 1.000[c] |
| Hypokalemia—% (no.) | 21.3 (26) | 20.0 (21) | 29.4 (5) | 0.357[c] |
| Hyponatremia—% (no.) | 10.7 (13) | 10.5 (11) | 11.8 (2) | 1.000[c] |
| Hypocalcemia—% (no.) | 6.6 (8) | 5.7 (6) | 11.8 (2) | 0.309[c] |

Moderate $QT_c$ prolongation was defined as 450 ms (men)/470 ms (women) ≤ $QT_c$ interval < 500 ms. Severe $QT_c$ interval prolongation was defined as $QT_c$ interval ≥ 500 ms (irrespective of gender).

[a]Mann–Whitney *U* test for independent samples.

[b]Pearson's Chi-squared test.

[c]Fisher's exact test.

AzCERT, Arizona Center for Education and Research on Therapeutics; eGFR, estimated glomerular filtration rate; IQR, interquartile range; no., number; $QT_c$, rate-corrected QT.

not taking $QT_c$-prolonging drugs. Risk factors especially for severe $QT_c$ prolongation have not been investigated to date.

In the present study, 92.7% of patients with $QT_c$ prolongation received at least one potentially $QT_c$-prolonging drug according to the AzCERT classification. In addition to age, which was set at ≥ 65 years as part of the inclusion criteria and which represents an independent risk factor for $QT_c$ prolongation, the prescription of AzCERT-listed drugs was the most frequent risk factor in our study population. Of note, at least one additional risk factor was identified in all patients, most notably cardiac diseases such as arterial hypertension and chronic heart failure, which affected 77.9 and 51% of patients, respectively. In general, patients in our study population displayed higher proportions of risk factors, especially cardiac diseases, than in the previous studies in the gerontopsychiatric setting. This may be explained by the fact that our investigation focused exclusively on patients with prolonged $QT_c$ intervals, but also emphasizes that not only $QT_c$-prolonging drugs but presumably a combination of different risk factors seems to be responsible for the development of $QT_c$ prolongation. We did not observe statistically significant differences between patients with moderate and severe $QT_c$ prolongation; however, there was a trend towards a higher number of drugs taken in the group with severe $QT_c$ prolongation. This opens avenues for follow-up studies with a prospective design, which should investigate whether polypharmacy represents a risk factor for severe $QT_c$ prolongation.

Four patients (3.3% of all patients with $QT_c$ prolongation) developed a cardiac event during their hospital stay, a proportion that was somewhat higher than in previous investigations (26, 32, 33). Yet, a causal relation to $QT_c$ prolongation was suspected in only one of these four cases.

To the best of our knowledge, our study is the first to investigate the frequency of treatment modifications as a consequence of $QT_c$ prolongation in geriatric psychiatry. Although 92.7% of the patients took at least one AzCERT-listed drug, the medication was changed in only 10.7% of cases as a consequence of $QT_c$ prolongation, with antipsychotic drugs being discontinued in 69.2% of treatment modifications. This suggests that $QT_c$ prolongations were often tolerated in clinical routine in view of the patients' high-risk profiles for $QT_c$ prolongation, and were less frequently causally attributed to the influence of medication. Nevertheless, antipsychotics in particular appeared to be often associated with $QT_c$ prolongation by the treating physicians.

In the present study, the majority of patients (69.7%) were taking more than one AzCERT-listed drug, which is comparable with findings by Das et al. (26). In our study, the largest proportion of AzCERT-listed drugs were those with a possible risk for $QT_c$ prolongation. These accounted for 20.7% of all drugs, which was markedly higher than the proportions of the other AzCERT categories. For example, drugs with a known risk for $QT_c$ prolongation only accounted for 2.3%. In previous studies, the proportion of drugs with a known risk for $QT_c$ prolongation was considerably higher than in our investigation (26, 33, 34).

The most frequently prescribed drugs with a known risk for $QT_c$ prolongation in our study were haloperidol and citalopram. In

previous studies in the psychiatric setting, these drugs were also among the most frequently prescribed substances in this category, along with levomepromazine and chlorpromazine (26, 32, 34). Pipamperone and mirtazapine were the most common drugs with a conditional risk in our study, whereas in other investigations these two drugs were prescribed infrequently, in contrast to lithium and aripiprazole, which were leaders in this category in previous reports (26, 32, 34). Moreover, the most frequently prescribed $QT_c$-prolonging drugs in our study were pantoprazole and risperidone, both of which convey a possible risk of $QT_c$ prolongation according to the AzCERT classification. Other studies identified quetiapine and sertraline as the most frequently prescribed drugs in psychiatric patients in this category (26, 33, 34).

Das et al. and Hefner et al. (26, 35) investigated the characteristics of drug interactions associated with $QT_c$ prolongation in psychiatric patients and identified pipamperone + risperidone and escitalopram + risperidone as the most frequent interaction pairs. Similarly, pipamperone + risperidone represented the most frequent combination with drug interaction potential in terms of $QT_c$ prolongation in our study, along with risperidone + torasemide. In addition to risperidone and pipamperone, quetiapine and pantoprazole were also frequently involved in potential interactions, suggesting a significant contribution of these drugs to $QT_c$ prolongation.

Of note, pantoprazole was frequently involved in drug interactions associated with potential $QT_c$ prolongation. Pantoprazole has been reported to increase $QT_c$ and has therefore been added to the list of "Drugs to be avoided in patients with congenital long QT syndrome" (36). Extended use (> 14 days) of proton pump inhibitors (PPIs) should be discouraged because of their inherent risk of TdP (37).

Our investigation is not without limitations. It was designed as a retrospective and unicenter analysis. Similarly, we did not evaluate the evolution of the $QT_c$ interval during the course of treatment and did not include the duration of drug intake. It should also be mentioned critically that we focused exclusively on patients with $QT_c$ prolongation in our statistical analyses, which led to a relatively small sample size with limited statistical power of the results. The results of our study need to be validated in future studies with a prospective and multicenter design and with larger sample sizes to allow for better generalizability.

In summary, the present study investigated the frequency and characteristics of severe compared to moderate $QT_c$ prolongation in geriatric psychiatry. It was striking that almost all patients also suffered from cardiac diseases and displayed other risk factors for $QT_c$ prolongation, suggesting a multifactorial genesis of $QT_c$ prolongation. Nevertheless, in individual cases, drugs may exert a decisive impact on the $QT_c$ interval and potentially result in life-threatening consequences such as TdP. In particular, combinations of drugs with a known risk for $QT_c$ prolongation (according to the AzCERT classification) should be re-evaluated critically. On the other hand, fears of $QT_c$ prolongation should not result in PPOs.

Strengths of our study were the high quality of ECG assessments (in contrast to previous studies) with stringent exclusion criteria, and analysis of potential differences between patients with moderate and severe $QT_c$ prolongation. The results of our work indicate that polypharmacy might be a potential risk factor for severe $QT_c$ prolongation, even though this needs to be verified in future studies. Furthermore, our investigation is the first to analyze therapeutic consequences of $QT_c$ prolongation. We were able to show that $QT_c$ prolongations are often tolerated by the treating physicians, suggesting that the therapeutic benefits of potentially $QT_c$-prolonging drugs frequently outweigh their risks in clinical practice. An additional advantage of our study was the comprehensive evaluation of drug interaction pairs which contributed to $QT_c$ prolongations in a real-world setting.

## Data availability statement

The original contributions presented in the study are included in the article/Supplementary material, further inquiries can be directed to the corresponding author.

## Ethics statement

The studies involving human participants were reviewed and approved by Ethics Committee of Hannover Medical School. The patients/participants provided their written informed consent to participate in this study.

## Author contributions

MSW and AG: conceptualized the study. MSW, AG, and JH: analyzed the data. JH: inferential statistics, language editing, provided expert advice in clinical pharmacology. MSW, AG, SS, TP, SB, KK, TK, KJ, and FW: provided expert advice in psychiatry and psychopharmacology. OK: provided expert advice in cardiology. MSW, AG, JH, and SS: interpreted the study results, drafted the first version of the manuscript, created the tables and figures. TP, KK, SB, TK, OK, KJ, and FW: assisted with the preparation of the manuscript. AG: supervised the project. All authors contributed to the article and approved the submitted version.

## Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

## Publisher's note



## Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2023.1157996/full#supplementary-material

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# Personalized training as a promoter for physical activity in people with depressive disorder—a randomized controlled trial in Germany

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**Introduction:** Adopting an active lifestyle is an important goal, but can be difficult to achieve for people with depressive disorders. Current guidelines recommend the integration of physical activity in the multimodal treatment of depressive disorders. However, the possibilities to provide individual support for physical activities are frequently limited. The aim of our study was to examine how physical activity can be increased in a real-world setting by combining physical training and psychological interventions.

**Materials and methods:** In this randomized-controlled interventional study, 31 outpatients diagnosed with moderate to severe depression were recruited from the region of Hannover. The intervention group ($n$=16) was offered six weekly individual sessions lasting between 60 and 90 min with a sports scientist, including Motivational Interviewing and accompanied exercise activities. The control group ($n$=15) received a written booklet with information on steps toward becoming more active. Moderate-to-vigorous physical activity (MVPA) as the primary outcome was analyzed using activity sensors before and after the 6-week intervention, and 3 months subsequently. Secondary outcomes included the Six-Minute Walk Test (6MWT), Sit-to-Stand test (STS), and mental health assessed with self-rating questionnaires.

**Results:** In the intervention group, MVPA increased significantly between baseline and the first follow-up and remained at an increased level at the second follow-up in comparison to decreased levels in the control group (difference of 15.5 min/day between groups over time, SE=6.2 min/day, 95%-CI[2.7, 28.3], $p$=0.020). The increased activity level was associated with markers of increased fitness (6MWT and STS) in the intervention group. Both groups showed comparable improvements in depressive symptoms, while the number of patients receiving antidepressants increased in the control group and decreased in the intervention group. Two patients dropped out of the intervention group during the trial.

**Conclusion:** The intervention proved to be a feasible and effective aid to promote a physically active lifestyle for patients diagnosed with depression. Furthermore, the higher level of physical activity was maintained for the follow-up period. Given the success of the approach evaluated in this project, individual support for physical activity should be investigated in larger sample sizes and potentially be considered in the multimodal treatment of depression.

**Clinical trial registration:** [https://clinicaltrials.gov/], identifier [DRKS00023257].

KEYWORDS

depression, exercise, physical activity, motivation, motivational interviewing, sport

# 1. Introduction

Achieving a change in exercise habits is an important goal in patient care for depression, but is frequently difficult to implement in practice. Loss of interest, energy, self-confidence and decisiveness are important determinants of major depressive disorder and impede patients in following an active lifestyle. Indeed, studies and meta-analyses demonstrate that people with depression tend toward sedentary lifestyles with decreased physical activity compared with healthy controls (1–4). There is also evidence for an inverse relationship between physical activity and depression [e.g., (5–8)] and an increased risk for inactivity-induced physical comorbidities [e.g., (9)]. However, the promotion of physical activity for patients suffering from depression harbors significant therapeutic potential (10). Starting an active lifestyle can lead to a multitude of positive effects through various biological or psychosocial pathways [e.g., (11)], but there is currently no established or accepted method to increase activity in already depressed and inactive people. In previous studies, we have analyzed the effects of exercise interventions on adipose tissue, muscle mass, cardiorespiratory fitness, metabolic syndrome and brain-derived neurotrophic factor in inpatients with major depressive disorder (12–15) and the effects of physical activity on the severity of depression and anxiety in company employees (16). Building on these findings, the present study evaluates how to increase physical activity in "real-world" settings in outpatients with depressive disorders.

Depressed mood and stress represent the main barriers to physical activity, as do poor levels of social support (17). Lack of time, physical illness, and poor health are also stated as limiting factors (18). Furthermore, a higher body mass index and a lower self-efficacy are associated with lower participation in physical activity (19). Professional assistance in setting goals, overcoming barriers and maintaining motivation (17), and the inclusion of health care professionals qualified in exercise prescription (20) are recommended strategies to assist patients with depressive disorder. The importance of increasing autonomous motivation (21) and self-efficacy (22) is recognized and Motivational Interviewing techniques can support behavioral change on the basis of patients' own decisions (23, 24). In previous studies, personal or telephone contact provided an opportunity for patients to speak about their goals and any potential reservations regarding exercise (25), and to explain the effects of physical activity (26). Further promising approaches identified in previous projects include personal coaching with individualized training schedules (27), a combination of supervised exercise with recommendations for home-based exercise (28), and a hybrid approach with telehealth options, web-based modules and smart technology [e.g., (29–31)]. In contrast to many previous approaches, our study neither focuses on group exercise [e.g., (32)] nor measures efficiency in reducing weight or symptom severity [e.g., (33)], but rather measures change in physical activity as the primary outcome. On the basis of previous work, we designed an intervention based on a combination of the supporting factors outlined above and techniques such as Motivational Interviewing, flanked by a new component of "accompanied activity." This involved the discussion of barriers such as those mentioned above, and limiting factors in personal conversations with the study participants.

The aim of this study was to examine how to promote a long-term increase in self-selected physical activity in the patients' daily life using this combination of physical training and psychological methods. We hypothesized a significantly greater increase in moderate-to-vigorous physical activity (MVPA) as measured with activity trackers when using this combined approach in the intervention group in comparison with the control group. The main focus was on the long-term effects of our intervention as assessed at the second follow-up visit, 3 months after the end of the intervention.

# 2. Materials and methods

## 2.1. Participants

We advertised for potential participants in Hannover (Lower Saxony, Germany) between November 2020 and February 2022. Initial details on the trial were distributed via posts on selected internet platforms (homepage of the "Patienten Universität an der Medizinischen Hochschule Hannover" and Hannover Medical School intranet) and on Hannover Medical School's social media channel. Handouts were made available by health care professionals in outpatient clinics (Wahrendorff clinical center and Hannover Medical School) and medical practices (in a radius of approximately 5 km of the study site). This resulted in 60 potential participants who were subsequently informed about the study in detail (see Figure 1). The inclusion criteria for patients were: a diagnosis of depression (F32, F33) according to ICD-10 (34), age between 18 and 60 years, and place of residence in the region of Hannover. Exclusion criteria were substance abuse, suicidal tendencies, lack of ability to understand information or give informed consent, pregnancy, lactation, or contraindications for unsupervised physical activity or tests. Written informed consent was obtained from all participants. The study was approved by the local ethics committee at the Hannover Medical School (NR8924_BO_S_2020), registered at "Deutsches Register Klinischer Studien"/WHO International Clinical Trials Registry Platform (DRKS00023257) and performed in accordance with the Declaration of Helsinki. Recruitment was stopped once the required sample size was reached.

Patients were randomly assigned to either the intervention group ($n = 16$) or the control group ($n = 15$). All participants continued with their usual medications. Changes in medication were not part of the study procedure, but were monitored at each study visit. Participants changed their medication in consultation with their therapists who were not part of the study team. Twenty-four patients were taking medication; of these 18 were taking antidepressants and six were taking only cardiac or thyroid dysfunction medication. Seven patients

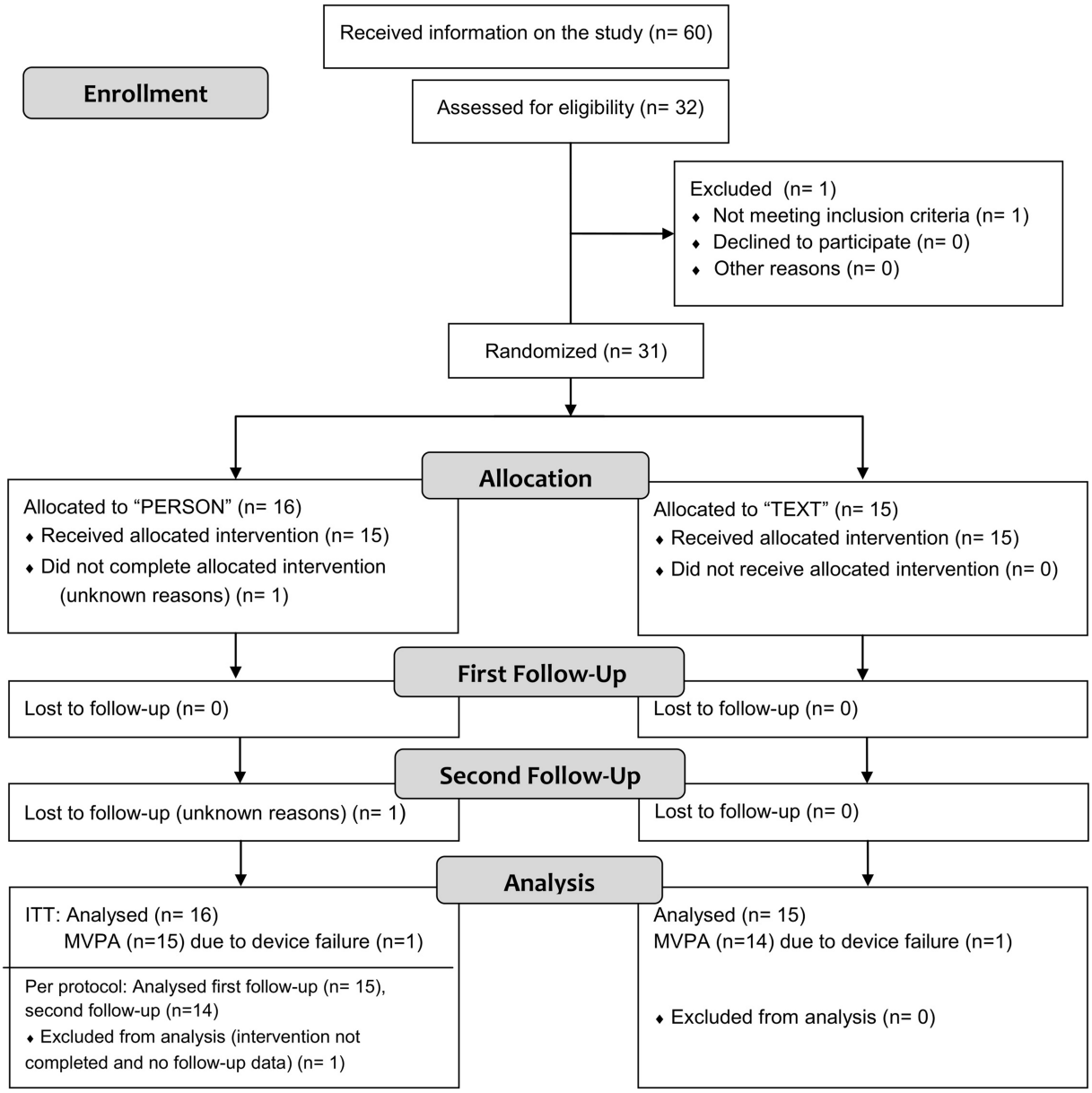


FIGURE 1
Flowchart of the numbers of participants and dropouts (for details on excluded and missing values, see paragraph "Statistical analysis" and Table 3. MVPA, moderate-to-vigorous physical activity).

were not taking any medication at baseline. The baseline characteristics of the groups are reported in Table 1.

## 2.2. Interventions

Patients in the intervention group participated in six individual sessions (one session per week) lasting between 60 and 90 min with a sports scientist, comprising Motivational Interviewing and accompanied physical activity. Sessions included theoretical and practical parts and were standardized with the help of pre-formulated lists of questions and exercises, as well as work sheets and written information. The practical part consisted of a multi-faceted exercise program under the guidance of an experienced sports therapist with training in Motivational Interviewing. The participants had the possibility to try out endurance and strength training, complementary exercises addressing flexibility, coordination, relaxation, and individually requested sports. Participants could individually select a preferred activity based on the guided testing or previous positive experiences. For the theoretical part, the participants' past exercise experiences and current status were evaluated; goals were defined, analyzed and divided into small tasks. Discrepancies between the current and desired physical activity status were identified. Together with the patient, the sports therapist discussed the advantages and disadvantages of increased sports activity, examined factors which might promote or complicate exercise, and formulated a daily and weekly plan. General information on healthy eating and the effects of sports and exercise on health was provided. The results from the

TABLE 1 Baseline characteristics of participants as mean ± standard deviation or absolute number in the two groups (intervention group, personalized training with Motivational Interviewing and accompanied activity, "person"; control group, written information, "text").

| | Descriptive statistics | |
|---|---|---|
| Baseline characteristic | Intervention group (person) | Control group (text) |
| Size of group (n) | 16 | 15 |
| Age (y) | 41.4 ± 10.6 | 41.1 ± 12.5 |
| Women/men (n) | 14/2 | 13/2 |
| Body weight (kg) | 83.2 ± 19.9 | 74.1 ± 13.4 |
| BMI (kg/m$^2$) | 28.8 ± 6.5 | 25.8 ± 4.4 |
| MADRS (points) | 21.5 ± 6.1 | 22.9 ± 5.6 |
| Employed yes/no (n) | 7/9 | 7/8 |
| Psychotherapy yes/no (n) | 11/5 | 13/2 |
| Antidepressants yes/no (n) | 12/4 | 6/9 |

Significant group differences occurred only in the number of participants under treatment with antidepressants.
y, years; kg, kilogram; m, meters; %, percent; n, number of participants with specific characteristic; BMI, body mass index; MADRS, Montgomery-Åsberg Depression Scale.

baseline assessments were explained and used to tailor the activities to the patient's individual health and fitness status. The overall goal was to meet general activity recommendations (35) and to find individual activities that the participants were interested in continuing on their own. The sports therapist was able to act as a sports companion and join the participant's selected activity, e.g., sports group, fitness center visit or walking tour at home (accompanied activity). The stepwise development of activities has parallels with behavioral activation strategies (36–38), regarding physical activity as a form of healthy behavior with the potential for positive experiences. Following previous studies (39, 40), the intervention is based on principles of self-determination theory (41) and uses Motivational Interviewing techniques (42, 43) (for a detailed description of the contents of the intervention, see Table 2).

Patients in the control group received written information after the results of the baseline assessments had been explained. It contained detailed information on safety, activity recommendations of World Health Organization (WHO) (35) and American College of Sports Medicine (ACSM) (44), training methods, sports disciplines, organization, sports equipment, tips for motivation, information on healthy eating and an exercise log. The control setting did not provide the option of any personal contact in the intervention period, or any individualization of the contents or accompanied activity; all other assessments were identical to those in the intervention group.

## 2.3. Assessment of physical activity

As shown in Figure 2, data was collected at baseline (visit 1), directly after the intervention period (visit 2, first follow-up), and after a three-month period following the intervention, during which no training or assistance was offered (visit 3, second follow-up).

Moderate-to-vigorous physical activity (MVPA) in min/day was defined as the primary outcome and was assessed with waist-worn activity sensors (GT9X Link, ActiGraph, Pensacola, Florida, United States). These are medical devices that measure acceleration in the vertical, medio-lateral and antero-posterior axis (45, 46). The activity was measured over 7 days according to a previously defined protocol. Data was processed and analyzed with ActiLife 6 (ActiGraph, Pensacola, Florida, United States) following the recommendations of a systematic review of previous studies (47). In order to detect measurement errors, participants were asked to record non-wear times, activities in water, or activities with high energy expenditure but low acceleration (e.g., stationary bicycle), as well as biking to recognize the use of e-bikes. In the results section we report the measured values without manual correction to minimize evaluator influence or bias.

In addition, the self-rating "Freiburger Questionnaire on Physical Activity" was used (48) to confirm measurements. This also allows the separate analyses of sports activities.

## 2.4. Secondary parameters of physical health

Changes in fitness were assessed using simple tests of everyday activities: Sit-to-Stand Test (STS) (49) and Six-Minute Walk Test (6MWT) (50) with standardized test protocols.

## 2.5. Secondary parameters of mental health

Self-rating questionnaires were used: World Health Organization Quality of Life-Bref (WHOQOL-Bref) (51), Beck Depression Inventory (BDI II) (52), and "Barriers and barrier management in physical exercise" (53). The Montgomery-Åsberg Depression Scale (MADRS) (54, 55) was used as an expert rating in order to measure the severity of depressive symptoms.

## 2.6. Power analysis

The required sample size for the primary outcome (MVPA) was 15 per group according to the *a priori* power analysis with SAS/STAT Software (SAS Institute Inc., Cary, United States) with the following assumptions: adjusted type I significance level of $\alpha = 0.05$, power of $1 - \beta = 0.8$, MVPA-differences between groups at visit 3 of 27 min/day, standard deviation 25 min/day. Expected values were based on literature research (10).

## 2.7. Statistical analysis

Statistical analysis was performed with IBM SPSS Statistics (Version 22, International Business Machines Corporation, Armonk, New York, United States). After testing for normal distribution (Kolmogorov–Smirnov test, Shapiro Wilk test and histogram), the groups were compared either by analysis of variance (ANOVA) or the Mann–Whitney-*U*-test. The effect of time and time x group interactions were analyzed using the general linear model for repeated measurements with three factor levels and Bonferroni-corrected post-hoc tests or the Friedman test as the appropriate nonparametric alternative (56). We focused on the results of the parametric tests because they are

TABLE 2 Contents of the intervention sessions targeted to individual needs.

| Week | Theoretical part | Practical part |
|---|---|---|
| 1 | • Oral information: explaining the results of visit 1 and deducing special therapeutic needs with regard to pre-existing diseases<br>• Written information: general recommendations for activity<br>• Motivational Interviewing: rating of importance of change and rating of confidence (evaluation of readiness for change), expectations, individual starting point<br>• Work sheet: "advantages and disadvantages of activity increase"<br>• Time for individual needs | • Accompanied activity/guided exercise program: active breaks<br>• Activity recommendation: interrupt sitting time with an active break<br>• Time for individual activity plans |
| 2 | • Oral information: effects of endurance training<br>• Written information: endurance training<br>• Motivational Interviewing: reflecting the experiences of last week, reasons for change, supporting factors, inducing "change talk"<br>• Work sheet: "what helps others, what helps me"<br>• Time for individual needs | • Accompanied activity/guided exercise program: endurance activity, e.g., walking, biking<br>• Activity recommendation: repetition of endurance activity or a second endurance activity or an individual self-selected activity<br>• Time for individual activity plans |
| 3 | • Oral information: effects of strength training<br>• Written information: strength training<br>• Motivational Interviewing: reflecting the experiences of last week<br>• Problem solving strategies: barriers and worries<br>• Work sheet: "barriers and ideas for solutions"<br>• time for individual needs | • Accompanied activity/guided exercise program: strength training, e.g., exercises in a fitness center or at home with resistance bands<br>• Activity recommendation: repetition of strength training activity or a second strength training activity or an individual self-selected activity<br>• Time for individual activity plans |
| 4 | • Oral information: possibilities of flexibility, coordination, relaxation exercises<br>• Written information: flexibility, coordination, relaxation exercises and "possibilities of support"<br>• Motivational Interviewing: reflecting the experiences of last week, talking about possible activities (list of sports activities) and the first step, inducing "change talk"<br>• Goal setting: defining an individual goal and dividing it into small tasks<br>• Work sheet: "step by step"<br>• Time for individual needs | • Accompanied activity/guided exercise program: flexibility, coordination, relaxation exercises<br>• Activity recommendation: repetition of the guided activities or an individual self-selected activity<br>• Time for individual activity plans |
| 5 | • Oral information: doses of activity and recovery<br>• Motivational Interviewing: reflecting the experiences of last week, talking about activity slots in a typical day or week, inducing "change talk"<br>• Work sheet: daily schedule, weekly schedule<br>• Time for individual needs | • Accompanied activity: individual self-selected activity<br>• Activity recommendation: endurance activity and activity with exercises (strength, flexibility, coordination and relaxation) and individual self-selected activity<br>• Time for individual activity plans |
| 6 | • Oral information: long-term training schedule<br>• Motivational Interviewing: reflecting the experiences of the intervention, rating of importance of change and rating of confidence, talking about future plans, inducing "change talk"<br>• Work sheet: "looking back and looking ahead"<br>• Time for individual needs | • Accompanied activity: -<br>• Activity recommendation: endurance activity and activity with exercises (strength, flexibility, coordination and relaxation) and individual self-selected activity<br>• Time for individual activity plans |

described as robust against violations of the normal distribution (57). As a measure of effect size, partial $\eta^2$ is reported ($\eta^2 \geq 0.01$: small effect; $\geq 0.06$: medium effect; $\geq 0.14$: large effect). Individual changes over time were compared between groups with analysis of covariance (ANCOVA) adjusted for baseline values. The difference between the means of both groups is reported as MD. The level of significance was $\alpha = 0.05$. In the results section, we report the results of the Intention-To-Treat (ITT) analysis to avoid an overestimation of effects (58). Missing values due to dropout were imputed using the baseline observation carried-forward method. Single missing values, e.g., as a result of device failure, were not imputed. The Spearman-Rho and Pearson correlation coefficients were calculated for the analyses of relationships between parameters. Covariates are stated in the results section.

# 3. Results

## 3.1. Participants

Figure 1 shows a flowchart of the number of participants and dropouts. Twenty-six women and four men with a mean age of $41 \pm 12$ years and a mean body mass index (BMI) of $28 \pm 6\,kg/m^2$

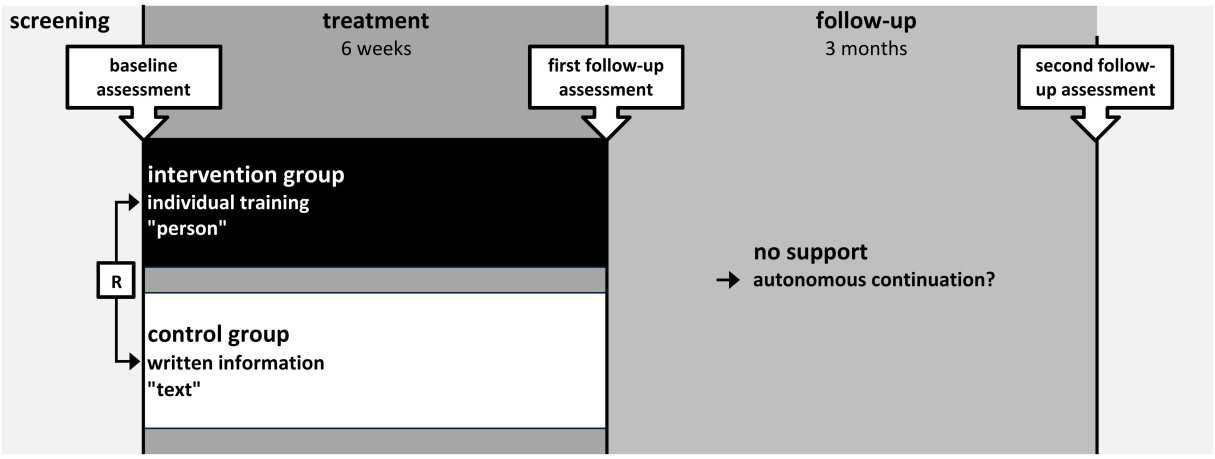


FIGURE 2
Timeline of the assessments and periods (R: randomization).

completed the study. Eighteen participants (58%) were overweight (BMI ≥ 25 kg/m$^2$), 11 Participants (35.5%) were obese (BMI ≥ 30 kg/m$^2$). The baseline comparisons between groups and additional baseline characteristics are given in Table 1. The differences between the groups did not reach statistical significance except for the treatment with antidepressants.

## 3.2. Dropouts

One patient dropped out due to missed appointments (intervention and first follow-up) for unknown reasons. Another patient in the intervention group was lost to follow-up (second follow-up, visit 3) for unknown reasons. The dropout rate over the study period, from baseline to the second follow-up, was 6%.

## 3.3. Intervention

Attendance, an indicator for compliance, was 96% in the intervention group. Two appointments were canceled because of the participants' workload, one was forgotten, and one did not take place due to dropout. Appointments were postponed in cases of scheduling difficulties or illness. In general, 73% of the appointments were held face-to-face, 27% were conducted via telephone, e-mail or video conference due to infection containment measures in the pandemic or to promote independent activity (six sessions).

The entire intervention period was impacted by the Covid-19 pandemic, for example lockdown of fitness centers. All activities had to be conducted in accordance with the varying official and individual safety precautions. Participants rated the influence of the pandemic situation on their physical activity with 7 out of 10 points (0: no influence and 10: significant influence) with 57% reporting reduced physical activity. In addition, patients rated the influence of the pandemic on their mental health with 7 out of 10 points (worsening of symptoms reported by 75%). The pandemic situation may also have influenced the choice of sports disciplines. Intervention records show that the main disciplines were walking and jogging, although 88% of the patients combined two activities. No team sports were chosen and a preference for individual disciplines was observed, e.g., swimming, yoga and fitness training. Ninety-four percent of the participants were active on their own; 75% joined a local sports group. Patients rated the intervention with 9 out of 10 points (0: not helpful; 10: very helpful). The items "personal contact" (9.6 points), "free of charge" (9.7 points) and "accompanied activity" (9.5 points) were rated as the most helpful aspects. When asked whether their physical activity was impacted by the intervention, 75% of the intervention group answered with "yes," while only 13% of the control group reported changes in activity. 81% of interventions resulted in the completion of a sports program and increase in physical activity, and were rated as successful by the sport therapist.

No serious adverse events occurred, but 14 adverse events were reported. Only two were caused by physical activity (twisted knee and heel spur) and occurred in the control group.

## 3.4. Physical activity

Results of the ANOVA with repeated measurements for all three time points revealed a significant interaction between group and time [$F(2, 54) = 4.283$, $p = 0.019$, partial $\eta^2 = 0.137$] as shown in Figure 3. Interactions remain significant after correction with the covariates baseline symptom severity or medication dose ($p = 0.029$ and $p = 0.035$, respectively).

Between baseline and the second follow-up, MVPA increased by 10.4 min/day (SE = 4.3 min/day) in the intervention group, but decreased by about 5.1 min/day (SE = 4.5 min/day) in the control group (MD = 15.5 min/day, 95%-CI[2.7, 28.3], $p = 0.020$). Between baseline and the first follow-up, MVPA increased by 9.8 min/day (SE = 3.4 min/day) in the intervention group, and decreased by 1.5 min/day (SE = 3.5 min/day) in the control group (MD = 11.3 min/day, 95%-CI[1.1, 21.4], $p = 0.031$). Between the first and second follow-up, MVPA increased by 0.6 min/day (SE = 4.8 min/day) in the intervention group, and decreased further by 3.6 min/day (SE = 4.9 min/day) in the control group (MD = 4.2 min/day, 95%-CI[−10.0, 18.4], $p = 0.247$).

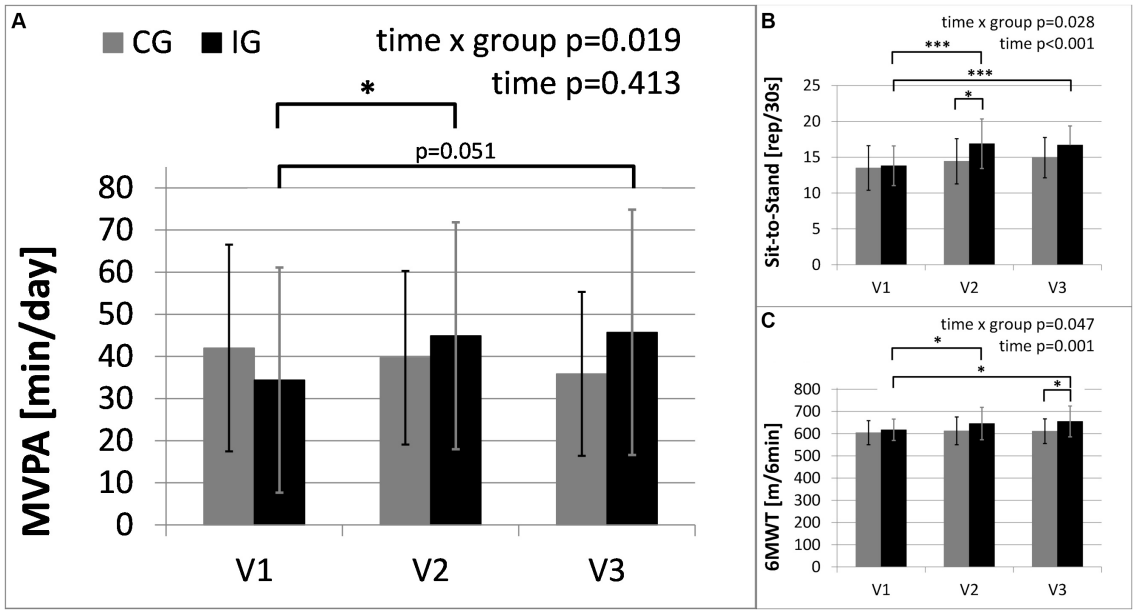


FIGURE 3
Main outcome of physical activity and secondary outcomes of physical health: **(A)** moderate-to-vigorous physical activity (MVPA) in minutes per day, assessed with activity sensors (CG, $n$=14; IG, $n$=15, due to failed measurements); **(B)** results of Six-Minute Walk Test (6MWT); **(C)** results of Sit-to-Stand Test. The intervention group (IG) is compared to the control group (CG) over the study period from baseline (V1) to the first follow-up visit (V2) directly after the intervention and the second follow-up (V3), 3months after the end of the intervention (*: significant time effect/group difference $p$<0.05; ***$p$<0.001).

