

PSYCHOCARDIOLOGY: EXPLORING THE BRAIN-HEART INTERFACE

EDITED BY: Kai G. Kahl, Marlies Elizabeth Alvarenga and Don Byrne
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PSYCHOCARDIOLOGY: EXPLORING THE BRAIN-HEART INTERFACE

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Editorial: Psychocardiology then and now – the genesis of a discipline

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Editorial on the Research Topic

Psychocardiology then and now – the genesis of a discipline

The poet Schiller, reflecting on the happiest of emotions, says:

The golden time of first love!

The eye sees the open heaven,

The heart is intoxicated with bliss;

[from The Song of the Bell (Das Lied von der Glocke), 1798]

And from a rather more melancholic disposition, the poet Keats writes:

My heart aches, and a drowsy numbness pains

My sense, as though of hemlock I had drunk ...

(from Ode to a Nightingale, 1819).

What then connects these exquisite lines? It is that the seat of such contrasting emotions has been placed explicitly in the human heart. Indeed, the range of emotions to which this attribution applies extends wider than these two poetic examples portray. Countless recorded works of poetry and prose, philosophy, and religion have held this view to be self-evidently true. And the compelling nature of the link remains with us now. But from the perspectives of both the psychological and cardiological sciences in the twenty-first century it is a conspicuous misattribution. It is, however, not difficult to understand how it could have occurred.

When we experience and identify an emotion, whether positive or negative, we are also reporting a set of explainable and measurable physiological events having their origins in the activation of key centers within the nervous system (1). The pioneering psychologist James (2) held that a consciously expressed emotion is little more than the subjective self-report of bodily changes arising from autonomic activation. And though challenged by Cannon (3) on neurophysiological grounds, this conceptualization prevailed for many decades as the dominant theoretical foundation for understanding and explaining human emotion.

The cardiovascular system has figured strongly in this causal reasoning. Activation of the autonomic nervous system can be subjectively experienced in a number of recognizable and disturbing cardiovascular events—rapid and irregular pulse, blushing and elevations of skin temperature, shortness or rapidity of breath, light-headedness, and syncope, all present themselves for consideration, but hemodynamic events reflecting fluid pressure in the circulatory system also enter this mix. The evidence for this assertion is now abundant and indisputable (4–6). But while the poet considers this link from an experiential viewpoint and concludes that the actual source of the feeling lies in the heart, the scientist, considering the same psycho-biological link, can now state with certainty, that while the heart reacts, the origins of the feeling lie clearly within the nervous system. So, for the purposes of the present discourse, while the heart is not the source of the feeling, it is undeniably a powerful barometer of that feeling.

The use of the term *psychocardiology* is relatively new (7, 8). But recognition of the role of psychological factors and risk or incidence of cardiovascular disease (CVD), goes much further back in history. A full analysis of the rise of psychocardiology over the past century is not intended of this Editorial. The sheer volume of contemporary literature documenting the heart/brain nexus is now formidable. Still, brief reference to some important milestones along the way will serve as a context for the presentation of the contemporary papers which will make up the substance of this Frontiers Special Issue exploring the heart/brain interface.

Passing over purely speculative references to the possibility of a heart/brain nexus which have appeared throughout medical history, the late nineteenth and early twentieth centuries began to see the more formal chronicling of that nexus based on systematic clinical observations. The extreme mental stress of military combat—the anticipation of a violent death in the immediate future—and its pathological impact on the heart, was first formally noted by Jacob Da Costa (9). The term *Soldier's Heart*, ultimately known as Da Costa's Syndrome, included palpitation, fatigue, breathlessness, chest pain, sighing, dizziness, and faintness (10). This constellation of physical symptomatology, at least contemporaneous with severe mental stress, is clearly indicative of significant cardiac distress, though there is no evidence either that it was protracted or that it gave rise to an elevated risk of clinically documented, acute cardiac events such as myocardial infarction. Nonetheless, clinical observation by military medical practitioners of the day did foreshadow, more than a century and a half ago, the possibility that the mind might seek expression through the cardiovascular system.

Looking to the general population more broadly, the pioneering Canadian physician William Osler (11) first noted, on the basis of clinical observation again, that a particular pattern of pressured and achievement driven behavior appeared to be conspicuously over-represented in patients presenting

clinically with angina pectoris—anticipating perhaps, as we will see a little later, the formulation of the Type A behavior pattern. A short time later, the emergence of psychoanalytic theory and practice in the early twentieth century came to provide a more grounded basis for understanding both mental and somatic phenomena through carefully systematized clinical observation, giving rise to the now recognized medical discipline of *psychosomatic medicine* (12). And within the specific domain of cardiovascular disease, the influential psychoanalyst Franz Alexander reported that hypertensive patients tended to be those suppressing disturbing and problematic experiences deeply into the subconscious without being able to externally recognize, accept, and resolve these experiences (13).

The heart/brain nexus became subjected to the methodological and statistical rigors of cardiovascular epidemiology several decades later with the landmark work of the cardiologists Rosenman and Friedman. Evidence from the now iconic Western Collaborative Group Study (WCGS) (14) demonstrated prospectively, that individual possession of the Type A behavior pattern—interestingly similar to Osler's earlier observations—endowed a risk of experiencing a major cardiac event by a factor of more than two-fold. The finding has, not surprisingly, been strongly disputed in recent times, both on methodological grounds and because of a subsequent failure to independently replicate the results of the WCGS. Nonetheless, it demonstrated for the first time that the heart/brain nexus was amenable to systematic epidemiological investigation, and that the nexus was more than simply observationally based conjecture.

But history takes us just so far in understanding the heart/brain interface. Empirical evidence—such as that which we first saw in the WCGS—as we now know, must completely replace clinical observation alone, and over the past 45 years, this evidence has appeared in abundance. It has been derived from studies utilizing a broad array of research settings and foci, spanning the basic bioscience and psychological laboratories, the working medical facilities of hospitals and clinics, and into the territory of the general population itself. It has drawn on a plethora of methodologies and approaches, covering the fundamental laboratory-based investigations of the biomedical sciences, the experimental paradigms of psychophysiology, the invasive techniques of interventional cardiology, the use of tightly controlled clinical trials, and the rigorous field work of prospective epidemiological studies. And importantly, it has been truly multi-disciplinary in nature, uniting the specific knowledge and skills of biological scientists working in fundamental biomedicine, cardiologists, psychiatrists and psychologists, epidemiologists and statisticians, each contributing uniquely but synergistically to a common purpose—to understand the heart/brain nexus and to translate this understanding into the better clinical management of those with, or at risk of, cardiac disease.

Historically, we therefore came to ask: is psycho-social stress reliably implicated in the risk or clinical incidence of cardiac disease? Recent reviews of empirical studies now allow some solid conclusions to be drawn. Dimsdale (15), reviewing evidence on the roles of both acute and chronic stressors in relation to CVD noted three clear conclusions: first, there is overwhelming evidence that stress negatively effects the heart at an acute level; second, the evidence is strongest for stressors as triggers of coronary events; and third, the evidence on stress as a causal factor in cardiovascular disease is less strong. Steptoe and Kivimäki (16) some years later, following a careful meta-analysis of the relative strengths of the stress/heart link, provide more conclusive findings linking workplace stress to both CVD risk and clinical incidence of cardiac events. This review highlighted the cardio-pathological effects of loneliness and social isolation, and noted the roles of both anger and depression as triggers of cardiac events. And in a very recent review specifically focusing on the neurobiological causal mechanisms linking stress to CVD, Osborne et al. (17) concluded that the evidence to date now warrants the clinical use of stress reduction approaches in the mitigation of CVD risk. Each of these reviews concedes deficiencies both in the definitions and measurement of stress. Moreover, the definitive prospective study of stress and CVD in a completely unselected general population has yet to be done. Nonetheless, we have come far in the last five decades from a situation of hopeful speculation regarding stress and the heart, to a point where the systematic empirical evidence linking the two can no longer be discounted.

More recently however, attention appears to have turned to examining the more specifically experienced negative emotions, and principally depression, anxiety, and anger, usually when evident to a pathological degree, as possible causal precursors to CVD. Contemporary reviews of the evidence suggest that this was a useful move away from the more broad-brush focus on stress. Depression is clearly concomitant with clinical cardiac events for many patients. Moreover, depression is known to predict poorer outcomes in patients after diagnosed cardiac events (18). However, recent meta-analytic reviews of methodologically strong prospective studies of CVD risk clearly link major depression prospectively with both elevated risk of CVD and elevated mortality levels in those with existing incident CVD (19). This has been recently confirmed in a large (>145,000 participants) multi-center study of depression and both CVD morbidity and mortality over a 9-year period (20). It can be sensibly concluded therefore that depression, whether as a diagnosed state or as a collection of symptoms, endows some individuals with an elevated risk of both CVD morbidity and mortality. The strength of this evidence recently led the National Heart Foundation of Australia to take the position that depression must now figure among the more historically recognized risk markers for CVD (21).

The evidence is a little more equivocal in regard to anxiety and CVD, particularly in drawing causal conclusions (22, 23),

but the current evidence does not discount the link. Anxiety, like depression, is clearly concomitant with clinical cardiac events, and appears related both to onset and prognosis (24). However, reviews by both Batelaan et al. (25) and Reinart et al. (26) indicated the possibility of a prospective relationship between anxiety states and an elevation in CVD incidence over time. And arguably the most persuasive evidence on anxiety and CVD comes from studies on Post-Traumatic Stress Disorder (PTSD) and CVD—the accumulation of evidence here now establishes a compelling case for that causal link (27). Perhaps the weakest evidence thus far is for the link between anger and CVD, though it is still sufficiently interesting to remain in contention. Contemporary work supports a prospective link between CVD and destructive anger (28), anger in response to stress (29), and anger proneness (30). Nonetheless, the most persuasive view of anger presently is that of a trigger to, rather than a cause of incident CVD (31, 32).

But perhaps the most contentious issue in this emerging domain of evidence addresses the postulated links between serious mental illness (psychosis) and CVD. Symptoms of psychosis—including Schizophrenia and Bipolar Disorder—have been contemporaneously linked with CVD risk or incidence (33–35). However, issues of causality remain unresolved, and it has been proposed that if such a link exists, it may be mediated through the coexistence of unhealthy or risky lifestyle factors such as cigarette smoking, inadequate nutrition and physical neglect, or even through the lipid-elevating side effects of some anti-psychotic medications (35). The possible link between psychosis and CVD risk is, therefore, yet to be fully explored.

Evidence is also now accumulating on the role of childhood adversities in the development of future health risk. This perspective, integrating findings from different disciplines, links mental disorders with CVD, and paves the way for a lifespan perspective in psychocardiology. Multiple stressors during child development affect the developed adult, thereby partly structuring their phenotypes. Adverse childhood experiences are now increasingly recognized as factors modulating health and illness across the life-course. In a landmark study (36) childhood adversities were found to increase the risk of mental disorders, CVD, and unhealthy lifestyles such as smoking, eating behaviors and low physical activity.

One theory aiming to explain the long-term sequelae of chronic stressors in childhood is the concept of *allostasis* (37). Allostasis describes the physiological responses to stressors evolved to maximize the probability of survival while limiting somatic damage. Unfortunately, such beneficial defensive responses come at a cost and, over time, repeated allostatic activity, particularly activation of stress hormone systems (38), leads to systemic somatic damage and loss of resilience to additional stressors. This damage accumulates and is known as allostatic load (39).

The notions of childhood adversities and allostasis, therefore, may stimulate a whole new theoretical direction of research, with clinical implications for both diagnosis (assessment of childhood adversities and comorbid mental disorders in patients with CVD), treatment and prevention strategies.

In this broad context then, the Special Issue of *Frontiers in Psychiatry, Psychocardiology: Exploring the Brain-Heart Interface* was conceived—and 26 original and peer reviewed papers in the area are now presented. Authors were not constrained by any pre-ordained structure—their brief was simply to report on contemporary evidence, either as original research or as critical reviews, bearing on this interface. Nonetheless, examination of the accepted submissions indicates that they aggregate under several albeit loosely bordered categories. *Early developmental psychosocial precursors* typically childhood trauma, and emotional and physical abuse (but interestingly, less so sexual abuse) were identified in relation to thromboembolic pulmonary hypertension (Lepsey et al.), pulmonary arterial hypertension (Park et al.) and congenital heart disease (Proskynitopoulos et al.) manifested later in adulthood. The over-representation of *psychological disorders* (typically as *depression and anxiety disorders*) and *stress*, in patients with thromboembolic pulmonary hypertension (Dering et al.) and those experiencing sudden cardiac arrest (Batelaan et al.) are also reported. And dysfunctional meta-cognitions more broadly are linked to pulmonary arterial hypertension (Caldarone et al.). Though causal inferences cannot be drawn for these data. Attention is also drawn, beyond the recognized effects of anxiety and depression, to the phenomenon of more broadly characterized cardiac distress in relation to longer-term recovery after a cardiac event (Jackson et al.). And we are also reminded that cognitive dysfunction too may follow cardiac events requiring surgical intervention (Vu and Smith).

Possible *psycho-biological mechanisms* also figure in the papers presented here. The central role of brain monoamines in those with both anxiety and depression has now been conclusively linked to CVD (Esler et al.). Elevated deposits of visceral adipose tissue have also been linked to CVD, possibly *via* inflammatory processes (Stapel et al.). And consistent with already published evidence, increased stress reactivity to psychosocial stimuli in the laboratory has been associated with primary hypertension (Balint et al.). This challenge-based methodology did not, however, generalize to Yohimbine induced heart rate variability in unmedicated depressed patients (Deuter et al.). The impact of CVD on both employment and Quality of Life (QoL) has been documented in patients with pulmonary hypertension (Fuge et al.; Olsson et al.) and survived myocardial infarction (Burnos and Wrzosek), and decreased QoL has also been associated with heart failure (Zormpas et al.; Anthony et al.).

The *COVID-19 pandemic* has also stimulated recent research into CVD. Papers alerting us to the impact of the pandemic on

the availability of medical services to patients with congenital heart disease (Akkermann et al.), and the negative consequences of COVID lockdown on physical activity and sleep patterns of children (as potential future CVD risk; Olive et al.) raise areas of future research. The pandemic did not, however, appear to negatively impact on mental distress or QoL in patients with Pulmonary Arterial Hypertension (Park et al.).

And finally, it was pleasing to see that *interventions for mental illness* in patients with cardiac conditions featured prominently in contributions to this Special Issue. Interventions using psychotropic medications remain important though, in the light of well-demonstrated cardio-toxicity in some agents, they must be used with considerable caution (Kahl et al.). There is also a raft of (relatively) cardio-specific issues to do with adherence to medication which must be recognized (Halling et al.). Psychotherapeutic interventions for both anxiety and depression in patients with CVD are, however, now becoming increasingly employed, and both Meta-cognitive Therapy (Wells et al.; Gebhardt et al.; Caldarone et al.) and Transdiagnostic CBT (Tully et al.) show significant promise as effective psychocardiological interventions.

In this light, we believe that our Special Issue gives rise to inspiring new ideas concerning all aspects of psychocardiology. Screening for mental disorders, disease associated distress, and childhood trauma is recommended in the workup of patients. Psychotherapeutic interventions are recommended at all levels of cardiovascular treatment, and in severe cases, psychopharmacological drug treatment can carefully be considered. However, more research is clearly merited to ensure fully convincing evidence able to be integrated into current treatment guidelines.

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DB, KGK, and MA made substantial contributions to the conception and idea of the Editorial, drafted the work and revised it critically for important intellectual content, provided approval to the final version, and agreed to be accountable for all aspects of the work.

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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Prevalence of Mental Disorders and Impact on Quality of Life in Patients With Pulmonary Arterial Hypertension

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Objective: Mental health may affect the quality of life (QoL) in patients with pulmonary arterial hypertension (PAH). However, mental disorders have not been systematically assessed in these patients. We examined the prevalence of mental disorders using structured interviews and determined their impact on QoL in patients with PAH.

Methods: This study included 217 patients with PAH from two German referral centers. Psychiatric disorders were assessed using the structured clinical interview for DSM-V. QoL was assessed using the WHO Quality of Life questionnaire (short form). The diagnostic value of the Hospital Anxiety and Depression Scale was evaluated by receiver operating characteristic curve analysis.

Results: More than one third of the patients had psychological disorders with current or past adjustment disorder (38.2%), current major depressive disorder (23.0%), and panic disorder (15.2%) being the most prevalent mental illnesses. About half of the patients with a history of adjustment disorder developed at least one other mental illness. The presence of mental disorders had a profound impact on QoL. The Hospital Anxiety and Depression Scale ruled out panic disorder and depression disorder with negative predictive values of almost 90%.