After adjusting for baseline values, MVPA at the second follow-up was significantly greater in the intervention group compared with the control group [$F(1, 26) = 6.157$, $p = 0.020$, partial $\eta^2 = 0.191$].

The statistical results were confirmed when applying nonparametric tests (for variables with missing normal distribution) and analyzing the according-to-protocol population.

The results of the "Freiburger Questionnaire on Physical Activity" showed that sports activity significantly increased by 2.7 kcal/kg/week (SE = 1.2 kcal/kg/week) in the intervention group, but decreased by 1.6 kcal/kg/week (SE = 1.2 kcal/kg/week) in the control group between baseline and the second follow-up (MD = 4.3 kcal/kg/week, 95%-CI[0.8, 7.8], $p = 0.019$).

## 3.5. Secondary outcomes

Table 3 provides the results of the exploratory analysis for selected secondary outcomes. Significant time x group interactions occurred in the results of the Sit-to-Stand Test (STS) and Six-Minute Walk Test (6MWT), representing the changes in physical fitness. In the intervention group STS and 6MWT increased by 21 and 6%, respectively. Both groups show significant improvements in the severity of depressive symptoms. Furthermore, Table 3 shows changes in the use of antidepressants. The changes in medication reflected a reduced number of patients taking antidepressants in the intervention group and an increased number of patients taking antidepressants in the control group (see Figure 4). No significant interactions were found between changes in depressive symptoms, physical activity and medication. In the "Barriers and barrier management in physical exercise" questionnaire, significant improvements were seen in barrier management in the intervention group (16% increase) with a significant time x group interaction for barrier management, but not for barrier severity. The management of barriers is significantly correlated with sports activity at visit 2 ($r = 0.597$, $p = 0.001$) and visit 3 ($r = 0.489$, $p = 0.007$). The perception of barriers to physical activity at baseline ($r = -0.412$, $p = 0.024$) and the results of 6MWT at baseline ($r = -0.364$, $p = 0.048$) correlated significantly with age, while all other parameters did not show significant correlations with age. No significant correlations with BMI or symptom severity were found.

# 4. Discussion

This study demonstrates a feasible and effective way to promote a long-term increase in self-selected physical activity in a real life setting for patients with depression, combining both physical training and psychological methods.

## 4.1. Effectivity for the increase in moderate-to-vigorous physical activity

The intervention group showed a greater increase in moderate-to-vigorous physical activity than the control group. Since the control group was offered the same information via a written booklet and the same assessment visits, this difference can be attributed to the personal contact in combination with accompanied physical activity and an individualized, flexible approach to determine the best way to start activity in the Motivational Interviewing conversations. In addition to measured physical activity increases and the supporting results from

TABLE 3 Secondary outcomes as mean±standard deviation in the intervention group and control group before (visit 1), directly after the intervention (visit 2) and at the second follow-up 3months after the end of the intervention (visit 3).

| | Intervention group (person) | | | | Control group (text) | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | n | Visit 1 | Visit 2 | Visit 3 | n | Visit 1 | Visit 2 | Visit 3 | Time × group interaction |
| PA FQ (kcal/kg/week) | 16 | 25 ± 20 | 34 ± 19* | 28 ± 18** | 15 | 25 ± 15 | 22 ± 13 | 25 ± 14 | $F(2, 58) = 2.454$, $p = 0.095$, partial $\eta^2 = 0.078$ |
| SA FQ (kcal/kg/week) | 16 | 1 ± 3 | 9 ± 10 | **6 ± 6**** | 15 | 6 ± 12 | 4 ± 6 | **2 ± 3** | $F(2, 58) = 5.060$, $\boldsymbol{p = 0.014}$, partial $\eta^2 = 0.149$ |
| STS (rep/30 s) | 16 | 14 ± 3 | **17 ± 4** | 17 ± 3*** | 14 | 14 ± 3 | **14 ± 3** | 15 ± 3 | $F(2, 56) = 3.862$, $\boldsymbol{p = 0.028}$, partial $\eta^2 = 0.120$ |
| 6MWT (m/6 min) | 16 | 618 ± 48 | 646 ± 73 | **655 ± 69**** | 14 | 604 ± 54 | 613 ± 62 | **611 ± 56** | $F(2, 56) = 3.243$, $\boldsymbol{p = 0.047}$, partial $\eta^2 = 0.104$ |
| BDI II (points) | 16 | 30 ± 12 | 23 ± 13 | 26 ± 13* | 15 | 26 ± 10 | 23 ± 8 | 22 ± 12 | $F(2, 58) = 0.568$, $p = 0.570$, partial $\eta^2 = 0.019$ |
| MADRS (points) | 15 | 22 ± 6 | 17 ± 8 | 14 ± 10* | 15 | 23 ± 6 | 17 ± 7 | 13 ± 8*** | $F(2, 56) = 0.308$, $p = 0.736$, partial $\eta^2 = 0.011$ |
| PA-barriers (points) | 16 | 33 ± 7 | 32 ± 6 | 32 ± 6 | 15 | 34 ± 5 | 34 ± 5 | 32 ± 6 | $F(2,58) = 0.467$, $p = 0.591$, partial $\eta^2 = 0.016$ |
| Management (points) | 16 | 32 ± 5 | **38 ± 8** | 37 ± 6* | 14 | 34 ± 6 | **31 ± 9** | 32 ± 8 | $F(2, 56) = 4.753$, $\boldsymbol{p = 0.012}$, partial $\eta^2 = 0.145$ |
| WHOQOL psychol. (points) | 16 | 29 ± 14 | 38 ± 16 | 29 ± 18* | 15 | 38 ± 13 | 38 ± 14 | 36 ± 18 | $F(2, 58) = 1.969$, $p = 0.149$, partial $\eta^2 = 0.064$ |
| WHOQOL physical (points) | 16 | 47 ± 16 | 54 ± 17 | 51 ± 14* | 15 | 56 ± 14 | 55 ± 14 | 54 ± 17 | $F(2, 58) = 2.759$, $p = 0.072$, partial $\eta^2 = 0.087$ |
| Antidepressants (n) | 16 | **12** | 11 | 10 | 15 | **6** | 8 | 9 | – |

The presented results were confirmed by non-parametric analyses for not normally distributed parameters. *p*-values are not corrected for multiple testing (MVPA, moderate-to-vigorous physical activity; PA FQ, Physical Activity Freiburger Questionnaire; SA FQ, Sports Activity Freiburger Questionnaire; STS, Sit-to-Stand Test; 6MWT, Six-Minute Walk Test; BDI II, Beck Depression Inventory II; MADRS, Montgomery-Åsberg depression rating scale; PA-Barriers, barriers to physical exercise; WHO QOL, World Health Organization Quality of Life. *Time effect in repeated measurements ANOVA $p < 0.05$; **$p < 0.01$; ***$p < 0{,}001$; bold: difference between groups in *t*-test $p < 0.05$).

the questionnaires, nearly 75% of the participants of the intervention group reported an increase in physical activity due to the intervention. Furthermore, we were able to show that parameters of physical health improved and medication with antidepressants was reduced in the intervention group in the course of the study period. Both groups showed decreased symptoms of depression. This was accompanied by a reduced use of antidepressants in the intervention group and an increased use in the control group. The periodic appointments for study assessments, together with the corresponding social contact and improved connection with the healthcare institution may have contributed to the improved mood in the control group.

In a study by Chalder et al., "physical activity facilitators" offered interviews including Motivational Interviewing techniques primarily via telephone (39, 40). This did not result in any significant reductions in depressive symptoms or medication dosage, but participants stated that they felt well and benefited from the intervention, although they would have wished for more active help. In our study, the increase in activity was smaller than expected, but baseline values were comparable to other measurements with similar activity sensors (10). Possible causes could be linked to the pandemic containment measures and fear of infection. In line with other studies (59), more than 50% of our participants reported reduced physical activity during the COVID-19 pandemic. The chosen activities, which showed a preference for activities which could be done alone and outside, and the rating of the influence of COVID-19 are both relevant in this context. However, despite the limited increase, current research has shown that even small gains in physical activity are effective in improving mental health (60).

## 4.2. Sustainability of effects

In contrast with the INSHAPE program which involved weekly contact with "health mentors" and a free sports program for 6 months leading to increased self-reported activity (61), participants in our project were not supported after the initial six weekly sessions. Nevertheless, the intervention group still showed an increased level of physical and sports activity at the second follow-up 3 months after the end of the intervention (see Figure 3). The parameters of physical health (STS and 6MWT) show similar improvements over time. In contrast, the secondary outcomes of mental health show different changes. Following an initial improvement in mental health during the intervention, they show a slight decline in the follow-up period when there was no contact with the study personnel. Thus, regular appointments and personal contact and support may be critical factors in improving patients' mental health. Continuous follow-up appointments at a higher frequency than 3-month intervals or alternative methods to increase social support may lead to improved outcomes.

## 4.3. Feasibility and safety

Adverse events caused by physical activity were reported only in the control group and may be explained by too little knowledge of training methods and too much training load without an appropriate habituation process. On the basis of these data, the intervention was deemed safe for the participants. The intervention was also deemed feasible: Symptoms of depression, the COVID-19 lockdown, family difficulties, professional activities, orthopedic problems and pain were reported as the main barriers, but the small dropout rate of 6%, the high attendance rate of 96% and the positive ratings of the components in the intervention group suggest a good feasibility and the effectiveness of motivational strategies for the participants. The dropout rate was smaller than expected and significantly below that reported in a meta-analysis (20) for people with depression (18%). The study was feasible even under pandemic conditions in which there were strict restrictions for sports activity due to the individual training mode chosen for the intervention, in contrast with other study concepts involving group exercise [e.g., (25)].

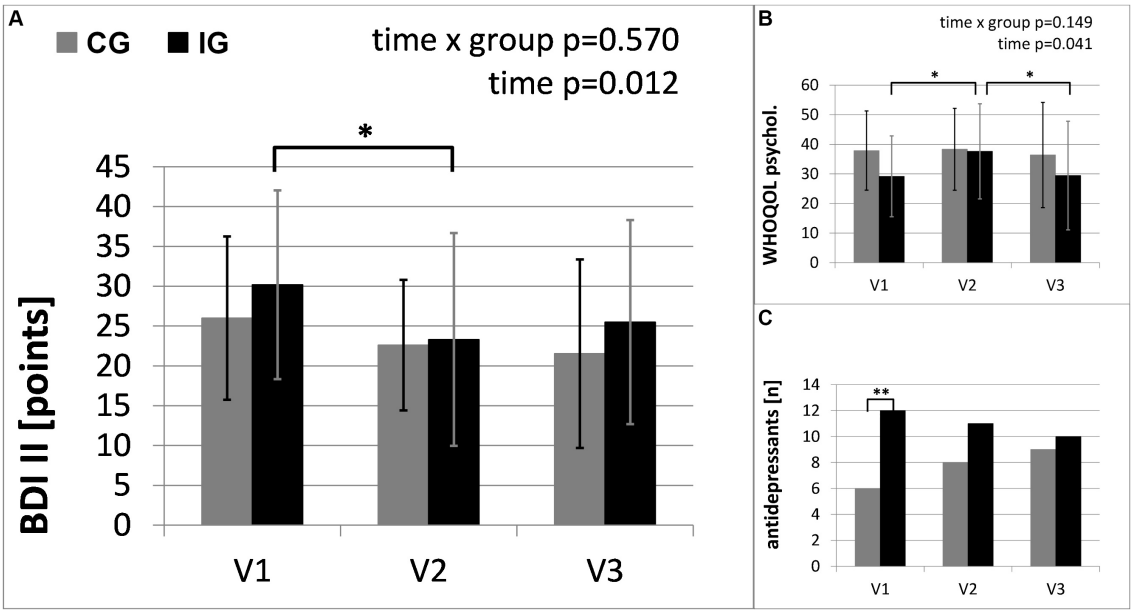


FIGURE 4
Secondary outcomes of mental health: **(A)** results of self-rating Beck Depression Inventory (BDI II); **(B)** results of World health Organization Quality of Life Questionnaire (WHOQOL-Bref); **(C)** number of participants taking antidepressants. The intervention group (IG) is compared to the control group (CG) over the study period from baseline (V1) to the first follow-up visit (V2) directly after the intervention and the second follow-up (V3), 3months after the end of the intervention (*: significant time effect/group difference $p<0.05$; **$p<0.01$).

## 4.4. Successful features of the intervention

Feedback from the patients in the intervention group showed that it was helpful that the intervention was free of charge, presented personally, and included accompanied activity. The analysis of training logs showed that structure, social connections and proximity to their place of residence were important factors. The planning and provision of short workout sequences which could be integrated in daily life and a planned structure for a 7-day period were seen as effective aids. Exploring possibilities for sport near the patient's place of residence, contacting existing groups or finding partners for sports activity in the family or among friends (to increase social support) were also reported as helpful strategies. Beyond that, feasibility could be further improved by allowing more flexibility in making appointments, e.g., individualizing the time intervals between the appointments. Additional factors for consideration are varying requirements for individual support and the need for extra support during challenging life situations, e.g., change of residence or occupation.

## 4.5. Implications for the implementation in health care

Not all barriers to an active lifestyle are related to the patients. Garvey et al. (24) identified barriers to the prescription of exercise on the part of healthcare providers: lack of knowledge on how to prescribe exercise and establish contact with trained physical activity specialists, concerns about the patient's ability to exercise, risk factors, such as comorbidities, or placing more stressors on their clients (24). Improvement in cooperation between the different professions is needed in addition to the establishment of routine referral methods with the possibility of individual support for physical activity. Physical exercise is recommended in the guidelines for the treatment of depression (62). Consequently, the translation of the treatment guidelines into clinical practice is the next important step. The German "Rezept für Bewegung" (translation: "prescription of activity") by the German Olympic Sports Confederation and German Medical Association or global health initiatives such as "Exercise is Medicine®" by the American College of Sports Medicine (ACSM) already pursue this goal, but physical activity is still underused in the therapy of patients with depression (18). A more widespread application is desirable, but would need to take account of differences in country-specific health care systems and lifestyles.

## 4.6. Limitations

The present study has some limitations: Both groups experienced changes in therapy and medication during the study participation. A critical point for the statistical analysis is the small sample size. While larger effects can be detected with sufficient power, it is possible that small to medium effects would only reach statistical significance in bigger samples. Also, fewer men than women participated. Although the primary outcome was measured with activity sensors, data for secondary outcomes were collected with self-rating questionnaires and therefore may have been influenced by social desirability. The activity sensors used in the study measured acceleration, but not heart rate or effort. Therefore, the classification of activity intensity may not be sufficiently accurate. However, to address this potential limitation, we used wear time and activity logs as well as activity questionnaires and checked each automatic analysis. It should be taken into consideration that absolute values measured with varying activity

sensors lack comparability between studies [e.g., (63)]. Our study procedure was furthermore impacted by the pandemic situation and its effects on physical activity (59) and the follow-up results were influenced by COVID-19 infections in two cases.

### 4.7. Perspectives

Future research should target motivational aspects of being physically active for people with mental illness and seek greater synergies between the fields of psychology and sports and training medicine. On a larger scale, projects are needed which analyze the cost–benefit ratio and test the implementation of programs supporting physical activities in the healthcare system (64). Additionally, larger samples would allow the comparison of single features of the interventions and the analysis of the influence of moderating factors and predictors of response.

### 4.8. Conclusion

Personalized training with Motivational Interviewing and accompanied physical activity was a feasible and effective aid to increase moderate-to-vigorous physical activity and improve physical performance as measured with Sit-to-Stand Test and Six-Minute Walk Test in people with depression. The combination of physical training and psychological methods focusing on individual activity preferences, needs, and possibilities in the everyday life of the participants resulted in a low dropout rate and improved management of barriers preventing physical activity. Participants in the intervention group showed improvements in depressive symptoms in spite of reductions in their pharmacological therapy. The integration of individual support regarding physical activity, including the successful methods evaluated in this project, should be considered for the multimodal treatment of depression.

## Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

## Ethics statement

The studies involving human participants were reviewed and approved by the Ethics Committee of Hannover Medical School. The patients/participants provided their written informed consent to participate in this study.

## Author contributions

KK-V, SH, AK, UT, and KK planned and designed the study. ES and AK recruited the participants. KK-V, ES, and KK collected the data. KK-V and SH were responsible for the analysis and interpretation of the data. KK-V wrote the first draft of the manuscript. SH, ES, AK, UT, and KK contributed to the discussion, reviewed, and edited the manuscript. All authors contributed to the article and approved the submitted version.

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## Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

## Publisher's note



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# Prevalence of post-traumatic stress and tests of metacognition as a PTSD risk marker in patients with coronary heart disease and elevated HADS scores: analysis of data from the PATHWAY RCT's in UK cardiac rehabilitation

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**Introduction:** Anxiety and depression in coronary heart disease (CHD) are associated with poorer health outcomes, greater healthcare use and reduced quality of life. Post-traumatic stress symptoms may be a particular concern as they are associated with increased mortality at follow-up. We examined prevalence of PTSD in patients with elevated anxiety/depression scores referred for cardiac rehabilitation (CR) across seven NHS sites in North-West England. We tested a possible mechanism (metacognition) linking CHD to PTSD symptom severity as implicated in the metacognitive model.

**Methods:** Data was collected at baseline as part of the NIHR funded PATHWAY trial of metacognitive therapy for anxiety and depression in CHD. Patients ($n$ = 572) with at least mild symptoms of anxiety and depression under routine screening (assessed with the Hospital Anxiety and Depression Scale) and attending CR were eligible for the study. A battery of questionnaires, including assessment of demographic variables, PTSD symptoms (using the IES-R) and metacognitive beliefs was administered prior to random allocation and intervention delivery.

**Results:** Rates of PTSD were high, with 48% of patients meeting threshold for PTSD and a further 15% partial PTSD. All five metacognition subscales were positively associated with PTSD vs. no PTSD, with beliefs about the uncontrollability and danger of worry and beliefs about need to control thoughts being most strongly related. For every unit increase in uncontrollability and danger metacognitions the odds of being in the PTSD group increased 30%, whilst the odds of partial PTSD increased 16%. Stepwise regression analysis using the metacognitive subscales along with demographic and health-related covariates found that uncontrollability/danger and need for control metacognitions explained unique variation in PTSD symptom severity, with unique contributions also for age, sex, and number of comorbidities.

**Conclusion:** PTSD symptoms appeared highly prevalent in the current CR sample. Metacognitive beliefs were individually associated with symptom severity with the strongest positive relationship observed for beliefs about uncontrollability and dangerousness of worry, followed by need to control thoughts. The results highlight the importance in assessing PTSD in CR patients and add support to implementing metacognitive therapy in CHD to target particular metacognition risk factors in anxiety, depression and PTSD.

KEYWORDS

**coronary heart disease, post-traumatic stress disorder (PTSD), metacognition, cardiac rehabilitation, metacognitive model, IES-R, metacognitions questionnaire, MCQ-30**

## Introduction

At least 1 in 3 coronary heart disease (CHD) patients experience anxiety and depression symptoms and anxiety and depression appear to be independent risk factors associated with the development and recovery from CHD (1, 2). Detailed assessment of psychological morbidity amongst cardiac rehabilitation patients suggests that as many as 45% could meet diagnostic criteria for a specific anxiety disorder, 20% could meet criteria for depression with 26% having at least two disorders (3). Additionally, in one study, the early age myocardial infarction (MI) group, showed rates of current psychiatric disorders, lifetime psychiatric disorders, and lifetime depressive disorders that were higher than the rates for the late age MI group (4).

The prevalence of PTSD in CHD has received particular attention, with rates estimated at between 0–35% (5). A meta-analysis of 13 studies involving 821 individuals after myocardial infarction (MI) concluded that the weighted prevalence of PTSD is 14% (range 0–25%) of patients (6). Estimates of PTSD in survivors of MI have been reported as 27% at a mean of 45 months after cardiac arrest (7). A substantial proportion of patients with implantable cardioverter defibrillators (ICDs) appear to have PTSD (8, 9) with a prevalence found to be 20% in ICD clinics (10). PTSD symptoms are a concern because they may be associated with increased mortality and morbidity in CHD (11), but they are not usually assessed or treated as part of cardiac rehabilitation (CR).

Following a cardiovascular event such as MI, clinical guidelines in the UK recommend that patients attend cardiac rehabilitation to reduce future cardiac risk and improve outcomes (12). In 2019 there were 89,573 patients taking up CR across 230 programmes, representing 50% of those offered CR (13). Routine assessment of psychological functioning in CR uses the Hospital Anxiety and Depression Scale (HADS) to assess anxiety and depression symptoms, but this is not designed to capture symptoms of PTSD (re-experiencing, hyperarousal, avoidance). As a result, routine psychological assessment is not geared to recognize PTSD symptoms and adjust to the needs of traumatized patients. An important issue therefore, concerns the prevalence and severity of PTSD in those patients who show at least mild general anxiety/depression symptoms under routine screening and whether greater attention to PTSD is indicated.

In the present study we aimed to assess the magnitude and prevalence of PTSD symptoms in patients endorsing at least mild anxiety/depression symptoms on the routinely administered Hospital Anxiety and Depression Scale (HADS). We also aimed to test the statistical predictors of PTSD symptoms based on metacognitive theory whilst controlling for known covariates. In particular, we examined age, sex, number of comorbidities as covariates and tested the contribution of hypothesized psychological mechanisms which are vulnerabilities for PTSD in the metacognitive model (14). The examination of theory-driven psychological mechanisms that could be risk markers for PTSD is valuable as it might contribute to treatment planning.

The metacognitive model of PTSD (14, 15) links traumatic experiences such as cardiac events to PTSD through the mechanism of excessive negative thinking caused by maladaptive metacognition. It proposes that acute stress symptoms are maintained by activation of a persistent thinking style dominated by worry/rumination, threat monitoring and counterproductive coping behaviors, that maintain a sense of current threat. This thinking style is modulated by metacognition; an array of higher-level structures and internal information involved in the regulation of thinking. An important feature of metacognition in this model is information about cognition on which processing relies. In particular, maladaptive knowledge or beliefs about the uncontrollability and dangerousness of thoughts are considered especially important in the unhelpful regulation of thinking and development of psychological disorder, including PTSD symptoms. Consistent with this prediction, maladaptive metacognitions have been found to be elevated across psychological disorders (16) and among individuals with PTSD (17, 18). A small number of studies suggest that such metacognitions are positively associated with greater anxiety and depression (19) and greater negative affectivity (20) in CHD, and poorer mental health in Pulmonary Arterial Hypertension (21). However, there is a gap in the literature concerning the contribution of metacognitive beliefs to PTSD in CHD patients.

Given these limitations in the literature and the potential value in understanding the extent and risk factors of PTSD in CR the present study aimed to assess: (1) the severity of PTSD symptoms and prevalence of PTSD in CR patients reporting elevated anxiety/depression; (2) the relative predictors of PTSD symptoms; (3) the contribution of biased metacognitions to risk

and symptom severity as hypothesized by metacognitive theory, when controlling for covariates. Addressing such issues can contribute to understanding the specific psychological needs of CR patients, support the tailoring of psychological provision to meet those needs and provide evidence of the potential contribution metacognition can make in predicting the risk of PTSD in heart disease patients with elevated anxiety/depression scores.

# Methods

## Participants and design

The present study is a secondary analysis of data from 572 participants (363 males) who participated in the NIHR-funded PATHWAY programme, which was conducted across seven CR services in the North-West of England. Participants completed baseline assessments prior to randomization in two separate controlled trials. Characteristics of sample participants are displayed in Table 1. The trials were single-blind multi-center tests of the effects of adding metacognitive therapy group treatment (trial 1) or adding self-help metacognitive therapy (trial 2) to usual CR (22, 23).

Eligible patients were referred to CR services and met the Department of Health or British Association for Cardiac Prevention and Rehabilitation CR eligibility criteria. Reasons for referral to CR were: acute coronary syndrome, after revascularization, stable heart failure, stable angina, after implantation of defibrillator, heart valve repair/replacement, heart transplant, and ventricular assist devices, adult congenital heart failure. Patients were required to have a minimum score of 8 (mild symptoms) on either the depression or anxiety subscale of the Hospital Anxiety and Depression Scale (HADs) (24), be aged 18 years or older, and have a competent level of English language comprehension (read, understand, and complete questionnaires in English).

## Outcome measures

At baseline assessment a battery of self-report measures was used. Included in the test battery and extracted for the present analyses were the following measures:

The Impact of Event Scale – Revised (IES-R) (25) is a 22-item self-report measure that assesses symptoms of PTSD, consistent with diagnostic criteria of DSM -IV (26), and is an extension of the IES. Items can be scored as a total score (0–88) or utilize the three subscales: avoidance, intrusion and hyperarousal. The IES-R can be used as a continuous measure and can also be considered using cut-offs to suggest clinical presence of PTSD, where scores 33 or above have been found to give the best diagnostic accuracy for probable PTSD, (27). Partial PTSD scores range between 24 and 32 or the absence of PTSD scores below 24 (28, 29). Although the IES was not originally designed as a diagnostic tool it has excellent sensitivity and specificity in identifying PTSD cases against diagnostic DSM-IV and ICD-10 screening (30). Similarly, the IES-R shows moderate agreement with a positive PTSD screen on DSM-IV and DSM-V (31). In the current sample the Cronbach alpha for the IES-R = 0.95.

The Hospital Anxiety and Depression Scale (24) is a 14-item self-report measure that assesses symptoms of anxiety and depression, is widely used in physical health and is a routine measure of anxiety and depression in CR in the UK. In the present study, Cronbach alpha for the anxiety subscale = 0.82 and for depression = 0.78.

The metacognitions Questionnaire 30 (32) is a 30-item measure of metacognitive beliefs implicated in the metacognitive model. It consists of 5 subscales, assessing the following metacognitive domains; positive beliefs about worry (Pos); negative beliefs about uncontrollability and danger of thoughts (Neg ud); need for control of thoughts (nfc); cognitive confidence (cc), and cognitive self-consciousness (csc). Each subscale is comprised of 6-items. The measure has been widely used in research testing the metacognitive model and has a stable factor structure and acceptable reliability. In CR patients the five factor and a bi-factor model (i.e., including the total score) have been tested for goodness of fit. Whilst it appears that the bi-factor solution may carry some small additional information beyond the 5 subscales alone, continued use of the more widely established 5-factors is currently recommended (18). The subscale Cronbach alpha's in the present sample were as follows: positive beliefs (Pos) = 0.87; Neg ud = 0.82; cc = 0.89; nfc = 0.71; csc = 0.78; MCQ total-score alpha = 0.90.

## Data analysis plan

Descriptive statistics (frequencies and percentages) were used to assess the range and distribution of PTSD symptom severity scores. Prevalence of PTSD was assessed using the IES-R cut-off scores as defined above for no PTSD, partial PTSD and PTSD case-ness. Scatter plots and Pearson's correlation coefficients were used to test associations between metacognitive beliefs and PTSD symptoms (continuous outcome).

To assess if metacognitive beliefs predicted PTSD caseness (defined as: no PTSD, partial, yes), we conducted a multinomial regression. Along with the measures of metacognitions this analysis included a pre-specified set of demographic- and health-related covariates known to be associated with PTSD: age, sex, previous cardiovascular events (yes/no), number of comorbidities and previous diagnosis/treatment of anxiety (yes/no), and/or depression (yes/no). For this analysis we report the relative risk ratios (RR) for the raw subscale and total MCQ scores but we also rescaled the MCQ total and subscale scores to all range from 0–100, to provide directly comparable measures of relationships with PTSD.

To investigate relationships between metacognitive beliefs and degree of PTSD symptomology we conducted a series of linear regression models using IES-R in its continuous form as the dependent variable. An initial "reference" model consisted solely of the pre-specified covariates. Subsequent models included the covariate set plus one MCQ-30 subscale of interest, repeating until the total score and each subscale had been tested individually. Likelihood ratio tests were used to determine if the change in the

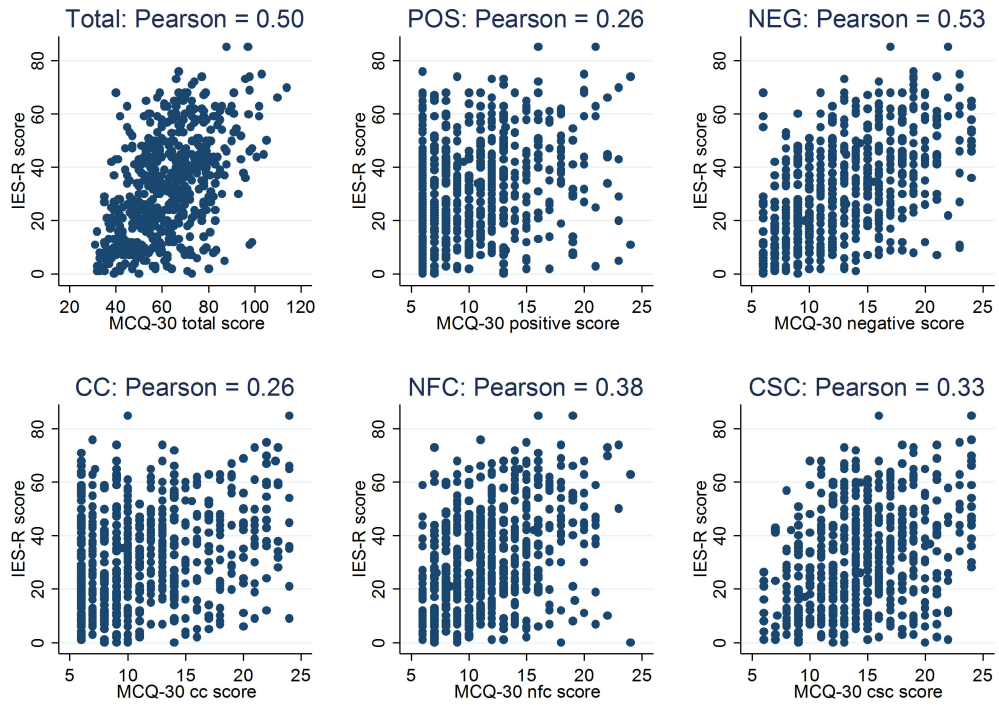


FIGURE 1
Scatter plots of MCQ-30 (and its subscales) and PTSD symptom severity (IES-R) scores.

adjusted R-squared when adding each MCQ-30 subscale score into the model was statistically significant.

We also sought to determine the subset of MCQ subscales which, after controlling for the covariate set could account for unique variation in trauma-symptom severity (IES-R) using hierarchical multiple regressions. To do so we determined whether forward-stepwise regression and backward-stepwise regressions gave rise to the same final subset of MCQ predictors and covariates. All analysis was conducted using Stata version 14 and an alpha level of 5% for statistical significance.

# Results

## Sample overview

Participant characteristics are summarized in Table 1 for the entire sample and are further broken down by PTSD classification based on IES-R cut-offs. The table presents descriptives for the covariates and the MCQ30 subscales.

## Prevalence of PTSD in cardiac rehabilitation patients

While 211 patients (36.9%) did not meet the cut-off score for PTSD, 85 patients (15%) had partial PTSD (i.e., scored between 24–33 on the IES-R), and 276 patients (48.25%) met the cut-off score for PTSD. Table 2 details the prevalence rates of PTSD by type of cardiac event.

## Relationship between metacognitive beliefs and PTSD severity

Metacognitive beliefs were positively associated with symptoms of PTSD (as measured by the IES-R total score), such that greater dysfunctional metacognitive beliefs were associated with increased symptoms, see Figure 1. Correlations were moderate for the MCQ total, $r = 0.50$, $p < 0.001$, and negative beliefs regarding uncontrollability and danger, $r = 0.53$, $p < 0.001$. Weaker correlations were noted between PTSD severity and need for control, $r = 0.38$, $p < 0.001$, cognitive confidence $r = 0.26$, $p < 0.001$, cognitive self-consciousness, $r = 0.33$, $p < 0.001$, and positive metacognitive beliefs, $r = 0.26$, $p < 0.001$.

## Metacognitive predictors of PTSD category

Relative risk ratios and confidence intervals for the MCQ30 subscale and total scores analyzed as predictors of PTSD caseness are summarized in Table 3. After adjusting for covariates, each subscale of the MCQ and the total score were significantly related to being classified as PTSD rather than no PTSD. The MCQ-neg subscale was most strongly associated with being in the PTSD category (as compared to the no PTSD category); for a one-unit increase in MCQ neg, the likelihood of being in the PTSD category increased by 30%, whilst the likelihood of being in the partial PTSD category increased by 16%. The next largest association was for MCQ need for control, followed by MCQ cognitive self-consciousness. Inspection of the rescaled RR values shows that the

TABLE 1 Participant characteristics.

| Characteristic | Total | No PTSD | Partial PTSD | PTSD |
|---|---|---|---|---|
| Sex, *n* (%) | | | | |
| Male | 363 (63%) | 153 (73%) | 55 (65%) | 155 (56%) |
| Female | 209 (37%) | 58 (27%) | 30 (35%) | 121 (44%) |
| Age, mean (SD) | 60.5 (10.9) | 63.1 (11.0) | 61.3 (9.9) | 58.2 (10.5) |
| Previous anxiety | 190 (33%) | 41 (19%) | 28 (33%) | 121 (44%) |
| Previous depression | 190 (33%) | 42 (20%) | 30 (35%) | 118 (43%) |
| Number of comorbidities, mean (SD) | 4.6 (2.3) | 4.1 (2.0) | 4.5 (2.4) | 5.0 (2.4) |
| 0 | 15 (3%) | 5 (2%) | 3 (4%) | 7 (3%) |
| 1–3 | 193 (34%) | 83 (39%) | 29 (34%) | 81 (29%) |
| 4–6 | 244 (43%) | 98 (46%) | 33 (39%) | 113 (41%) |
| 7 or more | 120 (21%) | 25 (12%) | 20 (24%) | 75 (27%) |
| Number of additional cardiac events, mean (SD) | 0.7 (1.1) | 0.7 (1.0) | 0.7 (1.0) | 0.7 (1.1) |
| 0 | 333 (58%) | 119 (25%) | 48 (56%) | 166 (60%) |
| 1 | 122 (21%) | 52 (25%) | 20 (24%) | 50 (18%) |
| 2 or more | 117 (21%) | 40 (19%) | 17 (20%) | 60 (22%) |
| Marital status | | | | |
| In a relationship | 343 (60%) | 138 (65%) | 46 (54%) | 159 (58%) |
| Separated | 132 (23%) | 46 (22%) | 22 (26%) | 64 (23%) |
| Single | 96 (17%) | 27 (13%) | 17 (20%) | 52 (19%) |
| MCQ-30, mean (SD) | 61.7 (15.5) | 53.4 (13.3) | 61.0 (13.0) | 68.2 (14.7) |
| Positive subscale | 10.6 (4.4) | 9.4 (3.8) | 10.7 (4.6) | 11.5 (4.5) |
| Negative (ud) subscale | 13.1 (4.6) | 10.4 (3.7) | 12.9 (3.9) | 15.1 (4.3) |
| cc subscale | 11.7 (5.0) | 10.3 (4.3) | 11.3 (4.7) | 12.8 (5.2) |
| nfc subscale | 11.8 (3.9) | 10.4 (3.6) | 11.2 (3.2) | 13.1 (3.9) |
| csc subscale | 14.5 (4.2) | 12.9 (4.0) | 14.9 (4.0) | 15.6 (4.0) |
| IES-R, mean (SD) | 32.1 (18.7) | 12.7 (6.6) | 27.7 (2.6) | 48.3 (11.4) |

MCQ, metacognitions questionnaire; ud, uncontrollability and danger; cc, cognitive confidence; nfc, need for control; csc, cognitive self confidence; IES-R, Impact of Events Scale-Revised.

total MCQ score had a slightly higher risk ratio than the MCQ-neg subscale when their respective scores were rescaled between 0–100.

## Metacognitive predictors of PTSD symptom severity

Summary statistics for the linear regression models are presented in Table 4. The pre-specified covariate set explained 14% of the variance in IES score, and entering each of the MCQ30 subscales and the MCQ total individually alongside the covariates resulted in a statistically significant increase in the variance explained. Models including the MCQ-30 total score or the negative subscale (uncontrollability and danger) accounted for the largest amount of overall variance in the IES-R (30.8% and 31.9% respectively). Compared to the covariates alone, adding negative beliefs concerning uncontrollability and danger (ud) into the model explained an additional 18.1% of variance (i.e. 31.9% compared to 13.8%) whilst need for control (nfc) explained an additional 10.6%, and cognitive self-consciousness (csc) 7.8%. Adding the MCQ positive beliefs and cognitive confidence (cc) subscales to the covariates led to smaller increments in variance accounted for (4.3% and 3.9% respectively).

The results of the stepwise regression analysis to determine the optimal subset of predictors are summarized in Table 5. Both forward entry and backward elimination resulted in the same two MCQ subscales remaining in the equation; negative beliefs (ud) and need for control (nfc), along with the three covariates; age, sex, and number of comorbid disorders.

# Discussion

Among heart disease patients attending CR and scoring at least mild anxiety/depression symptoms under routine screening with the HADs, we found high mean PTSD symptom scores and a high prevalence of PTSD cases based on IES-R thresholds. There was no evidence of higher PTSD being associated with type of cardiac event, with rates similar across acute coronary syndrome, heart-valve repair/replacement or other event

classifications. PTSD symptom severity was positively correlated with each metacognitive subscale, with beliefs concerning the uncontrollability and dangerousness of thoughts (MCQ-neg UD) making the strongest contribution individually after controlling for covariates.

Rates of PTSD were high, with 48% of patients meeting the threshold for PTSD and a further 15% partial PTSD. Thus, almost two-thirds of the sample met criteria for symptoms of potential "clinical concern" as defined by IES-R cut-off scores. These rates are higher than those reported previously of up to 35% (5), which is probably accounted for by the preselection in the current sample of patients who have at least mild anxiety/depression on the HADS. These results highlight the importance of assessing specific psychological morbidity and PTSD in particular in patients showing elevated anxiety/depression scores. All metacognitive subscales were associated with increased likelihood of a PTSD classification, with uncontrollability and danger the strongest predictor. These results are consistent with metacognitive theory, where beliefs about loss of control and harmfulness of cognition in particular, are core factors behind psychological vulnerability and poor adaptation to stress (33). Taking the raw MCQ-30 subscale scores, for every unit increase in MCQ negative belief (uncontrollability and danger) the odds of being in the PTSD group increased by 30%, whilst the likelihood of being in the partial PTSD group increased by 16%. Thus, small increments in MCQ uncontrollability and danger were associated with large increments in the odds of having PTSD. The rescaled MCQ scores allow a level comparison of the relative effects of total MCQ score against the MCQ subscales and show that total score has a risk ratio (RR) that is only slightly above the RR of uncontrollability and danger.

TABLE 2 PTSD category by type of cardiac event.

| Cardiac event | PTSD category | Frequency (percentage) [95% CI] |
|---|---|---|
| Any | No PTSD | 211 (37%) [33 to 41%] |
| | Partial PTSD | 85 (15%) [12 to 18%] |
| | PTSD | 276 (48%) [44 to 52%] |
| Acute coronary syndrome | No PTSD | 139 (36%) [31 to 41%] |
| | Partial PTSD | 64 (17%) [13 to 21%] |
| | PTSD | 182 (47%) [42 to 52%] |
| Heart valve repair/replacement | No PTSD | 13 (31%) [18 to 41%] |
| | Partial PTSD | 8 (19%) [9 to 34%] |
| | PTSD | 21 (50%) [34 to 66%] |
| Other | No PTSD | 126 (36%) [31 to 41%] |
| | Partial PTSD | 51 (14%) [11 to 19%] |
| | PTSD | 175 (50%) [44 to 55%] |

TABLE 4 Adjusted R squared values for regression models of IES-R using covariates alone (demographic and heath factors), and covariates plus each of the MCQ-30 scores (total and subscale scores) individually.

| | Adjusted $R^2$ | Significant improvement over covariates only (LR test) |
|---|---|---|
| Covariates only | 0.138 | Reference |
| MCQ total score | 0.308 | <0.001 |
| MCQ positive | 0.181 | <0.001 |
| MCQ neg ud | 0.319 | <0.001 |
| MCQ cc | 0.177 | <0.001 |
| MCQ nfc | 0.244 | <0.001 |
| MCQ csc | 0.216 | <0.001 |

MCQ, metacognitions questionnaire; neg ud, negative beliefs/uncontrollability and danger, cc, cognitive confidence, nfc, need for control; csc, cognitive self confidence.

TABLE 3 Relative risk ratio and confidence intervals for metacognitive beliefs as predictors of PTSD.

| MCQ scale | IES class | Relative risk ratio | 95% CI | P | Rescaled relative risk | 95% CI |
|---|---|---|---|---|---|---|
| MCQ total | Partial PTSD | 1.04 | 1.02 to 1.06 | <0.001 | 1.03 | 1.02 to 1.05 |
| | PTSD | 1.08 | 1.06 to 1.10 | <0.001 | 1.06 | 1.05 to 1.08 |
| MCQ positive | PartialPTSD | 1.08 | 1.02 to 1.15 | 0.015 | 1.01 | 1.00 to 1.03 |
| | PTSD | 1.12 | 1.07 to 1.18 | <0.001 | 1.02 | 1.01 to 1.03 |
| MCQ Neg-ud | Partial PTSD | 1.16 | 1.08 to 1.25 | <0.001 | 1.03 | 1.01 to 1.04 |
| | PTSD | 1.30 | 1.23 to 1.38 | <0.001 | 1.05 | 1.04 to 1.06 |
| MCQ cc | Partial PTSD | 1.04 | 0.98 to 1.10 | 0.170 | 1.01 | 1.00 to 1.02 |
| | PTSD | 1.11 | 1.06 to 1.16 | <0.001 | 1.02 | 1.01 to 1.03 |
| MCQ nfc | Partial PTSD | 1.06 | 0.99 to 1.15 | 0.111 | 1.01 | 1.00 to 1.02 |
| | PTSD | 1.22 | 1.15 to 1.29 | <0.001 | 1.04 | 1.03 to 1.05 |
| MCQ csc | Partial PTSD | 1.13 | 1.06 to 1.21 | <0.001 | 1.02 | 1.01 to 1.03 |
| | PTSD | 1.18 | 1.12 to 1.24 | <0.001 | 1.03 | 1.02 to 1.04 |

MCQ, metacognitions questionnaire; positive, positive metacognitive beliefs; neg ud, negative metacognitive beliefs concerning uncontrollability and danger; cc, cognitive confidence; nfc, need for control; csc, cognitive self confidence.

TABLE 5 Summary of optimal stepwise regression model for IES-R scores.

| Variable | Coefficient | 95% CI | *P* |
|---|---|---|---|
| MCQ nfc | 0.72 | 0.33 to 1.11 | <0.001 |
| MCQ neg ud | 1.56 | 1.21 to 1.91 | <0.001 |
| Age | −0.26 | −0.38 to −0.13 | <0.001 |
| Sex | 3.86 | 1.09 to 6.62 | 0.006 |
| Previous cardiac event | −0.77 | −3.44 to 1.89 | 0.57 |
| Number comorbidities | 1.08 | 0.40 to 1.77 | 0.002 |
| Previous anxiety | 1.48 | −1.95 to 4.90 | 0.40 |
| Previous depression | −0.31 | −3.73 to 3.11 | 0.86 |

Adjusted $R^2 = 0.33$. MCQ, metacognitions questionnaire; nfc, need for control; neg ud, negative beliefs/uncontrollability and danger.

In testing for an optimal set of independent predictors for PTSD symptom severity we found that MCQ-neg (uncontrollability and danger) and MCQ need for control made significant unique contributions. There were also contributions from other covariates. In sum, greater PTSD symptom severity was associated with being female, younger, having more comorbidities, and reporting elevated MCQ-neg and MCQ-nfc scores. This pattern of results is potentially informative in developing a profile of heart disease patients with elevated HADS scores who are likely to be suffering from post-traumatic stress.

The potential limitations of the current study method should be considered in interpreting the findings. We did not use diagnostic interviews in screening for PTSD as these are expensive and not routinely available in cardiac services, instead we relied on the IES-R for detecting symptoms and making clinically relevant cut-offs for cases. The IES-R shows good to excellent ability to identify PTSD cases when validated against DSM-IV or DSM-V criteria (27, 31), but we cannot rule-out that PTSD in the current sample may differ in some respects from PTSD defined by diagnostic interview. The current sample includes patients with scores of at least 8 on a HADS subscale at initial screening, and therefore the results should not be interpreted in the context of all CHD patients. Our sample is likely to give higher estimates in comparison with the overall proportion of CHD patients with PTSD. However, the data show that for those with at least mild anxiety and depression symptoms, there is a high prevalence of PTSD symptoms meeting thresholds of probable clinical importance.

The identification of PTSD symptoms in CHD and when implementing CR is valuable if interventions are going to be sensitive to and effectively tailored to meet the psychological needs of patients. In particular, PTSD may impact on outcomes and attendance at CR and may itself be affected by the components of CR. For example, attending CR may increase the severity of PTSD symptoms such as intrusive memories which are highly distressing for some patients. An implication is that assessment of PTSD symptoms would contribute to adjusting delivery of CR to accommodate the psychological needs of the individual.

Whilst we cannot infer causality from the current cross-sectional data, the results demonstrate that specific metacognitions are associated with a greater likelihood of having PTSD in patients with cardiac disease. The metacognitions identified as associated with highest trauma symptomatology correspond to those considered to have a central causal/maintaining role in the metacognitive model (15). The results support the potential application of the model to understanding and treating traumatic stress symptoms in cardiac patients. Specifically, the results are consistent with the idea that interventions that modify dysfunctional beliefs concerning the uncontrollability and dangerous effects of thoughts could have beneficial effects and reduce PTSD symptoms. In accordance with this, the addition of metacognitive therapy to CR, which focuses on modifying such beliefs has been found to be associated with significant improvements in anxiety, depression and PTSD symptoms in randomized trials of patients with CHD (22, 23).

In conclusion, the present findings have several potential implications for the management of psychological symptoms in CHD. First, they highlight a need for more specific assessment of PTSD in patients showing anxiety or low mood. Second, they suggest that general approaches to the management of anxiety/depression symptoms in CR may not meet the needs of a large proportion of patients who have underlying PTSD. Third, the results are consistent with application of the metacognitive model and metacognitive therapy aimed at modifying risk factors such as uncontrollability and danger metacognitions that are linked to both PTSD and other psychological morbidities. It appears that management of psychological symptoms in CR might take two different routes; (i) introduce specific PTSD-focused treatment methods for those service users that need them or; (ii) adopt a transdiagnostic treatment approach such as metacognitive therapy that is designed to target universal factors associated with multiple morbidities including PTSD. Metacognitive therapy is effective in mental health settings in treating PTSD (34) and within CR the inclusion of MCT is associated with significant improvements in HADs anxiety/depression and PTSD symptoms (22, 23). The results of the present study add further support for improving psychological outcomes in CHD by targeting metacognition.

## Data availability statement

The datasets presented in this article are not readily available because participants did not grant permission for public repository of their data. Requests to access the datasets should be directed to the study sponsor: Greater Manchester Mental Health and Social Care NHS Trust. Contact: researchoffice@gmmh.nhs.uk.

## Ethics statement

Ethical approval was obtained from the Preston Research Ethics Committee (REC Reference 14/NW/0163) and from the North West—Greater Manchester West Research Ethics Committee (REC Reference 16/NW/0786). The patients/participants provided their written informed consent to participate in this study.

## Author contributions

AW: study conception, grant writing, data analysis, interpretation, and manuscript writing. CH: statistical analysis

plan, data analysis, and manuscript writing. DR: grant writing, data-analysis, and manuscript writing. LC: manuscript writing, data analysis, and interpretation. All authors contributed to the article and approved the submitted version.

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## Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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# Improving mental well-being in psychocardiology—a feasibility trial for a non-blended web application as a brief metacognitive-based intervention in cardiovascular disease patients

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**Background:** Many patients with cardiovascular disease also show a high comorbidity of mental disorders, especially such as anxiety and depression. This is, in turn, associated with a decrease in the quality of life. Psychocardiological treatment options are currently limited. Hence, there is a need for novel and accessible psychological help. Recently, we demonstrated that a brief face-to-face metacognitive therapy (MCT) based intervention is promising in treating anxiety and depression. Here, we aim to translate the face-to-face approach into digital application and explore the feasibility of this approach.

**Methods:** We translated a validated brief psychocardiological intervention into a novel non-blended web app. The data of 18 patients suffering from various cardiac conditions but without diagnosed mental illness were analyzed after using the web app over a two-week period in a feasibility trial. The aim was whether a non-blended web app based MCT approach is feasible in the group of cardiovascular patients with cardiovascular disease.

**Results:** Overall, patients were able to use the web app and rated it as satisfactory and beneficial. In addition, there was first indication that using the app improved the cardiac patients' subjectively perceived health and reduced their anxiety. Therefore, the approach seems feasible for a future randomized controlled trial.

**Conclusion:** Applying a metacognitive-based brief intervention via a non-blended web app seems to show good acceptance and feasibility in a small target group of patients with CVD. Future studies should further develop, improve and validate digital psychotherapy approaches, especially in patient groups with a lack of access to standard psychotherapeutic care.

KEYWORDS

**psychocardiology, cardiovascular disease, anxiety, depression, mental health, metacognitive therapy, e-health, digital intervention**

# Introduction

Cardiovascular diseases (CVDs) belong to the largest group of civilization diseases worldwide and are the leading cause of mortality, representing 32% of all global deaths in 2019 (1). The associated life-threatening cardiac events, such as myocardial infarction, often lead to longstanding impacts upon people's lives (2). The accompanied stress reactions frequently result in pathological anxiety and depressive symptoms, often to the point of psychiatric conditions (3). Among patients entering cardiac rehabilitation, 18% suffer from clinically significant depression and 28% report anxiety (4). Quite commonly, cardiac patients are absent from employment for long periods of time due to physical, but also psychological impairment (5, 6). This leads to a high level of subjective suffering and places a burden on the healthcare system (7). Furthermore, depression and anxiety disorders worsen adherence of cardiac patients during treatment and thus contribute to increased mortality (8). After all, CVDs and mental disorders amplify each other reciprocally, creating a vicious cycle (9). The initial psychological symptoms may worsen and manifest over time if not treated (10). As a result, longer and more intensive interventions and medications are necessary (10). In the present study, we focus on anxiety and depression as the two major psychological comorbidities in CVD patients.

Therefore, current cardiological guidelines pay special attention to the identification of psychological symptoms among CVD patients (8, 11). Given the need to explore treatment options for psychological conditions in CVD patients, a third-wave psychotherapy method has recently gained attention, metacognitive therapy (MCT) (12). Similar to CBT, MCT focusses on negative beliefs as a major contributor of psychopathology. However, MCT solely focuses on beliefs about one's own cognition called metacognitions that determine the interpreting, monitoring, and controlling of the thinking process (12). The core of MCT is the Cognitive Attentional Syndrome (CAS), which is characterized by a perseverative type of thinking and inflexibility of attention. According to MCT, psychiatric symptoms occur when a person uses the CAS to process an ordinary stressful situation. Dysfunctional metacognitions will become entrenched, leading to even greater anxiety, worry and depressive thoughts (13). Those affected are caught in a self-reinforcing cycle and are mentally focused on their worries (14). The inflexibility of their attention control prevents them from breaking out of their symptoms. The effect of MCT on CVD patients has been investigated and demonstrated in several studies (15). Given that anxiety and rumination are common in cardiology patients, MCT appears to be successful in this group of patients due to the impact on dysfunctional metacognitions and coping strategies that support the CAS (16). MCT seeks to disrupt these supportive mechanisms by identifying their components and discussing their uselessness, as well as through several MCT techniques (12). One of them is called Attention Training Technique (ATT) and assumes that patients with psychiatric symptoms, such as anxiety and depression, cannot easily shift their attention, so they are unconsciously reinforcing pathological mechanisms (17). ATT is the first technique that helps break down the dysfunctional processes that support CAS. Another prominent method is Rumination/Worry Postponement, which challenges beliefs about the uncontrollability of worry and rumination (12). Through these and other techniques, patients are trained in detached Mindfulness (DM). In DM, patients have an observer role toward their own thoughts, they stop identifying with those thoughts and refrain from acting in response to them.

As of yet, there is evidence from several meta-analyses and RCTs in favor of face-to-face MCT (18, 19). However, for many patients, in-person visits can be a barrier. In addition, in Western countries, and especially in Germany, there are gaps in regional access to the therapy as well as lack of psychotherapists for the ever-increasing number of those in need (20–22). The SARS-CoV-2 pandemic has only worsened the deficit in psychological care (23, 24).

In this context, some studies have provided promising data, showing, that brief psychological interventions can help patients with CVDs get back into everyday activity (25). Recently, MCT has been also shown to be an encouraging approach for brief internet interventions (26, 27). In a recent case series from our own lab, patients with CVD and psychological distress underwent eight adapted video call sessions with a psychotherapist of 50 min each. These were designed to teach strategies for dealing with worry and rumination according to metacognitive therapy. The results of this study suggest that patients may benefit in terms of symptom reductions and an increase in metacognitive competence in themselves following these eight online video sessions (27).

Although brief MCT is effective and permits saving and rational use of available psychological aid resources, it is still face-to-face therapy and thus dependent on the availability of psychotherapists. The possibility of using digital solutions has already been explored for CBT (28–31). Comparisons have also been made as to whether a non-blended intervention is as effective as a blended one (32). The use of guided MCT for self-help in CVD was investigated by Wells et al. (15) in the recent PATHWAY program. In addition to video, audio, and text materials, patients were contacted by telephone by specially trained staff to discuss the content of the therapy. In evaluating the program, however, half of the patients indicated that they did not need the calls and even rated them negatively (26).

To our knowledge, metacognitive therapy using a digital intervention without psychological support has not been investigated. In this study, we developed a metacognitive therapy-based, non-blended web app specifically targeting patients suffering from CVD. The research objective of our study is to assess whether the approach of a web app is feasible.

# Methods

## Design

The present study was designed as an exploratory prospective observational single-arm feasibility trial. We here aim to translate a brief face-to-face metacognitive psychotherapy for CVD patients into the digital realm and explore the feasibility of that approach.

## Ethical approval

All study procedures were reviewed and approved by the local ethics committee of Hannover Medical School. Written informed consent in accordance with the Declaration of Helsinki was provided by all subjects prior to participation.

## Recruitment

Participants currently suffering from a diagnosed CVD were recruited at the Department of Cardiology and Angiology of Hannover Medical School. Patients were informed by the cardiologists of the listed departments about the purpose of the study and were screened for the following inclusion criteria: (a) confirmed diagnosis of a CVD, (b) age 18–65 years, (c) no diagnosed mental illness (previously or currently existing) and no corresponding psychotherapeutic intervention during the study, (d) not having psychiatric medication or being stable at medication for at least 3 months, (e) the ability to use a digital device (i.e., smartphone, tablet or desktop-PC with an internet browser), (f) consistent access to the internet, (g) suitable knowledge of German language. The exclusion criteria were: (a) acute suicidal tendencies, (b) acute psychotic symptoms. Besides the baseline inclusion visit, the entire study was conducted remotely. Patient flow is shown in CONSORT flow chart (Figure 1). From the total of 68 recruited CVD patients, 58 met the inclusion criteria and were included in the study. Patients that did not log in within 14 days ($n = 14$) got excluded and did not participate in the study at all, meaning after signing the initial informed consent, no data could be collected. This does not only include data from our non-blended web app itself, but also all questionnaires both pre and post web app usage. The same applies to patients who had not edited any content 14 days after logging in ($n = 26$). After patients dropped out of the study, they were asked to provide feedback via email about their reasons for withdrawing.

## Study procedures

All participants received verbal and written instructions regarding study participation and app usage at the baseline visit. An access link to the web app and a personal key for the digital module-specific survey as well as brief instructions on the study procedure were provided via mail. The participants were asked to complete the baseline questionnaires before starting the training program. After the training, the questionnaires had to be filled out and returned by mail. Supportive phone calls by the study team were made once a week to inquire about the status of data processing and any possible technical problems related to the usage of the web app. In addition, technical email support was provided. There was no contact with a psychotherapist at any point. No financial compensation was provided for participation in the study.

## MCT in form of a non-blended web app

The web app is based on preliminary work by our research group, in which the German version of metacognitive therapy (MCT) manual (12) was used to create a brief intervention for patients with CVDs (27). The web app can be used by patients across different platforms and devices, e.g., a smartphone, tablet, or computer. It consists of two main parts, learning and practicing. Following the brief instructions in the email, a patient enters the learning section, which consists of six modules based on the described short-term MCT intervention (27). Each module includes five to eight psychoeducational videos in which an animated character guides participants through the training program. The first module is an introduction to MCT, where patients learn the specific terms used in the program, as well as the storylines and thought patterns of simulated patients who report on certain CVDs. The second module introduces cognitive attentional syndrome (CAS), a chain of mechanisms that support anxiety and rumination (33). This module is essential since, even in conventional therapy, identifying the CAS is a challenging task on which the clinical effect of MCT relies. The third module provides information on ATT. The video with instructions for the German version of the ATT in this Module recommends that patients, after watching it, perform the attention training daily, in parallel with the learning part. In the fourth module the basics of the CAS model are explained, using one cardiac patient's CAS as an example. The fifth module covers techniques of DM. In addition, a new tool for addressing dysfunctional thoughts is presented—the Rumination/Worry Postponement and consolidates all learned materials and is followed by a glossary. Online ratings of the web app modules are collected using an external survey platform LimeSurvey (version 5.4.2; LimeSurvey GmbH., Hamburg, Germany) (34).

The practicing part of the app is structured threefold: (a) ATT, (b) DM, and (c) Rumination Postponement (33). If, when and how often subjects use the different exercises is a free choice of the user. Of note, the option to revisit materials is not restricted. During initial piloting of the app, it was shown that completion of all learning modules plus continued exercising as instructed takes approximately 14 days. The subjects were instructed to complete the learning part of the app in 14 days, but the access to the learning and practicing content of the app was not limited in time. The web app is only available in German language.

# Measures

## Hospital anxiety and depression scale

The Hospital Anxiety and Depression Scale (HADS) (35) is a self-reported tool for measuring the level of anxiety and depression in the past 7 days. It consists of 14 items, with seven each assigned to two subgroups. Each item is measured using a 4-point Likert scale from 0 to 3. A total maximum of 21 points is possible in each subscale. The summed points of the subscales correlate directly with the severity of anxiety and depression. HADS has good psychometric properties and is widely used on patients with somatic diseases (36, 37), including cardiology patients (38, 39). In our case, we used the German version (40).

## World Health Organization quality of life assessment

The World Health Organization Quality of Life Assessment (WHOQOL-BREF) (41) is a self-administered short version of the WHOQOL-100 (42) questionnaire and assesses an individual's quality of life in the past 2 weeks based on four domains: physical health, psychological domain, social relationships, and environment. In addition, there are two questions assessing the overall quality of life and perceived general health. The questionnaire includes 26 questions on a 5-point Likert scale, ranging from complete disagreement (1) to complete agreement (5) with the statement. The sum scores of the

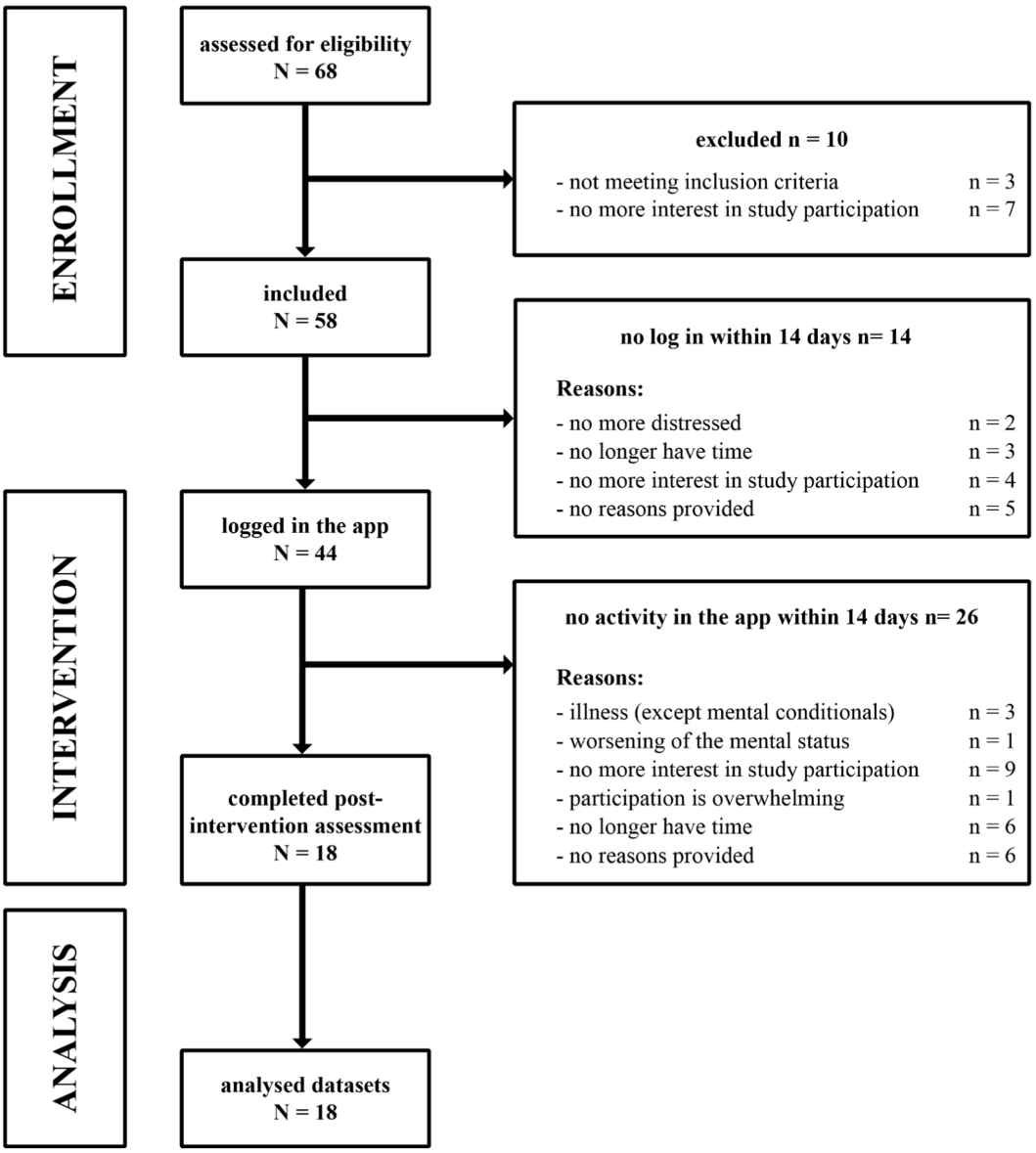


FIGURE 1
Patient flow during the study.

domains are transformed into a scale of 0–100. Higher scores on the questionnaire correspond to a higher quality of life. The questionnaire has good content validity, internal consistency, and test–retest validity (41). The German version of the questionnaire was used (43).

## Metacognitions Questionnaire-30

We used the German translation of the Metacognitions Questionnaire-30 (MCQ-30; 32) is a self-administered measurement tool that asseses several metacognitive parameters divided into five domains, each consisting of six items: (1) positive beliefs about worry, (2) negative beliefs about worry concerning uncontrollability and danger, (3) low cognitive confidence, (4) need to control thoughts, (5) cognitive self-consciousness. It consists of 30 items containing Likert scale ratings (1 do not agree to 4 agree very much), with higher scores indicating more dysfunctional metacognitive beliefs. All subscales of the MCQ-30 were highly consistent in cardiology patients, as well as the total score (Cronbach's alpha = 0.91) (44). The German version of the questionnaire was used (12).

## User version of the mobile application rating scale

The user version of the mobile application rating scale (uMARS) is the end-user version of the MARS (45) and represent a self-reported questionnaire to assess the quality of mobile health (mHealth) apps. It includes 20 items corresponding to five subscales: four for the objective quality: (a) engagement, (b) functionality, (c) esthetics, and (d) information quality and one subscale for the (e) subjective quality assessment. There is a further 6-items subscale for assessing the (f)

TABLE 1 Participants' demographic characteristics.

| Demographic factors | Entire sample ($N = 18$) | $n$ (%)/SD |
|---|---|---|
| **Gender** | | |
| Male | 10 | 56% |
| Female | 8 | 44% |
| **Age, mean (SD)** | 52 | (11) |
| **Employment status** | | |
| Employed | 10 | 56% |
| Unemployed, retired | 7 | 39% |
| Prefer not to say or N/A[a] | 1 | 5% |
| **Educational qualification** | | |
| Diploma/degree | 2 | 11% |
| School/vocational | 14 | 78% |
| Prefer not to say or N/A | 2 | 11% |
| **Documented CVD[b]** | | |
| GUCH (grown-up congenital heart disease) | 5 | 27% |
| Cardiac arrhythmia | 3 | 17% |
| Heart failure with reduced ejection fraction | 7 | 39% |
| Other (heart transplant, hypertrophic cardiomyopathy, idiopathic PAH) | 3 | 17% |
| **Self-reported psychiatric disease** | | |
| Yes | 2 | 11% |
| No | 16 | 89% |
| **Psychological therapy** | | |
| In the past or planed | 3 | 17% |
| Never | 15 | 83% |

[a]Not applicable.
[b]Cardiovascular disease.

TABLE 2 Average web app modules completion rates.

| Item | Mean | (SD) | $n^a$ |
|---|---|---|---|
| Learning | 91.2% | (18.8) | 18 |
| Practicing | 70.9% | (45.5) | 13 |
| Module 1 | 95.7% | (9.4) | 18 |
| Module 2 | 98.8% | (3.6) | 18 |
| Module 3 | 89.1% | (7.6) | 16 |
| Module 4 | 86.5% | (7.1) | 17 |
| Module 5 | 88.9% | (7.6) | 16 |
| Module 6 | 80.6% | (9.2) | 15 |
| Glossary | 66.7% | (11.4) | 14 |
| Web app usage duration (days) | 12.2 | (13.6) | 18 |

[a]Entire sample ($N = 18$).
100% could be achieved by completing all five learning modules and watching the closing video in module six. The duration of web app usage counts the time from starting the first video in module one to finishing the last learning video in module five.

user's perceived impact of the evaluated app. Each item uses a 5-point scale as in original MARS (1-inadequate, 2-poor, 3-acceptable, 4-good, 5-excellent) (45). The item of the (e) subjective quality subscale may be answered as not applicable (N/A) and are, in that case, not added to the total score. The uMARS scoring is based on mean scores for each subscale. The internal consistency and test–retest reliability of the uMARS total score and subscales were shown as excellent in the RCT (Cronbach's alpha = 0.90) (46). Here we used the German version of the uMARS, which uses items from the validated German version of the MARS (45)—MARS-G (47) includes similar items to the uMARS, so we adapted it for our study, using experience of other research groups (48, 49).

## Module specific survey

In addition to the uMARS, patients were asked to rate the content of each module on a 10-point scale directly after the respective module was completed. This questionnaire was integrated into the web app as a link to LimeSurvey (34). The questions can be found in Supplementary Figure S1.

## Statistical analysis

Exploratory analyses were conducted in SPSS software (version 29; IBM Corp., Armonk, NY, United States). uMARS and rating scale data are presented descriptively. As part of exploratory analyses within the context of our feasibility study, we investigated changes in WHOQOL-BREF, HADS and MCQ-30 from baseline to post web app using $t$-tests for dependent measures (alpha of 0.05, two-tailed). Note, that these analyses are intended to explore the feasibility of translating into a non-blended web app rather than rejecting or accepting a hypothesis as in a RCT.

# Results

## Sample description

Eighteen participants with documented CVD completed the trial. Demographic data and details on the underlying cardiac conditions are shown in Table 1.

## Web-app usage data

Participants took an average of 12 days (SD 13.6) to work through the learning area as shown in Table 2. The completion rate of the learning content was on average 91.2% (SD 18.8). Thirteen participants used the practicing area and completed it with the mean rate of 70.9% (SD 45.5).

## Changes after web app-usage

After completing the web app modules, there was an improvement in the patients' perceived general health [WHOQOL-BREF general health; $t$ (17 = 2.72, $p = 0.015$, Cohen's d = 0.64)] and in

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the psychological domain [WHOQOL-BREF psychological; $t$ (16 = 2.23, $p$ = 0.041, Cohen's d = 0.54) see Figure 2]. Furthermore, anxiety decreases significantly from pre- to post-training [HADS-A; $t$ (17 = 2.49, $p$ = 0.02, Cohen's d = 0.59)], while depression did not decrease [HADS-D; $t$ (17 = 0.73, $p$ = 0.48)]. Regarding changes in metacognitions, there was no change in the MCQ-30 total score [$t$ (17 = 1.33, $p$ = 0.20)]. The score in the MCQ-30 subscale cognitive self-consciousness changed from 12.78 to 11.78 [MCQ-30 cognitive self-consciousness; $t$ (17 = 1.91, $p$ = 0.07, Cohen's d = 0.45)]. There were no effects regarding the other subscales of the MCQ-30 (all $p$-values > 0.21).

## Rating of the web app

The assessment of the general acceptability of the users regarding the web-app-based training program was based on the uMARS scale and the module-specific questions. An overview of the ratings of the perceived engagement, functionality, esthetics, information, app subjective quality, the user's perceived impact and the app quality mean score of the evaluated app is presented in Figure 3. According to the uMARS scoring participants rated the app as acceptable on average (mean score of 3.1 from 5 possible points) (Table 3). The results of the module specific questionnaires are shown in Supplementary Figure S1. The results of uMARS participant's individual feedback can be found in Supplementary Table S1.

# Discussion

Here, we developed an MCT-based brief intervention as a web app with learning content based on results of the former developed and tested face-to-face trial (27). We translated the individually tailored modular learning content into digital form, which includes video recording, creating animations and recording the audio content. Then, 18 patients diagnosed with a CVD tested the web app and provided extensive feedback on its functionality, the subjective quality of it and parts that may be improved. Moreover, anxiety and depression symptoms and metacognitive competency were assessed at baseline and after.

Overall, the web app approach seems to be accepted by users, with functionality rated best. On average, the participants needed 12 days to complete the training, however, with a range of 13.6 days. Among all the participants who engaged with the app, a moderate to high completion rate in the learning area was shown, while participants were more reluctant to practice. Additionally, we observed an improvement in the patient's perceived health and psychological health, reduction in anxiety symptoms, as well as nonsignificant trend toward improvement in cognitive self-efficacy.

These initial results suggest that it quite might be feasible to deliver a MCT-based brief intervention to patients in the form of an app. However, the effects on efficacy need to be further explored in larger randomized controlled trials with a correspondingly larger number of participants. The personal feedback in the uMARS questionnaire from the complete datasets showed that the content of

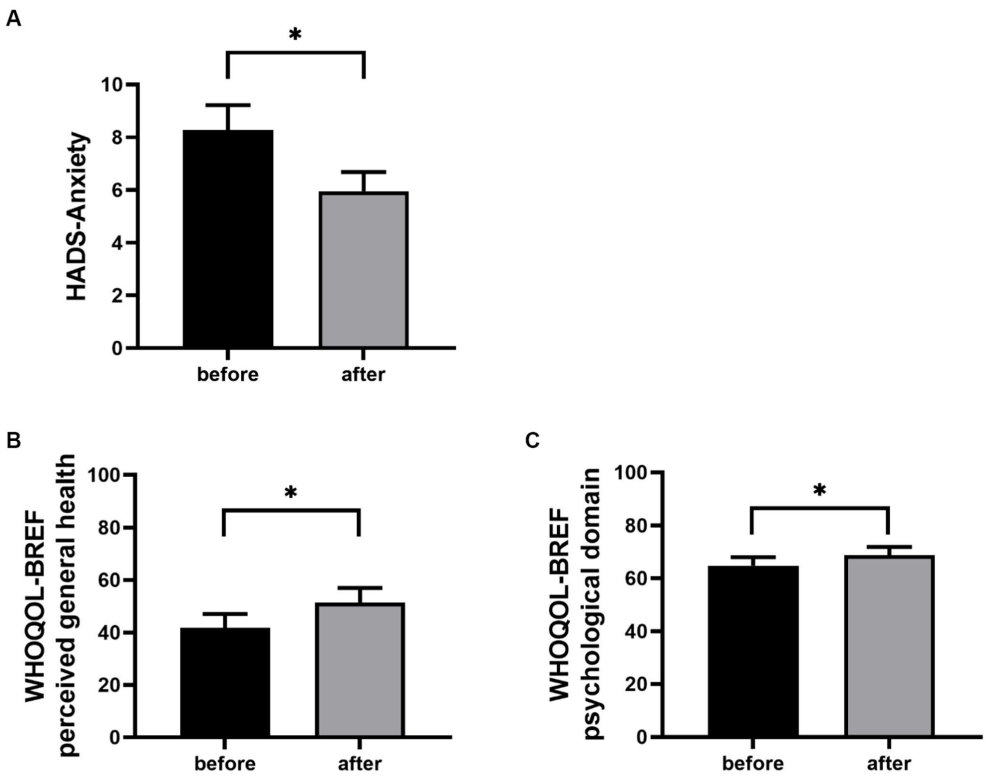


FIGURE 2
HADS-Anxiety **(A)**, WHOQOL-BREF perceived general health **(B)** and WHOQOL-BREF psychological domain **(C)** mean scores before and after using the web app are shown ±1 SEM. *$p$ < 0.05.

a web app could be processed by the participating CVD patients. The individual approach from the former trial seems to be well suited for this purpose (15). However, once again, further studies are needed in the future to appropriately examine the effect on larger and more heterogeneous groups. It would be interesting to investigate whether the initial nonsignificant trends shown in pre to post measures from the feasibility study can also be observed in larger numbers of cases. Especially given the shortage of psychotherapists, such non-blended web app-based approaches are promising to provide scalable opportunities in the future.