Conclusion: Mental disorders, in particular adjustment disorder, major depression, and panic disorder, are common in patients with PAH and contribute to impaired QoL in these patients. The Hospital Anxiety and Depression Scale may be used as a screening tool for the most common mental health disorders. Future studies need to address interventional strategies targeting mental disorders in patients with PAH.

Keywords: pulmonary arterial hypertension, anxiety disorder, adjustment disorder, psychocardiology, quality of life, depression disorder, panic disorder

INTRODUCTION

Pulmonary arterial hypertension (PAH) is a rare debilitating and life-threatening disease characterized by progressive pulmonary vascular remodeling and consecutive right-sided heart failure (1). Despite therapeutic advances, there is yet no cure for PAH. For the affected patients, experiencing the symptoms of the disease, especially the progressive impairment in exercise capacity, together with the uncertainties accompanying the usual diagnostic delay (2, 3) is often traumatizing. Receiving the diagnosis of PAH is frequently associated with conflicting emotions as patients may be relieved that an explanation for their symptoms has been found while realizing at the same time that they suffer from a severe, permanent, and potentially lethal disease, which will affect and change the rest of their lives. The consequences of receiving a PAH diagnosis are immense as the patients have to deal not only with their physical limitations but also with uncertainties about their future; the potential inability to continue working with all its financial, familial, and social consequences; the outlook of not being able to become pregnant or to raise children; the need for continued medical check-ups including invasive procedures; and the burden, complexities, and side effects of medical therapies including the possible need for lung transplantation.

Hence, it is not surprising that some patients may develop an adjustment disorder, which may evolve into other psychiatric conditions during the course of their illness. Symptoms of depression and anxiety have been reported in up to 50% of patients with PAH (4–12). It is likely that such symptoms have a profound effect on the quality of life (QoL) in the affected patients. However, to the best of our knowledge, all previous studies assessing mental disorders in patients with PAH have used self-rating questionnaires rather than structured expert face-to-face interviews, which are considered the gold standard of psychiatric assessment.

In the present cross-sectional study, we assessed the current prevalence of mental disorders in patients with PAH using structured face-to-face interviews using the structured clinical interview (SCID) for DSM-V (13). The prevalence of adjustment disorders after receiving the PAH diagnosis was assessed retrospectively in most cases. In addition, we analyzed the association between mental disorders and QoL. Finally, we investigated the usefulness of the Hospital Anxiety and Depression Scale (14), an established patient self-assessment tool, as a screening instrument for SCID-derived mental disorders in patients with PAH.

METHODS

Design and Study Setting

This cross-sectional observational multicentre study included patients with a confirmed diagnosis of PAH (WHO Group 1) according to current diagnosis criteria (1), age ≥ 18 years, and physical and mental capability to complete questionnaires and interview in German language. The study concept was developed in cooperation with patient organizations as suggested during the latest Pulmonary Hypertension World Symposium (15). Patients

were enrolled in two German pulmonary hypertension referral centers (Hannover Medical School and University of Gießen and Marburg). The study was approved by the local institutional review boards (Nr. 8540_BO_K_2019 for Hannover and Nr. 21119 for Gießen and Marburg), and all patients gave written informed consent.

Recruitment

In Hannover, all active patients with PAH deemed eligible were identified from a database and approached via mail. In Gießen, all patients with ambulatory visits between January 1, 2020 and March 31, 2020 were invited to participate. After providing written informed consent, patients completed a set of questionnaires and underwent a personal structured clinical interview for DSM-V.

Questionnaires and SCID

Assessment of anthropometric data [age, height, weight, body mass index (BMI)], lifestyle factors such as smoking habits (active, former, current, pack years), and current alcohol consumption (drinks per week) and psychosocial data with information regarding educational and employment status were assessed using self-rated questionnaires.

Psychiatric characterization was performed using the Structured Clinical Interview for DSM-V to determine axis-I psychiatric disorders and covered the past 4 weeks before the interview. The prevalence of adjustment disorders within 3 months after the PAH diagnosis was assessed retrospectively using the same set of questions given in the structured clinical interview. Further characterization comprised symptoms of panic disorder and depression with the Hospital Anxiety and Depression Scale (14), and QoL with the WHO Quality of Life questionnaire in short form (WHOQOL-BREF) (16). QoL was classified as overall, psychological, and physical QoL.

Psychiatric Diagnosis

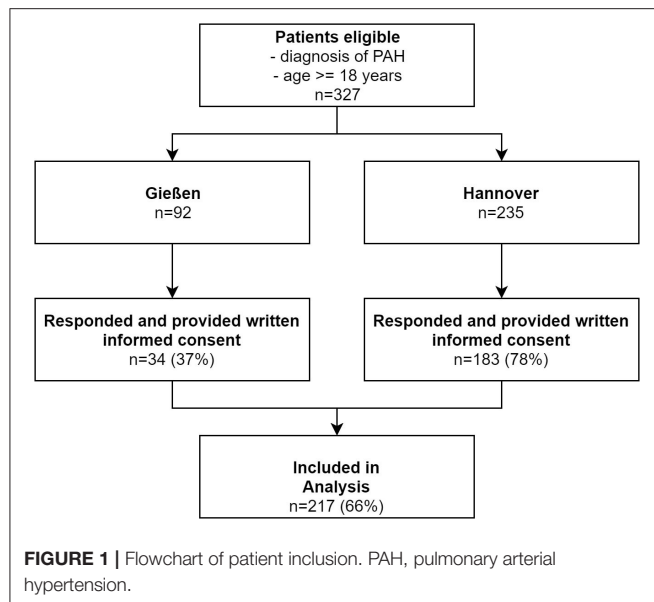
Mental disorders were defined according to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5).

Clinical Assessments

Clinical assessments at the time of the study included BMI, blood gas analyses, lung function tests including diffusion capacity of the lungs for carbon monoxide (DLCO), 6-min walk distance (6MWD), WHO functional class (FC), and serum levels of the N-terminal fragment of proBNP (NT-proBNP). Hemodynamic parameters at diagnosis were documented.

Comparison With General Population

To compare the prevalence of mental disorders in patients with PAH with the prevalence of mental disorders in the general population, data from a subsample aged 18–70 years of the mental health module of the German Health Interview and Examination Survey for Adults (DEGS1-MH; $n = 5,381$) were used (17).



Statistical Analysis

IBM SPSS Statistics 27.0 (IBM Corp, Armonk, NY, USA) and STATA 13.0 (StataCorp LP, College Station, Texas, USA) statistical software were used for analysis of the data. Continuous variables are shown as median and interquartile range (IQR) or as mean and SD, as appropriate. Categorical variables are shown as n and percent (%) unless indicated otherwise. To compare groups, χ^2 test, Mann-Whitney *U* test, or *t*-test was used as appropriate. Prevalence rates of mental disorders in PAH and a representative German population (DEGS1-MH study) were compared using χ^2 test. Point estimates with 95% CIs and differences between the two populations were calculated. To assess effect sizes, Cohen's *d* for continuous or risk ratios for categorical variables were calculated. To examine the impact of mental disorders on QoL, linear regression models were calculated to assess determinants on QoL (psychological, physical, and overall QoL were used as dependent variables). Using receiver operating characteristic (ROC) curve analysis with calculation of the area under the curve (AUC), the best cut-off values of Hospital Anxiety and Depression Scale A (for anxiety) and D (for depression) with the corresponding sensitivity and specificity on the structured clinical interview-derived outcomes panic disorder and depression disorder were calculated. *P*-values < 0.05 were considered statistically significant.

RESULTS

Participant Characteristics

Patients were contacted and interviewed between September 2019 and March 2020. A total of 327 patients were approached. Overall, 217 patients (66%) agreed to participate in the study, provided written informed consent, and took part in the interview (**Figure 1**). The patient characteristics are shown in **Table 1**.

Patients with mental disorders were younger, more likely to receive combination therapies for PAH, had a higher diffusion capacity of the lung for carbon monoxide, and were more likely to smoke than patients without mental disorders (**Table 1**). Disease severity as determined by FC, 6MWD, and NT-proBNP, hemodynamics at the time of PAH diagnosis, and alcohol consumption did not differ between the groups.

Prevalence of Mental Disorders in PAH

In this cross-sectional study, current mental disorders were detected in more than one third of the patients, with major depressive disorder and panic disorder being the most prevalent mental illnesses (**Table 2, Figure 2**). Major depressive disorder and panic disorder were about 3 times and 8 times, respectively, more frequent in patients with PAH than in the general population. In contrast, the prevalence of other psychiatric illnesses was similar in patients with PAH and in the general population (**Table 2, Figure 2**).

Of note, 38.2% of PAH patients showed signs and symptoms of adjustment disorder after receiving the PAH diagnosis, and 53% of these patients suffered from at least one other psychiatric disorder at the time of the psychiatric assessment.

Male and female patients with PAH did not differ concerning prevalence rates of any mental disorder (data not shown).

Diagnostic Value of the Hospital Anxiety and Depression Scale in Patients With PAH

At a cut-off value of ≥ 10 points, ROC curve analysis showed an AUC of 82.6% of the Hospital Anxiety and Depression Scale-A (95% CI 75.7–89.4%; $p < 0.001$) for the detection of panic disorder (**Figure 3A**). This resulted in a sensitivity of 63%, specificity of 85%, a positive predictive value of 42.9%, and a negative predictive value of 88.1%.

The AUC for the Hospital Anxiety and Depression Scale-D was 83.1% (95% CI 76.3–89.8%; $p < 0.001$) with an optimal cut-off of ≥ 9 points for the detection of major depressive disorder (**Figure 3B**). Sensitivity was 62%, specificity 80%, the positive predictive value was 47.7%, and the negative predictive value was 87.5%.

Quality of Life in PAH

The overall QoL of patients with PAH assessed by the WHOQOL-BREF tool was 50 (38–75) points. Patients with PAH and psychological disorders had a significantly lower QoL than those without psychological disorders: median, 38 (IQR, 25–63) points vs. median 63 (IQR, 50–75) points, $p < 0.001$. QoL for physical and psychological subscores were both significantly worse in patients with psychological disorders (**Table 1, Figure 4**). This was true notwithstanding the fact that the severity of PAH as determined by FC, 6MWD, and NT-proBNP at the time of the psychiatric assessment did not differ between patients with and without major mental disorders (**Table 1**).

Determinants of QoL

By linear regression analysis, WHO FC, 6MWD, and mental disorders were significant determinants of overall and physical QoL. Each increase in WHO FC was associated with a 10-point

TABLE 1 | Characteristics of the patients at baseline.

	All patients <i>n</i> = 217	Patients with depression or panic disorder <i>n</i> = 63 (29%)	Patients without depression or panic disorder <i>n</i> = 154 (71%)	<i>p</i> -value	Effect size (Cohen's <i>d</i> ^c or risk ratio ^d)
Age (years)	56 (44–66)	49 (39–59)	59 (49–68)	0.001	0.549 ^c
Female sex (%)	155 (71%)	46 (73%)	109 (71%)	0.741	1.03 ^d
BMI (kg/m ²)	26 (23–31)	26 (23–31)	25 (23–31)	0.569	−0.085 ^c
Diagnosis					
IPAH, <i>n</i> (%)	122 (56%)	31 (49%)	91 (59%)	0.076	0.83 ^d
HPAH, <i>n</i> (%)	25 (12%)	12 (19%)	12 (8%)	–	2.38 ^d
Associated PAH, <i>n</i> (%)	70 (32%)	20 (32%)	50 (33%)	–	0.97 ^d
Time since PAH diagnosis (years)	6 (3–11)	6 (2–11)	7 (3–12)	0.069	0.273 ^c
WHO FC					
I/II, <i>n</i> (%)	112 (52%)	26 (41%)	86 (57%)	0.134	0.72 ^d
III, <i>n</i> (%)	93 (43%)	35 (56%)	58 (38%)	–	1.47 ^d
IV, <i>n</i> (%)	10 (5%)	2 (3%)	8 (4%)	–	0.75 ^d
6MWD (m)	439 (353–521)	429 (344–525)	445 (359–523)	0.787	0.042 ^c
NT-proBNP (ng/L), <i>N</i> = 62	184 (88–517)	199 (64–801)	181 (100–469)	0.455	−0.119 ^c
DLCO (% pred.)	62 (47–74)	66 (57–75)	56 (42–73)	0.021	−0.426 ^c
paO ₂ , mmHg	67 (60–75)	68 (61–77)	66 (58–75)	0.072	−0.273 ^c
Hemodynamics at diagnosis					
mPAP (mmHg)	48 (41–57)	48 (41–56)	49 (40–58)	0.720	0.066 ^c
PAWP (mmHg)	9 (6–12)	8 (6–11)	9 (6–12)	0.231	0.189 ^c
CI (L/min/m ²)	2.4 (2.0–2.9)	2.4 (2.2–3.0)	2.4 (2.0–2.9)	0.512	0.103 ^c
PVR (dyn·s·cm ^{−5})	707 (501–947)	698 (510–958)	710 (500–930)	0.884	0.023 ^c
PAH medication					
Monotherapy	44 (20%)	10 (14%)	34 (24%)	0.037	0.58 ^d
Double combination	102 (47%)	26 (41%)	76 (49%)	–	0.84 ^d
Triple combination	71 (33%)	27 (43%)	44 (29%)	–	1.48 ^d
Smoking status					
Active, <i>n</i> (%)	24 (11%)	12 (19%)	12 (8%)	0.027	2.38 ^d
Former, <i>n</i> (%)	31 (14%)	11 (18%)	20 (13%)		1.38 ^d
Never, <i>n</i> (%)	162 (75%)	40 (64%)	122 (79%)		0.81 ^d
Pack years	14 (5–25)	11 (5–19)	15 (5–26)	0.151	0.385 ^c
Sociodemographic items					
Drinking (drinks per week) ^a	0.8 ± 2.0	0.9 ± 2.8	0.8 ± 1.5	0.600	−0.082 ^c
Exercise score (points)	3 (2–4)	3 (2–3)	3 (2–4)	0.565 ^b	0.107 ^c
HADS-A (points)	6 (2–9)	10 (7–12)	4 (2–7)	<0.001	−1.46 ^c
HADS-D (points)	5 (2–8)	9 (5–13)	4 (2–6)	<0.001	−1.344 ^c
QoL-overall (points)	50 (38–75)	38 (25–63)	63 (50–75)	<0.001	0.686 ^c
QoL-psych (points)	71 (58–79)	50 (41–67)	75 (63–83)	<0.001	0.853 ^c
QoL-physical (points)	57 (45–75)	46 (32–64)	64 (50–75)	<0.001	0.818 ^c

Continuous variables are stated as median and interquartile ranges (IQR) and categorical variables are stated as *n* and percent (%), unless indicated otherwise.

^aMean and SD because of distribution of the data.

^bNon-parametric Mann–Whitney *U* test because of ordinal scale of the variable.

^cCohen's *d*.

^dRisk ratio.

BMI, body mass index; QoL, quality of life; HADS-A, Hospital Anxiety and Depression Scale—anxiety; HADS-D, Hospital Anxiety and Depression Scale—Depression; I/HPAH, idiopathic or heritable pulmonary arterial hypertension; WHO FC, World Health Organization Functional Class; 6MWD, 6-min walking distance; BNP, brain natriuretic peptide; NT-proBNP, N-terminal fragment of pro-brain natriuretic peptide; DLCO, diffusion capacity of the lung for carbon monoxide; paO₂, mmHg, arterial pO₂; mPAP, mean pulmonary arterial pressure; PAWP, pulmonary artery wedge pressure; CI, cardiac index; PVR, pulmonary vascular resistance; IQR, interquartile range. Statistically significant values as bold.

TABLE 2 | Prevalence of common mental disorders of PAH in comparison with data from the general German population (DEGS1-MH).

	PAH <i>n</i> = 217	DEGS1-MH <i>n</i> = 5318	<i>p</i> -value	Risk ratio
Any current mental disorder	38.2 (32.0–44.9)	27.7% (26.3–29.2)	<0.001	1.38
Alcohol abuse	0.4% (0.08–2)	1.8% (1.4–2.3)	— ^a	0.22
Alcohol dependence	1.3% (0.4–3)	3.0% (2.5–3.6)	— ^a	0.43
Schizophrenia	0.4% (0.08–2)	2.6% (2.1–3.2)	— ^a	0.15
Major depressive disorder	23% (17–29)	7.7% (6.9–8.6)	<0.001	2.99
Bipolar 1 disorder	0.4% (0.08–2)	1.0% (0.7–1.4)	— ^a	0.40
Panic disorder	15.2% (11–20)	2.0% (1.6–2.5)	<0.001	7.60
Agoraphobia	5.9% (3.5–9.9)	4.0% (3.4–4.7)	0.147	1.48
Social phobia	3.6% (1.8–7.1)	2.7% (2.2–3.4)	0.387	1.33
Generalized anxiety disorder	2.7% (1.2–5.8)	2.2% (1.8–2.8)	0.580	1.23
Specific phobia	10.6% (7.1–15.4)	10.3% (9.3–11.3)	0.889	1.03
PTSD	4.1% (2.2–7.7)	2.3% (1.8–2.8)	0.078	1.78
Obsessive compulsive disorder	5.9% (3.5–9.9)	3.6% (3.1–4.4)	0.066	1.64
Anorexia nervosa	0% (0–1.7)	0.7% (0.5–1.1)	— ^a	0.00
Bulimia nervosa	0.4% (0.1–2)	0.2% (0.1–0.3)	— ^a	2.00

Psychological disorder prevalence rates per group stated as percent (%) and 95% CIs and risk ratios.

^aSamples do not satisfy the standard binomial requirement.

PTSD, posttraumatic stress disorder; DEGS1-MH, Studie zur Gesundheit Erwachsener in Deutschland (German study of health status in adults)—Mental Health; PAH, pulmonary arterial hypertension. Statistically significant values as bold.

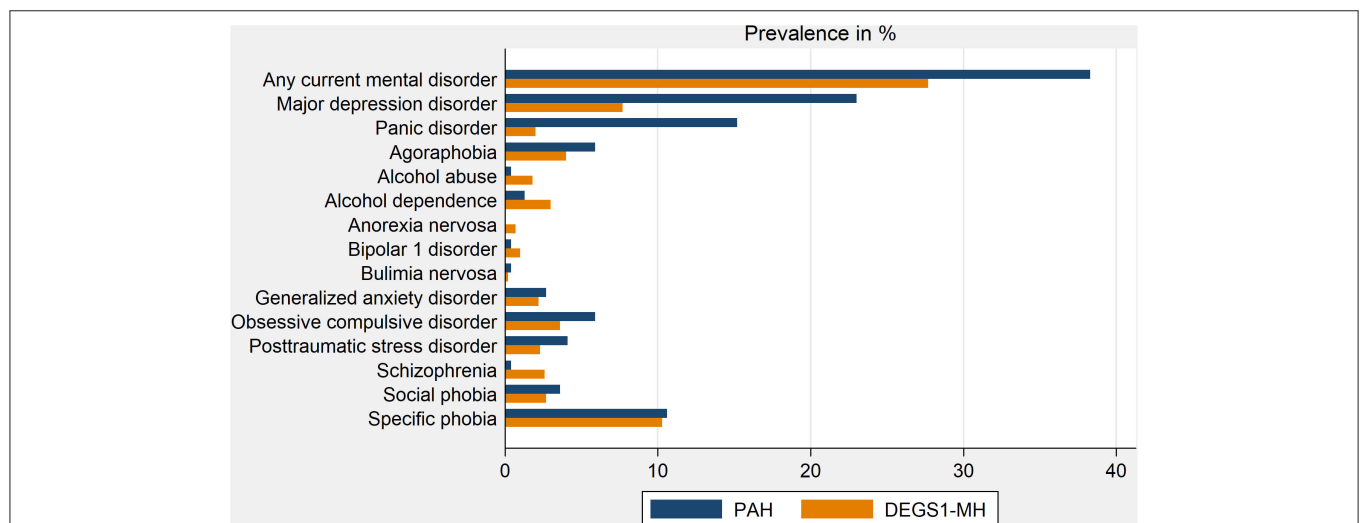


FIGURE 2 | Comparison of mental disorders prevalence in patients with PAH and the German population. DEGS1-MH, Studie zur Gesundheit Erwachsener in Deutschland (German study of health status in adults)—Mental Health; PAH, pulmonary arterial hypertension.

decline in the overall QoL, and a decline in 6MWD by 10 m was accompanied by a 0.3-point decline in QoL. The presence of depression was associated with a 13-point decline in QoL and the presence of panic disorder was associated with an 8-point decline in QoL. Physical QoL decreased by 9 points per WHO FC worsening, by 14 points in the presence of depression, and by 8 points in the presence of panic disorder. Psychological QoL was determined mainly by the presence of depression disorder (−20 points) and panic disorder (−10 points), but also by 6MWD (0.4 points per 10 m).

DISCUSSION

To the best of our knowledge, this was the first study to systematically assess the prevalence of psychiatric disorders in patients with PAH by structured face-to-face interviews. The main findings can be summarized as follows: (1) more than one third of our patients had psychiatric disorders, mainly major depressive disorder and panic disorder, exceeding the prevalence of these mental disorders in the general population; (2) the presence of psychiatric disorders had a substantial impact on

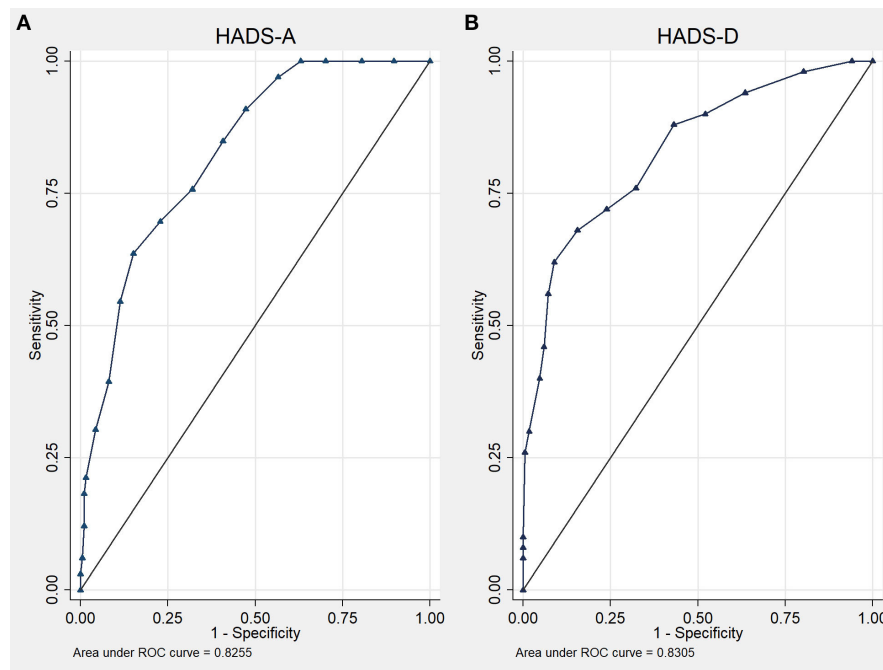


FIGURE 3 | Receiver operating characteristic curves of the Hospital Anxiety and Depression Scale (HADS) for the detection of panic disorder **(A)** and depression disorder **(B)**.

QoL; using linear regression analysis, major depression disorder was associated with a 13-point decline in the overall QoL on an ordinal scale ranging from 0 to 100 points, and the presence of panic disorder reduced QoL by 8 points; (3) more than one third of the patients under study reported signs and symptoms of adjustment disorder within the first 3 months after receiving the PAH diagnosis, and more than half of these patients developed other psychiatric disorders during the course of the disease; and (4) the Hospital Anxiety and Depression Scale may be a useful screening tool for the identification of probable cases of major depressive disorder and panic disorder in patients with PAH.

The high prevalence of psychiatric disorders in our cohort of patients with PAH was driven by depression and panic disorder, which were about 3 times and 8 times, respectively, more frequent than in the general population. This is in line with previous observations in patients with other chronic cardiovascular diseases such as congenital heart disease and heart failure (18, 19) and in other chronic diseases such as diabetes mellitus type 1 (20) or chronic obstructive pulmonary disease (21). In contrast, the prevalence of other major psychiatric disorders such as schizophrenia, bipolar disorders and alcohol dependence was not increased in our patients. Not unexpectedly, psychiatric disorders, foremost depression, had a major impact on QoL in our patients, contributing as much as the physical impairment to the reduced QoL. Hence, psychiatric disorders may become targets of therapy in this patient population.

To better understand and treat psychiatric disorders in patients with PAH, several key points have yet to be addressed. First, longitudinal assessment starting at the time of diagnosis

is needed to distinguish between pre-morbid conditions and disorders that develop after the PAH diagnosis. Second, the role of adjustment disorders in the development of psychiatric disorders needs to be further clarified. In our study, 38.2% of the patients reported signs and symptoms associated with adjustment disorders after they received the PAH diagnosis. It is conceivable that this may have been the best time for therapeutic intervention, which may have prevented the development of manifest psychiatric disorders in some patients. Recently, successful psychological treatment of a patient with newly diagnosed PAH suffering from severe adjustment disorder using metacognitive treatment was described (22). Metacognitive treatment belongs to the wide spectrum of “third wave” cognitive behavioral therapies (23) and has the advantage of relatively short treatment duration. However, systematic studies and RCTs are not available at the moment, leading to the third key point, that the effects of psychotherapeutic interventions on psychiatric disorders and QoL in patients with PAH need to be studied in more detail.

Fourth and final, a proper diagnosis of psychiatric disorders in patients with PAH is a prerequisite for therapeutic interventions. Patients with PAH are mostly treated by cardiologists and pneumologists, i.e., physicians with limited experience in the detection of psychiatric disorders. As structured psychosomatic support is not yet part of the standard management of these patients in most pulmonary hypertension centers, a validated diagnostic tool might prove useful to identify or rule out the presence of psychiatric disorders. In the present study, we investigated the Hospital Anxiety and Depression Scale. This

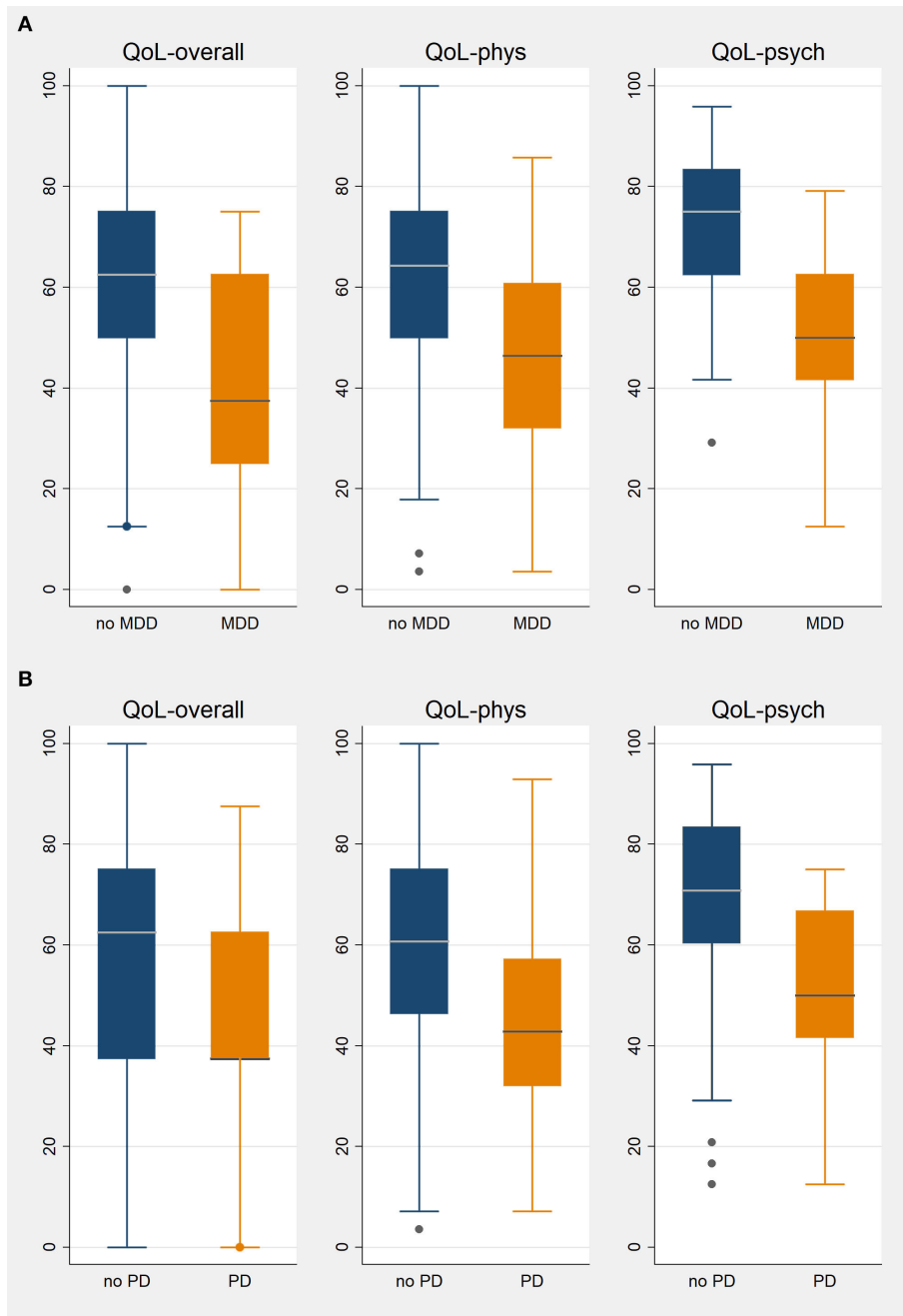


FIGURE 4 | Quality of life in PAH patients with or without major depression disorder **(A)** or panic disorder **(B)**. QoL, quality of life; phys, physical; psych, psychological; MDD, major depression disorder, PD, panic disorder; box plots show medians and interquartile ranges.

diagnostic tool was originally designed for medical inpatient patients and represents an established self-rating scale for non-psychiatric patients to detect depression and anxiety as a comorbidity (14). Several studies evaluated the diagnostic value of the HADS for various medical conditions. As a common feature, diagnostic accuracy varied according to the heterogeneity of patient groups and the underlying medical condition chosen, raising questions regarding its validity and concerning the

optimal diagnostic cut-off points for particular physical diseases (24, 25). For example, in a recent study lower cut-off points for the detection of anxiety disorders and major depressive disorder were proposed for adults with congenital heart disease compared with the originally published cut-offs (19). In our study, the Hospital Anxiety and Depression Scale was found to have positive predictive values of 47.7 and 42.9%, respectively, and negative predictive values of 87.5 and 88.1%, respectively,

for the detection of depression and panic disorder. Hence, the Hospital Anxiety and Depression Scale may be used as screening tool which may help non-experts to rule out the presence of depression and panic disorders, the most frequent psychiatric abnormalities in the present study. Pending further data, it might be advisable to recommend psychiatric or psychosomatic evaluation in patients with suspicious findings on the Hospital Depression and Anxiety Scale. However, it may be even more useful to develop specific questionnaires for patients with PAH, including tools with a high sensitivity for adjustment disorders, which can be used during the first 3 months after the diagnosis has been established.

Our study has strengths and limitations. The main strength is the inclusion of a relatively large set of patients with PAH who all underwent a structured face-to-face interview, which is considered the gold standard of psychiatric assessment. Limitations include the fact that only two centers from a single country participated. In addition, this cross-sectional study did not provide longitudinal data on the course of psychiatric disorders and also no data on the presence of psychiatric disorders before the development of PAH. In addition, the diagnosis of adjustment disorder after the PAH diagnosis was mainly based on retrospective assessments and may be confounded by recall bias.

In summary, our study showed a high prevalence of psychiatric disorders, especially major depressive disorder and panic disorder, in patients with PAH. The presence of these psychiatric disorders was associated with a profound reduction in QoL. In addition, our study found hints for a high prevalence of adjustment disorders after the diagnosis of PAH has been received. In some patients, adjustment disorders might be a starting point for the development of major mental disorders and may therefore provide an opportunity for early psychotherapeutic interventions. Further studies are needed to better understand the development of mental disorders in patients with PAH, to obtain reliable screening tools, and to assess therapeutic interventions.

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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 Ethics committee, Hannover Medical School, Hannover, Germany. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

KMO was responsible for study design, implementation of the study, data collection, statistical analysis, data interpretation, and drafting the manuscript. TM was responsible for study design, implementation of the study, data collection, conducting the interviews, statistical analysis, data interpretation, and drafting the manuscript. JF was responsible for implementation of the study, data collection, statistical analysis, data interpretation, and drafting the manuscript. JCK and MJR were responsible for implementation of the study, data interpretation, and revising the manuscript. HG was responsible for study design, implementation of the study, data collection, data interpretation, and revising the manuscript. HAG was responsible for implementation of the study, data collection, data interpretation, and revising the manuscript. PF, RS, H-DK, IH, NL, and M-RD were responsible for study design, data interpretation, and revising the manuscript. MMH and KGK were responsible for study design, implementation of the study, statistical analysis, data interpretation, and drafting the manuscript. All authors contributed to the article and approved the submitted version.