This is the first prototype of the web app, which still lacks, above all, the possibility of personalized customization. A plan for further development includes programming the web app in a way that allows each user to customize a learning path for themselves.

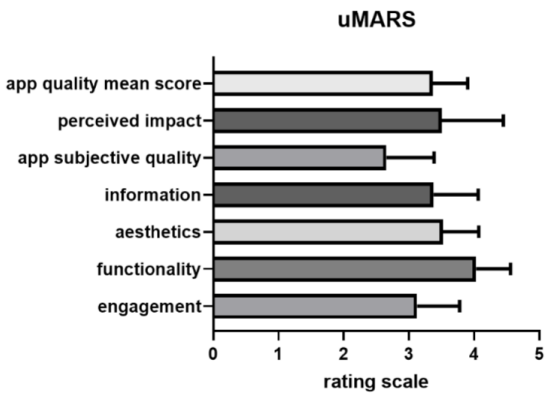


FIGURE 3
Participants uMARS ratings of the web app for all sections from 1 to 5 points are shown ±1 SEM.

## Effects on depression and anxiety

Patients with CVD often suffer from pronounced anxiety, whether it is fear of reinfarction in patients after myocardial infarction, or otherwise (50). A digital tool capable of reducing anxiety and easily accessible at any time, especially when experiencing acute symptoms of anxiety, offers a solid backup option beyond the clinical setting. This could be an important strength of future digital apps, making them complementary to professional psychological treatment.

In our study, we were able to observe first effects with regard to symptom improvement. At baseline, CVD patients showed mild

TABLE 3 Assessment scores for baseline and post-intervention measures.

| | Baseline | | Post-intervention | |
|---|---|---|---|---|
| Scores | Mean | SD | Mean | SD |
| World Health Organization Quality of Life Assessment (WHOQOL-BREF) | | | | |
| Domains | | | | |
| Physical | 59.73 | 18.40 | 62.5 | 18.81 |
| Psychological* | 64.71 | 13.43 | 68.7 | 12.86 |
| Social relationships | 60.65 | 19.76 | 62.5 | 21.25 |
| Environment | 75.20 | 14.79 | 76.6 | 10.76 |
| Perceived QOL[a] | 61.11 | 19.60 | 62.5 | 12.86 |
| Perceived general health* | 41.67 | 22.69 | 51.4 | 23.44 |
| Hospital Anxiety and Depression Scale (HADS) | | | | |
| Subscales | | | | |
| HADS - Anxiety* | 8.28 | 3.98 | 5.94 | 3.10 |
| HADS - Depression | 5.72 | 3.68 | 5.22 | 3.83 |
| HADS - Total score | 14.00 | 6.55 | 11.17 | 6.41 |
| Metacognitions Questionnaire-30 (MCQ-30) | | | | |
| Subscales | | | | |
| Positive beliefs about worry | 9.72 | 2.76 | 10.06 | 2.13 |
| Negative beliefs about uncontrollability and danger of worry | 11.22 | 4.14 | 10.83 | 3.82 |
| Cognitive confidence | 11.28 | 4.35 | 10.89 | 4.17 |
| Need for control | 12.22 | 4.41 | 11.06 | 3.37 |
| Cognitive self-consciousness | 12.78 | 3.95 | 11.78 | 3.06 |
| MCQ-30 total score | 57.22 | 16.09 | 54.61 | 13.09 |

[a]Quality of Life.
*$p < 0.05$.

anxiety symptoms. After the use of the web app, anxiety symptoms were much less pronounced on average. This initially promising data should be replicated and validated, preferably using a larger patient sample as well as a randomized and controlled design.

Before the start of the intervention, no depression symptoms were measurable in the participants. After app usage no decrease could be proven here either. Hence, a floor effect seems likely with regard to no effect of the web app on depression. Future studies in CVD patients with and without depression are needed to fully evaluate potential effects of such web apps on it.

For the MCQ-30 scale a non-significant trend in cognitive self-awareness could be observed. However, more data is needed using similar web app designs, preferably compared to traditional CBT or MCT interventions to shed light on the working mechanisms of the improvements in symptomology. Currently, the modules of the web app have a uniform design for all users. In previous studies, authors suggested that a specific MCT intervention should be adapted for any type of CVD separately to be able to address the pathomechanisms of mental disorders more individually (12, 27). The lack of significant changes in participants' metacognitive status can also be due to further reasons. It may mean that the learning content was not understood, completion rates in exercises were too low, or that participants had no previous pathological metacognitions. Integrating better and clearer instructions into the web app is one possible solution. Since at least improvement tendencies have been shown, it is possible that the effects of MCT techniques are too low in healthy individuals. Therefore, a larger study involving patients with a CVD and anxiety and depression assessed with validated psychological instruments may provide additional insights.

## User behavior

The major aim during development was to bring a face-to-face intervention into a digital learning program, with a structure that allows the training to be completed entirely non-blended and to communicate the challenging content of the MCT-based learning modules to patients in the most comprehensible way.

Overall patients made substantial progress in the training program, and we registered a mean completion rate of 91.2% in the learning area calculated from the rates of all 18 participants and a mean completion rate of 70.9% performed by at least 13 participants. The remaining five participants did only complete the modular learning area. Wells et al. (26) showed a completion rate of 50–70% of at least four modules while being guided. This supports the assumption that CVD patients are quite capable of handling digital learning. We observed that the patients comprehended the structure of the web app prototype and worked through the learning content completely on their own. There was no additional guidance from the study team at any point. For this reason, the accepted app structure should be retained as far as possible and slightly adapted. Areas for learning and for practice should continue to be separated, and the modular structure should be retained. Likewise, the basic elements, such as introduction, learning section, and summary and repetition of learning content should remain consistent in each module.

However, the effect of MCT results from the confluence of learning and practice together, suggesting that practice must be adequate and regular. Dammen et al. (51) demonstrated that ATT exercise, which is also a part of our web app in particular leads to significant improvement in anxiety and depression symptoms. The exercise area was introduced in a module in the middle of the training program where the participants were instructed to practice regularly. From that point onwards, participants had access to the practice area at any time and could practice at their own discretion. Unfortunately, our data on details on for the lack of motivation to practice is limited. We received some hints from the uMARS optional comment section, which can be found in Supplementary Table S1. While three patients reported being satisfied with the exercises, two participants lacked details about the mechanisms of action of the exercises. One participant described the exercises as too extensive. Furthermore, three patients missed interactive parts, as well as gamification elements. Another patient would like a tool to record progress after exercises.

These points must be considered in the development of future web apps. Overall, the importance of practicing must be made especially clear to users. A revision of the explanatory video, as well as implemented reminders upon completion of each learning module, could remedy this. Patients could also receive daily motivating messages on their mobile devices tracking their progress and encouraging them to continue practicing. Furthermore, an integrated concept of gamification could increase the overall motivation of the patients. At present, interactive elements are rarely used in existing mental health but patients seem to wish for it according to feedback (52). In addition, the link to the exercises in the learning area should be integrated more frequently, as some patients described that they were confused and did not know when exactly to practice.

In the present study, we also experienced an increase in anxiety and depression in two male patients. The first patient left the study after completing the learning part at 100%. The reason was that using the app and intensely interacting with the own negative thoughts caused him to feel poorer. The second patient left the study for the same reasons as the first but returned to the study 4 weeks later and completed it. Both patients were contacted by a psychotherapist and were provided with support and recommendations. Thus, future research should consider risk factors for deterioration in order to prevent them. At this point, it is not irrelevant that studies devoted to psychological aid publish positive results, while deterioration of psychological well-being remains unreported (53). As with any other effective intervention, psychotherapy contains the potential for deterioration of the mental state of the patient (54), which is necessarily discussed before the start of the intervention. Regarding the negative effects of Internet-based therapy in anxiety and depression among patients in the treatment group, adverse effects can vary from 4 to 10% (55, 56). It is important to note that in the control group, side effects are reported more frequently, suggesting that the benefits of therapy outweigh the possible negative effects (57, 58).

For the sake of completeness, it should be noted that we noticed two particularly critical points within the patient flow, as shown in Figure 1. Out of a total sample of 58, 14 patients did not log into the web app and of those who did log in, 22 did not start the training. The reasons for this varied widely. The most frequently cited reasons were no longer having interest in study participation ($n = 13$) and no longer having time ($n = 9$), while 11 patients did not want to give a reason. Just from these results, one must ask about the motivation

of the patients to participate in such a training and how it could be increased. Since the participants were not proven to have depression or anxiety, the important next step is to investigate the motivation for training in a patient group with a higher level of psychological distress.

### Technical implementation

The technical implementation of the first version was rated overall with three out of five points, which shows that there is still room for improvement here in any case. The functionality of the prototype was rated the best suggesting that the web app works satisfyingly, the menu is clearly structured and thus comprehensible navigation is provided.

On this basis, it is possible to improve the attractiveness of other web app focuses, that have received a lower rating, like the visual quality of the web app, which was rated with 3.5 of 5 points. A uniform design must be created professionally here, which must be a necessary process in the development of a native app in any case. Multimedia content, i.e., graphics, animations, videos and sound recordings, must either be revised or completely recreated based on the original content.

### Limitations

Some general aspects of study design should be considered and changed in future studies. A larger sample size and comparison to a randomized control group could provide further information to generalize the results. However, the purpose of this study was primarily to evaluate the functionality of the web app and if its application is feasible. In future, these preliminary results can be used as a basis for appropriate changes to provide patients with the most efficient tool possible.

The second point is the limitations of the web app. Depending on the web platform provider, it is possible to get a wide range of functionality sufficient to create a training program. However, the web app provides limited opportunities to create interactive elements, such as gamification (59). Many internet interventions use interactive elements to maintain motivation and reinforce the desired effect of the intervention (60). In addition, regular reminders that appear directly on the end device could increase activity and participation (61). As the present study had multiple dropouts, it is necessary to develop a native mobile app to overcome the disadvantages of the web app described above.

Another point is the diversity of the sample. The study was focused on patients with various CVD pathology, and the presence of depression and anxiety was not an obligatory criterion for inclusion. Thus, the effects of the app-based MCT in the sample with anxiety and depression need to be investigated. Further research should also consider gender matching since women are more inclined to ruminate than men (62). Furthermore, different age groups participated in our study (mean age 52, SD 11). Research indicates that CVD patients <56 years old were four times more likely to use any mobile technology than those >69 years old and three times more likely to use technology for medical purposes (63). Regarding the technology use levels, some participants generally use more mobile devices and apps than others. However, some potential participants had neither mail addresses nor internet access. These factors should be taken into account in the planning of subsequent studies.

## Conclusion

The feasibility study suggests that a non-blended metacognitive therapy-based web app may offer a promising approach for future randomized controlled trials. The results of the study can be improved by developing a native app, with more options for customization to meet the needs of CVD patients. In addition, future research should focus on further exploring the app and its effects based on the results of this study in larger trials.

## Data availability statement

The original contributions presented in the study are included in the article/Supplementary material, further inquiries can be directed to the corresponding author.

## Ethics statement

The studies involving humans were approved by ethics board of Hanover Medical School, Hanover. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

## Author contributions

KL and EP were responsible for study design and technical implementation, conducted the study, performed data collection and processing, statistical analysis, and drafted the manuscript. DD and MW-B implemented and supervised the data collection. The informatics implementation was carried out by OW, ND, NM, AS, MB, and MM. KK was responsible for study design, conduct of the study, and data interpretation. IH was responsible for study design, conduct of the study, statistical analysis, data interpretation, and draft of the manuscript. All authors contributed to the article and approved the submitted version.

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## Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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## Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2023.1138475/full#supplementary-material

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# The pathophysiology and management of depression in cardiac surgery patients

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**Background:** Depression is common in the cardiac surgery population. This contemporary narrative review aims to explore the main pathophysiological disturbances underpinning depression specifically within the cardiac surgery population. The common non-pharmacological and pharmacological management strategies used to manage depression within the cardiac surgery patient population are also explored.

**Methods:** A total of 1291 articles were identified through Ovid Medline and Embase. The findings from 39 studies were included for qualitative analysis in this narrative review.

**Results:** Depression is associated with several pathophysiological and behavioral factors which increase the likelihood of developing coronary heart disease which may ultimately require surgical intervention. The main pathophysiological factors contributing to depression are well characterized and include autonomic nervous system dysregulation, excessive inflammation and disruption of the hypothalamic–pituitary–adrenal axis. There are also several behavioral factors in depressed patients associated with the development of coronary heart disease including poor diet, insufficient exercise, poor compliance with medications and reduced adherence to cardiac rehabilitation. The common preventative and management modalities used for depression following cardiac surgery include preoperative and peri-operative education, cardiac rehabilitation, cognitive behavioral therapy, religion/prayer/spirituality, biobehavioral feedback, anti-depressant medications, and statins.

**Conclusion:** This contemporary review explores the pathophysiological mechanisms leading to depression following cardiac surgery and the current management modalities. Further studies on the preventative and management strategies for postoperative depression in the cardiac surgery patient population are warranted.

KEYWORDS

**postoperative depression, cardiac surgery, autonomic nervous system dysregulation, hypothalamic pituitary adrenal axis dysregulation, inflammation, cognitive behavioral therapy, antidepressant, statins**

## 1. Introduction

Cardiovascular disease (CVD) is a leading cause of mortality, accounting for over 18 million deaths globally in 2019 (1). As a management modality, over 2 million cardiac surgeries are performed globally *per annum* (2). Common examples of cardiac surgery include coronary artery bypass graft (CABG), valve replacements and heart transplantation. Given the aging population,

patients who undergo cardiac surgery are more likely to be older and possess significant medical comorbidities such as hypertension and diabetes mellitus (3). Cardiac surgery intends to offer definitive management for persistent cardiovascular disease which is refractory to medical management. Successful cardiac surgery significantly improves quality of life, which in turn improves psychological outcomes. Depression is a mood disorder with a lifetime prevalence between 2 and 21% (4). Within the cardiac surgery population, the prevalence of depression is significantly higher. The prevalence of pre-operative depression ranges from 20 to 47% while postoperative depression affects 23–61% of patients following cardiac surgery (5–11). The disparity in prevalence between pre- and postoperative depression may be attributed to differences in modalities used to detect depression (different questionnaires vs. psychiatric interviews), differences in parameters used to define depression and differences in post-operative follow-up. Moreover, patients may display somatic symptoms such as fatigue and sleep disturbances which can be difficult to discern from depression (12). Both pre-operative and post-operative depression are underpinned by the same pathophysiological mechanisms and are associated with poor clinical outcomes. Psychiatric assessment should occur pre-operatively and post-operatively. Prior to operating on a patient with pre-operative depression, it may be worthwhile offering additional counseling or support. During the postoperative period, the patient's psychiatric state should be monitored. Reductions in depression symptoms are expected postoperatively and associated with improvements in quality of life. Conversely, increases in postoperative depression may be attributed to the occurrence of complications or major adverse cardiovascular events (MACE) (13). Hence, there is significant interest in understanding the underlying pathophysiology of depression following cardiac surgery and investigating effective preventative and management modalities within this population.

## 1.1. Risk factors for depression

Risk factors for postoperative depression following cardiac surgery include female gender (5, 14, 15), younger age (16), previous depressive episodes or family history of depression (17) and history of pre-operative depression (18, 19). Social factors such as lower educational levels, lower levels of social support or social isolation also increase the risk of postoperative depression. Social support during the first month following surgery may reduce the likelihood of postoperative depression and impairments in activities of daily living (ADL) at 6 months (20). Naturally, emergency surgery and an extended length of hospital stay contribute to the likelihood of developing postoperative depression (15, 21).

Risk factors for developing preoperative depression are similar to the above, but uniquely include dyspnea upon exertion and at rest (contributing to a higher NYHA classification) (8, 22) and previous myocardial infarction (22). The identification of these contributory factors may allow early recognition of vulnerable patients and early referral for psychiatric assessment.

## 1.2. Screening questionnaires for depression in cardiac surgery patients

The following questionnaires are commonly utilized in depression studies involving cardiac surgery patients.

### 1.2.1. Patient Health Questionnaire 9

The Patient Health Questionnaire 9 (PHQ-9) is a nine-item self-administered questionnaire used to assess depressive symptoms over the previous 2 weeks using the Diagnostic and Statistical Manual of Mental Disorders 5th Edition (DSM-5) criteria. The PHQ-9 assesses affective, cognitive, and somatic symptoms. Four items are related to somatic symptoms (sleeping difficulties, fatigue, reduced appetite and psychomotor agitation/retardation) (23). The PHQ-9 has high specificity, but low sensitivity for detecting depression in patients with CVD (24, 25). McManus et al. reported a 54% sensitivity and 90% specificity for detecting depression when using a score of $\geq$10 as the cut-off. This questionnaire may be administered over telephone/telehealth to reliably assess for depressive symptoms (26).

In 2008, the American Heart Association recommends screening for pre-operative depression in patients with coronary heart disease (CHD) with the PHQ-2 or PHQ-9 (preferred). Patients with a positive PHQ-2 screen are asked to complete a PHQ-9 questionnaire, whereas those with a positive PHQ-9 questionnaire should be referred for psychiatric evaluation (27). Patients with a positive PHQ-9 depression screen were at increased risk of MACE at 6 months (OR: 2.16, 95% CI: 0.98–4.74) and five times more likely to receive anti-depressant medication (28). Stenman et al. demonstrated screening with the PHQ-9 in cardiac surgery patients was practically feasible and economically viable, with 64% of elective patients completing the questionnaire prior to surgery (29). Similarly, Gorini et al. reported over an 80% completion rate of the PHQ-9 for pre-operative screening (30). To improve the response rate, the PHQ-9 may be included in the preadmission screen.

### 1.2.2. Centre for Epidemiological Study of Depression scale

The Centre for Epidemiological Study of Depression (CES-D) is a 20-item self-administered questionnaire which measures common depressive symptoms through a 4-point Likert scale. It comprises an amalgamation of previously validated depression questionnaires. The CES-D has a high internal consistency, as evidenced by a Cronbach's alpha score of 0.85 (31). For each question, a score of 0 represents minimal symptoms, and a score of 4 represents depressive symptoms most of the time (32). A score greater than 16 indicates clinically significant depression. Uniquely, the CES-D includes several items which assesses interpersonal problems. However, the DSM-5 does not include interpersonal problems within their assessment of depression and interpersonal problems are more likely to occur in psychopathologies such as social anxiety (33).

### 1.2.3. Beck Depression Inventory

The Beck Depression Inventory (BDI) is a 21-item questionnaire which assesses depressive symptoms over the past 2 weeks. Each answer is recorded on a scale of 0–3, with higher scores indicating more severe depressive symptoms. Studies commonly define depressive symptoms by a score of greater than 10 or greater than 14 (34, 35). A cognitive-affective subscale may be created by adding up the scores from the first 13 items. Conversely, a somatic subscale may be produced by summing the scores from the remaining 8 items (36). Used in over 2,000 studies, the BDI has high internal consistency evidenced by a Cronbach $\alpha$ of 0.82 in a non-psychiatric population (37). The BDI is available and validated in numerous other languages. The BDI is copyrighted, and payment is required to access the forms, which may lead to accessibility issues in resource poor nations (35).

#### 1.2.4. Hospital Anxiety and Depression Scale

The Hospital Anxiety and Depression Scale (HADS) is a 14-question survey, with 7 questions pertaining to depression and anxiety, respectively. Each question is scored between 0 and 3. For the depression subscale, a score less than 8 generally indicates no depression, and a score greater than 11 associated with likely depression (38). The HADS predominantly focuses on cognitive and psychological symptoms rather than somatic features to reduce the potential compounder of somatic features during a hospital admission (39). The HADS was initially designed for the inpatient setting, but can reliably detect anxiety and depression in the primary care and general population (40).

#### 1.2.5. Cardiac Depression Scale

Hare and Davis developed the Cardiac Depression Scale (CDS) specifically for cardiac patients in Australia to account for the range of depressive symptoms, including adjustment disorder with depressed mood. The CDS is a 26-item questionnaire with a Likert scale rating system ranging from 1 to 7, with a score of 1 representing "strongly disagree" while a score of 7 represents "strongly agree." Higher total scores represent more severe depressive symptoms (41). A CDS cut-off score equal to or greater than 95 provided 97% sensitivity and 85% specificity (42). Findings from the CDS have correlated strongly with the BDI ($r = 0.73$) (41, 43).

#### 1.2.6. Limitations

Self-administered depression screening questionnaires should not replace structured clinical interviews. Several questionnaires, such as the BDI, are restricted by copyright, which may limit access to certain institutions. Additionally, the depression questionnaires should be validated in various languages for different cultures to determine appropriate cut-offs for a positive result. Furthermore, stigma surrounding depression in different cultures may subconsciously influence an individual's responses to the questionnaires. Finally, studies use different parameter points to define the presence and severity of depression. This makes it difficult to conduct meta-analyses to pool the data for cardiac surgery patients.

### 1.3. Clinical implications of depression

Both pre-operative and post-operative depression with poor clinical outcomes. Psychiatric assessment should occur pre-operatively and post-operatively.

Depression is an independent risk factor for the development of cardiac disease. The risk of death due to cardiovascular disease (CVD) is two times greater in depressed patients (44). The depressed state is associated with poor nutritional choices, limited exercise, tobacco use, and reduce compliance to medications (45–48). This may exacerbate cardiac disease, resulting in the patient requiring surgical intervention. Prior to operating on a patient with pre-operative depression, it may be worthwhile offering additional counseling or support. Preoperative depression is associated with poor functional status (49) poorer quality of life (50), a longer length of hospital stay ($p < 0.001$) (10) and increased level of postoperative pain (51). These patients are less likely to return to work in both a fulltime (OR: 9.43, CI: 3.15–28.21) or part time capacity (OR: 5.44, 95% CI: 1.60–18.53) (52) and are more likely to be re-hospitalized for a cardiovascular cause at 6 months postoperatively ($X^2 = 4.24$, $p < 0.04$) (53). Pre-operative depression is also associated with increased mortality following CABG and valve surgery (54–57).

During the postoperative period, the psychiatric state should be monitored. Improvements in physical functioning and quality of life are expected postoperatively and would likely be associated with improvements in depression symptoms. Postoperative depression is associated with higher pain levels up to weeks post discharge (34), lack of functional improvement in patients 6 months post-surgery (58, 59), two fold increased risk of re-admission (60) and substantial risk of atherosclerotic progression (OR 1.50, 95% CI 1.08 to 2.10, $p = 0.02$) (61). Postoperative depression is also associated with increased mortality following coronary artery bypass grafting (CABG) (62). Overall, postoperative depression is an increased 10-year mortality rate following cardiac surgery (HR: 1.8, $p = 0.04$) (44).

## 2. Methods

A literature search using OVID Medline and Embase was performed for studies included in this narrative review. Keywords for depression include depression; pre-operative depression, post-operative depression, depress*. The following keywords for cardiac surgery were included: cardiac surgery; heart surgery; cardiac operation; cardiothoracic surgery; coronary artery bypass graft; CABG; revascularisation surgery; valve replacement and valve repair. Limits included English language, human studies and adults only.

The identification and selection of studies is depicted in Figure 1. Study designs of interest included observational cohort studies and randomized controlled trials. Thirty-nine studies were qualitatively assessed (heart rate variability: 5, inflammation: 4, hypothalamic adrenal axis dysregulation: 2, education: 5, cardiac rehabilitation: 3, cognitive behavioral therapy: 4, prayer: 3, biobehavioral feedback: 1, antidepressants: 7, statins: 2, alternative care: 3). Background information was obtained through references from the search-strategy, and from references within studies.

## 3. Pathophysiology

The pathophysiology underlying depression in CHD patients includes autonomic nervous system (ANS) dysregulation, inflammation and hypothalamic pituitary adrenal (HPA) axis dysregulation. Surgical trauma may also contribute to postoperative depression through the pathophysiological mechanisms mentioned above. The depressed state may contribute to behavioral factors which may exacerbate CHD. These behavioral and pathophysiological factors are summarized in Figure 2.

### 3.1. Dysregulation of the autonomic nervous system

#### 3.1.1. Overview of heart rate variability

Heart rate may be controlled through sympathetic and parasympathetic mechanisms. Sympathetic autonomic activation increases the heart rate, while parasympathetic activation reduces the heart rate (63). Heart rate variability (HRV) refers to the oscillation in

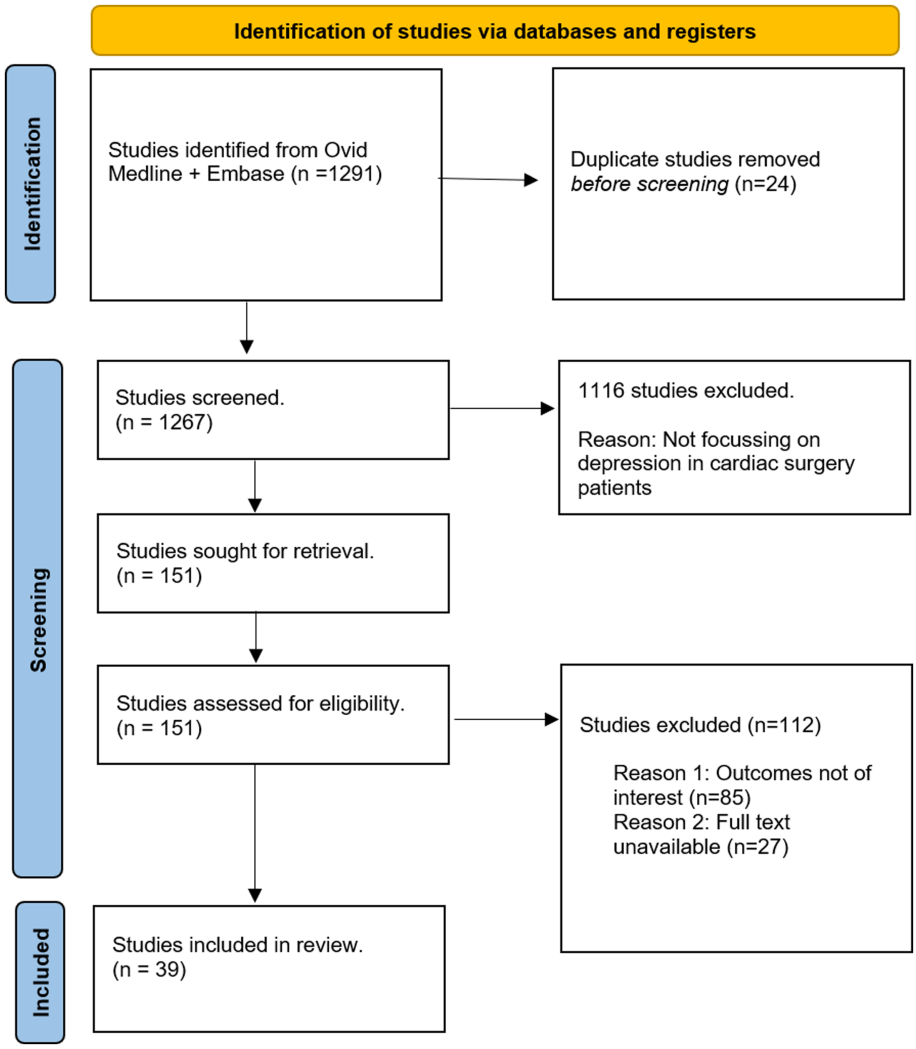


FIGURE 1
Inclusion of studies for qualitative analysis.

time intervals between heart beats (64). HRV is predominantly recorded using electrocardiography (ECG) and physiological monitors such as the Nexus 10 BioTrace equipment. Generally, during the recording process, patients are asked to keep their eyes open and keep their wrists still. Occasionally, the investigator will read pleasant travel excerpts to keep patients relaxed. This standardized process has been previously shown to mimic normal waking states of arousal (65). Moreover, patients are usually excluded from studies if they are not in sinus rhythm, given the increased difficulty in determining HRV (66).

Physiologically, HRV reflects the overall balance between the sympathetic and parasympathetic systems on the cardiovascular system (67, 68). A higher HRV is generally indicative of a well-functioning autonomic nervous system that is responsive to physiological and psychological stressors. Conversely, a low HRV may represent excessive sympathetic nervous system activation, or inadequate vagal tone (64). Additionally, a low HRV may predict acute cardiac complications and sudden cardiac death in patients with acute myocardial infarction and major pulmonary resections (69, 70).

HRV may be calculated using the time domain, or the frequency domain (64). The time domain measurements of HRV quantify the time between heart beats. HRV may be calculated as the standard deviation of the mean R-R or N-N interval (SDNN) on ECG in milliseconds. The SDNN accounts for cyclical components responsible for HRV such as respiration and blood pressure fluctuations (71). Additionally, HRV may also be calculated as the root of the mean square differences in the N-N intervals (rMSSD). This parameter represents the short-term heart rate variability and acts as an index of vagal outflow (72). Power spectral analysis can quantify the contribution of autonomic cardiac regulation to HRV using the knowledge of frequency and power (the energy signal found within a frequency band) (73). Very Low Frequency (VLF) power is defined as <0.04 Hz, Low Frequency (LF) power is between 0.04–0.15 Hz and High Frequency (HF) power is between 0.15–0.40 Hz HF power represents parasympathetic activity, whereas LF power represents sympathetic and some parasympathetic activity (64). Thus, a ratio of LF / HF ($ms^2/ms^2$) assesses overall autonomic balance.

An increase in the LF/HF ratio suggests sympathetic dominance, whereas a decrease reflects a parasympathetic dominance (74, 75). Autonomic dysregulation may result in electrical instability of myocytes and predispose patients to arrhythmias, myocardial

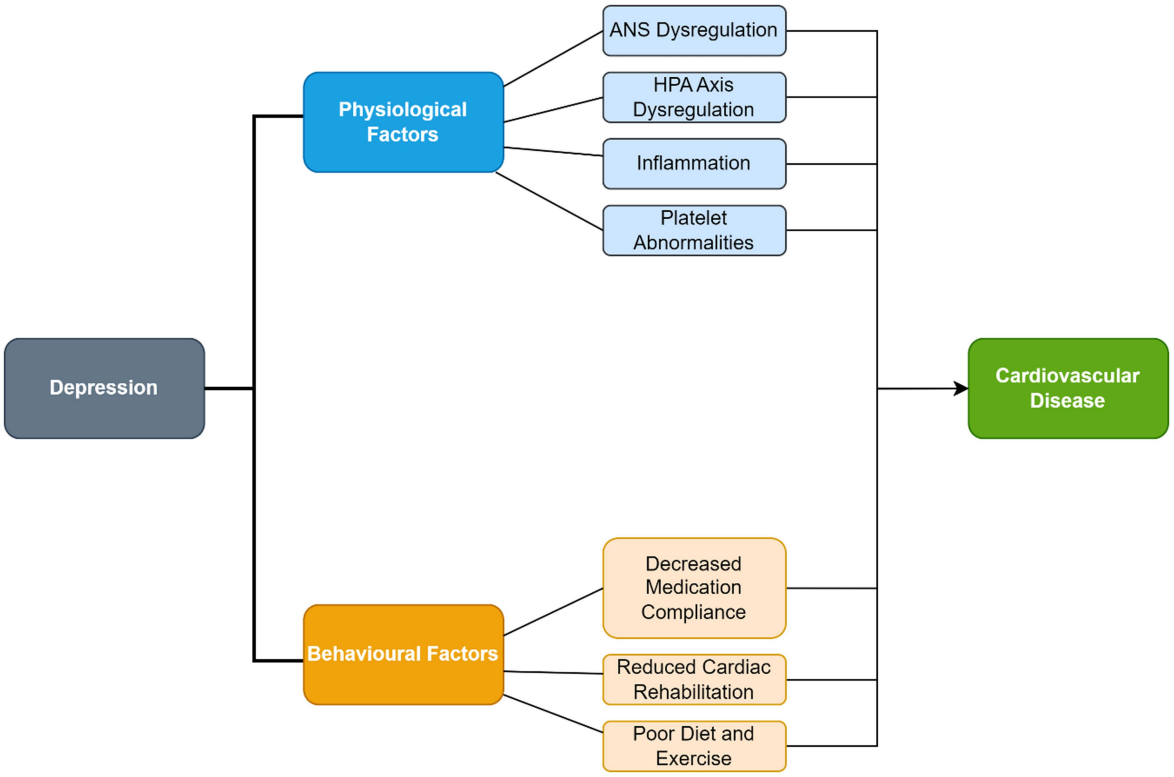


FIGURE 2
Summary diagram of relationship between depression and coronary heart disease.

ischemia, and sudden cardiac death (76, 77). Depressed patients exhibit features of ANS dysregulation through elevations in plasma and urinary catecholamines such as noradrenaline, decreased HRV and an elevated basal HR compared to non-depressed patients (78, 79). Consequently, there is a likely link between CHD, depression and ANS dysregulation.

### 3.1.2. Depression reduces vagal outflow following cardiac surgery

Depression affects the sympathovagal balance following cardiac surgery, specifically with reduced vagal outflow. Studies assessing the pathophysiology of depression in the cardiac surgery population are summarized in Table 1.

Dao et al. proposed autonomic cardiovascular dysregulation as a potential mechanism in the development of depression following cardiac surgery (80). ANS dysregulation was defined as a high basal HR, low HRV and high levels of plasma norepinephrine. The depressed + CABG group had a significantly lower HRV and higher basal HR compared to the other groups, but there were no differences in the level of plasma norepinephrine. This lack of difference may be reflective of the autonomic state of the arm rather than systemically, as blood was taken from the cubital fossa. Additionally, patients with depression + CABG had a longer length of stay compared to non-depressed patients. This suggests that autonomic dysregulation resulting from depression may negatively affect CABG outcomes.

Within the cardiac surgery population, ANS dysregulation is driven by an attenuated vagal response. In a study of 33 patients, Patron et al. demonstrated a reduction in HRV as calculated by SDNN in patients with depression (CES-D greater than16) following cardiac surgery (17.5 ms vs. 36.7 ms, $p = 0.02$) (81). Depressed cardiac surgery patients exhibited an attenuated vagal response, as demonstrated by a reduced high-frequency power and subsequently an increased LF/HF ratio (Depressed: 3.6 vs. non-Depressed: 0.9, $p = 0.08$). This suggests reduced vagal outflow, rather than sympathetic hyperactivity, is the corresponding factor between depression and CHD in the cardiac surgery population. Anxiety may also be associated with a reduction in HRV (85). However, Patron et al. demonstrated HRV reductions in depressed patients following cardiac surgery was independent of anxiety, using the STAI Y1 and STAI Y2 tests.