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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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Impact of SARS-CoV-2-Pandemic on Mental Disorders and Quality of Life in Patients With Pulmonary Arterial Hypertension

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Background/Objective: Covid-19 pandemic may affect mental health and quality of life (QoL) in patients with pulmonary arterial hypertension (PAH). We assessed changes in anxiety and depression, quality of life (QoL) and self-described impact of Covid-19 in patients with PAH during the Covid-19 pandemic.

Methods: This study included 152 patients with PAH from two German referral centers. Anxiety and depression were assessed using the Hospital Anxiety and Depression Scale (HADS-A and HADS-D) at two different timepoints before and during the Covid-19 pandemic with a median of 232 days between baseline and follow-up. QoL was assessed using EQ-5D and emPHasis-10. Perceived impact of Covid-19 and related regulations and measures were assessed using a set of specific questions and statements.

Results: More than two thirds of patients had an unsuspicious HADS-A and HADS-D. Median scores did not differ from baseline for both HADS-A and HADS-D ($p = 0.202$; $p = 0.621$). Overall, no significant changes in HADS-A or HADS-D categories from baseline to follow up were observed ($p = 0.07$; $p = 0.13$). QoL did not change between baseline and follow-up. The Covid-19 pandemic had little impact on access to medical care and established PAH therapy. Patients were in agreement with governmental measures and regulations and felt sufficiently safe.

Conclusion: First waves of Covid-19 pandemic had little impact on anxiety, depression and QoL in patient with PAH. Established PAH therapy and access to medical care were not affected. Further studies on the impact of prolonged duration of the ongoing Covid-19 pandemic are needed.

Keywords: Covid-19 pandemic, pulmonary arterial hypertension, mental disorder, depression, anxiety

INTRODUCTION

Since the first confirmed case of coronavirus disease 19 (Covid-19) caused by the novel beta-coronavirus SARS-CoV-2 was reported in January 2020, the disease has had great impact on every aspect of German society (1). In March 2020 the World Health Organization (WHO) declared Covid-19 a pandemic. The incidence in Germany has increased to over 2.29 Mio. cases including over 60,000 deaths so far (2). In response to the rising number of cases and deaths attributed to Covid-19, nationwide governmental measures such as mandatory quarantine, lockdown and physical distancing guidelines were implemented. Covid-19 has greatly affected the economy, employment and public health. Recent studies indicate implications of Covid-19 pandemic on mental health with higher levels of perceived stress, anxiety and depression (3–7). Bauerle et al. found increased anxiety and depression symptoms during the Covid-19 outbreak Germany. Covid-19 related fear proved to be a strong predictor of changes in mental health before and during the Covid-19 pandemic (8).

Pulmonary arterial hypertension (PAH) is a rare progressive pulmonary disease characterized by remodeling of pulmonary vasculature leading to increased pulmonary vascular resistance and left untreated to death by right heart failure (9, 10). Patients with PAH experience symptoms such as dyspnea on exertion, fatigue, syncope and clinical signs of heart failure impairing physical activities and quality of life (QoL) (11). Despite vast advances in therapeutic options over the last decades and subsequent improvements in clinical outcomes, PAH remains a life-threatening illness (12).

Only few studies have addressed the prevalence of psychiatric disorders in PAH patients (13, 14). Lowe et al. demonstrated a high prevalence of anxiety and depression with disease progression (15). Frequency of adjustment disorders, anxiety and depression correlate with intensity of symptoms and functional impairment in patients with PAH (16). Olsson demonstrated a higher prevalence of anxiety and depression disorders in PAH compared to levels in the German general public (17, 18). Yogeswaran et al. found significant negative impact of the Covid-19 pandemic on access to medical care for patients with suspected pulmonary hypertension (PH) due pandemic related restrictions in Germany (19).

The present study aimed to assess changes on mental health and QoL during the Covid-19 pandemic and the impact of the pandemic in a PAH cohort with a higher prevalence of anxiety and depression disorder.

METHODS

This prospective, exploratory observational multicenter study included patients with confirmed PAH of a cohort previously described in the PEPPAH-study (18), at two participating PH referral centers (Hannover Medical School and University of Giessen, both in Germany). This study was conducted from May 7th, 2020 to August 4th, 2020 by a self-administrated questionnaire. All patients gave written informed consent. The study was approved by local institutional review board (Nr. 8540_BO_K_2019). The questionnaire was mailed to study participants together with a free postage reply envelope.

Patient Setting and Clinical Parameters

All patients who had previously participated in the PEPPAH study where reapproached *via* mail. Patients were selected based on diagnosis of PAH according to current criteria (9) and age ≥ 18 years. Baseline assessment defined as timepoint of PEPPAH also included hemodynamics from right heart catheterization at time of diagnosis, 6-min walk distance (6MWD), WHO functional class (FC), and serum levels of N-terminal fragment of pro-brain natriuretic peptide (NT-proBNP). Follow up assessment was defined as last available clinical data not older than 90 days at time of questionnaire. Risk assessment for our cohort was based on three variables FC, 6MWD, and BNP/NT-proBNP as previously described (20, 21). Each variable was graded with a number as low risk (1), intermediate risk (2) and high risk (3). The average risk was calculated by dividing the sum of the grades by the number of available variables and rounding to the next integer (22). Hospital-wide Covid-19 regulations restricted in-person care to urgent or emergency outpatient visits. To compensate for this, we provided remote monitoring of symptoms, general condition and medication *via* phone or email for our outpatients.

Assessment of Mental Disorders and Covid-19 Implications

We assessed symptoms of anxiety and depression, health-related quality of life (HRQoL) and Covid-19 pandemic related questions. Participants completed the following set of questionnaires: the Hospital Anxiety and Depression Scale (HADS) (23), the EuroQoL EQ-5D subscored in EQ-5D-3L and EQ-VAS (24), emPHasis-10 (25), and Covid-19 pandemic related questions (Table 2). The HADS questionnaire is divided into subscales for anxiety (HADS-A) and depression (HADS-D), each containing 7 questions for a maximum of 21 points per subscale. The higher score indicating a more severe anxiety or depression. Zigmond and Snaith (23) proposed a score >11 per subscale to be associated with significant anxiety or depression. A cut-off score of 8 or above for both HADS-A and HADS-D was validated, showing probable signs of anxiety or depression (26, 27). The EQ-5D-3L has five dimensions. Higher scores indicate a better quality of life. The EQ-VAS is a scale with a range from 0 (the worst health you can imagine) to 10 (the best health you can imagine). The emPHasis-10 is a PH specific HRQoL questionnaire. The emPHasis-10 score ranges from 0 to 50 with higher scores indicating worse HRQoL. Covid-19 related questions applying a

Abbreviations: 6MWD, 6-minute walk distance; BNP, brain natriuretic peptide; Covid-19, coronavirus disease 19; FC, World Health Organization functional class; HADS, Hospital Anxiety and Depression Scale; HRQoL, health-related quality of life; NT-proBNP, N-terminal fragment of probrain natriuretic peptide; PAH, Pulmonary arterial hypertension; PEPPAH, Psychische Einschränkungen bei Patienten mit pulmonal arterieller Hypertonie (Prevalence of mental disorders and impact on quality of life in patients with pulmonary arterial hypertension); PH, pulmonary hypertension; QoL, quality of life; SARS, Severe acute respiratory syndrome; SD, standard deviation; WHO, World Health Organization.

6 point Likert scale (1 = strongly disagree to 6 = strongly agree) ranged from subjective impact on everyday life, general anxiety to PH-therapy and opinion on governmental regulations during the Covid-19 pandemic (see **Supplementary Material**). Frequency of outpatient visits at the time of this study were compared to the same timeframe in 2019.

Statistical Analysis

IBM SPSS Statistics (version 27.0, IBM Corp., Armonk, New York) and Stata 13.0 (State Corp LP, College Station, Texas, USA) statistical software programs were used for statistical analysis. All analyses were descriptive and there was no formal study hypothesis. Categorical data were presented as counts with percentages. Continuous variables were presented as median with the first and third quartile (Q1 and Q3) or as mean and standard deviation (SD). For group comparisons Chi-square, Fisher's exact-test or McNemar Bowkers-Test, paired *t*-test or Wilcoxon-test were used as appropriate. All tests were two-sided, a *p*-value of < 0.05 was considered statistically significant.

RESULTS

The questionnaires were employed on the May 7th, 2020 for Hannover and May 18th, 2020 for Giessen, respectively. The last questionnaire was returned on July 3rd, 2020. Data collection was conducted ~7 months after the PEPPAH study. A total of 204 patients were approached in this study. One hundred and fifty-two patients (75%) (27 from Giessen and 125 from Hannover) agreed to participate and returned their self-administered questionnaires. One patient died shortly before mailing arrived and one patient refused participation. Patient characteristics are shown in **Table 1**. The majority of patients were female (*n* = 111, 73%); median age was 58 (49–67) years. All patients were treated with PAH medications, most of them (74%) with dual combination therapy.

Clinical Parameters

ESC/ERS risk status, disease severity (FC, 6MWD, NTproBNP), reported subjective condition and stair-climbing performance did not differ between baseline and follow-up (see **Table 2**).

Psychological Effects During the Covid-19 Pandemic

The majority of patients (68%) had an unsuspicious HADS-A with an overall median score of 6. One third were classified suspected (22%) or probable (11%) for an anxiety disorder. Median HADS-A score did not differ from baseline (*p* = 0.202). For HADS-D the majority of patients was unsuspicious (78%), and 22% had signs of suspected or probable depression disorder (see **Table 2**). Median HADS-D score did not differ from baseline (*p* = 0.621). Overall, no significant changes in HADS-A or HADS-D categories from baseline to follow up were observed (*p* = 0.07 and *p* = 0.13, respectively). For both HADS-A and HADS-D, more patients were classified with a suspected score at follow-up and less people with a probable score. Transitions in HADS-A and HADS-D categories are shown in **Figure 1**. For HADS-A, 25 patients (16%) and HADS-D 21 patients (14%)

TABLE 1 | Patient characteristics.

All patients— <i>n</i>	152
Site—<i>n</i> (%)	
- Hannover	125 (82%)
- Giessen	27 (18%)
Sex—<i>n</i> (%)	
- Female	111 (73%)
- Male	41 (27%)
Age—median (IQR)	58 (49–67)
Diagnosis—<i>n</i> (%)	
- 1.1 IPAH	80 (53%)
- 1.2 HPAH	17 (11%)
- 1.4 Associated PAH	53 (35%)
- 1.6 PVOD/PCH	2 (1%)
PH-Therapy—<i>n</i> (%)	
- PDE5i	126 (83%)
- ERA	121 (80%)
- PCA (Selexipag and Treprostinil)	42 (28%)
- TKI	5 (3%)
- sGCs	15 (10%)
- CCB	21 (14%)
Time—median (IQR)	
- From diagnosis to baseline—years	8 (4–14)
- From baseline to follow up—days	232 (204–240)

Continuous variables are stated as median and interquartiles ranges (IQR) and categorical variables are stated as *n* and percent (%), unless stated otherwise. I/HPAH, idiopathic or heritable pulmonary arterial hypertension; PVOD/PCH, pulmonary veno-occlusive disease/pulmonary capillary hemangiomatosis; PDE5i, phosphodiesterase-5 inhibitors; ERA, endothelin receptor antagonists; PCA, prostacyclin receptor agonists; TKI, tyrosine kinase inhibitor; sGCs, stimulators of soluble guanylate cyclase; CCB, calcium channel blocker.

changed categories. Measured by emPHasis-10, HRQoL was significantly lower on follow-up (18 points) than at baseline (14 points). HRQoL measured by EQ5D-3L and EQ-VAS did not differ between baseline and follow-up (see **Table 2**).

Covid-19 Pandemic Related Questionnaire and Outpatient Care

The majority of patients felt affected in their everyday life (mean 3.93 ± 1.55) due to the pandemic. Anxiety about Covid-19 did not have implications on patient's everyday life (2.44 ± 1.65). The majority of patients stated that their PH therapy did not suffer during the Covid-19 pandemic (mean 1.70 ± 1.27). Most of them were in agreement with governmental regulations and the ability to self-protect during the Covid-19 pandemic (mean 4.89 ± 1.31 ; mean 4.76 ± 1.40 , see **Figure 2**). The Covid-19 pandemic showed little impact on fear of worsening of existing mental illness (mean 1.89 ± 1.23). Patients did not see a need for more phone or video consultations from their physician (mean 1.89 ± 1.51). Access to medical care and medication was perceived as unproblematic (Likert scales prior and during the Covid-19 pandemic for medical care 1.46 vs. 2.16 and medication 1.53 vs. 1.79). Outpatient visits during Covid-19 pandemic decreased by 46% from March to June 2020 reaching its lowest rate in

TABLE 2 | Comparison of psychological, clinical parameters and HRQoL.

	Baseline	Follow-up	p-value
HADS-A-Score—median (IQR)	6 (2–9)	6 (3–8)	0.202
- Unsuspicious	100 (66%)	103 (68%)	0.070*
- Suspected	26 (17%)	33 (22%)	
- Probable	26 (17%)	16 (11%)	
HADS-D-Score—median (IQR)	5 (2–7)	4 (2–7)	0.621
- Unsuspicious	117 (77%)	118 (78%)	0.135*
- Suspected	15 (10%)	22 (15%)	
- Probable	20 (13%)	12 (8%)	
emPHasis10—median (IQR)	14 (8–25)	18 (11–29)	0.009
EQ5D-3L—median (IQR)	8 (7–9)	8 (6–9)	0.181
EQ-VAS—median (IQR)	7 (6–8)	7 (5–8)	0.366
Subjective condition—n (%)			0.899*
- Better	5 (9%)	15 (10%)	
- Stable	44 (79%)	116 (76%)	
- Worsened	7 (13%)	21 (14%)	
Stair climbing—n (%)			0.276*
- >2	11 (33%)	35 (23%)	
- 2	8 (24%)	52 (35%)	
- 1	13 (39%)	47 (31%)	
- 0	1 (3%)	16 (11%)	
WHO FC—n (%)			0.766*
- I	16 (11%)	6 (12%)	
- II	72 (48%)	26 (51%)	
- III	63 (41%)	19 (37%)	
6MWD—median (IQR)	452 (365–532)	457 (367–528)	0.132
NT-proBNP (ng/l) —median (IQR)	179 (84–419)	314 (123–1024)	0.836
ESC/ERS risk status—n (%)			-
- Low	40 (67%)	41 (55%)	
- Intermediate	20 (33%)	33 (44%)	
- High	0 (0%)	1 (1%)	

Continuous variables are stated as median and interquartiles ranges (IQR) and categorical variables are stated as n and percent (%), unless stated otherwise. *Chi²-Test HADS, Hospital Anxiety and Depression Scale; WHO FC, World Health Organization Functional Class; 6MWD, six-minute walking distance; NT-proBNP, N-terminal fragment of pro-brain natriuretic peptide; ESC, European Society of Cardiology, ERS, European Respiratory Society.

March 2020 with 32% of ambulatory visits compared to the same timeframe in 2019.

DISCUSSION

The present study showed a limited impact of the Covid-19 pandemic on anxiety, depression and QoL in patients with PAH. Olsson identified higher prevalence of depression and panic disorder in patients with PAH contributing to impaired QoL (18). Psychological distress in PAH results from impact on daily life due to physical limitations, unclear prognosis and unemployment (28, 29). Our study revealed transitions between HADS-A and HADS-D categories from baseline to follow-up. Whereas there were no significant changes between groups overall, individual patients moved from unsuspicious to

suspected and for HADS-D even one patient from unsuspicious to probable, indicating an individual risk of mental health deterioration. For HADS-A these individual transitions also showed a trend for overall changes between category groups ($p = 0.07$). It remains unclear if changes in mental health assessment stem from normal range variations or if they imply an impact of the Covid-19 pandemic.

Overall QoL did not differ prior to and during the Covid-19 pandemic, which may have been related—at least partly—to the fact that access to medical care was not impaired. While some changes in QoL were detected using emPHasis-10, QoL remained stable with a median well below 20 points for both baseline and follow up. The changes were mainly driven by emPHasis-10 subscores for confidence in public places (subscore 7) and independency (subscore 9), indicating effects of Covid-19 pandemic related regulations such as social distancing measures.

In a recent study Ammar et al. demonstrated negative effects on mental well-being and emotional status caused by social distancing and self-isolation during the Covid-19 pandemic using an international cross-disciplinary online survey. However, only 21% of the participants came from Europe and there was (and is) a wide regional variation in Covid measures and access to medical care (30). In line with our study, unpublished data from a lung cancer cohort of our hospital showed little effect on mental health during the Covid-19 pandemic which might also be due to the consistent and stable medical care of this patient population.