The mechanisms underlying a reduction in HRV in depressed patients following cardiac surgery is poorly understood. Patron et al. assessed whether emotional regulation strategies such as cognitive reappraisal or emotional suppression contributed to autonomic dysfunction in depressed patients following cardiac surgery. Cognitive reappraisal refers to the reframing of an emotion-provoking situation to a neutral thought (86). Conversely, emotional suppression strategies refer to the self-inhibition of negative and intrusive thoughts (87). Within this study, depressed patients were more likely to use emotional suppression strategies, and this coping mechanism was associated with autonomic dysfunction following cardiac surgery (82). Additionally, Patron et al. examined the effect of pleasant, neutral or unpleasant emotional imagery on depressed patients following cardiac surgery. They found depressive patients had increased vagal withdrawal in response to unpleasant emotional imagery, as measured by high-frequency power ($p = 0.003$) (83). These results complement the literature, and suggest depressive patients demonstrate mood

TABLE 1 Studies assessing the association between autonomic dysregulation and depression in the cardiac surgery population.

| Study | Aim | Surgery type | Study type | Patient number | Patient groups | Intervention | Definition of depression | Findings |
|---|---|---|---|---|---|---|---|---|
| Dao et al. (80) | To assess the potential mechanism between autonomic dysregulation and depression in CABG patients | CABG ± valve procedure | Prospective observational study | $n = 180$ | CHD + depression<br>No CHD + depression<br>CHD + no depression<br>No CHD + no depression | Measure HR and HRV after 12 h fast, and assessment of plasma noradrenaline | Diagnosis of MDD as per MINI | CHD + depressed patients had a lower heart rate variability compared to patients with CHD and no depression (OR: 0.597, 95% CI: 0.497–0.718)<br>CHD + depressed patients had a higher heart rate compared to patients with CHD and no depression (OR: 1.12, 95% CI: 1.02–1.04) |
| Patron et al. (81) | To assess the association between depression and heart rate variability following cardiac surgery | Cardiac surgery (not defined) | Prospective observational study | $n = 33$ | Depressed ($n = 11$)<br>Non-depressed ($n = 22$) | Assessment of HR and HRV | CES-D > 16 | Depressed patients had a reduced HRV, as calculated by SDNN, in patients with depression following cardiac surgery (17.5 ms vs. 36.7 ms, $p = 0.02$). |
| Patron et al. (82) | To assess the relationship between depression, emotional regulation and autonomic dysfunction following cardiac surgery | Cardiac surgery (not defined) | Prospective observational study | $n = 68$ | Depressed ($n = 25$)<br>Non-depressed ($n = 43$) | Assessment of affective evaluation through a questionnaire, followed by HR and HRV recording | CES-D > 16 | Depressed patients were more likely to use emotional suppression strategies and this may mediate sympathovagal imbalance [$F(1, 65) = 5.31$, $p < 0.03$] |
| Patron et al. (83) | To assess whether unpleasant imagery may mediate ANS dysregulation in depressed patients who have undergone cardiac surgery | Cardiac surgery (not defined) | Prospective observational study | $n = 28$ | Depressed ($n = 14$)<br>Non-depressed ($n = 14$) | Patients completed an emotional imagery test including listening to a pleasant, neutral and unpleasant script. HR and HRV are measured following | CES-D > 16 | Depressed patients had a greater reduction in high frequency power during unpleasant emotional imagery ($p = 0.003$, Cohen's $d = 1.34$) |
| Gentili et al. (84) | To assess whether a multi-feature analysis can predict the CES-D score of patients and automatically classify them as depressed or non-depressed. | CABG ± valve procedure | Prospective observational study | $n = 31$ | Single group of post cardiac surgery patients | Authors developed a model to predict CES-D scores | CES-D > 16 | The multi-variate model predicted the CES-D score in all 31 patients, with a variance of 89.93%. The model could also discriminate between whether patients were depressed or non-depressed with 86.75% accuracy. |

CABG, coronary artery bypass graft; CES-D, centre for epidemiological studies; CHD, coronary heart disease; HR, heart rate; HRV, heart rate variability.





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congruent bias and are more likely to react negatively to negative stimuli (88, 89).

Gentili et al. developed a regression model using HRV features in time and frequency, as extracted from five-minutely ECG recordings to predict cardiac surgery patients' CES-D score, and consequently the presence and severity of depressive symptoms. The model could predict the CES-D score in all 31 patients, with a variance of 89.93%. Additionally, they could discriminate whether patients were depressed or non-depressed with 86.75% accuracy (84). This model should be tested, and validated in a larger population. If successful, it may be feasible to collect HRV measurements automatically at the bedside and use this parameter as a screening tool to detect patients with depression. This would be a useful tool in hospitals where psychological evaluation of patients following cardiac surgery is unavailable.

## 3.2. Inflammation

### 3.2.1. Link between inflammation and depression in cardiac surgery patients

There is a bidirectional relationship between inflammation and depression (90). In the cardiac surgery population, inflammation drives the pathophysiology of the underlying CHD but may also manifest because of cardiac surgery itself. This pro-inflammatory state may affect serotonergic neurotransmission through the Kynurenine pathway and contribute to depression (91). Pro-inflammatory cytokines within the peripheries may enter the brain by crossing the blood–brain barrier, or indirectly facilitate activation of microglia within the brain. Hence, excessive peripheral inflammation may contribute to neuroinflammation and potentially to depression (92, 93). On the contrary, depression may contribute to inflammation through the upregulation of pro-inflammatory cytokines and acceleration of the atherosclerotic process (94).

#### 3.2.1.1. Inflammatory nature of coronary heart disease

Atherosclerosis is a chronic inflammatory process which leads to the buildup of plaque within the arterial wall (95). Atherosclerosis is the main pathophysiological contributor to CHD. The pathogenesis of atherosclerosis involves the following key steps: endothelial damage and the formation of foam cells, fatty streaks, intermediate lesions, atheroma and finally, atherosclerotic plaques (96, 97).

Firstly, endothelial insults may be caused by reactive oxygen species, turbulent blood flow (particularly at arterial branch points), hyperglycemia and hyperlipidemia. Low-density lipoproteins may penetrate the injury site and migrate into the tunica intima (98). This triggers a pro-inflammatory process which upregulates the expression of cell-adhesion molecules such as VCAM-1 upon the endothelial surface (99). Monocytes adhere to the endothelial surface and migrate into the subendothelial spaces. Subsequently, the macrophages phagocytose oxidized low-density lipoprotein to form foam cells. The accumulation of foam cells leads to fatty streaks, which may remain stable and ultimately form atherosclerotic plaques or regress (100).

#### 3.2.1.2. Association between inflammation and cardiac surgery

During cardiac surgery, factors which may contribute to a systemic inflammatory response include surgical trauma, blood surface interactions with the cardiopulmonary bypass circuitry, endotoxemia, and ischemic reperfusion injuries. These initiating factors trigger a series of responses from the complement system, neutrophils, cytokines, the coagulation cascade, and the vascular endothelium which result in a systemic inflammatory response. In addition, excessive inflammation may cause organ dysfunction (101–103).

#### 3.2.1.3. The kynurenine hypothesis of depression

Tryptophan is an essential amino acid with two predominant fates – conversion into kynurenine or 5-hydroxytryptamine (serotonin) (104, 105). Over 95% of consumed dietary tryptophan undergoes degradation through the kynurenine pathway (106). The conversion of tryptophan into kynurenine is catalyzed by hepatic tryptophan 2,3-dioxygenase (TDO) and extra-hepatic Indolamine 2,3-dioxygenase (IDO) (107).

From here, kynurenine has three possible fates. Firstly, within microglia, kynurenine may be consumed to facilitate the formation of 3-hydoxykynurenine and its metabolites 3-hydroxyanthranilic acid and quinolinic acid. Quinolinic acid is a glutamate N-methyl-D-aspartate (NMDA) agonist which has excitotoxic and neurotoxic properties associated with depression (108–110). Secondly, also within microglia, kynurenine may also be converted to anthranilic acid, which may be implicated in depression or schizophrenia (111–113). Thirdly, kynurenine may be consumed within the skeletal muscles or peripheries to form kynurenic acid. Kynurenic acid has neuroprotective, antidepressant and anticonvulsant properties, by acting as a non-competitive NMDA receptor blocker (114, 115).

In stressful and pro-inflammatory states, tryptophan is preferentially converted to kynurenine. This is represented by an elevated plasma kynurenine to tryptophan ratio (K/T ratio) (116). An elevated K/T ratio has been observed in CHD depressive patients (117). Perturbations in the metabolism of tryptophan have also been associated with metabolic syndrome risk factors, such as hypertension, obesity and dyslipidemia (91). Inflammation suppresses intrahepatic TDO, while extrahepatic IDO is expressed. Hence, inflammation is associated with an increased production of neurotoxic substrates from the kynurenine pathway which may contribute to depression (118). Moreover, the shunting of tryptophan down the kynurenine pathway depletes serotonin levels, supporting the monoamine hypothesis of depression whereby low serotonin levels contribute to low mood (119). Consequently, there is significant interest in examining inflammation as a pathophysiological mechanism in driving depression in cardiac surgery patients.

### 3.2.2. Commonly assessed inflammatory markers

Psychological and psychosocial stressors facilitate the release of pro-inflammatory cytokines (120). Magnocellular neurons are sensitive to stress and neuroendocrine changes and facilitate the release of pro-inflammatory cytokines into the general circulation via the neurohypophysis (121). Studies have primarily assessed whether there is a relationship between the peripheral concentration of pro-inflammatory markers such as c-reactive protein (CRP), interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α) and the development of depression. Elevated inflammatory markers may also attenuate the response to antidepressant therapy (122, 123).

CRP is an acute phase reactant which increases during inflammation (124, 125). CRP is an established cardiovascular risk

factor, with higher levels associated with poorer cardiovascular outcomes (126). A large proportion of studies assessing the association between inflammation and depression use CRP as their marker of inflammation. IL-6 is a multifunctional cytokine involved in immunological processes such as hematopoiesis, immune modulation and acute inflammation (127, 128). It is produced by numerous cells including macrophages, neutrophils, and lymphocytes (129). Given its multisystem involvement, IL-6 has been previously suggested to play a large role in the pathophysiology of depression (130). Excessive levels of IL-6 may affect the HPA axis and may be associated with left ventricular dysfunction and poor outcomes following open cardiac surgery (131, 132). Studies of inflammation and depression in the cardiac surgery population are summarized in Table 2.

### 3.2.3. Inflammatory markers may predict depression following cardiac surgery

Studies assess different inflammatory markers on the development of depression, making it difficult to draw definitive conclusions about their effect. Measuring the levels of CRP may identify patients at risk of developing depression following cardiac surgery. Yang et al. reported that for an increase in each standard deviation of logarithmically transformed high sensitivity pre-operative CRP, there was an increased odds of developing depression pre-operatively (OR: 1.16, $p = 0.001$) and at 6 months post-operatively (OR: 1.15, $p = 0.002$). This relationship was maintained even after adjusting for confounding variables and risk factors such as gender, education level, medications such as statins, and occurrence of major cardiac adverse events (133). Similarly, Poole et al. demonstrated that elevations in the level of CRP measured between postoperative days 4–8 significantly contributed to the depression status and longer hospital stay ($t = 2.62$, $p = 0.010$) (134). In contrast, Ivankovic et al. did not demonstrate a relationship between preoperative depression status and postoperative CRP levels (135).

Additionally, Streptoe et al. reported that early postoperative interferon γ (IFN-γ) levels which were in the upper tertile (mean concentration: 56.68 ± 7.5 pg./mL) was associated with depressive symptoms at 12 months (OR: 4.32, $p = 0.024$) (136). In contrast, there was no association between IL-6 and the development of postoperative depressive symptoms. Previous studies have demonstrated a correlation between the level of IL-6 and development of depressive symptoms (130, 137). IFN-γ is directly involved in the induction of indoleamine 2,3-dioxygenase, which is involved in the catabolism of tryptophan to products such as kynurenine (138). Elevated concentrations of kynurenine increase the likelihood of deleterious downstream effects as mentioned previously.

### 3.2.4. Relationship between depression, inflammatory markers, and length of hospital stay

#### 3.2.4.1. Association between depression and length of hospital stay

The association between depression status and length of hospital stay following cardiac surgery is unclear. Length of hospital stay is a common proxy measure of acute physical recovery (139). Poole et al. reported that patients with elevated preoperative depressive symptoms (BDI greater than 10) prior to CABG were significantly more likely to stay in the hospital for longer than a week, compared to non-depressed patients (OR 3.51, 95% CI: 1.415–8.693, $p = 0.007$) (134). This relationship is likely mediated by an elevation in the level of CRP measured between postoperative days 4–8 ($t = 2.62$, $p = 0.010$). These results suggest pre-operative depression may promote excessive inflammation and lead to poorer outcomes and extended hospital stays. On the contrary, Ivankovic et al. did not detect a significant association between elevated preoperative depression scores (BDI greater than 13) and extended postoperative length of stay (greater than 7 days) (135). Additionally, within the same study, Ivankovic and colleagues subsequently stratified the patients' preoperative BDI scores into depressed or non-depressed by applying the same cutoff as Poole et al. (Non-depressed: BDI less than 10; depressed: BDI greater than 10). Even with this filter, Ivankovic did not detect a significant association between binary BDI scores, and the length of postoperative hospital stay. The average EuroSCORE in Poole et al., study was 4.21 ± 2.79, while the median in Ivankovic et al.'s study was 1.1 with a range between 0.7 and 2.0. This may have contributed to the differences in postoperative recovery and length of hospital stay.

## 3.3. Disruption of the hypothalamic pituitary adrenal axis

### 3.3.1. Overview of the HPA axis

Consisting of the hypothalamus, pituitary gland and adrenal gland, the HPA axis is responsible for regulating the mammalian stress response, immunity, metabolic functioning, neurogenesis, neuronal survival and the emotional appraisal of events (140). Stressful stimuli trigger the production of corticotrophin-releasing hormone (CRH) and arginine vasopressin (AVP) by the paraventricular nucleus of the hypothalamus (141). CRH is a 41 amino acid peptide found within the central nervous system (142). Conversely, AVP is a cyclic nonapeptide with two forms, with one responsible for blood pressure regulation and the other responsible for the stress response (143). Following the binding of CRH to the CRH receptors within the anterior pituitary, adrenocorticotrophic hormone (ACTH) is released. Subsequently, ACTH will travel via the blood stream to act on the adrenal gland receptors to facilitate the release of glucocorticoids such as cortisol, mineralocorticoids such as aldosterone and androgens such as testosterone (144).

The HPA axis is regulated through a negative feedback mechanism. High concentrations of cortisol inhibit the further release of CRH and ACTH from the hypothalamus and pituitary gland, respectively, (145). Rapid increases in the concentration of cortisol also inhibit the HPA axis (146). On the contrary, glucocorticoids have been demonstrated to increase the concentration of CRH in limbic regions such as amygdala (147). Elevated expression of CRH within the limbic region has been associated with depressive symptoms (148, 149).

### 3.3.2. Dysregulation of the HPA axis in depression

Dysregulation of the HPA axis is commonly seen in MDD. Firstly, chronic emotional stress and MDD is associated with elevated cortisol secretion (150, 151). Normally, the HPA axis reacts appropriately through negative feedback mechanisms and reduce excess cortisol secretion. However, with HPA axis dysregulation, the negative feedback loop is impaired by reduced sensitivity of glucocorticoid receptors. This leads to hyperactivity of the HPA axis and further secretion of cortisol (152, 153). Cortisol hypersecretion is associated

TABLE 2 Studies assessing the association between inflammation and depression.

| Study | Aim | Surgery type | Study type | Patient number | Patient groups | Intervention | Definition of depression | Findings |
|---|---|---|---|---|---|---|---|---|
| Yang et al. (133) | To assess the contribution of preoperative high sensitivity CRP levels on the development of both pre and post-operative depression | Elective CABG | Prospective observational study | $n = 232$ | No pre-operative depression ($n = 190$)<br>Pre-operative depression ($n = 42$) | PHQ completed 3 days before surgery and 6 months postoperatively.<br>High sensitivity CRP collected at baseline | PHQ $\geq 10$ | Each standard deviation increase in preoperative logarithmically transformed high sensitivity CRP levels was associated with an increased odds of developing pre-operative depression (OR: 1.16, $p = 0.001$) and postoperative depression at 6 months (OR: 1.15, $p = 0.002$). |
| Poole et al. (134) | To assess the association between postoperative CRP, depressive features and length of hospital stay | CABG ± valve procedure | Prospective observational trial | $n = 145$ | No pre-operative depression ($n = 100$)<br>Pre-operative depression ($n = 45$) | Postoperative CRP measured between day1-3, then between day 4 and 8.<br>BDI assessed prior to surgery | BDI $\geq 10$ | Patients with pre-operative depression are 3.5x more likely to stay in a hospital for a week following surgery ($p = 0.007$)<br>Every unit of increase in high sensitivity CRP measured between postoperative day 1–3 increased the odds of an increased length of stay by 1% ($p = 0.030$)<br>Elevations in the level of CRP measured between postoperative days 4–8 significantly contributed to depression status and longer hospital stay ($t = 2.62$, $p = 0.010$) |

*(Continued)*





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TABLE 2 (Continued)

| Study | Aim | Surgery type | Study type | Patient number | Patient groups | Intervention | Definition of depression | Findings |
|---|---|---|---|---|---|---|---|---|
| Ivankovic et al. (135) | To assess the contribution of both pre and post-operative CRP levels to preoperative depression symptoms and length of hospital stay | Elective CABG | Prospective observational trial | $n = 212$ | No pre-operative depression ($n = 186$) Pre-operative depression ($n = 26$) | Postoperative CRP measured between day1 and 3, then between day 4 and 6. BDI assessed prior to surgery | BDI $\geq 13$ | 73.1% of patients with pre-operative depression had a length of stay over 7 days. In comparison, 56.5% of patients without preoperative depression had a length of stay over 7 days. Following stratification of preoperative BDI scores into depressed or non-depressed (BDI $< 10$), there was no association between binary BDI scores and length of postoperative hospital stay. Post-operative CRP measured at postoperative day 4–6 was associated with a prolonged hospital stay (OR: 1.017, 95% CI: 1.005–1.029, $p = 0.009$). No association detected between pre-operative BDI scores and CRP levels |
| Streptoe et al. (136) | To assess the association between the level of inflammatory markers and depressive symptoms | Elective CABG | Prospective observational trial | $n = 145$ | Not specified | Depressive symptoms measured 1 month prior to surgery and 12 months following surgery Plasma IL-6 and Interferon gamma were measured between postoperative days 1–3 | BDI cut off not specified | Early postoperative IFN-γ levels which were in the upper tertile (mean concentration: $56.68 \pm 7.5$ pg./mL) was associated with depressive symptoms at 12 months (OR: 4.32, $p = 0.024$). In contrast, there was no association between IL-6 and the development of postoperative depressive symptoms |

BDI, beck depression inventory; CABG, coronary artery bypass graft; CRP, c reactive protein; IFN- γ; interferon gamma; IL-6, interleukin-6; PHQ, patient health questionnaire.



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with depression following cardiac surgery (154). Poole et al. demonstrated a steeper change in cortisol concentration throughout the day (steeper cortisol slope) measured at 2 months post CABG is associated with a reduced odds of developing depression (defined as BDI greater than 10) at 12 months following surgery (OR: 0.661, 95% CI: 0.437–0.998, $p = 0.049$) (155).

Elevated CRH concentrations are observed in MDD, but not in psychopathologies such as schizophrenia and bipolar disorder (156, 157). Upon resolution of MDD, the CRH levels appear to normalize (158). Additionally, in response to exogenous CRH administration, there is a reduction in ACTH secretion (159–161). This may be attributed to the downregulation of CRH receptors within the hypothalamus. Disturbances in the HPA axis may lead to structural changes to the effectors of this axis. Hypersecretion of CRH due to impairment of the negative feedback loop may lead to pituitary hypertrophy (162, 163). Hippocampal changes in response to MDD have been an area of interest given this structure contains a high concentration of glucocorticoid receptors. A reduction in hippocampal volume is associated with the chronicity of disease, the severity and frequency of MDD episodes (164, 165). Reports of alterations to the size of the amygdala in MDD has been conflicting (166–168). HPA axis hyperactivity is associated with the development of classic cardiovascular risk factors including hypertension, dyslipidemia, impaired glucose tolerance and truncal obesity (169, 170). Hence, HPA axis dysregulation is a likely link between depression and cardiovascular disease.

#### 3.3.3. Effect of dexamethasone on depression following cardiac surgery

Dexamethasone is a glucocorticoid receptor agonist with anti-inflammatory properties. Prolonged use is associated with neuropsychiatric deficits such as postoperative cognitive dysfunction, depressive symptoms and mania (171). Studies of dexamethasone in the cardiac surgery population are summarized in Table 3. Kok et al. assessed the effectiveness of administering a single intraoperative dose of intravenous dexamethasone, a glucocorticoid receptor agonist, on depression and post-traumatic stress disorder (PTSD) following cardiac surgery (172). Compared to the placebo, a single intraoperative dose of dexamethasone (1 mg/kg of bodyweight up to a maximum of 100 mg) did not affect the overall prevalence of depression following cardiac surgery. The overall rates of PTSD were similar between the groups. However, dexamethasone demonstrated long-lasting protective effects against the development of depression and PTSD in women. Six women who received dexamethasone developed depression, while 20 women who received placebo developed depression ($p < 0.003$). Similarly, 4 women who received dexamethasone developed PTSD, while 16 women who received placebo developed PTSD ($p < 0.004$). Women are more likely to be affected by HPA axis dysregulation and to have a higher basal cortisol concentration (174, 175). Additionally, gender may differentially affect HPA axis activation and glucocorticoid sensitivity, which in turn modulates the pro-inflammatory cytokine production (176, 177).

Genetic polymorphisms in the glucocorticoid receptor may significantly influence an individual's susceptibility to develop depression and dictate their therapeutic response to antidepressant therapy (178, 179). Kok et al. assessed five common, single nucleotide polymorphisms on the glucocorticoid receptor including: rs41423247, rs10052957, rs6189, rs6195, and rs6198. They not identify polymorphisms which conferred protection against depression following cardiac surgery. On the contrary, three single nucleotide polymorphisms in the glucocorticoid receptor were required for dexamethasone to exert its protective effects against PTSD, including the rs41423247, rs10052957, and the rs6189 polymorphisms (173). The glucocorticoid receptor single nucleotide polymorphism rs6189 has been associated with reduced glucocorticoid receptor sensitivity and a faster response to treatment in MDD patients (180, 181). Thus, it is unclear why the protective effects of dexamethasone did not interact with this glucocorticoid receptor in the study. This is the largest study to date examining the genetic variability of the HPA axis in response to the administration of intraoperative dexamethasone in the cardiac surgery population. Future studies should also assess the concentration of CRH, ACTH and serum/salivary cortisol to gain a holistic view of HPA axis functioning.

## 4. Preventative and management strategies

The preventative and management strategies for depression following cardiac surgery are summarized in Figure 3. Management strategies may be divided into pharmacological or non-pharmacological strategies.

### 4.1. Preventative strategies

#### 4.1.1. Preoperative education

Preoperative education is effective in reducing depressive symptoms following cardiac surgery. Education may be delivered at the bedside, in a group, via phone call, or even through social media platforms. Long wait times for surgery, particularly in the elective setting, contributes to mental distress (182, 183). Preoperatively, patients should be informed of the surgical process and risks involved with the procedure, required investigations, secondary prevention through risk factor modification as well as any other concerns or expectations. Patients should also be informed of whether surgical access will be achieved via median sternotomy or through minimally invasive methods (e.g., lateral thoracotomy). Access via median sternotomy is known to cause anxiety and addressing this concern may reduce the risk of anxiety and depression (184).

Preoperative education should also involve psychological support and setting health and recovery expectations (185). Conversely, postoperative education should focus on the recovery and rehabilitation process. Centers should provide both preoperative and postoperative education to reduce depression and anxiety. The results of educational interventions in the cardiac surgery setting are discussed below.

##### 4.1.1.1. Preoperative education alone

Three studies were identified which examined preoperative education alone (Table 4). Two of the studies supported preoperative education in reducing depressive symptoms. In an RCT of a Chinese population, Guo et al. reported that compared to usual care, preoperative education was associated with a significant reduction in depressive symptoms at 7 days postoperatively as measured by HADS

TABLE 3 The effect of dexamethasone on improving depression in cardiac surgery patients.

| Study | Aim | Surgery type | Study type | Patient number | Patient groups | Intervention | Definition of depression | Findings |
|---|---|---|---|---|---|---|---|---|
| Kok et al. (172) | To assess the effectiveness of administering a single intraoperative dose of dexamethasone against preventing depression and PTSD following cardiac surgery | Assorted cardiac surgery (CABG or valves) | Follow up of randomized controlled trial | $n = 1{,}125$ | Dexamethasone ($n = 561$)<br>Placebo ($n = 564$) | Patients received a high intraoperative dose of dexamethasone (1 mg/kg) or placebo | BDI >13.5 | 69 patients receiving dexamethasone developed depression, whereas 78 patients receiving placebo developed depression (OR: 0.92, 95% CI: 0.64–1.31).<br>Six women who received dexamethasone developed depression, while 20 women who received placebo developed depression ($p < 0.003$). Similarly, 4 women who received dexamethasone developed PTSD, while 16 women who received placebo developed PTSD ($p < 0.004$). |
| Kok et al. (173) | To assess whether common hypothalamic pituitary adrenal axis polymorphisms would protect against the development of PTSD and depression following dexamethasone | Assorted cardiac surgery (CABG or valves) | Follow up of randomized controlled trial | $n = 996$ | Single group who completed were enrolled in the dexamethasone for cardiac surgery randomized controlled trial | Patients received a high intraoperative dose of dexamethasone (1 mg/kg) or placebo<br>Genotyping assessed rs41423247, rs10052957, rs6189, rs6195 and rs6198. | Not specified | Did not identify polymorphisms which conferred protection against depression following cardiac surgery.<br>On the contrary, three single nucleotide polymorphisms in the glucocorticoid receptor were required for dexamethasone to exert its protective effects against PTSD, including the rs41423247, rs10052957 and the rs6189 polymorphisms |

BDI, beck depression inventory; CABG, coronary artery bypass graft; PTSD, post-traumatic stress disorder.





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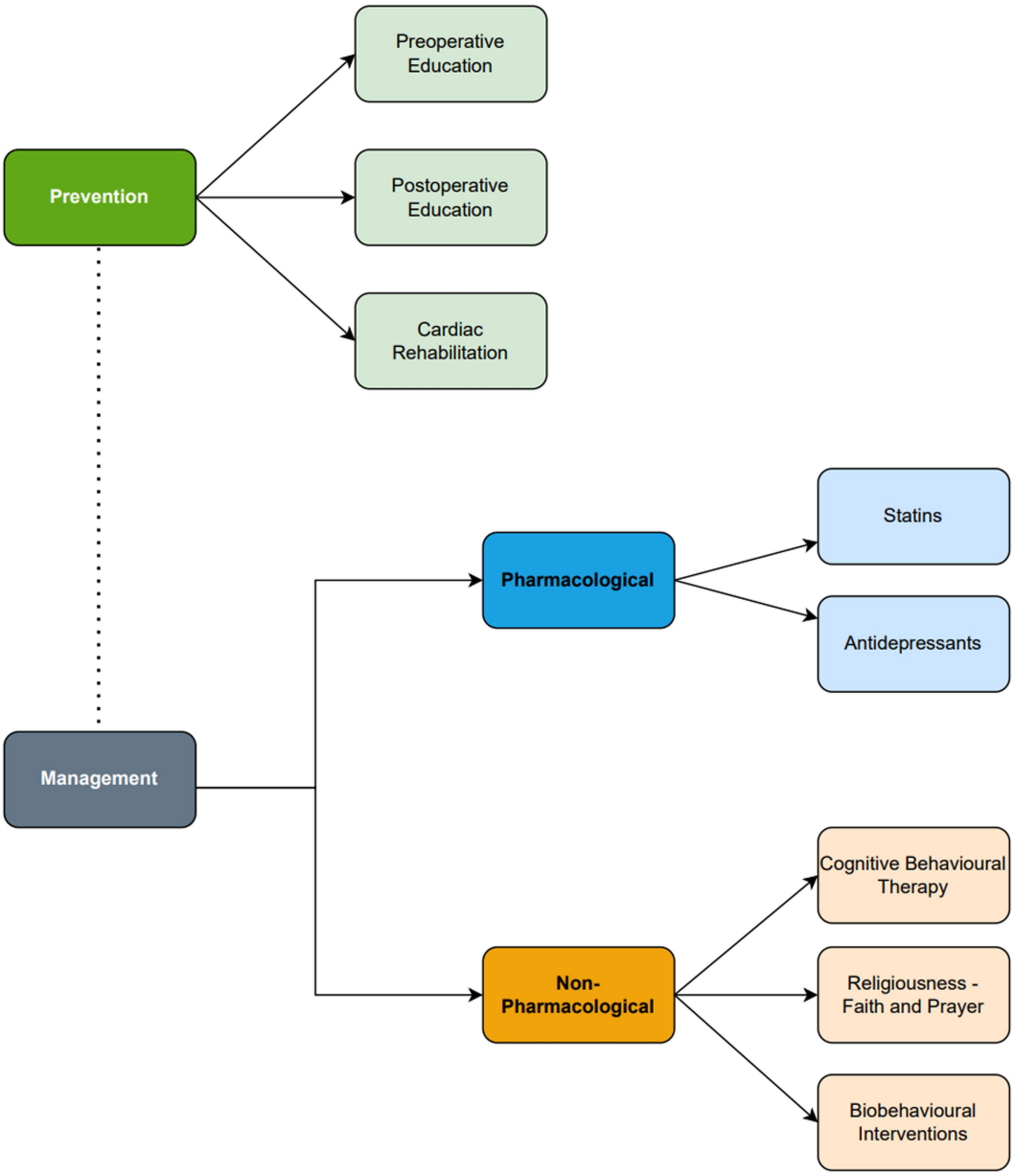


FIGURE 3
Summary diagram of the prevention and management of depression following cardiac surgery. Antidepressant and cognitive behavioral therapy are the core management for depression following cardiac surgery. Statins, religiousness/spirituality and biobehavioral interventions are emerging adjuncts which should only be considered in clinical practice following further evidence.

(Mean Difference: 2.1, 95% CI: −3.19 to −0.92, $p < 0.001$) (186). Their preoperative education intervention involved the distribution of a flyer and an accompanying explanation of what to expect from preadmission through to surgery and postoperative recovery. In comparison, the usual care group received general advice from the surgeon and anesthetist the day prior to their surgery. Preoperative education may have benefitted this population for several reasons. Firstly, patients undergoing cardiac surgery in several Chinese hospitals are admitted 1 week pre-operatively, contributing to the build-up of anxiety and depressive symptoms. Secondly, Chinese cardiac patients tend to be less informed about the finer details of their procedure. A qualitative analysis revealed surgeons generally discussed the severity of cardiac disease with the patient, but not the risks of surgery (which they limited to the patients' family members) (189). However, surgeons should discuss risks with patients, as one reported "knowledge is comforting, with the more [they] knew, the less anxious [they] became" (190). Patients undergoing cardiac surgery should be placed in nearby beds to allow patients to support each other.

Additionally, Furze et al. demonstrated that a nurse-led educational and cognitive behavioral intervention (HeartOp Programme) prior to surgery significantly reduced the severity of depressive symptoms, compared to usual care at 6 months postoperatively as measured by the CDS (Mean difference: 7.79, 95% CI: 2.04–13.54, $p = 0.08$) (187). Both groups initially received a 1-h interview in the outpatient clinic, followed by phone calls 1, 3, and

TABLE 4 The effect of preoperative education on improving depression following cardiac surgery.

| Study | Aim | Surgery type | Study type | Patient number | Patient groups | Intervention | Definition of depression | Findings |
|---|---|---|---|---|---|---|---|---|
| Guo et al. (186) | To assess whether preoperative education is effective in reducing anxiety and depression in Chinese cardiac surgery patients | Elective cardiac surgery (CABG, valve or congenital surgery) | Randomized controlled trial | $n = 135$ | Usual care ($n = 67$)<br>Preoperative education ($n = 68$) | Patients in the preoperative intervention group received an information booklet about heart surgery and verbal advice at around 2–3 days prior to surgery<br>Usual care group received unstructured verbal advice | Not specified, but measured using HADS | Preoperative education was associated with a significant reduction in depressive symptoms at 7 days postoperatively as measured by HADS (Mean Difference: 2.1, 95% CI: −3.19 to −0.92, $p < 0.001$) |
| Furze et al. (187) | To assess the effect of a brief, home based cognitive behavioral program (HeartOp) compared to only preoperative nurse counseling | Elective first time CABG | Randomized controlled trial | $n = 204$ | HeartOp group ($n = 100$)<br>Control group ($n = 104$) | HeartOp programme discusses cardiac myths and misconceptions, reducing risk factors for secondary prevention, and what to expect during the hospital stay. Goals are set to reduce cardiovascular risk and increase physical activity. The patient is followed up via phone call to check in on goals<br>General nurse led counseling involves providing generic advice, but no attempt at dispelling myths and misconceptions | Not specified, but measured using CDS | HeartOp Programme prior to surgery significantly reduced the severity of depressive symptoms, compared to usual care at 6 months postoperatively as measured by the CDS (Mean difference: 7.79, 95% CI: 2.04–13.54, $p = 0.08$) |
| Shuldham et al. (188) | To assess the benefit of preoperative education on improving postoperative pain, anxiety and depression | First time CABG | Randomized controlled trial | $n = 269$ | Education group ($n = 124$)<br>Control ($n = 145$) | Education was provided in a group setting (10–15 people) and covered pre-operative events and likely recovery process. The control group received informal one on one standard education. Questionnaires were sent, preoperatively, and at 6 weeks, 3 months and 6 months post-operatively | Not specified, but measured using HADS | There was no benefit from preoperative education ($n = 124$) on improving depressive symptoms measured by HADS compared to the usual care group ($n = 145$) at 3 days, 3 months and 6 months postoperatively (Mann–Whitney U: −11,886, Z: −0.50, $p = 0.62$) |

CABG, coronary artery bypass graft; CDS, cardiac depression scale; HADS, hospital anxiety and depression scale.



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6 weeks later and then monthly communication until the procedure. In the HeartOp group, nursing staff addressed common cardiac misconceptions, discussed risk factor alterations for secondary prevention and expectations within the hospital setting. They also facilitated goal setting for risk factor reduction. The program appears to be economical, costing £288.83 per quality adjusted life year. Common myths and goal setting was not addressed in the usual care group.

Conversely, Shuldham et al. did not demonstrate a benefit from preoperative education ($n = 124$) on improving depressive symptoms measured by HADS compared to the usual care group ($n = 145$) at 3 days, 3 months and 6 months postoperatively (Mann–Whitney U: −11,886, Z: −0.50, $p = 0.62$) (188). Education was delivered through a 4-h group session with 10–15 patients and involved discussion of the pre/post-operative period and rehabilitation. In contrast, the usual care group received informal verbal advice at the time of admission. The lack of benefit is likely attributed to an optimal standard of preoperative education already provided by the hospital. On the other hand, shy and reserved patients may not have sufficiently engaged in group discussions despite having the opportunity. Future studies should also compare pre-operative education in a group setting compared to a regular patient consultation.

#### 4.1.1.2. Combination of pre-operative and post-operative education

In a Turkish population, Yaman Aktas et al. demonstrated preoperative and discharge education ($n = 33$) was effective in reducing HADS scores compared to usual care ($n = 33$) at 10 days and 4 weeks post-discharge following cardiac surgery ($F = 19.23$, $p < 0.01$) (191). Patients in the education group were provided one preoperative and four postoperative educational sessions. Preoperative education involved an informational pamphlet, an explanation of CHD, an overview of CABG and what to expect postoperatively. Postoperative education was commenced on postoperative day 3 to account for drowsiness and weakness immediately following surgery. Postoperative education involved an explanation of the recovery process, rehabilitation exercises, activities to avoid and when to re-present to hospital. The average education time per patient was 113.3 min, which appears justified given the reduction in depressive symptoms.

### 4.1.2. Cardiac rehabilitation

Cardiac rehabilitation programs are focused on restoring a patient's physical capacity following surgery, decreasing the likelihood of further cardiac events, and improving psychological wellbeing. Patients who develop postoperative depression while attending cardiac rehabilitation are commonly affected by comorbidities such as poor lifestyle choices, diabetes, chronic pain, or angina (192). These patients are more resistant to improvements in mental health. Future cardiac rehabilitation programs should aim to address these comorbidities.

Cardiac rehabilitation is effective in reducing depressive symptoms following cardiac surgery (Table 5) (193–195). The cardiac rehabilitation interventions have been variable in focus as well as timing. Hojskov et al. conducted early physical rehabilitation and psychoeducation following CABG over 4 weeks. The physical intervention consisted of deep breathing exercises, peak flow spirometry, walking, neck/shoulder and cycling exercises, whereas psychoeducation was provided over four face-to-face consultations with a focus on mindfulness (193). On the other hand, Ma et al. conducted a 12-month intervention involving not only physical exercise guidance, but also counseling on CAD-related health education, risk factor controls strategies and psychological monitoring (194). Cardiac rehabilitation has also been shown to be effective in reducing depressive symptoms even if the patient completes it from home (195). This significantly increases the accessibility of services, particularly for patients with transport or logistical difficulties when attending outpatient appointments.

## 4.2. Non-pharmacological management

### 4.2.1. Cognitive behavioral therapy

Cognitive behavioral therapy (CBT) is effective, evidence-based psychotherapy for the management of psychopathologies such as depression and anxiety (196). CBT has several advantages. Firstly, the efficacy of CBT rivals that of anti-depressants in managing depression. Secondly, the concurrent use of CBT with antidepressants enhances the pharmacological effect of the medication and improves adherence to medications and rehabilitation plans (197, 198). Thirdly, the anti-depressive effect of CBT may last longer in comparison to anti-depressants and prevent relapse (199). Moreover, early initiation of CBT may halt the progression of new cases of depression. Persistent depressive symptoms are associated with a reduced chance of recovery. For example, the chance for recovery within the next 6 weeks if a patient has had depressive symptoms for 3 and 23 weeks is 40% and 5%, respectively, (200). CBT is limited by the necessity for patients to take ownership of their management, significant time commitments, travel requirements to clinic and limited focus on social networks (201, 202).

CBT sessions generally last an hour and run over several weeks. Within these sessions, trained mental health professionals will assist patients to identify automatic negative thoughts. They also aim to challenge and restructure negative thinking patterns and cognitive distortions with a goal to improve affect. In subsequent sessions, strategies aimed at maintaining psychological wellbeing are explored (203, 204). Following cardiac surgery, patients generally experience an improvement in psychological symptoms as their symptoms and quality of life significantly improve. However, postoperative pain, complications and slower than expected recovery may demotivate patients (205). This may also contribute to dysfunctional thoughts, loss of self-efficacy and fear of progression with rehabilitation exercises. CBT may directly address these cognitive distortions. Despite the clearly documented benefit of CBT in managing depression, there have been few studies exploring the efficacy of CBT in the cardiac surgery population (Table 6).

Standard delivery of CBT over a 12 week period appears to be effective at inducing sustained remission of depression following CABG compared to supportive stress management or usual care ($\chi^2 = 11.95$, $p = 0.003$) (206). To overcome the large time commitment required by traditional CBT models, a brief form of CBT such as the 'Managing Anxiety and Depression Using Education and Skills' (MADES) model have been proposed. For example, in the study by Dao et al., patients would attend 2 sessions preoperatively and 2 sessions within the first postoperative week. Compared to the usual care group, patients undergoing MADES had a shorter hospital stay (7.9 days ±2.6 days vs. 9.2 ± 3.5 days, $p = 0.049$) and demonstrated

TABLE 5 The effect of cardiac rehabilitation on improving depression following cardiac surgery.

| Study | Aim | Surgery type | Study type | Patient number | Patient groups | Intervention | Definition of depression | Findings |
|---|---|---|---|---|---|---|---|---|
| Hojskov et al. (193) | Assess the effect of early cardiac rehabilitation (4 weeks following CABG) compared with usual care on 6 min walk time, anxiety and depression, physical and emotional scores and pain | CABG | Randomized controlled trial | $n = 326$ | Early rehabilitation ($n = 163$).<br>Usual care ($n = 163$) | Rehabilitation consisted of deep breathing exercises, peak flow spirometry, walking exercises, neck/shoulder exercises and cycling. | HADS ≥8 | Early physical rehabilitation and psychoeducation following CABG decreased mean depression scores compared to usual care, as measured by HADS-D (Rehab: 3.7, Usual: 4.3)<br>No effect on 6-min walk time |
| Ma et al. (194) | To assess the effect of a 12 month long comprehensive rehabilitation and intensive education program in patients with unprotected left main CAD who underwent CABG | CABG | Randomized controlled trial | $n = 300$ | Rehabilitation program ($n = 150$)<br>Usual care ($n = 150$) | Intervention consisted of CAD-related health education, physical exercise guidance, risk factor control strategies and psychological monitoring. Exercise guidance involved exercise selection and a prescription of frequency, intensity and duration of exercise. Conversely, usual care involved generic discharge education and information about their medications. | HADS ≥8<br>Evaluated at 3 months, 6 months and 12 months following admission | There was no significant difference in HADS-D score at baseline, 3 months, 6 months, and 9 months postoperatively. However, there was a reduction in HADS-D score at 12 months in the intervention group (mean value: −1.3±1.7) compared to the usual care group (mean value: −0.6±1.5, $p < 0.001$). |
| Takroni et al. (195) | To compare the effectiveness of home-based cardiac rehabilitation against outpatient based cardiac rehabilitation and usual care in a population of Saudi Arabian patients | CABG | Randomized controlled trial | $n = 73$ | Home based cardiac rehab ($n = 24$)<br>Outpatient based cardiac rehab ($n = 25$)<br>Usual care ($n = 24$) | The outpatient cardiac rehabilitation group completed a physiotherapist-supervised program 3 times per week, with each session consisting of 15 min of warm-up, 20 min of progressive aerobic exercise and 10 min of cool-down.<br>The home rehabilitation group completed a similar intervention, but selected exercises from an exercise library and received a weekly support call. | HADS ≥8<br>Evaluated at baseline at 8 weeks and 12 weeks. | Both the home-based and outpatient-based cardiac rehabilitation programs were effective in reducing HADS-D scores at 8 weeks (outpatient: 4.32, home: 4.88).<br>However, the HADS-D score in the home-based rehabilitation program continued decreasing at the 4-week post-intervention follow-up (outpatient: 4.12, home: 3.79).<br>High compliance rate in both the outpatient and home-based cardiac rehabilitation program at 91.7 and 87.5% respectively |

CABG, coronary artery bypass graft; CAD, coronary artery disease; HADS, hospital anxiety and depression score.





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TABLE 6 Studies of cognitive behavioral therapy in improving depression following cardiac surgery.

| Study | Aim | Surgery type | Study type | Patient number | Patient groups | Intervention | Definition of depression | Findings |
|---|---|---|---|---|---|---|---|---|
| Freedland et al. (206) | To compare the effect of CBT against supportive stress management and usual care on the management of depression following CABG | CABG | Randomized controlled trial | $n = 123$ | CBT ($n = 41$)<br>Supportive stress management ($n = 42$)<br>Usual care ($n = 40$) | CBT sessions were hourly sessions once per week, over 12 weeks<br>Supportive stress management aimed to improve the patient's ability to cope with stressful life events through classes on breathing and relaxation techniques.<br>Outcomes were measured at 3, 6, 9, and 12 months | HAM-D > 7<br>BDI ≥ 10 | CBT (51%) was more effective than supportive stress management (33%) or usual care (15%) for inducing sustained remission of depression following CABG ($\chi^2 = 11.95$, $p = 0.003$).<br>Improvements in major depression were only seen in the CBT group. In contrast, improvements in mild depressive symptomatology were observed in the CBT and supportive stress group—albeit the effect was greater in the CBT group.<br>Supportive stress management was superior to usual care in reducing depressive symptoms at 3 months, but there was no difference at 6 or 9 months. |
| Dao et al. (207) | To assess the feasibility and accessibility of a brief tailored CBT intervention (MADES) on managing pre-operative depression | CABG | Randomized controlled trial | $n = 97$ | MADES ($n = 48$)<br>Usual care ($n = 49$) | The MADES group attended four sessions, including two preoperative and two postoperative sessions (within the week following cardiac surgery). | BDI ≥ 14 | Compared to the usual care group, patients undergoing MADES had a shorter hospital stay (7.9 days ±2.6 days vs. 9.2 ± 3.5 days, $p = 0.049$).<br>MADES was also associated with a reduction in depressive symptoms as confirmed by BDI, whereas patients receiving usual care demonstrated an increase in postoperative depressive symptoms.<br>Low attrition rate ($n = 1$) |

*(Continued)*



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TABLE 6 (Continued)

| Study | Aim | Surgery type | Study type | Patient number | Patient groups | Intervention | Definition of depression | Findings |
|---|---|---|---|---|---|---|---|---|
| Doering et al. (208) | To assess the efficacy of early CBT conducted in the home environment by nurses in patients 1 month following CABG | CABG | Randomized controlled trial | $n = 81$ | CBT ($n = 45$)<br>Usual care ($n = 36$) | 8 week CBT intervention | BDI $\geq 10$ | CBT group had a greater decrease in BDI scores compared to the usual care group.<br>The BDI in the usual care group increased over the 8-week period ($\beta = 1.41$, 95% CI: 0.81–2.02).<br>More CBT patients ($n = 29$, 64%) experienced remission from depression compared to the usual care group ($n = 9$, 25%). |
| Berensvaite et al. (69) | To assess the effect of CBT on HRV and its effectiveness on improving health related quality of life in patients 2 months following cardiac surgery | CABG | Randomized controlled trial | $n = 89$ | CBT ($n = 43$)<br>Usual care ($n = 46$) | 9 month CBT intervention. | Not specified | At baseline (2 months postoperatively), the Mann–Whitney U test demonstrated the HRV was slightly lower in the CBT group compared to the usual care group (21.8 ms vs. 32.9 ms, U = 591.5, $p = 0.047$).<br>At the final follow-up, there was a significant increase in the HRV within the CBT group compared to baseline (21.8 ms vs. 34.5 ms, $p = 0.022$). Conversely, the HRV decreased within the usual care group from baseline (32.9 ms vs. 29.2 ms, $p > 0.05$). Hence, CBT may improve the overall adaptability of autonomic nervous system.<br>The LF/HF ratio did not significantly change for either group, suggesting that CBT did not alter overall autonomic balance. |

BDI, beck depression inventory; CABG, coronary artery bypass graft; CBT, cognitive behavioral therapy; HAM-D, hamilton depression rating scale.





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reduced depressive symptoms (207). However, the MADES model requires validation in a larger cardiac surgery population prior to widespread use. Furthermore, CBT has been shown to be effective in reducing depressive symptoms following cardiac surgery even when delivered at a patient's home by nurses. This significantly eliminates accessibility and travel barriers required for patients to attend outpatient clinics (208). However, it should be noted that within this study, the number of females were under-represented within the CBT. This is a significant limitation as females have been shown to be more resistant to the effects of CBT (209). Lastly, a 9 month long CBT intervention following CABG has also been shown to be effective in improving the overall adaptability of the autonomic system. However, CBT did not improve vagal outflow (69).

#### 4.2.2. Religiousness, faith, and prayer

The lead up to cardiac surgery induces anxiety in many patients. Patients may cope using active or maladaptive coping strategies. Active coping strategies include behavioral or cognitive strategies. Behavioral coping strategies include actions to improve a situation, while cognitive strategies involve mental activities such as changing one's perspective on the situation, and positive reappraisal (210). Maladaptive coping strategies include actions which do not attempt to improve the situation, but rather ignore it or make it worse.

Religion is an unrecognized psychosocial factor and coping mechanism which may affect recovery following cardiac surgery (211). Religiousness refers to the belief in religious doctrines or the involvement in religious practices such as attending services or prayer (212). Religious involvement is postulated to improve postoperative recovery. Attending religious services is associated with increased social support, leading to greater connection with congregation members. Secondly, regular attendance of religious services may influence cognitive appraisal processes, which may therefore modulate immunological, autonomic and neuroendocrine activity (213).

The effect of religion and prayer on health outcomes in patients following cardiac surgery is not well established (Table 7). Contrada et al. reported stronger religious beliefs were associated with reduced postoperative complications and a shorter length of hospital stay. However, when postoperative complications were controlled for, there was no relationship between religion and length of stay (211). Religious involvement was also associated with an improvement in depressive symptoms. However, attendance at religious events was associated with poorer recovery and increased length of hospital stay. This may be attributed to whether a patient has a positive or negative religious coping style. Negative religious coping styles are seen in patients with religious struggles, and who have an insecure relationship with their god. Individuals with spiritual conflicts report poorer wellbeing scores, including depression (216).

Ai and colleagues postulated that the use of prayer when faced with a medical issue draws allows an individual to draw upon one's inner spirituality, and does not necessarily relate to specific religion or faith (214). Particularly in spiritual patients, the use of prayer may indicate a survival instinct and may also reduce anxiety (217). Patients who engaged in private prayer postoperatively had a lower level of distress 1 year following surgery (214). Ai et al. reported that private prayer prior to CABG was associated with higher levels of hope and optimism before their surgery (215). In contrast, Contrada and colleagues did not find an association between prayer and health outcomes or quality of life (211). They documented the frequency of prayer, but not the intent behind it. Clinicians should recognize that spirituality, religion, and prayer may be effective methods of coping. Spiritual guidance and services from a hospital chaplain or pastor should be offered to all patients.

#### 4.2.3. Postoperative education alone

Postoperative education has been uniquely delivered via an online format. Ma et al. compared an internet-based education and rehabilitation program ($n = 70$) against standard care ($n = 70$) for patients following CABG (218). They designed an educational rehabilitation program on the social media platform WeChat, the main communication modality in China (219). A 12-month intervention delivered by nurses involved health education, rehabilitation guidance, exercise supervision and psychological care. Health education involved the delivery of weekly videos on post-CABG management/recovery and modification of cardiovascular risk factors. Videos demonstrating rehabilitation exercises were created. Additionally, patients received fortnightly calls from nurses to discuss their psychological wellbeing. In comparison, the usual care group received once-off verbal advice prior to discharge and a call every month to discuss further rehabilitation guidance. At 12 months postoperatively, the HADS score was significantly lower in the WeChat group compared to the usual care group ($5.2 \pm 2.5$ vs. $6.1 \pm 3.1$, $p = 0.048$). Internet-based rehabilitation programs are more convenient for patients and are not limited by travel requirements. These interventions are cost-effective and patient queries are promptly answered. It is important to monitor adherence to medication or rehabilitation, as internet-based education may result in reduced patient engagement.

#### 4.2.4. Biobehavioral interventions

Respiratory sinus arrythmia refers to the rhythmic increases and decreases in heart rate associated with respiration. Given respiratory sinus arrythmia is largely driven by vagal outflow and the pathophysiology of depression involves autonomic dysfunction, it reasonable to target this underlying mechanism. Patients in the biofeedback group may be trained to breathe abdominally and at a slower rate to synchronize their heart rate and abdominal breathing.

Despite limited data, Patron et al. found that biofeedback training to increase respiratory sinus arrythmia appears to be effective in decreasing depressive symptoms following cardiac surgery (220). However, given no follow up studies were conducted, it is unknown whether the improvements in depressive symptoms are long lasting. Additionally, it is also unclear whether depressive symptoms are reduced due to an improvement in autonomic regulation, or by another pathway. No other recent studies have been identified to examine the effect of biobehavioral interventions on depression following cardiac surgery.

### 4.3. Pharmacological management

#### 4.3.1. Antidepressants

The management of moderate to severe depression may involve psychological or pharmacotherapy. Psychotherapy has been shown to be equivalent pharmacotherapy in managing depression. Over 50% of patients do not respond to their initially prescribed antidepressant, and over 30% of patients do not respond to subsequent management

TABLE 7 Studies assessing the effect of religion on depressive features in patients undergoing cardiac surgery.

| Study | Aim | Surgery type | Study type | Patient number | Patient groups | Intervention | Definition of depression | Findings |
|---|---|---|---|---|---|---|---|---|
| Contrada et al. (211) | To assess the effect of religiousness on depressive symptoms following cardiac surgery | CABG ± valve surgery | Prospective observational trial | $n = 142$ | Single group | Religious and psychological factors measured 1 week prior to surgery | Not defined<br>Measured using BDI | Stronger religious beliefs were associated with reduced postoperative complications and length of stay<br>However, once postoperative complications were controlled for, there was no relationship between religion and length of stay.<br>More frequent religious attendance is associated with poorer recovery and increased hospital stay<br>Depressive symptoms are associated with longer hospital stay |
| Ai et al. (214) | To assess the role of private prayer and religiousness on depressive symptoms following cardiac surgery | CABG | Retrospective observational trial | $n = 151$ | Single group | Questionnaires sent at 6 months and 1 year post cardiac surgery | Not defined<br>Measured using Symptom Checklist-90R | Patients who prayed were less likely to be depressed at 1 year postoperatively, even when controlling for depression at 1 month post-operatively. |
| Ai et al. (215) | To assess the effect of private prayer as a coping mechanism and its relationship with optimism in patients undergoing cardiac surgery | CABG | Prospective observational trial | $n = 226$ | Single group | First in person interview was conducted 2 weeks prior to surgery. Optimism was measured the day before surgery via telephone. | Not defined<br>Measured using CES-D | Private prayer prior to CABG was associated with higher levels of hope and optimism before their surgery |

BDI, beck depression inventory; CABG, coronary artery bypass graft; CES-D, center for epidemiological studies depression scale.





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(221). The most used antidepressants include selective serotonin reuptake inhibitors (SSRIs), serotonin and noradrenaline reuptake Inhibitors (SNRIs) and tricyclic antidepressants (222). For cardiac surgery patients, SSRIs and SNRIs are most commonly used (12). Examples of SSRIs include escitalopram, citalopram, fluoxetine, paroxetine and sertraline (222). Tricyclic antidepressants are largely avoided given their cardiotoxic nature (223).

The main aim of antidepressant therapy is to reduce psychological and physical symptoms and improve their functional capacity. Antidepressants should be used in conjunction with psychotherapies (224). SSRIs competitively inhibit the presynaptic uptake of serotonin, consequently increasing the level of serotonin within the brain (222). Moreover, they have also been reported to attenuate autonomic dysfunction through improvements via HRV and have anti-inflammatory effects (225). Recent evidence suggests that anti-depressants may exert cardioprotective properties the attenuation of platelet function by interfering with serotonin uptake within platelets. This may reduce the development and progression of atherosclerotic lesions, and thus reduce the risk of CHD (226).

#### 4.3.1.1. Efficacy

Despite limited evidence, SSRIs appear to be efficacious in reducing depression following cardiac surgery (Table 8) (227, 228). Prophylactic treatment with 10 mg of Paroxetine for 10 days in individuals identified to be at high risk of postoperative depression (older than 70 years and underwent emergency surgery) was associated with significantly lower CES-D scores (15.2 ± 7.8) compared to the control group (21.8 ± 7.5, $p = 0.0018$). The incidence of depression was significantly higher in the non-paroxetine group compared to the paroxetine group (64.4% vs. 12.1%, $p < 0.0001$) (227). Similarly, prophylactic treatment with 10 mg of escitalopram daily for 6 months was effective in reducing the mean BDI score from baseline compared to placebo in CABG patients ($p = 0.015$) (228). Moreover, the use of escitalopram in patients with pre-operative depression reported swifter improvements in quality of life and reduced postoperative pain. It should be noted that escitalopram was imitated starting 2–3 weeks prior to surgery to account for the delay period before the beneficial effects of SSRIs become clinically apparent (234).

#### 4.3.1.2. Safety profile

Studies of the safety profile of antidepressants in the cardiac surgery population have mainly involved assessment of morbidity, mortality, and the risk of bleeding.

***Mortality:*** The evidence describing the effect of SSRI/SNRIs on mortality in patients following cardiac surgery has been conflicting. Tully et al. reported that use of SSRI/SNRIs at the time of cardiac surgery did not increase all-cause mortality (HR: 1.03, 95% CI: 0.62–1.72, $p = 0.91$) or cardiac mortality (HR: 0.31, 95% CI: 0.04–2.26, $p = 0.25$) (230). Chocron et al. also did not report a difference in mortality between patients who were taking 10 mg of escitalopram and the control group (228). Similarly, Kim et al. reported no significant difference in the composite endpoint of hospital mortality and bleeding in patients who used antidepressants (9.4% vs. 8.2%, OR: 1.03, 95% CI: 0.60–1.78) (229). A systematic review comprising 162,001 patients (with 9,751 using SSRIs) revealed that the use of SSRIs pre-operatively or postoperatively did not increase 30-day hospital mortality or long-term mortality (235).

Conversely, Xiong et al. reported that use of SSRIs before CABG was associated with a higher risk of long-term mortality and rehospitalization following surgery (HR: 1.52, 95% CI: 1.30–1.77, $p < 0.0001$) (232). Notably, patients in the SSRI group were more likely to be affected by diabetes, dyslipidemia, hypertension, cerebrovascular disease, peripheral vascular disease, and a family history of coronary artery disease. These metabolic syndrome risk factors may have contributed to the poorer health of the patients in the SSRI group. Additionally, Xiong and colleagues did not adjust for potential covariates such as renal dysfunction and left ventricular dysfunction, factors which may significantly contribute to the increased mortality. Moreover, they only reported 5.1% of patients used SSRIs prior to surgery, while the prevalence of preoperative depression in CABG is estimated to be approximately 20% (12). This means patients may be underdiagnosed and undertreated, which inherently lead to poorer outcomes. Additionally, Stenman et al. also observed that preoperative antidepressant use was associated with increased mortality (HR: 1.45, 95% CI: 1.18–1.77) following adjustment for diabetes, COPD and ventricular dysfunction (233). This is concerning and warrants further investigation into the safety of SSRIs in the cardiac surgery population.

***Bleeding:*** Concerns have been raised regarding the potential bleeding risk of SSRIs/SNRIs. Bleeding risk is particularly heightened in a cardiothoracic surgery population given they are at increased risk of rhythm disorders and are likely already on anti-platelet or anti-coagulants. SSRIs do not appear to increase bleeding risk in the vulnerable cardiac surgery population. Kim et al. performed a sub-analysis within their study which demonstrated no increased bleeding risk in patients already on anti-platelets or direct oral anticoagulants (229). However, patients on warfarin were not included in this sub-analysis, warranting future investigations into this common cardiac surgery demographic. Similarly, Tully et al. did not report increased bleeding risk from SSRIs, even in patients receiving anti-platelet therapy ($p > 0.20$) (230). Lastly, Heimisdottir et al. demonstrated that there was no significant difference in the mean 24-h chest drain output (SSRI/SNRI: 815 mL vs. Control: 877 mL, $p = 0.26$), the number of packed red blood cell transfusions (SSRI/SNRI: 2.2 vs. Control: 2.2, $p = 0.99$) and the re-operative rate (SSRI/SNRI: 4.1% vs. Control: 6.0%, $p = 0.61$) (231).

***Other adverse reactions:*** The rate of adverse drug reactions to SSRIs/SNRIs appears to be low. Some examples of more common adverse reactions include diarrhea, nausea, vomiting, constipation, shivering and peripheral neuropathy (228). Notably, Tully and colleagues observed an increased requirement for renal dialysis in patients receiving SSRI/SNRI (OR: 2.18, 95% CI: 1.06–4.45, $p = 0.03$) and an increased duration of mechanical ventilation postoperatively (OR: 1.69, 95% CI: 1.03–2.78, $p = 0.04$) (230). However, these are novel results and should be interpreted with caution. SSRIs, especially citalopram, have also been associated with QTc prolongation. Rarely, they are associated with ventricular arrythmias and Torsade's-de-Pointes. Consequently, the United States Food and Drug Administration do not recommend dosing citalopram higher than 40 mg/day (223).

TABLE 8 Studies assessing selective serotonin reuptake inhibitors in cardiac surgery patients.

| Study | Aim | Surgery type | Study type | Patient number | Patient groups | Intervention | Definition of depression | Findings |
|---|---|---|---|---|---|---|---|---|
| Hata et al. (227) | To assess the efficacy of prophylactic management with selective serotonin reuptake inhibitors in females identified as high risk of developing depression postoperatively | Cardiac surgery | Case control | $n = 117$ | Prophylactic SSRI ($n = 58$)<br>No prophylactic SSRI ($n = 59$) | Intervention group received prophylactic treatment with 10 mg paroxetine in the first postoperative day, for 10 days. Patients in this group were also >70 years or undergone emergency surgery. | CES-D > 16 | Depressive symptoms (mean ± SD) were measured using the CES-D at 10 days postoperatively. The group receiving paroxetine had significantly lower CES-D scores (15.2 ± 7.8) compared to the control group (21.8 ± 7.5, $p = 0.0018$).<br>The incidence of depression was significantly higher in the non-paroxetine group compared to the paroxetine group (64.4% vs. 12.1%, $p < 0.0001$). The length of hospital stay was also significantly shorter in the prophylactic paroxetine group compared to the control group (15.9 days vs. 23.4 days, $p = 0.0102$). |
| Chocron et al. (228) | To assess the effect of prophylactic treatment with escitalopram on depression | CABG | Randomized controlled trial | $n = 361$ | Escitalopram ($n = 182$)<br>Placebo ($n = 179$) | Patients randomized (1:1) to escitalopram or placebo. Patients received 10 mg escitalopram 2–3 weeks prior to surgery, which continued until 6 months postoperatively. | BDI ≥ 4 | 10 mg of escitalopram daily reduced the mean BDI score more quickly from baseline at the six-month postoperative follow-up compared to placebo in CABG patients ($p = 0.015$). Moreover, the use of escitalopram in patients with pre-operative depression reported swifter improvements in quality of life and reduced postoperative pain.<br>No differences in morbidity and mortality at 12 months. |

*(Continued)*





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TABLE 8 (Continued)

| Study | Aim | Surgery type | Study type | Patient number | Patient groups | Intervention | Definition of depression | Findings |
|---|---|---|---|---|---|---|---|---|
| Kim et al. (229) | To assess the safety of SSRIs in patients who have undergone CABG | CABG | Retrospective observational study | $n = 1,380$ | SSRIs ($n = 1,076$)<br>No SSRIs ($n = 304$) | Primary endpoint was defined as a composite of in hospital mortality, bleeding events | Not defined | No significant difference in the occurrence of the primary endpoint between the groups (9.4% vs. 8.2%, OR: 1.03, 95% CI: 0.60–1.78).<br>Subgroup analysis of patients on antiplatelet and anticoagulation therapy did not reveal increased rate of bleeding. Patients on warfarin not included in subgroup analysis. |
| Tully et al. (230) | To assess the effect of SSRI/SNRIs on surgical morbidity and mortality following CABG | Primary isolated CABG | Prospective observational study | $n = 4,136$ | SSRI/SNRI ($n = 105$)<br>Non-SSRI/SNRI ($n = 4,031$) | Morbidity and mortality outcomes were recorded from electronic database of patients undergoing cardiothoracic surgery between 1996 and 2008 | Not defined | Median follow up time was 4.7 years (interquartile range 2.3–7.9 years)<br>Use of SSRI/SNRIs at the time of cardiac surgery did not increase all-cause mortality (HR: 1.03, 95% CI: 0.62–1.72, $p = 0.91$), cardiac mortality (HR: 0.31, 95% CI: 0.04–2.26, $p = 0.25$) or bleeding, even in patients receiving concomitant anti-platelet therapy ($p > 0.20$).<br>There was an increased requirement for renal dialysis in patients receiving SSRI/SNRI (OR: 2.18, 95% CI: 1.06–4.45, $p = 0.03$) and an increased duration of mechanical ventilation postoperatively (OR: 1.69, 95% CI: 1.03–2.78, $p = 0.04$). |

*(Continued)*





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TABLE 8 (Continued)

| Study | Aim | Surgery type | Study type | Patient number | Patient groups | Intervention | Definition of depression | Findings |
|---|---|---|---|---|---|---|---|---|
| Heimisdottir et al. (231) | To assess the effect of SSRI/SNRIs on bleeding following CABG | Primary isolated CABG | Retrospective observational study | $n = 1,237$ | SSRI/SNRIs preoperatively ($n = 97$) Reference group ($n = 1,140$) | Bleeding assessed using 24 h chest tube output, number of packed red blood cells transfused and reoperation for bleeding | Not defined | There was no significant difference in the mean 24-h chest drain output (SSRI/SNRI: 815 mL vs. Control: 877 mL, $p = 0.26$), the number of packed red blood cell transfusions (SSRI/SNRI: 2.2 vs. Control: 2.2, $p = 0.99$) and the re-operative rate (SSRI/SNRI: 4.1% vs. Control: 6.0%, $p = 0.61$). |
| Xiong et al. (232) | To assess the long term outcomes resulting from SSRI use prior to CABG | CABG | Prospective observational study | $n = 4,794$ | SSRIs preoperatively ($n = 246$) No SSRIs ($n = 4,548$) | Morbidity and mortality data was collected between 1999 and 2003 | Not defined | Median follow up time: 3 years Use of SSRIs before CABG was associated with a higher risk of long-term mortality and rehospitalization following surgery (HR: 1.52, 95% CI: 1.30–1.77, $p < 0.0001$) |
| Stenman et al. (233) | To assess the association between preoperative antidepressant use and survival following CABG | Primary, isolated non-emergent CABG | Retrospective observational study | $n = 10,884$ | Anti-depressants pre-operatively ($n = 1,171$) No pre-operative antidepressants ($n = 9,713$) | Morbidity and mortality data collected between 2006 and 2008 using the SWEDHEART registry | Not defined | Preoperative antidepressant use was associated with increased mortality compared to patients without anti-depressants (Adjusted HR: 1.45, 95% CI: 1.18–1.77) following adjustment for diabetes, COPD and left ventricular dysfunction Antidepressant use was also associated with an increased risk of rehospitalization (HR 1.40; 95% CI 1.19–1.65) |

BDI, beck depression inventory; CABG, coronary artery bypass graft; CES-D, center for epidemiological studies of depression scale; HR: hazards ratio, SNRI, serotonin and norepinephrine reuptake inhibitors; SSRI, selective serotonin reuptake inhibitor.





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### 4.3.2. Statins

Statins are predominantly used to manage hypercholesterolemia, a modifiable risk factor which strongly contributes to CHD (236). Mechanistically, statins reduce cholesterol biosynthesis within hepatocytes through competitive inhibition of 3-hydroxy-3-methyl glutaryl- coenzyme A (HMG-CoA) reductase (237). This results in an increased hepatic uptake of cholesterol from the bloodstream, reduced concentration of total cholesterol, and slightly increased concentration of high-density lipoprotein (HDL). Statins have also been associated with a myriad of pleiotropic effects such as anti-inflammatory, anti-sclerotic, antioxidant and anti-depressant activity (238).

The brain is a metabolically demanding and lipophilic organ which is highly susceptible to reactive oxygen species and oxidative stress (239). Statins, particularly atorvastatin, can act as an antioxidant to counteract the imbalance of reactive oxygen species, preventing further neuronal damage (240). Additionally, statins have been demonstrated to regulate glutamate excitotoxicity, another potential contributor to the pathophysiological mechanism of depression (240). Interestingly, the antidepressant effects of statins are also dependent on serotonergic modulation. However, this mechanism is unclear.

Statins may be classified as lipophilic or hydrophilic. Examples of lipophilic statins include atorvastatin, simvastatin and fluvastatin. On the contrary, examples of hydrophilic statins include pravastatin and rosuvastatin (241). Generally, lipophilic statins readily penetrate the blood brain barrier (BBB). Notably, simvastatin can pass through the BBB at least six times more easily compared to atorvastatin. Simvastatin's stronger ability to penetrate the BBB may explain the result of studies where simvastatin was found to protect against the onset of Alzheimer's Dementia compared to other statins such as lovastatin (242). Statins are well tolerated and a safe drug. The common adverse drug reactions (over 1% incidence) include myalgia, gastrointestinal symptoms, sleep disturbances and transient elevations in liver function tests. More significant drug reactions include rhabdomyolysis (particularly if taken with other cytochrome p450 inhibitors), hepatic dysfunction and peripheral neuropathy. There are few drug–drug interactions with statins (222).

#### 4.3.2.1. Anti-inflammatory effect of statins

As previously discussed, depression may result in a pro-inflammatory state, which contributes to CHD. In turn, CHD and cardiac surgery itself is associated with a potentially a deleterious systemic inflammatory response which may contribute to neuroinflammation (101). Studies have demonstrated the anti-inflammatory properties of statins, even in the cardiac surgery population. Statins may indirectly attenuate the pro-inflammatory state through the reduction in LDL cholesterol (243). Chello et al. reported administration of atorvastatin (20 mg daily, n = 20) for 3 weeks in patients undergoing on-pump CABG resulted in significantly lower levels of IL-6 and IL-8 at four, and 24 h postoperatively ($p = 0.02$) compared to placebo ($n = 20$). They also observed a reduction in neutrophil CD18/CD11b expression at 4 h ($p = 0.004$) and 24 h ($p = 0.01$) postoperatively in the atorvastatin group compared to placebo. Chello and colleagues correlated this reduction in pro-inflammatory activity to reduced neutrophil adhesion in the saphenous vein endothelium (244). Similarly, a 2003 study by Chello and colleagues demonstrated an attenuation in neutrophil CD11b and endothelial P-selectin expression in the simvastatin group, compared with non-responders to simvastatin and the control group following on-pump CABG. This study supports the anti-inflammatory role of statins through a nitric oxide-mediated mechanism. Patients received statin therapy for a minimum of 3 months within this study to maximize the bioavailability of nitric oxide, but the average duration of treatment was not specified (245).

Moreover, the use of statins is associated with a reduction in CRP levels (246, 247). In a study comparing the effect of varying doses of atorvastatin (20 mg daily for 5 days, 80 mg for 4 days followed by 40 mg/day for a total of 5 days or no atorvastatin), the highest dose of atorvastatin was associated with a significant reduction in the CRP level (mean ± standard error of the mean). The CRP level in group B was 13,545 ± 959.9 mg/L.h (95% CIL 11,476 mg/L.h – 15,604 mg/L.h), whereas the CRP level in group A was 17,085 ± 858.4 mg/L.h ($p = 0.01$) (248).

#### 4.3.2.2. Efficacy of statins in preventing or reducing depression

Statins should only be used as adjuncts for depression when further evidence regarding their efficacy emerges. From preliminary evidence, statins appear to prevent and improve depressive symptoms in the cardiac surgery population (Table 9). Stafford and Berk demonstrated the use of statin therapy commenced upon discharge was associated with a 79% reduction in the likelihood of developing MDD at 9 months post-operatively (95% CI: 0.052–0.876, $p = 0.032$) (249). Patients were started on either atorvastatin ($n = 114$), simvastatin ($n = 29$) or pravastatin ($n = 14$). The study was limited by an unclear adherence rate to the statins at 9 months. Hence, it is unclear how much the statins contributed to the reduced likelihood of depression. Notably, the patient cohort also consisted of patients who were hospitalized for CABG and percutaneous transluminal angioplasty or myocardial infarction. Despite the inclusion of three different presentations, the authors treated these patients as one homogenous group given evidence suggests CHD is both an etiological and prognostic factor for depression (251). Additionally, Abbasi et al. demonstrated that after 6 weeks, patients receiving simvastatin (20 mg daily) experienced a reduction in depressive symptoms ($p = 0.026$) (250). While the average Hamilton Depression Rating Scale score was lower in the simvastatin group (4.95 ± 3.98) compared to the atorvastatin group (8.56 ± 6.50), there was no significant difference between the groups. Future studies should have a larger sample size to compare simvastatin against placebo, as well confirm the potential superiority of simvastatin to other statins in preventing or managing depression following cardiac surgery.

## 4.4. Alternative models of care

Collaborative Care is an emerging model of healthcare whereby a health professional, most commonly a nurse, acts as a case manager and facilitates communication between the patient and multi-disciplinary team. Based on Wagner's Chronic Care Model, the case manager acts under the supervision of a primary care physician to educate patients about their medical condition, actively listens to their concerns and treatment preferences, offers evidence-based management advice, liaises with the multi-disciplinary team and proactively monitors a patients' response to treatment (252).

TABLE 9 Studies assessing the efficacy of statins in preventing or reducing depression in cardiac surgery patients.

| Study | Aim | Surgery type | Study type | Patient number | Patient groups | Intervention | Definition of depression | Findings |
|---|---|---|---|---|---|---|---|---|
| Stafford and Berk (249) | To determine whether statins are associated with reduced risk of depression in patients who have undergone a cardiac intervention | CABG or angioplasty | Prospective observational study | $n = 193$ | Receiving statins at discharge ($n = 157$)<br>Not receiving statins ($n = 36$) | Patients followed up for total of 9 months. Assessed at 3 months and 9 months using the Mini international neuropsychiatric interview and HADS | HADS ≥8 | Use of statin therapy at discharge was associated with a 79% reduction in the likelihood of developing MDD at 9 months post-operatively (95% CI: 0.052–0.876, $p = 0.032$) |
| Abbasi et al. (250) | To compare the effect of simvastatin and atorvastatin on improving mild to moderate depression in patients who recently underwent CABG in the previous 6 months | CABG | Randomized, double blind, placebo-controlled trial | $n = 46$ | Simvastatin ($n = 23$)<br>Atorvastatin ($n = 23$) | 6 weeks of treatment with either simvastatin (20 mg daily) or atorvastatin (20 mg daily)<br>Patients were followed up at baseline, 3 weeks and 6 weeks | Hamilton depression rating scale used<br>Score for depression not defined | There was a significant reduction in depressive symptoms, as quantified by the HDRS compared to baseline in the simvastatin group ($p = 0.026$) at the final week of the study.<br>However, there was no significant reduction in depressive symptoms upon comparison between groups.<br>Moreover, Kaplan Meier estimation demonstrated a quicker reduction in depressive symptoms in the simvastatin group compared to atorvastatin group ($p = 0.026$) |

CABG, coronary artery bypass graft; HADS, hamilton anxiety and depression scale; HDRS, hamilton depression rating scale; MDD, major depressive disorder.



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The Bypassing the Blues (BtB) trial was an 8 month, RCT funded by the National Institute of Health (US) to assess the potential role of collaborative care in the management of depression following cardiac surgery (253, 254). Patients were allocated to either the usual care group ($n = 152$) or collaborative care group ($n = 150$). Collaborative care patients were contacted by case managers to receive psychoeducation and discuss preferred treatment options. Subsequently, treatment plans were formulated and reviewed by psychiatrists or family physicians. At the 8-month follow up, the proportion of patients with greater than a 50% reduction in depressive symptoms from baseline as measured by the Hamilton Depression Rating Scale were significantly higher in the collaborative care group ($n = 75/150$, 50%) compared to the usual care group ($n = 46/152$, 29.6%, $p < 0.01$). These results highlight the potential for collaborative care to facilitate the management of depression in cardiac surgery patients.

Post-hoc analysis of the BtB trial demonstrated that the benefits of collaborative care were not associated with adjustments in antidepressant medications through the 8-month period ($p = 0.06$) (255). Thus, the benefit of collaborative care is likely to be derived from additional time and rapport built with the care manager, rather than medication alterations. Through a 12-month cost-effectiveness study, collaborative care was associated with a median saving of $2068 US compared to the usual care group (256). However, this did not reach significance ($p = 0.30$). Given the potential healthcare savings and cost-effectiveness of collaborative care, primary care physicians should be involved in these emerging treatment approaches for managing depression following cardiac surgery.