Attitude toward governmental measures might have an impact on mental health during the Covid-19 pandemic. On March 22nd, 2020, lockdown measures such as restrictions on gatherings, social distancing restrictions and closure of non-essential businesses were put in place in Germany. Our study showed that our patients were mostly in agreement with these governmental regulations. While patients felt an impact on their everyday life, they were not afraid of worsening of mental illness. While Yogeswaran et al. (19) saw impacts on initial PH care and treatment initiation in patients with newly diagnosed PH, our cohort reported little impact on established PH-therapy. Even though we saw reduction in outpatient visits during the time of the study we can presume that established remote patient care was deemed sufficient in patients with stable disease.

Popularity of telemedicine has risen during the Covid-19 pandemic. Kayser et al. demonstrated video consultations as a valuable tool in quality health care in a selected patient group during the Covid-19 pandemic (31). Phone and email consultations as well as a repeat prescription online ordering service developed into a mainstay of patient care at our center during the Covid-19 pandemic and were readily accepted by our patients. This might explain why we did not see a need for additional video consultations.

There are several limitations to this study. The assessment was limited to the first wave of infection in Germany in a time of decreasing infections and a falling infection curve. This and the relatively short observation period may have led to underestimation of the psychological impact on the pandemic on patients with PAH. Still, the Covid-19 pandemic continued after a summer with low infection rates with a second wave and increasing rates in autumn 2020. Impact of the continuing

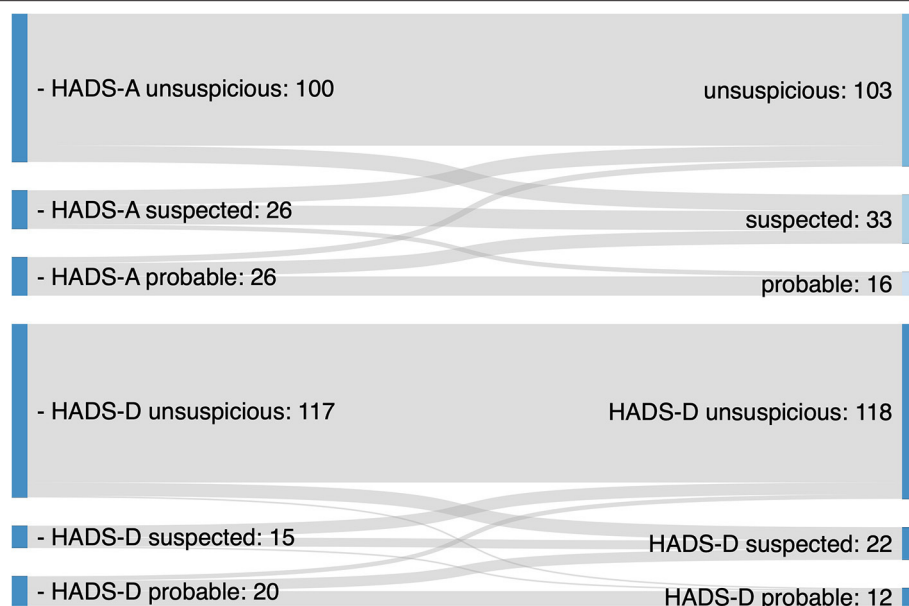


FIGURE 1 | Changes in HADS-A and HADS-D categories prior to and during the Covid-19 pandemic.

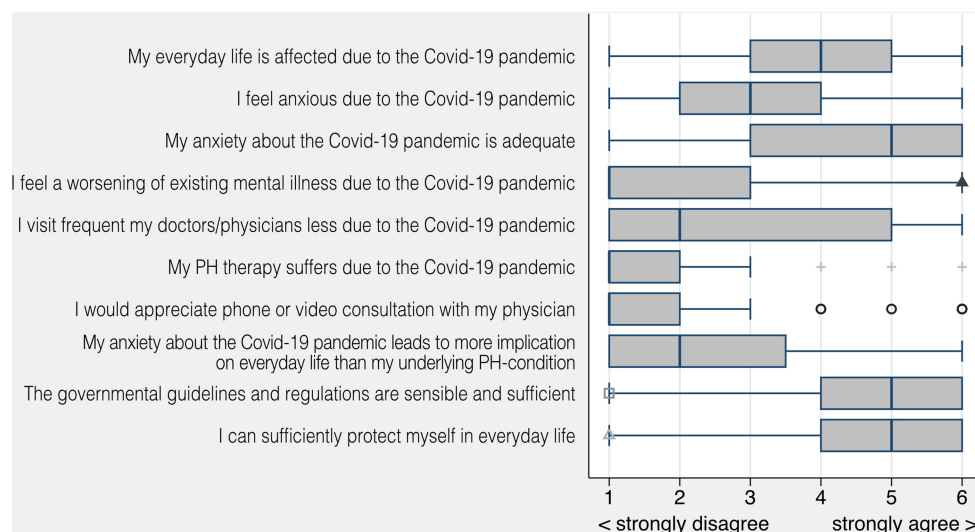


FIGURE 2 | Covid-19 pandemic specific questions; Likert scale 1 = strongly disagree to 6 = strongly agree.

Covid-19 pandemic including aspects of prolonged duration, further isolation and restrictions, economical and personal burden of family members or friends are not represented in this study. Availability of clinical parameters were limited. Questionnaires for both time points were sent by mail and interviews were conducted *via* phone. Ambulatory visits were not obligatory so nearby clinical data to the time points of the study were not always available. In addition, data on pre-existing mental disorders were not available.

The psychiatric tools used in the present study have not been validated in patients with PAH. HADS is a widely used tool

to assess anxiety and depression in non-psychiatric patients. In patients with heart disease, HADS shows high specificity for the detection of major depression but a limited sensitivity for mild depression disorder (32). Another limitation is potential selection bias. Although 75% of our patient responded, we cannot be certain that the results would have been different with a higher response rate. Further bias might be due to stigma or self-stigma which may cause serious problems in patients with mental disorders. We cannot rule out the possibility that patients with PAH are underscored in the administered self-rating scales, particularly the HADS (33–35).

In conclusion, the Covid-19 pandemic had little impact on intensity of anxiety or depression and overall QoL in our cohort of patients with PAH. While the number outpatient visits declined, access to medical care and established PAH therapy was felt appropriate. The impact of the ongoing Covid-19 pandemic with prolonged lockdown measures remains unknown and deserves further investigation.

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

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AUTHOR CONTRIBUTIONS

DHP and JF were responsible for study design, implementation of the study, data collection, statistical analysis, data interpretation, and drafting the manuscript. KO and MH were responsible for study design, implementation of the study, data interpretation, and critically revising the manuscript. JK, TM, and KK were responsible for data interpretation and revising the manuscript. HAG, HG, and MR were responsible for implementation of the study, data collection, data interpretation, and revising the manuscript. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: <https://www.frontiersin.org/articles/10.3389/fpsy.2021.668647/full#supplementary-material>

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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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Prevalence of Child Maltreatment in Adults With Congenital Heart Disease and Its Relationship With Psychological Well-Being, Health Behavior, and Current Cardiac Function

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Background: The prevalence of child maltreatment in adults with congenital heart disease (ACHD) has not been assessed so far. Child maltreatment is a major risk factor for unfavorable behavioral, mental, and physical health outcomes and has been associated with decreased quality of life. Given the increased survival time of ACHD, it is essential to assess factors that may worsen the quality of life and interact with classical cardiovascular risk factors and mental well-being.

Methods: In a cross-sectional study, 196 ACHD (mean age 35.21 ± 11.24 y, 44.4% female, 55.6% male) completed a thorough psychiatric and cardiac evaluation. Child maltreatment was assessed using the Childhood Trauma Questionnaire (CTQ) and rates were compared to already existing data from the German general population. Further psychological measurements included the WHO Quality of Life Questionnaire, Hospital Anxiety and Depression Scale (HADS) and assessment of lifestyle factors (exercise, smoking, alcohol consumption, body mass index). To identify a relationship between current cardiac function and child maltreatment, we used logistic regression.

Results: ACHD reported significantly higher rates of emotional neglect and emotional abuse and sexual abuse and lower rates of physical neglect when compared to the general German population. In addition, total CTQ-scores, emotional abuse, emotional neglect, physical abuse, and sexual abuse correlated with symptoms of depression, anxiety, and negatively correlated with QoL. Furthermore, CTQ scores contributed significantly in predicting higher New York Heart Association (NYHA) scores ($p = 0.009$).

Conclusion: Child maltreatment is more common in ACHD and associated with decreased quality of life and depression and anxiety. Furthermore, we found evidence that self-reported child maltreatment is associated with decreased cardiac function.

Given the longer survival time of patients with ACHD, identifying factors that may negatively influence the disease course is essential. The negative consequences of child maltreatment may be the subject of psychosocial interventions that have demonstrated efficacy in treating posttraumatic stress disorders.

Keywords: congenital heart disease, childhood maltreatment, quality of life, childhood trauma questionnaire, adults with congenital heart disease, ACHD, NYHA, CTQ

INTRODUCTION

Advancements in medical and surgical care lead to an increasing population of adults with congenital heart disease (ACHD). With an increase in life expectancy, CHD's long-term effects on both the quality of life (QoL) and the development of psychiatric disorders caused significant scientific interests. Even though the authors of a large-scale study regarded QoL in ACHD as "generally good" (1), it is crucial to consider physical, social, and psychological aspects in QoL assessment as mental disorders greatly influence a patient's mental health and well-being (2). For example, reduced QoL is present even in mild forms of major depressive disorder (3).

Although not uniformly, most studies have reported an increased risk and under-treatment of mood and anxiety disorders in ACHD (1, 3–6). Current mood and anxiety disorders have been associated with decreased quality of life in ACHD, and even mild forms of major depressive disorder led to reduced QoL in ACHD (7).

Parental mental health conditions are a well-known risk factor for child maltreatment that impacts families with children suffering from CHD. Studies have shown (8–14) that the child's burden concerning CHD is shared between family members, affecting the children's and parents' mental health and the child-parental interaction. In one study, CHD was identified as a substantial risk factor for mental health problems in children with CHD and their respective mothers (8). Depression, anxiety, somatization, and hopelessness were frequently found in parents of children with CHD, with mothers reporting more symptoms than fathers (9, 10). Multivariate analysis showed that distress, hopelessness, and the financial situation were more important in explaining diminished QoL than the children's heart condition (9). Another meta-analysis described a strong association between maternal depression and malicious maternal behavior in CHD (11). Furthermore, parental depression increases the risk of coercive and hostile parenting style as well as corporal punishment (12), while it was also shown that an improvement in maternal depression leads to an improvement in child depression and the child's functionality as assessed with the Columbia impairment scale (13). A study in women showed that child maltreatment was associated with poor overall health, physical, emotional, and functional disability, distressing physical symptoms, and a greater health risk behavior (14). In summary, having to care for a child with CHD is a significant burden for a family as it is associated with constant worrying about the child's health and future, frequent visits to health care institutions, frequent health care interventions and a potentially associated financial strain. These circumstances add to decreased

parental capacities and increased likelihood for neglectful or malicious behavior.

The higher prevalence of mental health issues in CHD children and parents and its negative impact on child-parent interaction suggest that adults with CHD report more traumatic experiences and abusive behavior from their parents when compared to the general population. Therefore, the objectives of the present study are:

1. To assess the prevalence of self-reported child maltreatment in a cohort of 196 ACHD patients using the Childhood Trauma Questionnaire
2. To compare the frequency of child maltreatment in ACHD with the prevalence estimates from the general population in Germany
3. To assess if child maltreatment is associated with symptoms of depression and anxiety, and with quality of life
4. To assess if self-reported child maltreatment is associated with worse cardiac function.

We hypothesized that the prevalence of child maltreatment is higher in ACHD patients than in the general population and that child maltreatment is associated with decreased quality of life and increased depression and anxiety.

MATERIALS AND METHODS

Participants

The PSYConHEART study is an ongoing project aiming at examining morbidity and mortality factors in ACHD (7). The study protocol conformed to the ethical guidelines of the declaration of Helsinki and was approved by the local ethics committee. All patients gave their informed written consent before study entry. Patients were recruited from the ACHD outpatient clinic of the Dep. of Cardiology and Angiology at the Hannover Medical School (Hanover, Germany). The inclusion criteria were as follows: (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 pregnancy and unstable cardiac conditions. Currently, 215 ACHD patients were recruited, of whom 19 had to be excluded due to incomplete data from at least one of the questionnaires. The final sample consists of 109 male and 87 female patients. Details of the underlying heart disease and treatment are given in Table 1.

Assessment of Child Maltreatment

Child maltreatment was assessed using the Childhood Trauma Questionnaire (15). The CTQ is a well-established instrument

TABLE 1 | Descriptive statistics regarding socio-demographics, questionnaires, and type of cardiac malformation of the current sample.

	Study sample (N = 196)
Males/Females (N/%)	109/87 (44.4%/55.6%)
Age (M/SD)	35.21 ± 11.24y
Smoker (N/%)	53 (27%)
Mean BMI	25.39 ± 4.97
Exercise level	3.28 ± 1.76
In a relationship	112 (57.14%)
School years	
Up to 9	31 (15.8%)
Up to 11 (junior high school)	94 (48%)
Up to 13 (secondary school)	71 (36.2%)
HADS-A (M/SD)	4.67 ± 3.36
HADS-D (M/SD)	3.48 ± 3.63
NYHA score (N/%)	
I	150 (76.5%)
II	35 (17.9%)
III	11 (5.6%)
IV	0
Bethesda score (N/%)	
1	106 (54.1%)
2	53 (27.0%)
3	37 (18.9%)
Cardiac malformation (N)	
Simple shunts	15
Atrioventricular septal defect	10
Mitral valve disease	4
Anomalous pulmonary venous connection	1
Bicuspid aortic valve	24
Subaortic stenosis	6
Coarctation	23
Congenital pulmonary stenosis	8
Double chambered right ventricle	2
Tetralogy of Fallot	30
Ebstein anomaly	7
Marfan Syndrome	16
D-Transposition: Atrial switch	24
D-Transposition: Arterial switch	1
Congenital corrected transposition	3
Fontan type circulation	16
Eisenmenger Syndrome	6

BMI, body mass index; HADS-A, hospital anxiety and depression scale, anxiety subscale; HADS-D, hospital anxiety and depression scale, depression subscale; NYHA, New York heart association score; M, mean; SD, standard deviation. All numbers are rounded to two decimal digits.

with a high internal consistency [Cronbach's $\alpha = 0.95$, (16)]. This self-administered questionnaire covers childhood adversities in five areas: emotional abuse, physical abuse, sexual abuse, emotional neglect, and physical neglect.

With reference to Walker et al. the items used to construct the five maltreatment scales were derived from the following definitions of abuse and neglect (14). Sexual abuse was defined

as “sexual contact or conduct between a child younger than 17 years of age and an adult or older person (at least 5 years older than the child).” Physical abuse was defined as “bodily assaults on a child by an adult or older person that posed a risk of, or resulted in, injury.” Emotional abuse was defined as “verbal assaults on a child's sense of worth or well-being or any humiliating or demeaning behavior directed toward a child by an adult or older person.” Physical neglect was defined as “the failure of caretakers to provide for a child's basic physical needs, including food, shelter, clothing, safety, and health care” (poor parental supervision was also included if it placed a child's safety in jeopardy). Emotional neglect was defined as “the failure of caretakers to meet the children's basic emotional and psychological needs, including love, belonging, nurturance, and support.” Groups (with either form of maltreatment/ no maltreatment) were constructed similar to the thresholds given in Walker et al. (14). To compare our sample with the German population, we used the data described by Iffland et al. (17). In their paper, the authors also used the thresholds presented by Walker et al. (14).

Assessment of Health Behavior and Symptoms of Anxiety and Depression and Quality of Life

Symptoms of anxiety and depression were assessed using the Hospital Anxiety and Depression Scale [HADS (18)] and the World Health Organization Quality of Life [WHO-QoL-BREF (19)] questionnaire for the assessment of quality of life. All three questionnaires have a high internal consistency [Cronbach's α : HADS-A = 0.83; HADS-D = 0.82 (20); WHO-QoL-BREF = 0.87 (21)]. Participants completed a demographic survey that included educational, marital and 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 as described elsewhere (22). Alcohol consumption was assessed as drinks per week and cigarette smoking by pack-years (cigarettes per day $\times$ years smoking)/20).

Assessment of Cardiac Disease

Echocardiography was performed in all patients to evaluate cardiac morphology and function by an experienced cardiologist. Cardiac defects were categorized regarding their complexity as simple, moderate, or great using the Warnes classification Bethesda score (23). Functional status was assessed by a cardiologist and determined according to the New York Heart Association (NYHA) class (24).