## 5. Future directions

Additional validation studies should be conducted for the commonly used depression questionnaires within the cardiac surgery population. This would allow for the establishment of definitive cut-offs for depression within this population. Further studies should also focus on whether somatic symptoms following cardiac surgery significantly overestimate the severity of depression, and hence whether different questionnaires need to consider this issue. Additionally, given anxiety is highly comorbid with depression, these two mood states should be assessed concurrently rather than separately.

There are limited studies assessing the pathophysiological mechanisms leading to postoperative depression in cardiac surgery patients. Further research into autonomic dysregulation and the mechanism between postoperative depression and cardiac surgery should be explored. Studies assessing HRV and autonomic dysregulation should control for respiratory rate and sinus arrhythmias, given they may affect HRV readings (257). HRV is not routinely collected in clinical practice. Institutions should consider using HRV biofeedback tools to track HRV and aim to normalize vagal outflow. Elevated levels of CRP are associated with postoperative depression and predicts the length of hospital stay. Studies should also assess the levels of other inflammatory markers such as IL-6, TNF-α and their association with postoperative depression. However, little is known about how this inflammatory state translates into postoperative depression. There should be increased examination of HPA dysregulation and the association with postoperative depression in cardiac surgery patients. Metabolic and genomic studies into this area may provide insight into the underlying mechanisms of HPA dysregulation and the association with depression. Studies should assess the concentration of CRH, ACTH and cortisol specifically in cardiac surgery patients to gain a holistic view of HPA axis functioning.

Future studies should assess the ideal duration and format of CBT (i.e., clinic vs. telephone based) to manage depression postoperatively. Given the costs associated with CBT, studies should attempt to identify which postoperative patients should undergo CBT. Very little is known about the mechanism of statins in reducing depressive symptoms, and thus, studies should also compare one statin at a time. For example, one statin should be compared to placebo, or another type of statin. Studies involving pharmacological agents should also include adherence rates, and how long patients were taking the medications for.

## 6. Conclusion

The understanding of the bidirectional relationship between depression and cardiac disease is limited. Depression is associated with several pathophysiological and behavioral factors which increase the likelihood of developing CHD. In addition, these factors may also contribute to postoperative depression. Additional studies are needed to elucidate these possible mechanisms, particularly within the cardiac surgery population who are highly susceptible to postoperative depression and a better understanding of such will further inform future prevention and management strategies.

## Author contributions

TV and JS conceptualized and designed the study. TV collected the data, analyzed the data, and produced the first draft of the manuscript. All authors contributed to subsequent drafts of the manuscript, including editing, and refining of the final manuscript and approved the final version of the manuscript for submission.

## Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

The handling editor MA declared a past co-authorship with the author JS.

## Publisher's note

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## Glossary

| | |
|---|---|
| ADL | Activities of Daily Living |
| ADR | Adverse drug reactions |
| BBB | Blood Brain Barrier |
| BDI | Beck Depression Inventory |
| BtB | Bypassing the Blues |
| CABG | Coronary Artery Bypass Grafting |
| CBT | Cognitive Behavioral Therapy |
| CDS | Cardiac Depression Scale |
| CES-D | Centre for Epidemiological Study of Depression |
| CRH | Corticotrophin Releasing Hormone |
| CRP | C-Reactive Protein |
| CVD | Cardiovascular Disease |
| DSM | Diagnostic Statistical Manual of Mental Disorders |
| HADS-D | Hospital Anxiety, Depression Score – Depression subset |
| HDL | High Density Lipoprotein |
| HMG-CoA | 3-Hydroxy-3-Methyl Glutaryl-Coenzyme A |
| HPA | Hypothalamic Pituitary Adrenal |
| HRV | Heart Rate Variability |
| IDO | Indolamine 2,3-Dioxygenase |
| IFN-γ | Interferon γ |
| IL-6 | Interleukin-6 |
| IL-8 | Interleukin-8 |
| LDL | Low-Density Lipoprotein |
| LF | Low Frequency |
| MACE | Major Adverse Cardiovascular Event |
| MADES | Managing Anxiety and Depression with Education and Skills |
| NMDA | N-methyl-D-aspartate |
| NYHA | New York Heart Association |
| PHQ | Patient Health Questionnaire |
| PTSD | Post Traumatic Stress Disorder |
| RCT | Randomized Controlled Trial |
| rMSSD | Root of Mean Square Difference in the N-N Intervals |
| TAVR | Transcatheter Aortic Valve Replacement |
| TDO | Tryptophan 2,3-Dioxygenase |
| TNF-α | Tumor Necrosis Factor α |
| SAVR | Surgical Aortic Valve Replacement |
| SNRI | Serotonin and Noradrenaline Reuptake Inhibitors |
| SSRI | Selective Serotonin Reuptake Inhibitors |
| SDNN | Standard deviation of mean R-R interval |
| VLF | Very Low Frequency |

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# Impact of relationship status on psychological parameters in adults with congenital heart disease

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**Objective:** Adult congenital heart disease (ACHD) is a growing disease entity, posing questions concerning psychosocial outcomes across the lifespan. Spousal relationships were shown to benefit cardiovascular and mental health in the general population. We assessed the association of relationship status with anxiety and depression in ACHD patients and determined whether patients considered disease-related concerns potential mediators of relationship problems.

**Methods:** *N* = 390 ACHD patients were included. Self-report questionnaires were used to assess relationship status, ACHD-related relationship problems, socio-demographic variables, and depression and anxiety scores. Further, clinical parameters concerning the heart condition were determined.

**Results:** *N* = 278 (71%) patients were currently in a relationship, while *N* = 112 (29%) were not in a relationship. Groups did not significantly differ regarding age, sex, and cardiovascular parameters. Two-way MANCOVA with relationship status and sex as independent variables, controlling for age, NYHA class, and NT-proBNP, showed an association of relationship status with depression, while sex was associated with anxiety. *N* = 97 (25%) patients reported disease-related adverse effects on a current or prior relationship. In detail, worries about body image (*N* = 57, 61%), own fears (*N* = 51, 54%), problems arising from wish to have children (*N* = 33, 35%), fears regarding a joint future (*N* = 29, 31%), partner's fears or lack of understanding (*N* = 28, 30%), and sexual problems (*N* = 21, 22%) were cited.

**Conclusion:** Relationships status was associated with depression, while sex was associated with anxiety in ACHD patients. Relationship status as well as potential relationship problems, and the importance of social support for mental and physical well-being, should be considered when treating ACHD patients.

KEYWORDS

**adult congenital heart disease, depression, anxiety, relationship status, cardiovascular disease**

## 1 Introduction

With a reported prevalence of 0.9–1% of live birth worldwide, congenital heart disease (CHD) represents the most commonly diagnosed congenital malformation in newborns (1, 2). With recent innovations in early diagnostic, interventional, and surgical procedures, the number of CHD patients that survive childhood and adolescence is steadily increasing. With up to 90% of patients reaching adulthood, factors that impact long-term cardiovascular

disease (CVD) risk become increasingly important in patients with adult CHD (ACHD) (3, 4). In this regard, a current meta-analysis that assessed CVD risk of CHD survivors in later life found an increased risk for overall CVD, albeit the study was unable to pinpoint whether CHD constituted an independent risk factor or whether the association was confounded by a CVD risk factor profile among ACHD patients (5).

Next, to the increased CVD risk, ACHD patients display a significantly higher prevalence of psychiatric disorders when compared to the general population, with mood- and anxiety disorders being the most frequent (6–8). As psychiatric disorders are in turn associated with a heightened risk for CVD in the general population and symptomatic depression and anxiety are associated with adverse outcome measures, including rehospitalization and mortality, in patients with established CVD (9, 10), it is of clinical importance to identify modifiable factors that might negatively impact mental well-being in ACHD patients.

Various studies have evaluated the impact of (marital) relationship status on CV parameters and CVD risk in the general population. A twin study conducted in Sweden showed that living alone was associated with an increased CVD risk (11). Similar findings were reported in other countries and cultural regions (12). This association is further supported by a recent meta-analysis, which concluded that individuals that were not in a relationship had a higher CVD risk compared to married individuals (13). Next to the association with CVD risk, relationship status has also been shown to be associated with the outcome following a cardiac event, as individuals that lived alone were found to have an increased risk for all-cause mortality, CVD death, and myocardial infarction compared to individuals that lived in a marital relationship (14). While data regarding underlying mechanisms are limited, social support received from the partner is thought to reduce psychosocial stress and to thereby play an important role in mediating the beneficial effect of spousal relationships (15). Additionally, individuals in a relationship are thought to seek healthcare earlier and more often, to show better adherence to prescribed treatment, and to be more susceptible to healthier lifestyle behaviors (15).

Next, to CV parameters, relationship status has been associated with mental health measures. In this regard, spousal relationships have been described to be associated with protection from depression and anxiety in the general population (16, 17).

While research regarding relationship status in the context of ACHD is currently limited, a study assessing quality of life (QOL) in ACHD patients showed that next to older age, lack of employment, and higher New York Heart Association (NYHA) functional class, no marriage history was associated with lower QOL (18). Furthermore, feeling of loneliness was found as a common predictor of depression and anxiety in patients with ACHD (7).

As ACHD has been associated with an increased risk for CVD as well as for mood and anxiety disorders (5–8) and relationship status has been found to impact CV parameters and CVD risk as well as mental well-being in the general population (13), relationship status presents a relevant issue in the growing population of ACHD patients. Nevertheless, the association of relationship status with depression and anxiety has not been previously examined in ACHD patients and disease-related factors that might affect relationship quality and thereby stability of a spousal relationship have not been previously assessed.

Therefore, we examined relationship status and its impact on symptoms of anxiety and depression in a sample of ACHD patients. Additionally, we describe frequency and characteristics of disease-related relationship problems in these patients.

# 2 Materials and methods

## 2.1 Subjects

The presented data were generated as part of the ongoing PSYConHEART study that aims to establish morbidity and mortality factors in ACHD patients (19–22). Data collection took place from August 2020 to February 2021 at the outpatient clinic of the Department of Cardiology at Hannover Medical School. The study was conducted in accordance to the ethical guidelines of the 1975 Declaration of Helsinki and ethical approval was obtained from the local ethics committee at Hannover Medical School. All participants gave their written informed consent before entering the study. Inclusion criteria were a structural CHD, the ability to read and agree to the consent form and to read and answer the German versions of the relevant questionnaires, and an age $\geq$ 18 years. Exclusion criteria were pregnancy and instability of the cardiac condition. For our analyses that focused on the effect of spousal relationships, we considered respective literature that indicates that the main source for social support in adults are spousal relationships while in adolescents parental support was found to be the most important with regards to parameters of mental well-being (23). As data from the German Federal Statistical Office indicate a mean age of 23.6 years for young adults to leave their parental home in Germany in 2021 (24) we only included patients with an age $\geq$ 25 years in the analyses.

Data from $N = 575$ patients were obtained. After exclusion of cases with an age < 25 years, and cases that were missing data regarding relationship status, NYHA class, NT-proBNP, and/or hospital anxiety and depression scale (HADS) score. $N = 390$ cases were included in the study sample. Supplementary Figure 1 shows the sample selection process.

## 2.2 Cardiovascular evaluation

A senior cardiologist examined all patients included in the study during their routine check-up. The functional status of patients was determined by use of NYHA class. Cardiac morphology and function, including LVEF, were assessed by echocardiography. To classify the complexity of the underlying heart condition, the Bethesda scale was used to divide the congenital defect into "simple," "moderate," or "complex" (25). Additionally, number of thoracotomies was documented.

## 2.3 Assessment of psychosocial status

All participants answered a demographic survey that included relationship status (defined as an intimate spousal relationship that was marriage-like). Symptoms of depression and anxiety were assessed using the HADS, with the anxiety (HADS-A) and the depression (HADS-D) subscores being used (26). Additionally, patients were

TABLE 1 Comparison of sociodemographic variables and CV measures in ACHD patients based on current relationship status.

| | Current relationship | | | |
|---|---|---|---|---|
| | No ($N = 112$) | Yes ($N = 278$) | Statistics | Value of $p$ |
| Age (years) | 38.8 ± 11.6 | 40.3 ± 11.0 | $U = 13892.5$, $Z = -1.664$ | $p = 0.096$ |
| Female sex ($N$ [%]) | 45 (40%) | 141 (51%) | $\chi^2(1) = 3.556$, $\varphi = 0.095$ | $p = 0.059$ |
| Number of thoracotomies | 1.6 ± 1.3 | 1.4 ± 1.1 | $U = 14645.0$, $Z = -0.793$ | $p = 0.428$ |
| Bethesda scale | | | $\chi^2(2) = 3.737$, $\varphi = 0.098$ | $p = 0.154$ |
| Bethesda I ($N$ [%]) | 9 (8%) | 28 (10%) | | |
| Bethesda II ($N$ [%]) | 29 (26%) | 96 (35%) | | |
| Bethesda III ($N$ [%]) | 73 (65%) | 152 (55%) | | |
| NYHA classification | | | $\chi^2(3) = 0.833$, $\varphi = 0.046$ | $p = 0.841$ |
| NYHA I ($N$ [%]) | 75 (67%) | 194 (70%) | | |
| NYHA II ($N$ [%]) | 27 (24%) | 65 (23%) | | |
| NYHA III ($N$ [%]) | 9 (8%) | 18 (7%) | | |
| NYHA IV ($N$ [%]) | 1 (0.9%) | 1 (0.4%) | | |
| LVEF (%) | 54.8 ± 10.3 | 56.3 ± 8.6 | $U = 11625.0$, $Z = -1.133$ | $p = 0.257$ |
| NT-proBNP (ng/L) | 252.5 ± 322.3 | 295.4 ± 444.8 | $U = 14,965,0$, $Z = -0.599$ | $p = 0.549$ |
| Psychotropic drug ($N$ [%]) | 6 (5%) | 15 (5%) | $\chi^2(1) = 0.000$, $\varphi = 0.000$ | $p = 0.997$ |

If not indicated otherwise mean ± standard deviation (SD) is depicted and asymptotic two-tailed $p$-values are shown. $p \leq 0.05$ was considered statistically significant. LVEF, left ventricular ejection fraction; NYHA class, New York Heart Association Functional classification, NT-proBNP, N-terminal pro b-type natriuretic peptide.

asked whether their heart defect had ever negatively impacted their relationship and to determine potential underlying issues, participants were asked to check either "yes" or "no" to the following suggested reasons: (1) negative body image, (2) own fears, (3) problems arising from wish to have children, (4) fears regarding a joint future, (5) fear or lack of understanding by the partner, and (6) sexual problems.

## 2.4 Statistical analyses

All statistical analyses were performed in SPSS 28 (IBM, Armonk, NY, United States). Shapiro Wilk Test was used for assessment of normality of data distribution. For group comparisons regarding anthropometric- and demographic data and CV parameters based on relationship status, non-parametric Mann–Whitney $U$-Test was used. Chi square test was performed for group comparisons of nominal data. To assess the association of relationship status and sex with depression and anxiety scores, two-way multivariate analysis of covariance (MANCOVA) was performed; HADS-D score and HADS-A score were imputed as dependent variables, relationship status and sex as independent variables, and age, NYHA class, and NT-proBNP as covariates. Sex was included as an independent variable based on dedicated literature that suggests distinct effects of relationship status on mental wellbeing in men and women in the general population (16). The respective covariates were included as prior studies reported conflicting results with regard to a potential association of disease severity and prognosis on psychological distress in ACHD patients (7, 27), and additionally an association of age, relationship status, and depression has previously been reported based on data from the general population (16). Two-tailed $p$-values are depicted and $p \leq 0.050$ was considered statistically significant.

# 3 Results

## 3.1 Relationship status, and sociodemographic variables, and CV measures

An overview regarding sociodemographic factors and cardiac parameters of the study sample is provided in the Supplementary Results. Table 1 compares sociodemographic variables and CV measures in patients that reported to be currently in a relationship ($N = 278$ [71%]) to those that reported to be not in a relationship ($N = 112$ [29%]). Both groups did not significantly differ in any of the reported parameters.

## 3.2 Association of relationship status and sex with depression and anxiety scores

Based on research indicating sex-specific effects of relationship status and social support on mental well-being (16), we assessed the association of relationship status and sex with HADS-D and HADS-A scores using two-way MANCOVA. To account for potential effects of age and disease severity, age, NYHA class, and NT-proBNP were included as covariates (7, 27). Two-way MANCOVA showed a statistically significant difference between relationship groups on the combined dependent variables [$F(2, 382) = 4.352$, $p = 0.014$, Wilk's $\Lambda = 0.978$]. Additionally, sex had a statistically significant effect on the combined term [$F(2, 382) = 4.371$, $p = 0.013$, Wilk's $\Lambda = 0.978$], while no significant interaction effect was found [$F(2, 382) = 1.217$, $p = 0.297$, Wilk's $\Lambda = 0.994$]. *Post hoc* univariate ANCOVAs were conducted for both dependent variables. Results show a statistically significant difference between relationship groups for HADS-D scores [$F(1,$

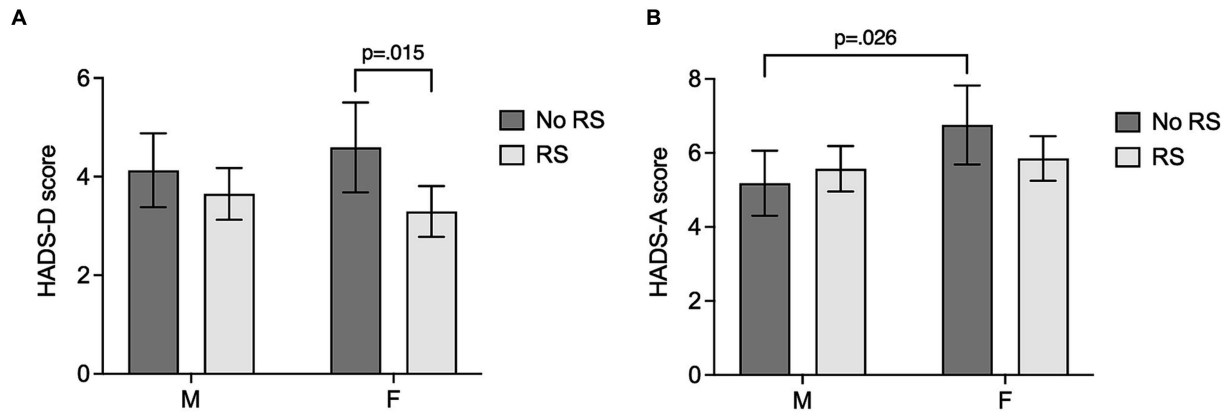


FIGURE 1
Depression and anxiety scores in ACHD patients in relation to relationship status and sex. Bar graphs depict estimated marginal means and 95% confidence intervals (calculated with age = 39.85, NYHA class = 1.39, and NT-proBNP = 283.12) of depressive symptoms measured by HADS-D score **(A)**, and anxiety symptoms indicated by HADS-A score **(B)**, dependent on relationship problems (No RS: no current relationship; RS: current relationship) and sex (M: male; F: female). Bonferroni-corrected two-tailed *p*-values for statistically significant pairwise group comparisons are depicted. $p \leq 0.050$ was considered statistically significant.

383) = 6.330, $p = 0.012$, $\eta^2 = 0.016$], while no significant difference for HADS-A score was found [$F(1, 383) = 0.383$, $p = 0.537$, $\eta^2 = 0.001$]. Contrarily, a statistically significant difference between sexes was found for HADS-A scores [$F(1, 383) = 5.020$, $p = 0.026$, $\eta^2 = 0.013$], while HADS-D scores did not significantly differ [$F(1, 383) = 0.022$, $p = 0.882$, $\eta^2 < 0.001$]. Pairwise comparisons based on estimated marginal means using Bonferroni-corrected *post hoc* test showed a significant difference of HADS-D scores based on relationship status only in women ($p = 0.015$, $M_{Diff} = 1.30$, 95%-CI [0.255, 2.345]) but not in men ($p = 0.308$, $M_{Diff} = 0.478$, 95%-CI [−0.442, 1.398]). Additionally, increased anxiety scores in women compared to men were only observed in the no relationship group ($p = 0.026$, $M_{Diff} = 1.575$, 95%-CI [0.192, 2.957]), but not in the relationship group ($p = 0.527$, $M_{Diff} = 0.279$, 95% -CI [−0.586, 1.144]). Results are visualized in Figures 1A,B.

## 3.3 ACHD-related relationship problems

Given the observed protective effect of a spousal relationship on depressive symptomology in our sample, we assessed whether the underlying heart defect could have potential, adverse effects on a patient's relationship. When asked, $N = 97$ (25%) of all ACHD patients in our sample reported that their heart disease had ever negatively impacted their relationship or prevented them from committing to a relationship, while $N = 292$ (75%) of patients reported no prior or current negative effect. Table 2 summarizes sociodemographic variables and CV measures of patients that had ever experienced a disease-associated adverse impact on their relationship compared to those who reported no previous or current impact. Patients that reported an adverse impact of their disease on their relationship did not significantly differ from those that were not affected with regard to current relationship status, age, or sex. However, patients that reported an adverse impact on their relationship presented with a higher disease severity indicated by a more complex underlying heart defect based on Bethesda class, a higher number of thoracotomies, a higher NYHA class and decreased LVEF. Additionally, patients that reported disease-related relationship problems had a prescription for at least one psychotropic drug more frequently.

## 3.4 Reasons for ACHD-related relationship problems

To determine potential underlying reasons for disease-related relationship problems, patients were asked to answer "yes" or "no" to six suggested potential reasons as detailed in section 2.5. $N = 94/97$ patients that had report prior or current disease-related adverse effects on their relationship completed the respective questionnaire. Patients that reported problems in their relationship indicated underlying reasons with the following frequencies: negative body image ($N = 57$ [61%]), own fears ($N = 51$ [54%]), problems arising from wish to have children ($N = 33$ [35%]), fears regarding a joint future ($N = 29$ [31%]), fear or lack of understanding by the partner ($N = 28$ [30%]), and sexual problems [$N = 21$ (22%)]. $N = 29$ (31%) patients cited only one of these reasons to be applicable, however, most patients reported more than one reason for their relationship problems ($N = 64$ [68%]) (Supplementary Figure 2).

# 4 Discussion

One main result of our study is the finding that patients without a current relationship reported higher depression scores. Additionally, woman that were not in a current relationship also reported higher anxiety scores compared to men without a current relationship.

The second main finding of our study is that one fourth of patients in the present sample reported a negative impact of their CHD on a prior or current relationship. These patients were characterized by a more complex underlying heart condition and a more severe heart disease.

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TABLE 2 Comparison of sociodemographic variables and CV measures in ACHD patients based on reported disease-related relationship problems.

| | Adverse impact on relationship | | | |
|---|---|---|---|---|
| | No (*N* = 292) | Yes (*N* = 97) | Statistics | *p*-value |
| Age (years) | 40.4 ± 11.8 | 38.3 ± 9.2 | $U = 13157.0$, $Z = -1.048$ | $p = 0.295$ |
| Female sex (*N* [%]) | 134 (46%) | 51 (53%) | $\chi^2(1) = 1.305$, $\varphi = 0.058$ | $p = 0.253$ |
| Number of thoracotomies | 1.4 ± 1.1 | 1.7 ± 1.3 | $U = 11611.5$, $Z = -2.554$ | $p = 0.011$ |
| Bethesda scale | | | $\chi^2(2) = 13.979$, $\varphi = 0.190$ | $p < 0.001$ |
| Bethesda I (*N* [%]) | 28 (10%) | 9 (9%) | | |
| Bethesda II (*N* [%]) | 108 (37%) | 17 (18%) | | |
| Bethesda III (*N* [%]) | 153 (53%) | 71 (73%) | | |
| NYHA classification | | | $\chi^2(3) = 13.744$, $\varphi = 0.188$ | $p = 0.003$ |
| NYHA I (*N* [%]) | 215 (74%) | 53 (55%) | | |
| NYHA II (*N* [%]) | 61 (21%) | 31 (32%) | | |
| NYHA III (*N* [%]) | 15 (5%) | 12 (12%) | | |
| NYHA IV (*N* [%]) | 1 (0.3%) | 1 (1%) | | |
| LVEF (%) | 56.3 ± 9.2 | 54.3 ± 8.8 | $U = 9301.5$, $Z = -2.360$ | $p = 0.018$ |
| NT-proBNP (ng/L) | 271.2 ± 416.0 | 320.1 ± 407.4 | $U = 12,810,5$, $Z = -1.409$ | $p = 0.159$ |
| Psychotropic drug (*N* [%]) | 9 (3%) | 12 (12%) | $\chi^2(1) = 12.234$, $\varphi = 0.178$ | $p < 0.001$ |

If not indicated otherwise mean ± standard deviation (SD) is depicted and asymptotic two-tailed p-values are shown. $p \leq 0.05$ was considered statistically significant. LVEF, left ventricular ejection fraction; NYHA class, New York Heart Association Functional classification, NT-proBNP, N-terminal pro b-type natriuretic peptide.

Our data indicate that patients with ACHD may benefit from a spousal relationship. In particular, our results suggest a greater benefit of being in a spousal relationship for women compared to men. In this regard, *post hoc* groupwise comparisons showed significant effects of relationship status on depression scores only in women but not in men and additionally, higher anxiety scores were detected in women that were not in a relationship compared to men with the same relationship status, while no effect of sex on anxiety scores was found in the relationship group.

While survival rates in patients have increased significantly over the last decades, ACHD patients with a moderate or complex underlying heart defect are often not cured and are confronted with medical complications and a shortened life expectancy (28–30). This might be associated with additional psychosocial challenges, which is reflected by the high frequency of depression and anxiety disorders in this patient population (6–8). In this regard, a study Kovacs and colleagues found that 50% of ACHD patients in the respective sample fulfilled criteria for at least one lifetime mood or anxiety disorder (7). Similarly, a prior study by our group found a prevalence of any mood disorder of 31% and of any anxiety disorder of 28% based on structured clinical interview in accordance to DSM-IV criteria (6). Therefore, the identification of factors that might protect from mood and anxiety symptoms is of importance.

Beneficial effects of spousal relationships on mental and on physical well-being have frequently been reported in the literature (31, 32). With regard to depression and depressive symptoms, various studies have found beneficial effects of marital relationships in the general population (16). An important factor that appears to confer beneficial effects of spousal relationships on protection from depression is perceived social support (23, 33). Perceived social support constitutes a subjective perspective of how individuals perceive the availability of material, psychological, and overall support offered by others (34). Perceived social support correlates well with various measures of mental health (35, 36). Of importance, social support is also characterized by the individuals that provide the support. In this regard, it is assumed that protective effects of social support vary depending on the provider, i.e., a spouse, relatives, or friends (23). A dedicated meta-analysis that reported on the association between social support and protection from depression found the strongest evidence for spousal support as a protective factor from depression in the adult population and especially emotional support was consistently found to be a protective factor (23).

Previous studies have found that ACHD patients experience mental health disorders, including depression and anxiety, with a higher prevalence than the general population (6–8). A study by Kovacs and colleagues found potential predictors for symptoms of depression and anxiety in these patients to be limited to feelings of loneliness and fear of negative evaluation as factors of social functioning, disease severity or functional class were not predictive (7). Contrarily, a recent publication reported a positive association of NYHA class and psychological distress (27). Our results are in line with the study by Kovacs et al. as no significant association of either NYHA class or NT-proBNP that were included as potential confounders in the MANCOVA, on HADS-D scores were detected in the present sample. While the impact of relationship status on depression and anxiety has not been previously evaluated in ACHD patients, prior studies have assessed relationship status in the context of quality of life in this patient population. Importantly, quality of life has been found to be significantly associated with anxiety and depression in ACHD patients (6). Previous studies have reported heterogenous effects regarding an association of marital relationship with QOL in patients with ACHD, with some studies reporting a significant association (18, 37, 38) while others failed to detect a significant effect (39). In line with our findings, a prior study reported that parameters of subjective functional status were only associated with the physical but not with the psychological domain of quality of

life, while family support and psychological distress were common denominators for most quality of life domains including the psychological domain (40).

Of note, our data suggest greater effects of relationship status on depressive symptoms in women with ACHD compared to male patients. This is in contrast to data from the general population that suggest a greater benefit from marital relationships for men when compared to women. A study conducted with data from a series of cross-sectional national health surveys in Canada found modifying effects of age and sex on the relationship of marital status and depression (16). In this study, women that were single, widowed, or divorced were found to be less vulnerable to depression than men (16). The authors hypothesized that women more frequently utilize larger and stronger networks of social support while men often appear to rely on spousal support (16). However, this might not be the case in patients with CVD, as data from patients post acute myocardial infarction suggest that women experience lower levels of social support compared to men (41). Additionally, our results are in line with findings from Chen and colleagues that assessed determinants of quality of life in ACHD patients. The authors found sex-specific differences in the psychological domain of quality of life, which could be attributed to underlying psychosocial factors (40). Whether the observed sex-differences regarding the association of relationship status on protection from depressive symptoms are a specific feature of ACHD patients or whether other factors not investigated in our sample, including relationship satisfaction and the quality of social support by the spouse as well as other sources of social support, contribute to the observed effect will be subject of follow-up studies.

Overall, our findings expand data from previous studies that found that being in a (marital) relationship was associated with higher levels of psychological well-being, indicated by lower rates of depression and substance abuse in the general population as well as in patients that suffer from mental health problems, to ACHD patients (42).

In our sample, 71% of ACHD patients reported to be currently in a spousal relationship, which is comparable to a study from the Netherlands that reported 69% of patients to be in a spousal relationship (43). In that study, the rate of individuals in a relationship was significantly lower in the ACHD group than that observed in the respective control sample, in which relationship rate was 89% (43).

Given the association of relationship status and depressive symptomology in ACHD patients, and considering findings by others that commonly reported an effect of relationship quality, i.e., marriage dissatisfaction or conflict, on cardiovascular parameters, CVD risk, and mental well-being (15, 44, 45), it is of importance to identify potential disease-related problems that ACHD patients might experience with regard to their spousal relationship.

Our data show that one fourth of the ACHD patients in our sample reported that their disease had previously negatively impacted their relationship and those patients were characterized by a more complex underlying heart condition and a more severe heart disease.

When asked for reasons underlying their perceived relationship problems, most patients cited one of the suggested reasons. However, more than half of the patients cited more than one reason. Contrarily, to the finding that disease-related relationship problems were more frequent in patients with a more severe underlying heart disease, the frequency with which the different suggested reasons for these perceived problems were cited did not depend on disease severity. Additionally, the respective reasons were cited with similar frequencies by male and female patients, with the exception of "problems arising from wish to have children" that was reported significantly more often by women (data not shown).

Overall, our data suggest protective effects of being in a spousal relationship on depressive symptoms in patients with ACHD. In light of literature that reports that ACHD patients are in spousal relationships at a lower rate than the general population (43), it appears of importance to identify factors, including those associated with the underlying cardiac defect, that might adversely affect relationship quality and stability. Our data show that a considerable percentage of patients has previously found their heart disease to adversely impact their relationship or prevented them from entering a relationship. Most patients cited at least one disease-related reason that could be attributed to the patient. Therefore, it might be considered to address relationship status as well as potential relationship problems, and the importance of social support for mental and physical well-being, when treating patients with ACHD.

## 4.1 Limitations

Our study has several limitations that should be considered. We only present cross-sectional data, which does not allow for temporal or causal inference. We did not assess whether patients that were not in a relationship were single, separated, or widowed. Therefore, we did not investigate any potential differences in these subgroups with regards to depression and anxiety scores, which is of importance, as literature suggests distinct effects on depression scores (16). Additionally, data regarding quality of social support by the spouse, as well as other sources of social support were not assessed in our sample. Finally, we did not assess current relationship quality, which could have impacted depression scores as literature suggests adverse effects of relationship conflict or dissatisfaction on mental health parameters (46–48).

# Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

# Ethics statement

The studies involving humans were approved by the local Ethics Committee at Hannover Medical School. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

# Author contributions

BS: Formal analysis, Visualization, Writing – original draft. NS: Formal analysis, Writing – original draft. TH: Investigation, Writing – review & editing. SA: Investigation, Writing – review & editing. IH: Formal analysis, Writing – review & editing. MW-B:

Conceptualization, Formal analysis, Project administration, Supervision, Writing – review & editing. KK: Conceptualization, Formal analysis, Project administration, Supervision, Writing – review & editing.

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## Conflict of interest

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The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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## Publisher's note



## Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2023.1260664/full#supplementary-material

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# Does coping style mediate the relationship between knowledge and psychosocial outcomes in women with atrial fibrillation?

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**Introduction:** In patients affected by atrial fibrillation (AF) disease-specific knowledge and coping style may be associated with psychosocial well-being. This study aimed to determine if coping style (problem-focused, emotion-focused, avoidance-focused) mediated the relationship between patient knowledge and three psychosocial outcomes (anxiety, depression and life satisfaction).

**Methods:** In 2021 a total of 188 women with reported AF, and ages ranging from 18 to 83 years (mean 48.7, sd 15.5 years), completed an online questionnaire consisting of sociodemographic, clinical and AF knowledge questions and psychosocial instruments (Anxiety and depression, the Hospital Anxiety and Depression (HADS) scale; life satisfaction, Satisfaction With Life Scale (SWLS); and coping style (Brief COPE). Using Jamovi statistical software three individual mediational models (for anxiety, depression and life satisfaction) were constructed assessing the direct and indirect relationships between knowledge, coping style and each psychosocial outcome. Age was a covariate in each model.

**Results:** The mediation analyses demonstrated significant direct negative associations between AF knowledge and HADS anxiety and depression and positive associations with SWLS. There were also direct associations between each of the three coping styles and the three psychosocial outcomes. There were significant indirect effects of coping style between AF knowledge and each of the three outcomes confirming partial mediation effects.

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**Discussion:** These findings highlight the crucial role of coping style in mediating the association between AF knowledge and psychosocial outcomes. As such, interventions aimed at increasing patient knowledge of AF may be more effective if adaptive problem-solving coping strategies are also demonstrated to these patients. Additionally, modification of maladaptive coping strategies as part of the psychological management of patients with AF is highly recommended.

KEYWORDS

atrial fibrillation, knowledge, coping, anxiety, depression, life satisfaction, mediation

## Introduction

Atrial fibrillation (AF) is the most common type of cardiac arrhythmia, affecting one in every four individuals at some point in their life (1). Cardiac arrhythmia refers to irregular heart rhythm and is caused by structural and electrical remodelling of the left atrium (2). The severity of AF ranges from brief paroxysmal episodes of electrical disturbance that terminate spontaneously within 48 hours to more regular episodes that last more than a week, and at the upper end of severity, into a permeant ongoing AF that causes cardiac remodelling, structural and electrophysiological remodelling of the tissue that provides substrates for maintenance of such arrhythmias, and functional impairment (3, 4). AF is a serious public health concern with an estimated prevalence of 5.35% in Australian adults over 55 years old (5). This is estimated to increase by 1.04% in the overall population aged >55 years by 2034 (5). In Scotland, Germany, and the USA, subjects aged 65 years or older show an AF incidence of 4.7, 4.1, and 28.3 per 1,000 person/years, respectively (6). Aside from age, 50% of AF cases can be explained by underlying risk factors that result in structural remodelling of the myocardium, including medical, demographic, psychological, behavioural, and social factors (2).

Both anxiety and depression play a central role in the onset and development of AF. Several prospective population-based studies demonstrate that anxiety (7) and depression (8–11) increase the risk of developing AF. Pre-operative anxiety has also been implicated in the onset of AF after coronary artery bypass graft surgery (12). Consistently, cross-sectional population studies demonstrate that the prevalence of AF increases with higher levels of perceived stress (13) and more traumatic life events (14).

Both anxiety and depression are also common consequences of AF. Rates of anxiety and depression reported in AF samples are significantly higher than seen in the general population (15–17). Anxiety has been consistently reported at around 30-35%, while depression rates vary substantially, between 20-45% (15–17). Evidence suggest that AF symptom severity co-occurs with increased levels of anxiety (13, 15, 18) and depression (15, 19, 20).

Given the strong association between AF and mental health, attention needs to be given to managing psychological wellbeing in AF patients. The 2020 European Society of Cardiology (ESC) Guidelines for the Diagnosis and Management of Atrial Fibrillation (21) highlight the importance of measuring the psychological consequences of AF such as anxiety, depression and quality of life. Consistently, an international consortium of AF patients and healthcare professionals has identified patient reported outcomes such as quality of life and emotional functioning as important measures in AF (22). Importantly, evidence from cross-sectional and longitudinal studies highlight that the associations between incident AF and poor psychosocial outcomes are particularly evident for women (16, 23–25).