Statistical Analysis

Data were analyzed using SPSS (Version 26, IBM, Armonk, NY, 2020). Group comparisons concerning the prevalence of childhood traumata (ACHD vs. general population) were determined by performing the Chi-square tests. We categorized values of the CTQ and its subscores using the threshold/cut-off described by Walker et al. (14), which was also used in a representative sample of the general German population presented by Iffland et al. (17).

TABLE 2 | Prevalence of child maltreatment in adults with congenital heart disease: comparison to data from the German population (25).

	ACHD		German population		<i>p</i>
	X/N	%	X/N	%	
CTQ-emotional abuse	51/196	26.0	254/2500	10.2	<0.001
CTQ-emotional neglect	68/196	34.6	348/2500	13.9	<0.001
CTQ-physical abuse	21/196	10.7	301/2500	12	n.s.
CTQ-physical neglect	49/196	25	1210/2500	48.8	<0.001
CTQ-sexual abuse	22/196	11.2	156/2500	6.2	0.007

ACHD, adults with congenital heart disease; CTQ, childhood trauma questionnaire; X, respective number of participants; N, total number of participants.

Pearson's correlation analysis was performed to demonstrate associations between total child maltreatment as assessed via total CTQ scores, different trauma types as assessed via CTQ subscores, behavioral (drinking and smoking behavior as well as physical exercise and BMI) and mental health factors (anxiety, depression and quality of life).

Logistic regression analysis was performed to assess the relationship between child maltreatment as measured by the overall CTQ score and current cardiac symptoms as determined via the NYHA score. To that end, we compared asymptomatic patients (i.e., NYHA I) with symptomatic patients (i.e., NYHA II and III). All data are shown as mean $\pm$ SD. An alpha of 0.05 was used for all analyses.

RESULTS

One hundred and ninety-six patients completed the questionnaires and fulfilled our inclusion criteria (109 males and 87 females/44.4% female, average age 35.21 years $\pm$ 11.24. According to the NYHA score, 150 patients were asymptomatic (NYHA I), and 46 were symptomatic (35 NYHA II and 11 NYHA III, no NYHA IV patients). For the demographics and details regarding underlying heart diseases, see **Table 1**.

Prevalence of Child Maltreatment in ACHD

Compared to a sample from the general German population using the same thresholds, patients with ACHD had significantly higher rates of emotional abuse [$\chi^2_{(1)} = 45.57$, $p < 0.001$] and emotional neglect [$\chi^2_{(1)} = 60.11$, $p < 0.001$]. Also, sexual abuse was more prevalent in the ACHD cohort [$\chi^2_{(1)} = 7.32$, $p = 0.007$] while physical neglect was more prevalent in the German population [$\chi^2_{(1)} = 39.98$, $p < 0.001$]. There was no difference regarding physical abuse [$\chi^2_{(1)} = 0.30$, $p = 0.58$] (see **Table 2**).

Correlation of Emotional Neglect, Emotional Abuse, and Sexual Abuse on Quality of Life, Psychological Well-Being, and Health Behavior

Using Pearson's correlation analysis (**Table 3**), overall CTQ-scores, emotional abuse, emotional neglect, physical abuse, and sexual abuse were correlated with anxiety symptoms and

negatively correlated with QoL. Furthermore, quality of life was negatively and depression was positively correlated with physical neglect.

Total CTQ and the emotional neglect and physical neglect subscore were negatively associated with drinks per week. Emotional abuse was negatively associated with BMI.

Results of the Regression Analysis

To assess the association between child maltreatment and current cardiac symptomatology, we used a logistic regression model with CTQ total score as the independent variable and NYHA class (asymptomatic [NYHA I] vs. symptomatic [NYHA II and III collapsed]) as the dependent variable. The model was statistically significant [$\chi^2_{(1)} = 6.85$, $p = 0.009$]. Goodness-of-fit was assessed using the Hosmer-Lemeshow-Test, indicating a good model fit [$\chi^2_{(8)} = 5.88$, $p = 0.661$]. CTQ contributed significantly in predicting NYHA severity ($p = 0.009$). Higher total CTQ scores increased the risk of having a higher NYHA class (OR = 1.031, 95%-CI [1.008, 1.055]).

DISCUSSION

In the current study, adults with CHD more frequently reported emotional neglect, emotional abuse, and sexual abuse compared to a representative sample from the German population. Furthermore, there was a significant positive association between overall child maltreatment, emotional abuse, emotional neglect, physical abuse, and sexual abuse on the one hand and decreased quality of life, increased anxiety and increased depression on the other hand. Moreover, there was a negative association between physical neglect and quality of life. Using logistic regression, we identified a negative relationship between child maltreatment and current cardiac function as assessed via the NYHA score.

However, and contrary to our hypothesis, physical neglect was significantly more frequent in the general German population, which could have numerous reasons. As Iffland et al. (17) point out, a different study on the psychometric properties of the German version of the CTQ argued that the physical neglect subscale has weak psychometric properties, is highly correlated with the other subscales, and has a weak internal consistency (17, 26). Furthermore, a study from 2018 has shown that older respondents who had experienced privation during the (post-) war years were more likely to report physical neglect (27). This could partly explain the difference between our sample and the findings reported by Iffland et al. (17), since their study was conducted in 2013 and the average age of all participants was 50.66 (SD = 18.56) as opposed to 35.21 years $\pm$ 11.24 in the present study. Nonetheless, comparisons of physical neglect should, therefore, only be made with caution.

Since we identified significantly higher emotional neglect, abuse and sexual abuse in ACHD, this could suggest that ACHD suffer from poly-victimization or multiple victimizations as defined by Finkelhor et al. (28). Several studies have shown that victims of poly-victimization have a higher risk for trauma symptoms (28), posttraumatic stress disorder, and depression (29, 30). One study (25) has described a dose-response relation between the number of potentially traumatic events experienced

TABLE 3 | Results of correlation analysis (Pearson's *r*) between child maltreatment, psychological well-being and health behavior (*N* = 196).

	HADS-D	HADS-A	QoL	BMI	Exercise	Drinks per week	Smoking behavior
CTQ-total score	0.32**	0.33**	−0.30**	0.14	−0.06	−0.18**	0.10
CTQ-emotional abuse	0.28**	0.27**	−0.26**	0.16*	−0.11	−0.14	0.10
CTQ-emotional neglect	0.32**	0.27**	−0.32**	0.10	−0.01	−0.14*	0.11
CTQ-physical abuse	0.22**	0.24**	−0.15*	0.14	−0.04	−0.12	0.08
CTQ-physical neglect	0.15*	0.14	−0.19**	0.13	−0.02	−0.14*	0.13
CTQ-sexual abuse	0.26**	0.29**	−0.20**	0.00	−0.08	−0.11	−0.03

BMI, body mass index; CTQ, childhood trauma questionnaire; HADS-A, hospital anxiety and depression scale, anxiety subscale; HADS-D, hospital and anxiety and depression, depression subscale; *N*, number of participants; QoL, quality of life. All numbers are rounded to two decimal digits.

***p* < 0.01.

**p* < 0.05.

and psychological distress. Participants who experienced an average of 10 types of trauma during their lives were at the most significant risk for PTSD scores and engagement in risky behavior such as substance use and suicidal behaviors. One meta-analysis and systematic review comprising 124 articles has concluded that the current evidence suggests a causal relationship between child maltreatment (non-sexual) and a range of mental disorders, substance abuse, suicidal behavior, and risky sexual behavior (31). Furthermore, a study on students in grades 9–12 has shown that past-year sexual violence victimization was related to health risk behaviors such as substance abuse, injury, risky sexual behavior, suicidal ideation, and feelings of sadness and hopelessness (32). It is well-established that depression is a risk factor for non-compliance with medical treatment: in one rigorous study (33), the odds were three times higher that patients suffering from depression will be non-compliant when compared with healthy controls. Furthermore, one randomized controlled trial study in recently hospitalized cardiac patients has shown that improvement of depression was consistently and independently associated with superior self-reported adherence to medications and secondary prevention behaviors across a 6-month span. Of note, in this study, improvement in anxiety did not show the same effect (34). Thus, it is very important to identify especially those who were the victim of multiple traumatization as they are at a high risk of developing depression. This could then influence therapy adherence and, subsequently, long-term prognosis.

The effect mentioned above of child maltreatment on therapy adherence could even translate into worse cardiac function and thereby increased mortality. In our study, using logistic regression, overall CTQ scores were associated with higher NYHA class. In ACHD, NYHA class predicts mid-to long-term mortality (35). Our results, therefore, suggest that child maltreatment could negatively influence morbidity and mortality in this specific patient population. One possible mechanism for this association could be the influence of traumatization and depression on therapy adherence. Therefore, it is reasonable to assume that therapy adherence could negatively influence long-term outcome and NYHA class. However, to the best of our knowledge, no study has yet identified the relationship between therapy adherence, mental disorders and cardiac function in ACHD. Rigorous studies investigating this proclaimed relationship are therefore needed.

Parental Factors

This study found a strong association between child maltreatment, emotional abuse, emotional neglect, physical abuse, and sexual abuse with higher anxiety and depression and lower QoL. Emotional neglect is considered to have a high prevalence rate and a significant impact on the child's health and development. Emotional neglect is determined by different factors such as child stigmata (e.g., a chronic disease), the well-being of parents, social factors (e.g., family income) and even culture and society factors (36). Most of the factors that influence the childhood neglect risk are parent-related (36–38). As disability can be regarded as one child-related risk factor for child neglect (39), one can assume that parents-related factors are more aggravating. This, in turn, could explain the higher prevalence of emotional neglect found in our study.

Indeed, some studies have shown that major depressive disorder poses a risk for child abuse (40) while some symptoms frequently occurring in anxiety and major depressive disorder are also associated with child neglect (37, 38, 41). Hence, the risk for mental disorders in both parents and the child caused by the child's CHD could partly explain the higher prevalence of emotional abuse and neglect reported in our study. Nonetheless, our report is limited because we did not test the patients' parents for mental disorders. In future studies, it would therefore be essential to assess mental disorders and childhood abuse in both children and their parents to assess the CHD's risk on the patients' mental health and potential abuse and neglect.

Since we have also identified a higher rate of experienced sexual abuse in patients with ACHD, it is plausible to raise the question if CHD poses a risk for sexual abuse. One could assume that childhood trauma and especially sexual abuse would increase the risk of developing a chronic illness later in adulthood, which was recently shown in an extensive surveillance system study analyzing 86,968 respondents from a population of 32 million people. In this study, the authors were able to show that young adults with high scores in adverse childhood experiences were at higher risk for the development of early-onset disease (42). Interestingly, parental factors and especially a problematic mother-daughter relationship put children at a greater risk for sexual abuse (43). As we have discussed above, some studies have shown that maternal major depressive disorder and specific psychiatric symptoms classified in the mood and

anxiety spectrum are associated with a higher risk for abuse of the respective child (37, 38, 40, 41). Sharing this common factor, namely a possible hazardous and problematic mother-child relationship, the increased prevalence identified in our study may be partly associated with this relationship's structure. However, we cannot conclude a possible causal relationship. It is still important to highlight the importance of further studies that could examine the risk of early-onset chronic illnesses and an association with childhood sexual abuse.

One conclusion that can be drawn from the results is that parents of children with CHD may be better integrated into the treatment process and should receive social and psychological help when necessary. In addition, helping parents cope with their children's disease may lead to decreased rates of emotional neglect. Thus, emotional neglect (and abuse) would be a modifiable variable that could reduce mental health burden in ACHD when addressed through early interventions of the patients' parents.

Some factors investigated in our study that are associated with child maltreatment influence morbidity and mortality, namely higher BMI, increased alcohol consumption and depression. In our study, BMI was negatively associated with emotional abuse. Contrary to the public belief that higher BMI is generally associated with higher mortality, in ACHD, higher body mass index is generally regarded as being associated with lower mortality (44, 45), especially in symptomatic patients with complex underlying cardiac defects, suggesting that cardiac cachexia could influence mortality. In a population-based study from the UK, BMI had a j-curved association to mortality in cardiovascular disease, among others, i.e., the mortality was higher in below and above average BMI values (46). However, it is essential to highlight that BMI does not directly translate into obesity and that lower BMI is associated with higher mortality, especially in patients suffering from CHD. Thus, the associations between BMI and emotional neglect and abuse in this patient collective need to be further elucidated and differentiated for cachexia, physiological BMI, and obesity.

Increased alcohol consumption is associated with higher mortality (47). In ACHD, one study has shown that self-reported depressive symptoms are associated with increased alcohol and tobacco use (48). In our study, however, we have found that overall CTQ scores and emotional neglect are negatively associated with drinks per week, i.e., the higher the reported child maltreatment the lower the number of drinks per week. Our study extends the existing literature and demonstrates that child maltreatment and its relationship to alcohol consumptions need further investigations. Nonetheless, a recent meta-analysis by Hughes et al. (49) demonstrated that child maltreatment is a major risk factor for many health conditions, such as physical inactivity, overweight, diabetes mellitus and obesity, poor self-rated health, heart disease and respiratory disease, to name a few. In their study, the highest associations were found for child maltreatment with sexual risk-taking, mental disorders, problematic alcohol use and interpersonal and self-directed violence (49). Furthermore, child maltreatment is negatively associated with adult education, employment, and income potential (50). Strengthening the understanding of the combined

effects of child maltreatment and physical diseases may induce multidisciplinary prevention programs focused on prevention. If child maltreatment is a relevant factor in developing mental disorders and quality of life, a short questionnaire concerning early traumatization may be part of a multidisciplinary approach to the patient.

Quality of Life

QoL is a complex phenomenon comprising different levels of physical, mental, and social levels of functioning (2) that has been the topic of many studies on ACHD. Two previous studies have shown that in ACHD patients, poor QoL is associated with the presence of mental disorders (7), older age, lack of employment, disability, no history of marriage, and poor NYHA class (1). However, both mentioned studies did not include any information on the presence of child maltreatment, which could influence the incidence and severity of mental disorders, thereby decreasing QoL. Hence, our study is the first that revealed a new factor that could influence the incidence of mental disorders and QoL in ACHD.

LIMITATIONS

To the best of our knowledge, the present study is the first study that addressed child maltreatment as assessed with the CTQ in ACHD. However, our study has some limitations that need to be discussed. We cannot deduce a causal relationship between reported child maltreatment and mental health because of our data's correlative nature. Further prospective studies in children with CHD may overcome this methodological flaw. Also, the reported child maltreatment values could be influenced by a recall bias (17), a general problem in retrospective studies. Finally, no assessment was done on the prevalence of mental disorders in the patients' parents, and thus the possible relationship between the parents' mental disorders and child maltreatment in the present sample remains unclear.

CONCLUSION

Child maltreatment, particularly sexual abuse, emotional neglect and emotional abuse, is more common in patients with ACHD. Total child maltreatment is associated with worse perceived quality of life and is associated with adverse physical (NYHA scores) and mental health (depression, anxiety and quality of life) outcomes, namely cardiac function and depression as well as anxiety and quality of life. Screening adult patients for history of child maltreatment can help both patients and professionals understand the underlying causes of health problems and enable better-informed treatment options. Psychosocial interventions that have proven efficacy in the context of trauma-related disorders (51, 52) can be applied to patients with a history of child maltreatment. A multidisciplinary approach to the patient that integrates past experiences and psychological problems is recommended in ACHD.

DATA AVAILABILITY STATEMENT

The raw 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 Committee, Hannover Medical School, Hannover, Germany. The patients/participants provided their written informed consent to participate in this study.

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AUTHOR CONTRIBUTIONS

PP and KK wrote the initial draft of the manuscript. MW-B and KK contributed to conception and design of the study. PP and IH performed the statistical analysis and revised the initial draft of the manuscript. All authors contributed to the final version and approved the manuscript.

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Heightened Stress Reactivity in Response to an Attachment Related Stressor in Patients With Medically Treated Primary Hypertension

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Background: A heightened stress reactivity to mental stress tasks has been shown in hypertensive patients and might contribute to a higher disease risk. We investigated this hyperreactivity with regard to an attachment related stressor that focuses on emotions instead of performance and we examined whether this effect can also be found in patients on antihypertensive drugs.

Materials and Methods: Fifty patients with primary hypertension, treated with at least one antihypertensive drug, were compared with 25 healthy individuals. After 10 min of rest, they participated in an attachment-related interview (Adult Attachment Projective picture system, AAP) and were exposed to an attachment-related stressor (Separation Recall, SR), a short-time stressor which activates attachment-related emotions and thoughts by talking 5 min about a personal experience of loneliness. Blood samples to measure adrenocorticotrope hormone (ACTH), cortisol, norepinephrine, epinephrine, and dopamine were taken. Blood pressure, heart rate and arterial stiffness were measured at rest, after AAP, after SR and 10 min after recovery. Standard deviation of normal-to-normal intervals (SDNN) and root mean square of successive differences (RMSSD) were calculated. Parameters were compared using Mann Whitney *U*-test and linear mixed-effects regression models controlling for age and body mass index (BMI) after logarithmic transformation if appropriate.

Results: Healthy test persons were younger and had lower BMI than patients. Comparing the two groups there were no significant differences in blood pressure and heart rate at rest. Both stressors provoked a significant response in almost all parameters. Results of the post-estimation of contrasts from linear mixed-effects regression models showed a steeper rise in systolic BP and arterial stiffness as well as a more pronounced decline in SDNN in hypertensive patients than in healthy controls. Levels of cortisol rose earlier and higher in hypertensive patients than in healthy controls.

Conclusion: Vascular, autonomic, and hypothalamic pituitary adrenal axis response is heightened in medicated subjects with hypertension in response to attachment-focused stressors compared to healthy subjects. We conclude that the remaining hyper-reactivity even with sufficient antihypertensive medication still poses a substantial risk for affected patients. New ways to diminish this risk should be developed.

Keywords: autonomic nervous system, hypothalamic pituitary adrenal axis, attachment, mental stress, antihypertensive treatment

INTRODUCTION

One out of three individuals is affected by hypertension in an industrial country like Germany (1). It is estimated to account for 7.6 million pre-mature deaths worldwide, and about 54% of strokes and 47% of ischemic cardiac diseases are a direct consequence of hypertension (2). Hence, it is a main risk factor for ischemic disease and death. In contrary to this and to decades of research, a breakthrough in prevention and therapy is not yet achieved. The amount of controlled hypertension is still only about 50% (1).

Higher resting blood pressure (BP) is correlated to higher risk of cardiovascular (CV) disease (3). Beyond resting BP, BP variability is a recognized risk factor (4). The response to stressors is of special interest in hypertension research. In normotensives, BP reactivity is predictive for the development of hypertension, and this has been shown for physical (5) as well as for mental stress (6–8). Also, sympathoadrenal stress reactivity predicts future BP (9). Cortisol responses to mental stress are as well-correlated with the incidence of hypertension (10). Stress response seems to be generally higher in individuals with systemic hypertension, not only in terms of a higher BP response, but also with regard to norepinephrine excretion and cortisol (11, 12). Overall, an enhanced CV response to mental stressors is associated with incident hypertension (13).

Existing studies are almost exclusively covering hypertensive patients without medication. Nevertheless, about one third of individuals with hypertension take antihypertensive medication (1). The results might differ from unmedicated subjects, as medication like beta-blocking agents should diminish the sympathetic hyperreactivity and drugs like angiotensin converting enzyme (ACE) inhibitors and AT1 receptor antagonists are found to reduce levels of adrenocorticotrophic hormone (ACTH) and cortisol (14). This is important, as the goal of medication is not merely to reduce BP, but to prevent further disease like myocardial infarction (MI). CV deaths can be triggered by stress (15), and a heightened cortisol response to mental stress is associated with the progression of coronary artery calcification (16). Therefore, it is important to know whether medicated individuals suffering from hypertension still show a hyper-reactive stress response.

Mental stressors commonly used for evoking a stress response are cognitive and performance-oriented like the mental arithmetic. The Trier Social Stress Test also includes a social component implementing a job interview (17). The majority of hypertensive patients is older than 65 years and has already

retired. Thus, this kind of performance-focused stressor seems to be inappropriate. Loneliness is a major risk factor for mortality (18), so we sought a stressor associated with (missing) interpersonal contact. This kind of stressor is the separation recall (SR) (19), which has been evaluated against mental arithmetic and has proven to be effective. Remembering and talking about a situation of loneliness and abandonment in one's own life triggers the memories and emotions linked to this situation. In order to broaden the context from loneliness and being abandoned to other attachment-related topics, we added an attachment-related interview, which is called adult attachment projective (AAP) (20). Nine different scenes of people being alone or with another person serve as stimuli for individual narratives and hereby activate the individual attachment patterns.

The present study aims at evaluating whether medicated patients with hypertension still show a heightened stress response to attachment/interpersonal-focused stressors.

MATERIALS AND METHODS

Study Population

Fifty hypertensive patients with primary hypertension, treated with at least one antihypertensive drug, were recruited from the Cardiologic Outpatient Clinic at the Ulm University Hospital. The following inclusion criteria were applied: age between 18 and 80 years and sufficient knowledge of the German language. Patients with heart insufficiency with ejection fraction <35%, severe valvular stenosis or insufficiency, end-stage renal disease with regular dialysis, current alcohol or drug abuse, chronic rheumatic diseases, obvious cognitive deficits following stroke, current psychosis and dementia, cortisol intake due to other comorbidities during the last 3 months, and those who received renal denervation for treatment of uncontrolled hypertension were excluded from the study.

Healthy participants were recruited by advertisement in the local newspaper. They were questioned by telephone about existing diseases and medication, those being criteria to be excluded from this study. People with asymptomatic substituted hypothyreosis were not excluded. We checked known diagnosis and medication again immediately before the stress test. Out of the initially recruited 31 healthy controls, one person took Trimipramin (Stangyl[®], Sanofi-Aventis, Germany), one suffered from diabetes (newly diagnosed), two were on cortisol medication (topic/inhalative), and two had arterial hypertension

(newly diagnosed). These individuals were excluded, leaving 25 individuals as healthy controls.

Procedures

The study protocol was approved by the ethical review board of Ulm University (no. 129/12) in accordance to the Helsinki Declaration. All subjects gave written informed consent. All subjects were instructed neither to smoke nor to drink coffee or black tea and to have lunch prior to 12 a.m. on the day of measurement. An overview of the experiment is shown in **Figure 1**. After arrival at the lab at 02:00 p.m., medication and medical history were assessed and a venous cannula was placed. Electrodes and BP cuffs were attached to the chest, both upper arms and both ankles, respectively. BP, brachial-ankle pulse wave velocity (baPWV), central PWV (cPWV) and central pulse pressure (cPP) were automatically measured at different points of time using an oscillometric sphygmomanometer (Vasera VS-1500N, serial number 50000071, Fukuda Denshi Co Ltd., Tokyo, Japan) on the right and the left upper arm and ankles as described below, while ECG was recorded continuously using NeXus-10 wireless physiological monitoring (serial number 0928100209, Mindmedia, Oldenzaal, Netherlands). In order to minimize artifacts via arm or leg movements, the whole procedure was conducted while the patient was lying. After 10 min of rest, an attachment-related interview (AAP) (20) and an attachment-related stressor (SR) (19) were performed. A short-time stressor which activates attachment-related emotions and thoughts by talking 5 min about a personal experience of loneliness. Blood samples were taken and sphygmomanometer measurements were performed after the AAP, the SR and 10 min of recovery. Mean HR was calculated for the penultimate minute of each time period (rest, AAP, SR, recovery). BP was calculated on the basis of the mean values of right and left arm measurement. Resting BP was calculated on the basis of the average of the two consecutive measurements.

The questionnaires described in the following section were completed after the measurement.

During SR three participants (two hypertensive, one healthy) were unable to identify an event when they felt lonely. Thus, no measurement results are available for them at time point 3.

Questionnaires

Physical activity was measured using the Freiburg Questionnaire of Physical Activity (21). The questions serve to specify physical activity during daily life in minutes per week, e.g., walking to the work place as well as doing sports. By applying metabolic equivalent of task (MET) estimates for every activity, a MET sum score can be calculated. We categorized the sum score in <500, 500–999, 1,000–1,499, and >1,500 MET-min/week according to Jeong (22).

Depressive and anxious symptoms were assessed using the German version of the Hospital Anxiety and Depression Scale (HADS-D, HADS-A) (23, 24). Seven items on each scale are rated on a three-point Likert scale and summed up, resulting in a range of 0–21. Higher scores indicate greater severity of symptoms.

Heart Rate Variability

HRV parameters were calculated using Kubios HRV Premium 3.3.1 (Kubios Oy, Kuopio, Finland). We chose to calculate HRV from a short time window of 60 s, preferably free of artifacts (3), which was available in most measurements. The 60-s-window was placed in the last of the 5 min prior to the four measurement time points and was manually screened for artifacts. If artifacts were present, the window was moved to find an artifact-free (preferably) period inside the 5-min-window. The maximum number of allowed artifact per minute was one. In addition to the manual screening and correction of artifacts, the automated artifact correction of Kubios, set to a low threshold, was applied. Five data sets could not be included due to technical reasons (missing data, corrupt data). Four individuals with hypertension had no constant sinus rhythm (2x atrial fibrillation, 1x trigeminus, 1x bigeminus), so the number of ECG valid for HRV calculation was 66 (41 hypertensives, 25 healthy). Of the included data, six measurements (9%) had one artifact per minute.

We calculated the time-domain parameters SDNN (standard deviation of normal-to-normal intervals) and RMSSD (root mean square of successive differences) as they can be calculated from a short time window of 1 min, which is not recommended for frequency-domain parameters like the low frequency band (25). SDNN reflects the global activity of the autonomic nervous system (ANS) and RMSSD represents the rapid changes in HR caused by the parasympathetic branch of the ANS (25).

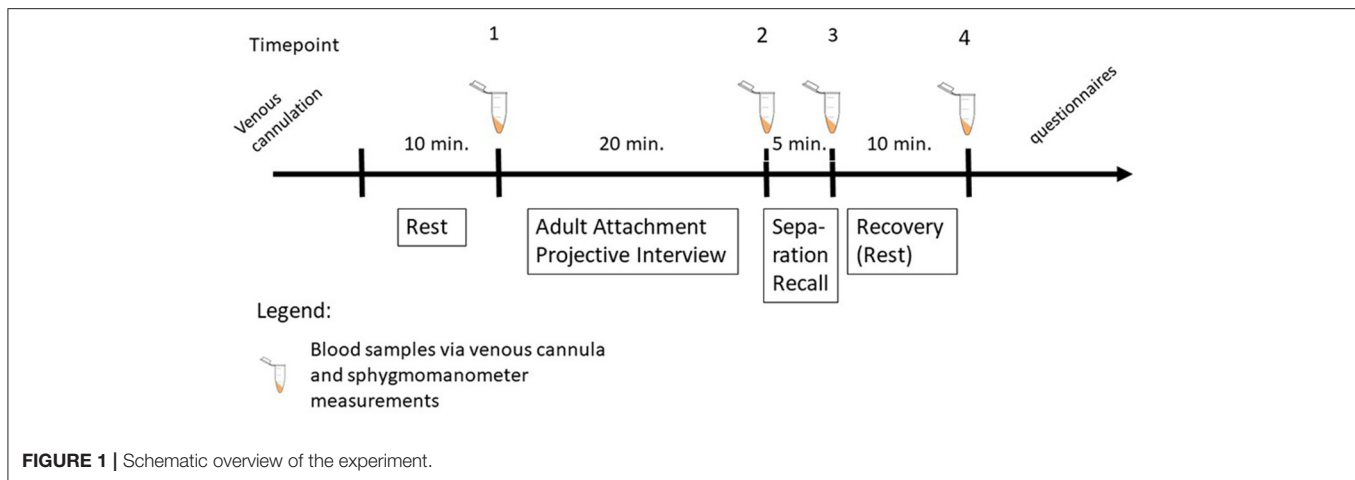
Blood Parameters

Venous cannulation was not successful in three hypertensive patients. In another three patients, blood could not be drawn from the cannula at later time points. We did not place a new cannula to avoid additional stressful stimuli during the experiment.

Blood samples were drawn from the venous cannula using a tube with coagulation activator (S-Monovette[®] Serum, Sarstedt, Nümbrecht, Germany) for ACTH and a tube containing EDTA for the other blood parameters (S-Monovette[®] EDTA, Sarstedt, Nümbrecht, Germany). The tubes were cooled directly before use and centrifuged immediately with 2,000 G and 3,570 U for 10 min (ACTH) and for 5 min (other blood parameters), respectively. Blood samples were frozen at –80 degree. Catecholamines (norepinephrine, epinephrine, dopamine) were measured using High Pressure Liquid Chromatography (CLC300, Chromsystems, Munich, Germany) and electrochemic detection (CLC100, Chromsystems, Munich, Germany). Plasma samples were analyzed using commercially available ELISA kits for ACTH (analytical sensitivity <1 pg/ml, intra-assay and inter-assay coefficients of variation <8.8%, IBL International, Hamburg, Germany) and Cortisol (analytical sensitivity <2.46 ng/ml, intraassay and inter-assay coefficients of variation <3.5%, IBL International, Hamburg, Germany).

Statistics

Parameters were compared using the non-parametric Mann-Whitney-U-test as not all descriptive parameters were normally distributed and Chi-square test (**Table 1**) where appropriate



(SPSS[®] Statistics 25, IBM, USA). A linear mixed-effects model with random intercepts were fitted using (STATA[®] 15.1, STATA Corp, USA). Dependent variables were SBP, DBP, HR, log(SDNN), log(RMSSD), log(ACTH), log(Cortisol), log(Norepinephrine), log(Epinephrine), log(Dopamine), baPWV, cPWV, log(cPP). Time was level 1, the individual level (Persons) was on level 2. A two-way-interaction between group (Healthy vs. Hypertensive) and time (rest [1], AAP [2], SR [3], recovery [4]) was modeled using restricted maximum likelihood. Regression parameters were normalized choosing the function that best approximates Gaussian/normal distribution as marked. Age and BMI differed significantly between hypertensives and healthy individuals and therefore were included in the models as covariates in the fixed effect part. Post-estimates from each model were contrasts of marginal linear predictions to test the effects of group, time, and their interaction (**Table 2**). A significance level of $p < 0.05$ was regarded significant. Marginal mean plots were calculated (**Figures 3–7**) at average at fixed values for group and time interaction and averaging over the remaining covariates age and BMI.

RESULTS

Study Population

Characteristics of the study population are shown in **Table 1**. Median age of hypertensive was 66 years (interquartile range: 57–72 years), while healthy controls were significantly younger (median age 61 years, interquartile range 54–65 years). A total of 76% of the hypertensives and 56% of the controls were male (difference insignificant). 85 and 76% were living in partnership, respectively. 86% of the hypertensive patients and 92% of controls reported physical activity of at least 500 MET-min/week, hereby meeting the minimum target of recommendations (26). Severe depressive or anxious symptoms were rare and only found in four (severe depressive symptoms), respectively six (severe anxious symptoms) hypertensive patients and in none of the control subjects. Hypertensive patients had higher BMI scores (median 28.1 kg/m², interquartile range 26.3–31.3 kg/m²) than

healthy controls (median 24.3 kg/m², interquartile range 22.7–27.4 kg/m²). There were no significant differences in SBP, DBP, and HR at rest between the two groups.

74% of hypertensive patients had already developed CAD. The median number of known diagnoses was 6 (interquartile range 4–7) and the mean number of drugs taken was 7 (interquartile range 5–9). Diabetes was prevalent in every fourth of the patients. Most of them took two ($N = 15$; 30%) or three ($N = 16$; 32%) antihypertensive drugs which were mostly ACE inhibitors or AT1 receptor antagonists ($N = 48$; 96%), followed by beta-blocking agents ($N = 39$; 78%). The antihypertensive medication is shown in detail in **Figure 2**.

Blood Pressure

Table 2 contains the results of post-estimation of contrasts from linear mixed-effects regression models for stress parameter reactivity. Complete regression tables are shown in **Supplementary Material 1**. **Figure 3** shows the stress response of hypertensive patients and healthy controls for SBP (**Figure 3A**) and DBP (**Figure 3B**). Linear mixed-effects regression models for SBP showed a significant time effect ($\chi^2 = 171.89$, $p < 0.001$), no group effect ($\chi^2 = 0.15$, $p = 0.703$) and a significant group*time-effect ($\chi^2 = 8.80$, $p = 0.032$) with hypertensive patients showing significantly higher values at time point three ($z = -2.81$, $p = 0.005$). For DBP, only a significant time effect ($\chi^2 = 149.83$, $p < 0.001$) was found, while group ($\chi^2 = 0.05$, $p = 0.819$) and group*time-effect ($\chi^2 = 5.92$, $p = 0.116$) were not significant.

Heart Rate and Heart Rate Variability

HR reacted significantly to the stressors (time effect: $\chi^2 = 260.04$, $p < 0.001$) without a significant group effect ($\chi^2 = 0.0$, $p = 0.993$) or group*time-effect ($\chi^2 = 7.69$, $p = 0.053$) (**Figure 4A**). The results were similar for RMSSD (time effect: $\chi^2 = 82.10$, $p < 0.001$; group effect: $\chi^2 = 0.69$, $p = 0.406$; group*time-effect: $\chi^2 = 4.25$, $p = 0.236$) (**Figure 4B**). In contrast, results for SDNN showed a significant group*time-effect ($\chi^2 = 18.05$, $p < 0.001$) with hypertensives showing lower values at time point two ($z = 2.70$, $p = 0.007$) and three ($z =$

TABLE 1 | Study population.