Psychosocial outcomes are also dependent upon patients' level of disease-specific knowledge. Evidence suggests that greater knowledge of the disease and its management can reduce uncertainty and alleviate anxiety (26). Patients' lack of knowledge about AF causes, symptoms and treatments, particularly at the time of diagnosis when the majority of treatment decisions are discussed and made (21), has been identified as a key barrier to therapy uptake and adherence (27, 28). In a study on the educational needs of people living with AF, clinicians indicated that patients' lack of understanding of AF treatments can contribute to anxiety, stress, and worry about the long-term impacts of medication management (29). While one study has shown that women with AF have less knowledge than men about AF detection, treatment and impacts (30), another found that women have better symptom knowledge than men (31).

Coping style has also been shown to influence psychological wellbeing. Adaptive coping is directed at managing or altering the problem causing the distress (problem-focused coping) whereas maladapting coping is directed at regulating the emotional response to the problem (emotion-focused coping) or avoiding the problem (avoidant coping) (32, 33). In studies of people with diabetes, cancer and endometriosis, greater engagement in maladaptive coping is associated with higher anxiety and depression, and poorer quality of life, whereas greater engagement in adaptive coping is associated with positive psychological outcomes (34–37).

Thus, both AF knowledge and coping style are likely to have a significant impact on how AF patients experience anxiety and process behavioural responses, which may ultimately affect their

quality of life. However, the mediational effects of coping style on the relationship between AF knowledge and psychosocial outcomes in women with AF remain unknown. Thus, the present study aimed to investigate the role of coping style in mediating the relationship between AF knowledge and anxiety, depression and life satisfaction in women with AF.

The specific hypotheses for this study were:

a) There will be significant associations between level of AF knowledge and the three psychosocial outcomes (negative for anxiety and depression, positive for life satisfaction).

b) Adaptive coping (problem-solving coping style) will be directly associated with the three psychosocial outcomes (negative for anxiety and depression, positive for life satisfaction).

c) Maladaptive coping (emotion-focused and avoidant coping styles) will also be directly associated with the three psychosocial outcomes, but in the opposite direction (positive for anxiety and depression, negative for life satisfaction).

d) Given that coping style may interact with level of knowledge and may also be directly associated with the outcomes, there will be significant indirect effects of the three coping styles mediating the relationship between AF knowledge and the three psychosocial outcomes.

# Methods

## Participants and procedures

This study was granted ethical approval through Federation University Research Ethics Committee (approval A21-056). Participants were recruited through advertisements on social media posts and forums, such as Facebook, Reddit, Survey Circle, and Instagram. These advertisements invited potential participants to take part in a confidential and anonymous online survey hosted on Qualtrics that could be accessed through the poster's hyperlink, weblink and QR code. Inclusion criteria stated that participants were required to be over 18 years of age, female, and Australian residents.

## Measures

The online questionnaire comprised sociodemographic questions, psychosocial measures (anxiety depression, and life satisfaction), self-rated knowledge of AF and coping style.

### Sociodemographic variables

Participants were asked to indicate their age, marital/partner status and education level, as well as weight (kg) and height (m) which was used to calculate Body Mass Index (BMI=kg/m2)).

### Anxiety and depression

Anxiety and depression symptoms were assessed using the Hospital Anxiety and Depression rating scale (HADS) (38). The HADS measures symptoms of anxiety (HADS-A; 7 items) and depression (HADS-D; 7 items). Items are rated on a 4-point (0–3) scale with higher scores indicating higher levels of symptoms. Scores range from 0 to 21 and are categorized as normal (0–7), mild (8–10), moderate (11–14), or severe (15–21), with scores >7 indicative of clinically-significant symptoms. The HADS has shown good internal consistency and good concurrent, criterion, and factorial validity with CVD patients (39) and has been used previously with atrial fibrillation patients (40, 41).

### Life satisfaction

The Satisfaction With Life Scale (SWLS) scale is a 5-item self-report questionnaire scored on a 35-point scale to measure sense of life satisfaction (42, 43). The SWLS has good internal consistency and excellent concurrent validity with other measures of wellbeing (44) and has been previously used to assess life satisfaction in CVD patients (45, 46).

### Knowledge of atrial fibrillation

Self-rated knowledge of AF was assessed using the following question specifically developed for this study: *"The following question is to get an understanding of how much you know about your condition. Let us know where you place yourself based on your knowledge on Atrial Fibrillation. How well is your understanding of Atrial Fibrillation?"* Responses were measured on a Likert-type scale ranging from 1 (no understanding) through to 5 (Excellent understanding).

### Coping style

Coping style was assessed using the Brief COPE scale which comprises 28 items rated on a four-point Likert scale, ranging from 1 = I usually don't do this at all, to 4 = I usually do this a lot. A total of 13 coping strategies are categorized into three main coping styles: problem-focused coping (active coping, instrumental support, positive reframing, and planning), emotion-focused coping (emotional support, venting, humour, acceptance, religion, and self-blame), and avoidant coping (self-distraction, denial, substance use, and behavioural disengagement) (47). Good internal consistency for the subscales have been reported in patients following an acute coronary syndrome (48) with the scale having been used previously with AF patients (49).

## Data analysis

After standardization, all variables were assessed for normality and kurtosis. Correlational analyses were undertaken to compare the relationship between standardized study variables. Three parallel process mediation models were run respectively using the outcomes SWLS, HADS-A and HADS-D continuous total scores (Y) (see Figure 1). The independent variable for each model was knowledge of AF (X) with age (years) included as a covariate. The

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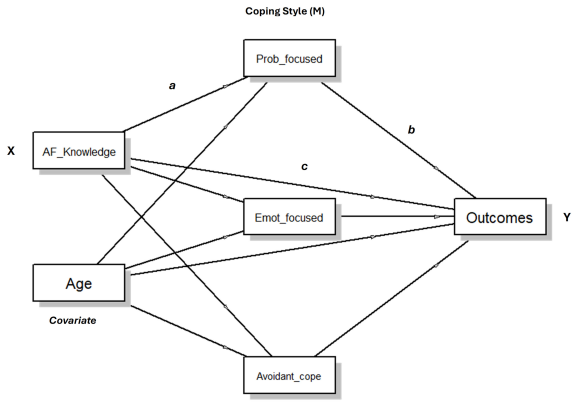


FIGURE 1
Conceptual model for the process mediation analyses.

proposed mediational variables (M) were the three main styles of coping (problem-focused, emotion-focused and avoidant coping). The proposed direct (c) and indirect effects (ab=a * b) were examined by estimating bias-corrected standardized regression coefficients (betas) using bootstrap analysis (5,000 bootstrap samples) as suggested by Biesanz, Falk, and Savalei (50). Since obesity is associated with occurrence of both atrial fibrillation (51–54) and poorer psychosocial indicators (55–57)a sensitivity analysis, was conducted for all three models with the addition of BMI as a covariate in addition to age. Since emotion-focused and avoidant coping correlated highly, analyses were repeated excluding emotion-focused coping and again excluding avoidant coping. For simplicity and ease of interpretation, these results are not presented as the main analysis. All mediation analyses were conducted using the jAMM module (58) for Jamovi (v2.3) (59).

## Results

A total of 188 females, with ages ranging from 18 to 83 years (mean 48.7, sd 15.5 years), completed the online questionnaire. Sociodemographic characteristics are presented in Table 1. Most participants had post-secondary education, two-thirds were married or living with a partner. Over half the participants were overweight or obese (BMI≥25). Only 40% of the sample rated their AF knowledge as good or excellent. Only a quarter of the sample rated their satisfaction with life as satisfied; 79.8% of the sample scored above the clinical HADS cutoff (HADS-A>7) for at least mild anxiety and 70.2% were above the cutoff (HADS-D>7) for at least mild depression.

After standardization, all variables used for the mediation analyses were assessed for normality and kurtosis and results fell within satisfactory ranges for subsequent statistical analysis. The relationship between the standardized variables is presented in Table 2. Correlation between the three major coping styles ranged from $r$=0.31 (problem-focused and avoidant coping) through to $r$=.71 (emotion-focused and avoidant coping). AF knowledge was moderately negatively correlated with anxiety ($r$ =-.50, $p$ <.001) and depression ($r$ =-.53, $p$ <.001) and moderately positively correlated

TABLE 1 Characteristics of participants (n=188).

| Characteristic | N (%) |
|---|---|
| **Age group (years)** | |
| 18-34 | 43 (23%) |
| 35-49 | 53 (28%) |
| 50-64 | 61 (32%) |
| ≥65 | 31 (17%) |
| **Education** | |
| Primary | 9 (5%) |
| Secondary | 35 (19%) |
| Trade or TAFE qualification | 41 (22%) |
| University diploma/degree/post-graduate | 103 (55%) |
| **Marital status** | |
| Never married | 40 (21%) |
| Widowed | 5 (3%) |
| Divorced or separated | 17 (9%) |
| Married or living with partner | 126 (67%) |
| **Body Mass Index (kg/m2)** | |
| Underweight (<18.50) | 5 (3%) |
| Healthy weight (18.5-24.9) | 74 (39%) |
| Overweight (25.0-29.9) | 44 (23%) |
| Obese (≥ 30.0) | 65 (35%) |
| **Atrial fibrillation knowledge** | |
| Little or none | 45 (23.9) |
| Moderate | 67 (35.6) |
| Good or Excellent | 76 (40.4) |
| Satisfaction With Life Scale | M 14.2 (SD 9.1) |
| HADS Anxiety | M 12.9 (SD 7.4) |
| HADS Depression | M 14.2 (SD 9.1) |

with life satisfaction ($r$=.40, $p$ <.001). Emotion focused coping and avoidant coping styles were significantly positively correlated with both anxiety and depression, and negatively correlated with life satisfaction. Age correlated positively with life satisfaction ($r$=.41, $p$ <.001) and negatively with anxiety ($r$= -.47, $p$ <.001) and depression scores ($r$= -.45, $p$ <.001). Since age correlated significantly with most variables it was included as a covariate in the mediation analyses. BMI was significantly negatively correlated with emotion focused coping and avoidant coping styles, and life satisfaction and positively correlated with both anxiety and depression.

## Mediation analyses

Three mediation models with standardized variables were tested (i.e., Model A: AF Knowledge → Coping style → life satisfaction;

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TABLE 2 Relationship between study variables. .

| | | Age | BMI | AFK | PC | EC | AC | SWLS | HADSA |
|---|---|---|---|---|---|---|---|---|---|
| Age | Pearson's r | — | | | | | | | |
| | p-value | — | | | | | | | |
| BMI | Pearson's r | 0.269 | — | | | | | | |
| | p-value | < .001 | — | | | | | | |
| AFK | Pearson's r | 0.372 | 0.300 | — | | | | | |
| | p-value | < .001 | < .001 | — | | | | | |
| PC | Pearson's r | 0.068 | 0.069 | 0.045 | — | | | | |
| | p-value | 0.355 | 0.344 | 0.544 | — | | | | |
| EC | Pearson's r | -0.291 | -0.297 | -0.228 | 0.629 | — | | | |
| | p-value | < .001 | < .001 | 0.002 | < .001 | — | | | |
| AC | Pearson's r | -0.345 | -0.452 | -0.398 | 0.313 | 0.705 | — | | |
| | p-value | < .001 | < .001 | < .001 | < .001 | < .001 | — | | |
| SWLS | Pearson's r | 0.409 | 0.408 | 0.401 | 0.100 | -0.292 | -0.498 | — | |
| | p-value | < .001 | < .001 | < .001 | 0.174 | < .001 | < .001 | — | |
| HADS-A | Pearson's r | -0.472 | -0.533 | -0.502 | -0.029 | 0.427 | 0.650 | -0.748 | — |
| | p-value | < .001 | < .001 | < .001 | 0.694 | < .001 | < .001 | < .001 | — |
| HADS-D | Pearson's r | -0.453 | -0.547 | -0.530 | -0.035 | 0.468 | 0.640 | -0.768 | 0.873 |
| | p-value | < .001 | < .001 | < .001 | 0.632 | < .001 | < .001 | < .001 | < .001 |

BMI, Body Mass Index; AFK, atrial fibrillation knowledge; PC, problem focused coping style, EC, emotion focused coping style, AC, avoidant coping style; SWLS, Satisfaction With Life Scale; HADS-A, Hospital Anxiety and Depression Scale – Anxiety; HADS-D, Hospital Anxiety and Depression Scale – Depression

Model B: AF Knowledge → Coping style → Anxiety; Model C: AF Knowledge → Coping style → Depression) with age (years) as a covariate in all analyses.

## Model A: knowledge of atrial fibrillation and life satisfaction

The individual regressions for direct and indirect components predicting total SWLS scores are presented in Table 3 with the statistical model presented in Figure 2. The first two requirements for the mediation procedure are that the independent variable (AF Knowledge) be related to the dependent variable (SWLS) and the mediator (three coping styles). Satisfying this requirement, there was a direct significant positive relationship between AF Knowledge and SWLS scores ($\beta$= .146, $p$ =.033) and a significant negative relationship between AF Knowledge and avoidance coping style ($\beta$ = -.313, $p$ <.001). This relationship between avoidant coping style and AF knowledge is common to all three models. The indirect relationship (AF Knowledge → Avoidant Coping style → life satisfaction) was significant (β =.124, p <.001). Thus, with three coping styles competing together, significant partial mediation effects were observed for avoidant coping style, but not for problem-focused or emotion-focused coping. There was, however, a direct positive relationship between problem-focused coping and higher SWLS scores ($\beta$= .266, $p$ =.007) and a direct negative relationship between avoidant coping and SWLS ($\beta$= -.397, $p$ <.001). The covariate age was positively related to higher SWLS scores ($\beta$= .172, $p$ = .026).

## Model B: knowledge of atrial fibrillation and anxiety

The individual regressions for direct and indirect components predicting total HADS-A scores are presented in Table 4 with the statistical model presented in Figure 3. There was a direct significant negative relationship between AF Knowledge and HADS-A scores ($\beta$= -.200, $p$ <.001). Of the three coping styles, only avoidant coping style was significantly associated with AF knowledge ($\beta$ =-0.313, $p$ <.001) and partial mediation was confirmed with the indirect effect ($\beta$= -0.152, $p$ <.001). Both problem-focused coping ($\beta$=-.255, $p$ <.001) and avoidant coping styles ($\beta$= .487, $p$ <.001) had direct associations with HADS-A scores. Age was negatively associated with HADS-A scores ($\beta$= -.169, $p$ =.004).

## Model C: knowledge of atrial fibrillation and depression

The individual regressions for direct and indirect components predicting total HADS-D scores are presented in Table 5 with the statistical model presented in Figure 4. AF knowledge was directly negatively associated with HADS-D total scores ($\beta$= -.247, $p$ <.001). As was the case with models A and B, only the partial mediation effect for avoidant coping style on the outcome variable was

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TABLE 3 Associations between knowledge of atrial fibrillation and Satisfaction With Life Scale total scores mediated by three styles of coping.

| Effect | Estimate | SE | Lower | Upper | β | z | *p* |
|---|---|---|---|---|---|---|---|
| **Indirect** | | | | | | | |
| AFK ⇒ PC ⇒ SWLS | 0.069 | 0.244 | -0.344 | 0.678 | 0.006 | 0.284 | 0.777 |
| AFK ⇒ EC ⇒ SWLS | 0.155 | 0.242 | -0.207 | 0.783 | 0.013 | 0.641 | 0.522 |
| AFK ⇒ AC⇒ SWLS | 1.439 | 0.421 | 0.724 | 2.402 | 0.124 | 3.414 | **< .001** |
| Age ⇒ PC ⇒ SWLS | 0.009 | 0.014 | -0.015 | 0.045 | 0.016 | 0.650 | 0.516 |
| Age ⇒ EC ⇒ SWLS | 0.014 | 0.020 | -0.021 | 0.061 | 0.023 | 0.677 | 0.498 |
| Age ⇒ AC⇒ SWLS | 0.053 | 0.021 | 0.019 | 0.103 | 0.090 | 2.487 | **0.013** |
| **Component** | | | | | | | |
| AFK ⇒ PC | 0.125 | 0.411 | -0.660 | 0.963 | 0.022 | 0.305 | 0.761 |
| PC ⇒ SWLS | 0.552 | 0.203 | 0.136 | 0.947 | 0.266 | 2.720 | 0.007 |
| AFK ⇒ EC | -1.185 | 0.642 | -2.430 | 0.089 | -0.139 | -1.844 | 0.065 |
| EC ⇒ SWLS | -0.131 | 0.176 | -0.451 | 0.238 | -0.096 | -0.745 | 0.457 |
| AFK ⇒ AC | -1.889 | 0.451 | -2.711 | -0.946 | -0.313 | -4.186 | **< .001** |
| AC⇒ SWLS | -0.761 | 0.145 | -1.040 | -0.476 | -0.397 | -5.271 | **< .001** |
| Age ⇒ PC | 0.017 | 0.024 | -0.031 | 0.063 | 0.059 | 0.712 | 0.477 |
| Age ⇒ EC | -0.103 | 0.036 | -0.173 | -0.033 | -0.239 | -2.905 | **0.004** |
| Age ⇒ AC | -0.070 | 0.024 | -0.117 | -0.024 | -0.228 | -2.963 | **0.003** |
| **Direct** | | | | | | | |
| AFK ⇒ SWLS | 1.685 | 0.791 | 0.148 | 3.238 | 0.146 | 2.132 | **0.033** |
| Age ⇒ SWLS | 0.101 | 0.045 | 0.016 | 0.194 | 0.172 | 2.232 | **0.026** |
| **Total** | | | | | | | |
| AFK ⇒ SWLS | 3.348 | 0.796 | 1.789 | 4.908 | 0.289 | 4.208 | **< .001** |
| Age ⇒ SWLS | 0.177 | 0.041 | 0.098 | 0.257 | 0.301 | 4.379 | **< .001** |

N=188; AFK, atrial fibrillation knowledge; PC, problem focused coping style, EC, emotion focused coping style, AC, avoidant coping style; SWLS, Satisfaction With Life Scale total score; significant associations in bold.

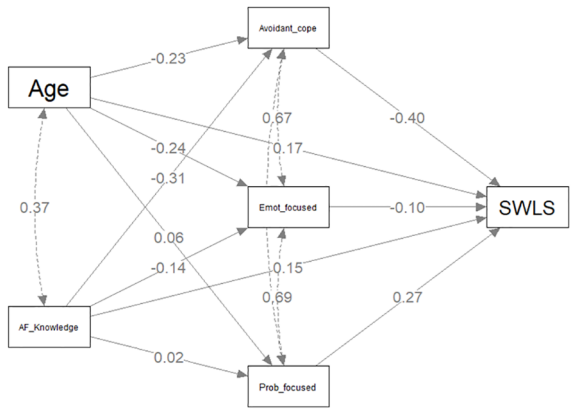


FIGURE 2
Mediation model predicting Satisfaction With Life Scale scores.

confirmed with a significant indirect effect ($\beta$= -.119, $p$ <.001). In contrast to models A and B, all three styles of coping had direct significant effects on HADS-D scores (Problem-focused $\beta$= -.340, $p$ <.001; Emotion-focused $\beta$= .325, $p$ <.001; Avoidant coping $\beta$= .380, $p$ <.001). Age was significantly negatively related to HADS-D scores ($\beta$= -.113, $p$ =.044).

## Sensitivity analysis

Analysis of all three models were repeated with the addition of BMI (kg/m2) as an additional covariate. BMI was negatively associated with HADS-A ($\beta$= -.201, $p$ <.001) and HADS-D ($\beta$= -.209, $p$ <.001) but was not significantly associated with SWLS score ($\beta$= .128, $p$ =.056). The partial mediation effects observed in the previous models were weakened but significance maintained with significant indirect effects only for avoidant coping style in all three

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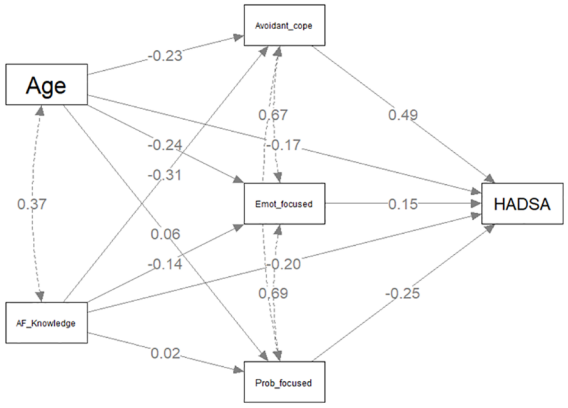


FIGURE 3
Mediation model predicting HADS Anxiety scores.

TABLE 4 Associations between knowledge of atrial fibrillation and HADS Anxiety total scores mediated by three styles of coping.

| Effect | Estimate | SE | Lower | Upper | β | z | *p* |
|---|---|---|---|---|---|---|---|
| **Indirect** | | | | | | | |
| AFK ⇒ PC ⇒ HADSA | -0.047 | 0.166 | -0.384 | 0.291 | -0.006 | -0.285 | 0.776 |
| AFK ⇒ EC ⇒ HADSA | -0.171 | 0.156 | -0.659 | 0.015 | -0.021 | -1.098 | 0.272 |
| AFK ⇒ AC⇒ HADSA | -1.256 | 0.369 | -2.115 | -0.640 | -0.152 | -3.407 | **< .001** |
| Age ⇒ PC ⇒ HADSA | -0.006 | 0.009 | -0.028 | 0.010 | -0.015 | -0.677 | 0.498 |
| Age ⇒ EC ⇒ HADSA | -0.015 | 0.012 | -0.047 | 0.001 | -0.036 | -1.272 | 0.203 |
| Age ⇒ AC⇒ HADSA | -0.046 | 0.017 | -0.084 | -0.018 | -0.111 | -2.740 | **0.006** |
| **Component** | | | | | | | |
| AFK ⇒ PC | 0.125 | 0.420 | -0.729 | 0.913 | 0.022 | 0.299 | 0.765 |
| PC ⇒ HADSA | -0.376 | 0.110 | -0.603 | -0.169 | -0.255 | -3.412 | **< .001** |
| AFK ⇒ EC | -1.185 | 0.646 | -2.432 | 0.037 | -0.139 | -1.833 | 0.067 |
| EC ⇒ HADSA | 0.144 | 0.096 | -0.028 | 0.352 | 0.149 | 1.506 | 0.132 |
| AFK ⇒ AC | -1.889 | 0.445 | -2.728 | -0.993 | -0.313 | -4.249 | **< .001** |
| AC⇒ HADSA | 0.665 | 0.107 | 0.450 | 0.863 | 0.487 | 6.221 | **< .001** |
| Age ⇒ PC | 0.017 | 0.023 | -0.028 | 0.064 | 0.059 | 0.718 | 0.473 |
| Age ⇒ EC | -0.103 | 0.035 | -0.171 | -0.033 | -0.239 | -2.957 | **0.003** |
| Age ⇒ AC | -0.070 | 0.023 | -0.117 | -0.025 | -0.228 | -3.000 | **0.003** |
| **Direct** | | | | | | | |
| AFK ⇒ HADSA | -1.651 | 0.442 | -2.554 | -0.802 | -0.200 | -3.735 | **< .001** |
| Age ⇒ HADSA | -0.071 | 0.025 | -0.118 | -0.020 | -0.169 | -2.875 | **0.004** |
| **Total** | | | | | | | |
| AFK ⇒ HADSA | -3.125 | 0.525 | -4.153 | -2.097 | -0.379 | -5.957 | **< .001** |
| Age ⇒ HADSA | -0.139 | 0.027 | -0.191 | -0.086 | -0.331 | -5.196 | **< .001** |

N=188; AFK, atrial fibrillation knowledge; PC, problem focused coping style, EC, emotion focused coping style, AC, avoidant coping style; HADSA, Hospital Anxiety and Depressions Anxiety Scale total score; significant associations in bold.

TABLE 5 Associations between knowledge of atrial fibrillation and HADS Depression total scores mediated by three styles of coping.

| Effect | Estimate | SE | Lower | Upper | β | z | *p* |
|---|---|---|---|---|---|---|---|
| **Indirect** | | | | | | | |
| AFK ⇒ PC ⇒ HADSD | -0.072 | 0.247 | -0.576 | 0.405 | -0.008 | -0.290 | 0.772 |
| AFK ⇒ EC ⇒ HADSD | -0.425 | 0.256 | -1.033 | -0.008 | -0.045 | -1.657 | 0.097 |
| AFK ⇒ AC⇒ HADSD | -1.118 | 0.328 | -1.869 | -0.558 | -0.119 | -3.410 | **< .001** |
| Age ⇒ PC ⇒ HADSD | -0.010 | 0.014 | -0.037 | 0.017 | -0.020 | -0.709 | 0.478 |
| Age ⇒ EC ⇒ HADSD | -0.037 | 0.016 | -0.078 | -0.012 | -0.078 | -2.281 | **0.023** |
| Age ⇒ AC⇒ HADSD | -0.041 | 0.016 | -0.075 | -0.014 | -0.087 | -2.655 | **0.008** |
| **Component** | | | | | | | |
| AFK ⇒ PC | 0.125 | 0.418 | -0.681 | 0.960 | 0.022 | 0.299 | 0.765 |
| PC ⇒ HADSD | -0.572 | 0.110 | -0.801 | -0.367 | -0.340 | -5.198 | **< .001** |
| AFK ⇒ EC | -1.185 | 0.641 | -2.433 | 0.088 | -0.139 | -1.848 | 0.065 |
| EC ⇒ HADSD | 0.359 | 0.092 | 0.179 | 0.537 | 0.325 | 3.922 | **< .001** |
| AFK ⇒ AC | -1.889 | 0.447 | -2.764 | -1.025 | -0.313 | -4.229 | **< .001** |
| AC⇒ HADSD | 0.591 | 0.104 | 0.373 | 0.786 | 0.380 | 5.679 | **< .001** |
| Age ⇒ PC | 0.017 | 0.023 | -0.029 | 0.062 | 0.059 | 0.730 | 0.465 |
| Age ⇒ EC | -0.103 | 0.035 | -0.171 | -0.034 | -0.239 | -2.963 | **0.003** |
| Age ⇒ AC | -0.070 | 0.024 | -0.115 | -0.024 | -0.228 | -2.977 | **0.003** |
| **Direct** | | | | | | | |
| AFK ⇒ HADSD | -2.317 | 0.449 | -3.248 | -1.475 | -0.247 | -5.159 | **< .001** |
| Age ⇒ HADSD | -0.054 | 0.027 | -0.107 | -2.70 | -0.113 | -2.010 | **0.044** |
| **Total** | | | | | | | |
| AFK ⇒ HADSD | -3.931 | 0.593 | -5.092 | -2.770 | -0.419 | -6.635 | **< .001** |
| Age ⇒ HADSD | -0.142 | 0.030 | -0.201 | -0.083 | -0.297 | -4.705 | **< .001** |

N=188; AFK, atrial fibrillation knowledge; PC, problem focused coping style, EC, emotion focused coping style, AC, avoidant coping style; HADSD, Hospital Anxiety and Depressions Depression Scale total score; significant associations in bold.

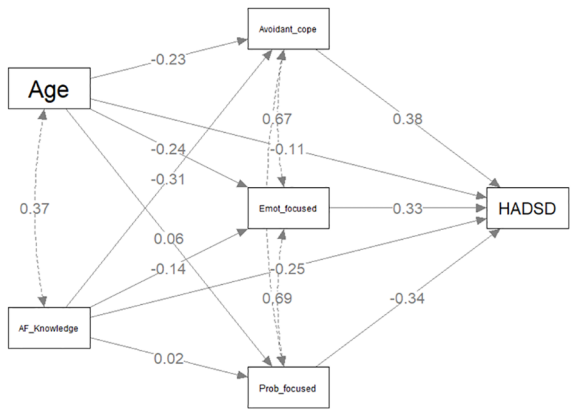


FIGURE 4
Mediation model predicting HADS Depression scores.

sensitivity models (SWLS $\beta$= .083, $p$ =.009; HADS-A $\beta$= -.098, $p$ =.003; HADS-D $\beta$= -.072, $p$ =.007). Since avoidant coping and emotion-focused coping correlated highly ($r$=0.7), the analysis of all models was repeated excluding emotion-focused coping and again excluding avoidant coping. The key results (significant partial mediating effect of avoidant coping) did not change when emotion-focused coping was removed from all three models. When avoidant coping was removed from all three models, no partial mediation effect was observed for either problem-focused coping or emotion-focused coping, regardless of whether BMI was included or excluded as a covariate. With exclusion of avoidant coping from the models, the direct relationship between emotion-focused coping and the three outcomes also became significant.

The indirect effect of avoidant coping on psychosocial outcomes was also examined for a subset of participants who had good or excellent AF knowledge (Table 6). Participants who scored above the median on avoidant coping performed significantly worse on all

TABLE 6 Effect of low versus high avoidant coping and problem focused coping on psychosocial outcomes for subset of participants with good or excellent atrial fibrillation knowledge.

| | Satisfaction With Life | | HADS Anxiety | | HADS Depression | |
|---|---|---|---|---|---|---|
| | Mean | SD | Mean | SD | Mean | SD |
| Low avoidant coping (n=52) | 20.1 | 8.2 | 9.1 | 5.4 | 6.9 | 5.5 |
| High avoidant coping (n=24) | 13.5 | 8.1 | 14.5 | 6.0 | 13.5 | 6.9 |
| Significance | F=10.9, df $_{1,74}$, $p$ =.002 | | F=15.2, df $_{1,74}$ $p$ =<.001 | | F=19.6, df $_{1,74}$ $p$ <.001 | |
| Low problem focused coping (n=35) | 16.3 | 9.1 | 11.3 | 6.2 | 9.5 | 7.1 |
| High problem focused coping (n=38) | 19.6 | 8.2 | 10.6 | 6.1 | 8.7 | 6.6 |
| Significance | F=2.64, df $_{1,71}$, $p$ =.109 | | F=0.24, df $_{1,71}$. P =.627 | | F=0.24, df $_{1,71}$, $p$=.629 | |

three psychosocial outcomes than those who scored low on avoidant coping (SWLS F=10.9, df(1,74), $p$ =.002; HADS-A F=15.2, df(1,74) $p$ =<.001; HADS-D F=19.6, df(1,74) $p$ <.001). By contrast, for problem focused coping, which did not have a significant indirect effect on outcomes, there were no significant differences between those who scored low versus high.

## Discussion

The present study investigated the relationships between AF knowledge, coping and psychological outcomes. To our knowledge, these findings are the first to quantitatively demonstrate moderate positive associations of AF knowledge with life satisfaction and moderate negative associations of AF knowledge with anxiety and depression. These findings are consistent with those of previous qualitative work (29) and also with previous findings that demonstrate inadequate knowledge is associated with uncertainty and stress (26).

Problem-solving coping style was also directly associated with the three psychosocial outcomes, being negative for anxiety and depression, and positive for life satisfaction. In contrast, the maladaptive emotion-focused and avoidant coping styles were directly associated with higher anxiety and depression and lower life satisfaction. These findings are consistent with those from studies of patients with various chronic conditions that have found poorer psychosocial outcomes in patients with maladaptive coping styles compared to better psychosocial outcomes with positive or adaptive coping styles (34–37). Given the cross-sectional design of our study, we are unable to eliminate the possibility that the presence of depressive symptoms may have influenced maladaptive coping styles, specifically avoidant coping. This notion aligns with findings from a prior study conducted by Trivedi and colleagues in stable heart failure patients (60). Their research revealed significant associations between depressive symptoms and avoidant coping, low perceived social support, and pessimism. Notably, it's worth mentioning that in their study, the majority of participants were male (67%), who often report lower depression rates than females (61).

Importantly, the current study provided support for a crucial role of coping styles in mediating the association between AF knowledge and psychosocial outcomes. Mediation analyses revealed that avoidant coping style partially mediated the relationship between AF knowledge and psychosocial outcomes. Specifically, when avoidant coping is low, there is the expected positive linear relationship between AF knowledge and life satisfaction scores. When avoidant coping is high, this linear association is significantly diminished and overall satisfaction with life is lower. When avoidant coping is high, AF knowledge is less influential on lowering anxiety or depression scores. Coping style, therefore, appears to have a crucial impact on how patients experience anxiety and process their behavioural response (32, 33).

The present findings have important clinical implications in terms of the development and trailing of interventions to improve AF knowledge as a means of improving psychological outcomes in AF patients. Previous studies have shown improved quality of life in AF patients who were supported to improve their knowledge of their condition (62–64). In addition to patient education, the findings of this study also highlight the potential importance of problem-solving coping strategies in improving psychosocial outcomes in patients with AF. Effective patient education has the potential to improve patients' understanding of their condition and its management, leading to improved coping strategies and better psychosocial outcomes. Adaptive problem-solving coping strategies in particular can help patients manage the problem causing their distress and reduce anxiety and depression, while enhancing satisfaction with life (65, 66). In contrast, maladaptive coping has been associated with poorer psychosocial outcomes in other patient groups such as heart failure patients (60) and has the potential to negate the potentially beneficial effects of patient knowledge.

In relation to both adaptive and maladaptive coping, psychotherapy offers a structured and supportive environment for patients to explore and develop coping strategies that can enhance their ability to manage the emotional challenges associated with AF (67). By addressing issues such as anxiety, depression, and the fear of sudden cardiac events, psychotherapeutic approaches like cognitive-behavioural therapy (CBT), relaxation techniques, and stress management can equip patients with the tools to better navigate the psychological impact of their condition (68–70). Further, randomised trials have shown that interventions aimed at improving patient education and knowledge about AF result in enhanced patient adherence, decreased treatment-related complications (71) and enhanced quality of life (72, 73). This finding is consistent with research on other health conditions on the impact of knowledge on anxiety and stress levels (74–76).

## Limitations

In common with cross-sectional online surveys such as this, the measures of anxiety, depression, satisfaction with life and knowledge of AF all relied on self-report, with no objective measure of these. This study relied on self-reported perceived knowledge of AF and did not use one of the several validated instruments available to assess AF knowledge (77). In addition, there was no measure of AF symptom severity. Our patients were all women and were sourced via social media and reported higher levels of anxiety and depression than would be expected from hospital sourced samples (78). Since our analyses involved continuous scale scores instead of clinical categories of anxiety and depression, it is unlikely that the mediation analysis would have been adversely affected by this limitation. This study did not explore the potential influence of potential confounders, such as socioeconomic status, medication use or comorbidities, on the relationship between AF knowledge and psychosocial outcomes. Given the self-selected nature of the sample, the findings should be interpreted cautiously until they can be replicated in a consecutive representative sample of confirmed diagnosed AF patients.

# Conclusions

It is notable that current Atrial Fibrillation Guidelines (3, 21, 79, 80) provide scant or no attention whatsoever to the psychological aspects of living with AF. The results of the current study add to a growing body of literature that highlights the psychological challenges of living with AF and indicate that such issues could be incorporated into comprehensive management guidelines. More specifically, these findings highlight the need for adequate psychological screening of cardiac patients as well as effective psychotherapeutic interventions to empower patients to better understand and cope with the emotional and psychological aspects of their condition.

# Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

# Ethics statement

The studies involving humans were approved by Federation University Ethics Committee. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

# Author contributions

MG: Data curation, Formal Analysis, Writing – original draft. MS: Investigation, Writing – review & editing. LS: Formal Analysis, Writing – review & editing. BM: Supervision, Writing – review & editing. AJ: Formal Analysis, Methodology, Writing – original draft. MA: Conceptualization, Funding acquisition, Investigation, Project administration, Writing – original draft.

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# Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

# Publisher's note



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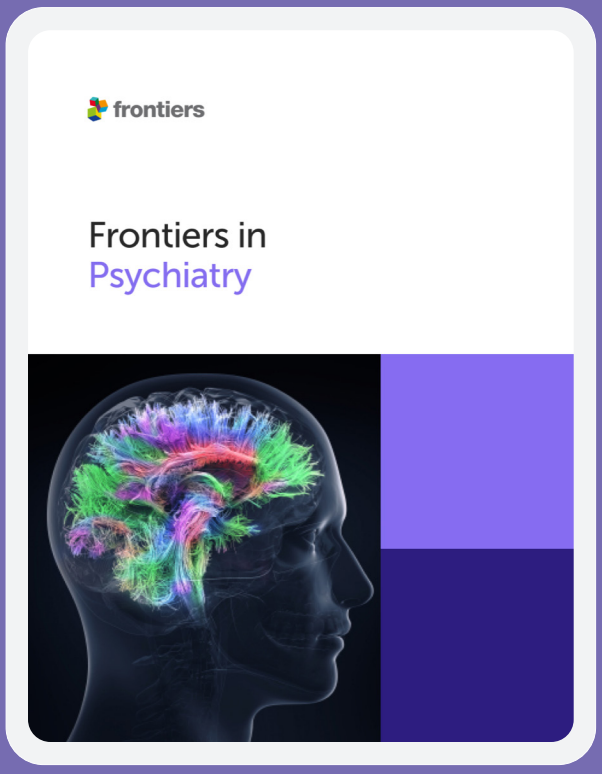


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