	Hypertensive patients <i>N</i> = 50		Healthy controls <i>N</i> = 25		<i>P</i> -value
	Median/ <i>N</i>	Interquartile range/%	Median/ <i>N</i>	Interquartile range/%	
Age [years]	66	57–72	61	54–65	0.018
Sex (male)	38	76%	14	56%	0.111
In partnership	41	85%	19	76%	0.347
Higher education	12	24%	10	4%	0.183
Physical activity >500 MET-min/week	43	86%	23	92%	0.768
BMI [kg/m ²]	28.1	26.3–31.3	24.3	22.7–27.4	<0.001
HADS anxious symptoms	6	2–8	6	1.5–7	0.566
HADS severe anxious symptoms	4	8%	0	0	0.590
HADS depressive symptoms	4	2–8	3	1.5–5	0.130
HADS severe depressive symptoms	6	12%	0	0	0.354
Systolic blood pressure [mmHg] (rest)	133.0	127.3–142.1	129	121.5–140.0	0.222
Diastolic blood pressure [mmHg] (rest)	78.8	75.8–83.6	79.5	73.0–88.0	0.800
Heart rate [bpm] (rest)	60.4	56.2–67.8	59.6	57.0–65.0	0.783
Number of diagnoses	6	4–7	0	0	
Number of medication	7	5–9	0	0	
Number of antihypertensive medication	3	2–4	0	0	
Coronary artery disease	37	74%	0	0	
History of myocardial infarction	20	40%	0	0	
Obesity (BMI >30 kg/m ²)	19	38%	0	0	
Diabetes	13	26%	0	0	
Smoking	4	8%	0	0	
Medication:					
ACE Inhibitor/AT1 Receptor Antagonist (mostly Ramipril/Candesartan)	48	96%	0	0	
Beta-blocking agent (mostly Metoprolol)	39	78%	0	0	
Diuretics (mostly Hydrochlorothiazid)	25	50%	0	0	
Calcium channel blocker (mostly Amlodipin)	24	48%	0	0	

P-values calculated with Mann Whitney U-test for metric and chi square test for dichotomous variables.

3.84, $p < 0.001$), further a significant time effect ($\chi^2 = 91.81$, $p < 0.001$) and no group differences ($\chi^2 = 1.69$, $p = 0.194$) (Figure 4C).

Hypothalamic-Pituitary-Adrenal Axis

Figures 5A,B show the response of ACTH and cortisol. Neither group ($\chi^2 = 1.25$, $p = 0.265$) nor time ($\chi^2 = 3.57$, $p = 0.312$) nor group*time-effect ($\chi^2 = 4.98$, $p = 0.173$) were significant for ACTH. In contrast, post-estimation of contrasts revealed for cortisol next to the expected significant time effect ($\chi^2 = 38.66$, $p < 0.001$) a significant group effect ($\chi^2 = 7.48$, $p = 0.006$) with higher values in hypertensive patients and a significant group*time-effect ($\chi^2 = 42.76$, $p < 0.001$) with hypertensives showing an earlier peak at time point 3 ($z = -4.3$, $p < 0.001$), while the cortisol levels of healthy individuals rose at time point four ($z = 2.1$, $p = 0.036$).

Catecholamines

Post-estimation of contrasts from linear mixed-effects regression model for dopamine showed a significant group effect with hypertensive patients showing lower levels of dopamine than

healthy controls (Figure 6A), but neither a time nor a group*time-effect (group effect: $\chi^2 = 15.50$, $p < 0.001$; time effect: $\chi^2 = 2.61$, $p = 0.455$; group*time effect: $\chi^2 = 3.95$, $p = 0.267$). Norepinephrine reacted significantly to the stressors ($\chi^2 = 21.17$, $p < 0.001$) without a significant group effect ($\chi^2 = 1.87$, $p = 0.172$) and without a group*time-effect ($\chi^2 = 2.40$, $p = 0.493$) (Figure 6B). The results for epinephrine were similar to dopamine, but with higher levels of epinephrine in patients with hypertension (group effect: $\chi^2 = 4.04$, $p = 0.045$; time effect: $\chi^2 = 2.36$, $p = 0.502$; group*time effect: $\chi^2 = 0.27$, $p = 0.965$) (Figure 6C).

Arterial Stiffness

Figure 7 shows the results of baPWV (Figure 7A), cPWV (Figure 7B), and cPP (Figure 7C). All three parameters showed a significant time effect ($\chi^2 = 34.49$ for baPWV, $\chi^2 = 67.02$ for cPWV, $\chi^2 = 18.43$ for cPP, all $p < 0.001$) without significant group ($\chi^2 = 0.30$, $p = 0.585$; $\chi^2 = 0.38$, $p = 0.540$; $\chi^2 = 1.43$; $p = 0.232$) or group*time effects ($\chi^2 = 2.84$, $p = 0.418$; $\chi^2 = 5.83$, $p = 0.120$; $\chi^2 = 1.39$; $p = 0.709$).

TABLE 2 | Post-estimation of contrasts from linear mixed-effects regression model for stress parameter reactivity.

Dependent variables	Group (df = 1)		Time (df = 3)		Group*time (df = 3)	
	chi2	p	chi2	p	chi2	p
Systolic blood pressure	0.15	0.703	171.89	<0.001	8.80	0.032
Diastolic blood pressure	0.05	0.819	149.83	<0.001	5.92	0.116
Heart rate	0.00	0.993	260.04	<0.001	7.69	0.053
log(SDNN)	1.69	0.194	91.81	<0.001	18.05	<0.001
log(RMSSD)	0.69	0.406	82.10	<0.001	4.25	0.236
log(ACTH)	1.25	0.265	3.57	0.312	4.98	0.173
log(Cortisol)	7.48	0.006	38.66	<0.001	42.76	<0.001
log(Dopamine)	15.50	<0.001	2.61	0.455	3.95	0.267
log(Norepinephrine)	1.87	0.172	21.17	<0.001	2.40	0.493
log(Epinephrine)	4.04	0.045	2.36	0.502	0.27	0.965
baPWV	0.30	0.585	34.49	<0.001	2.84	0.418
cPWV	0.38	0.540	67.02	<0.001	5.83	0.120
log(cPP)	1.43	0.232	18.43	<0.001	1.39	0.709

Post-estimation of contrasts from linear mixed-effects regression model with random intercepts.

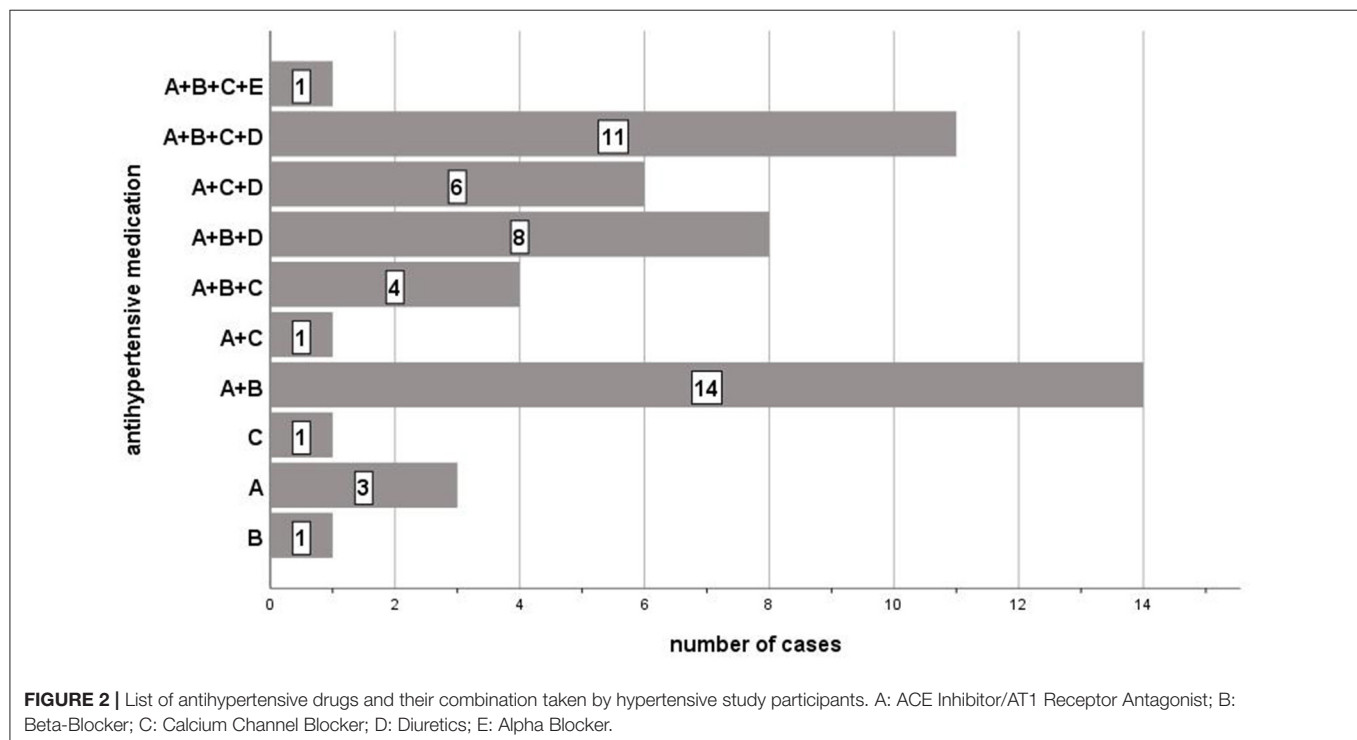
Covariates included in the models: age, body mass index.

Time was level 1, the individual level (Persons) were on level 2.

A two-way-interaction between group (Healthy vs. Hypertensive) and time (rest [1], AAP [2], sSRr [3], recovery [4]) was modeled using restricted maximum likelihood.

Significance level: $p < 0.05$.

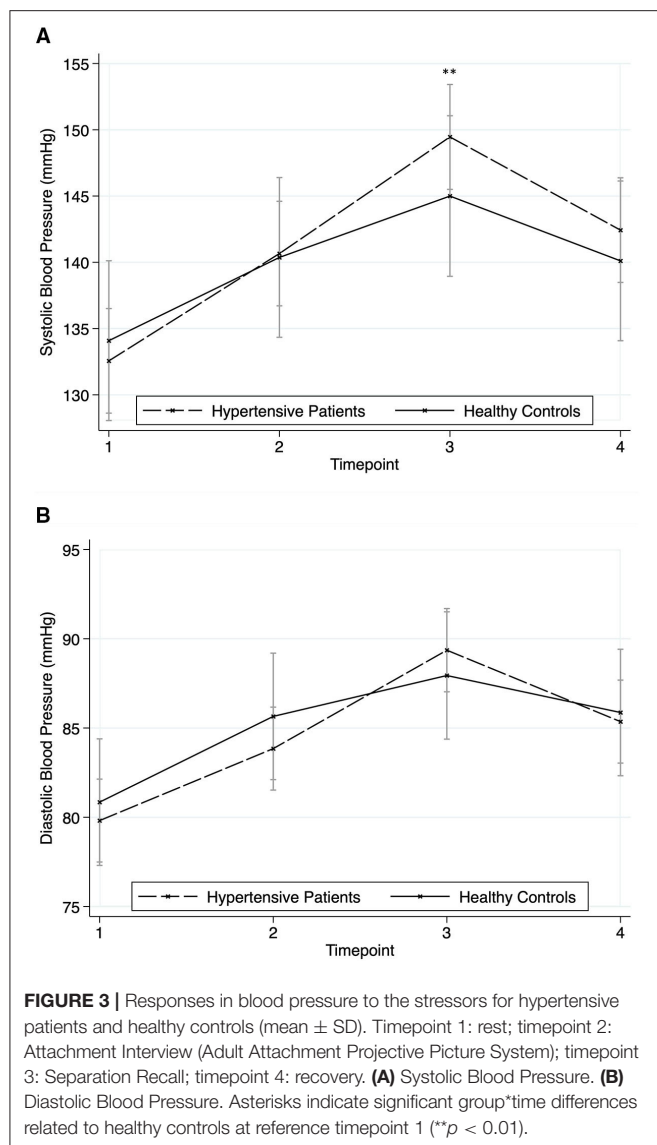
SDNN, standard deviation of normal to normal R-R intervals; RMSSD, root mean square of successive differences; ACTH, adreno-corticotrope hormone; baPWV, brachial-ankle pulse wave velocity; cPWV, central pulse wave velocity; cPP, central pulse pressure; df, degrees of freedom.



DISCUSSION

We showed that medicated subjects with hypertension still show a heightened stress response to attachment/interpersonal-focused stressors with differences in the CV, hypothalamic-pituitary-adrenal (HPA) axis and autonomic reactivity compared

to healthy subjects. This heightened reactivity might contribute to disease risk in patients with hypertension even though in rest, BP values might be within the normal range. It might represent the pathophysiological link for the finding of Kivimäki et al. that in men with cardiometabolic disease, job strain contributes significantly to risk of death, even in the group who had achieved



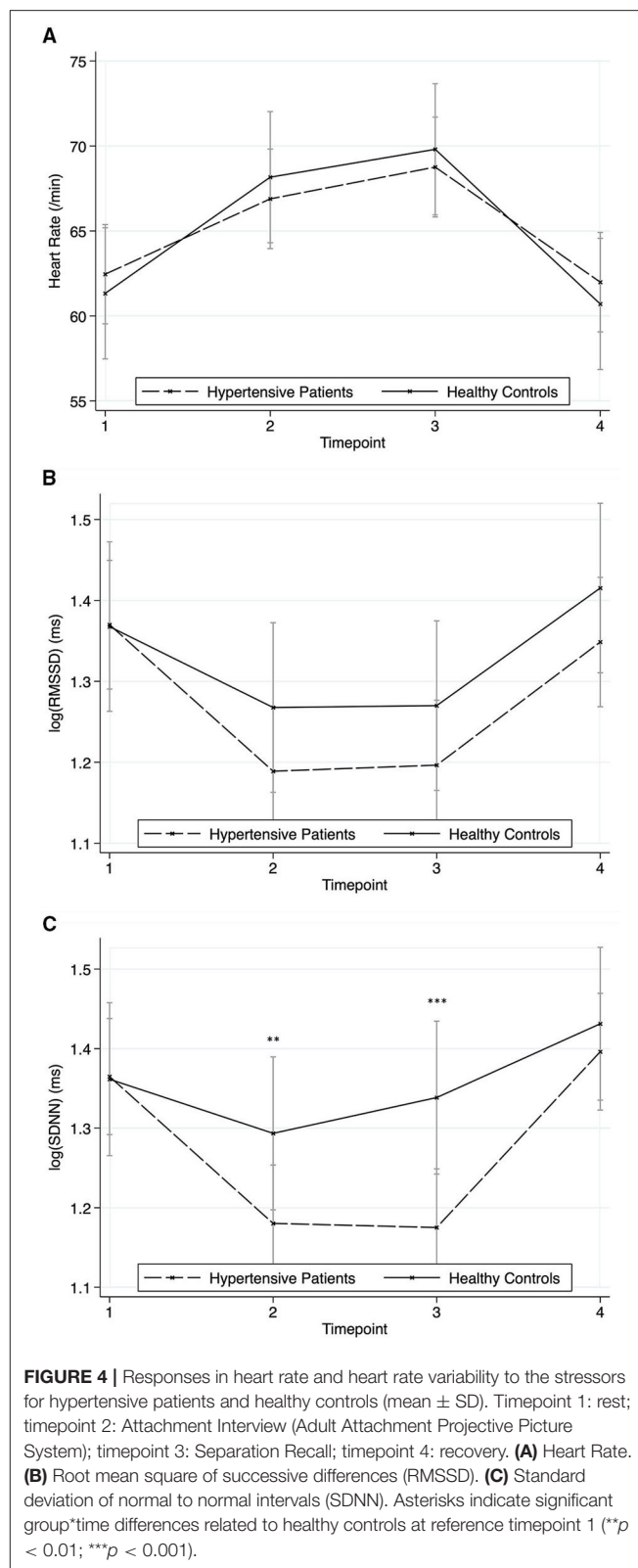
treatment targets, while no risk was found in men without cardiometabolic disease (27).

The relation between laboratory stress and ambulatory blood pressure levels has been shown (28, 29). There is even evidence that the response to specific real life stressors is higher obtained in real life than in the laboratory (30).

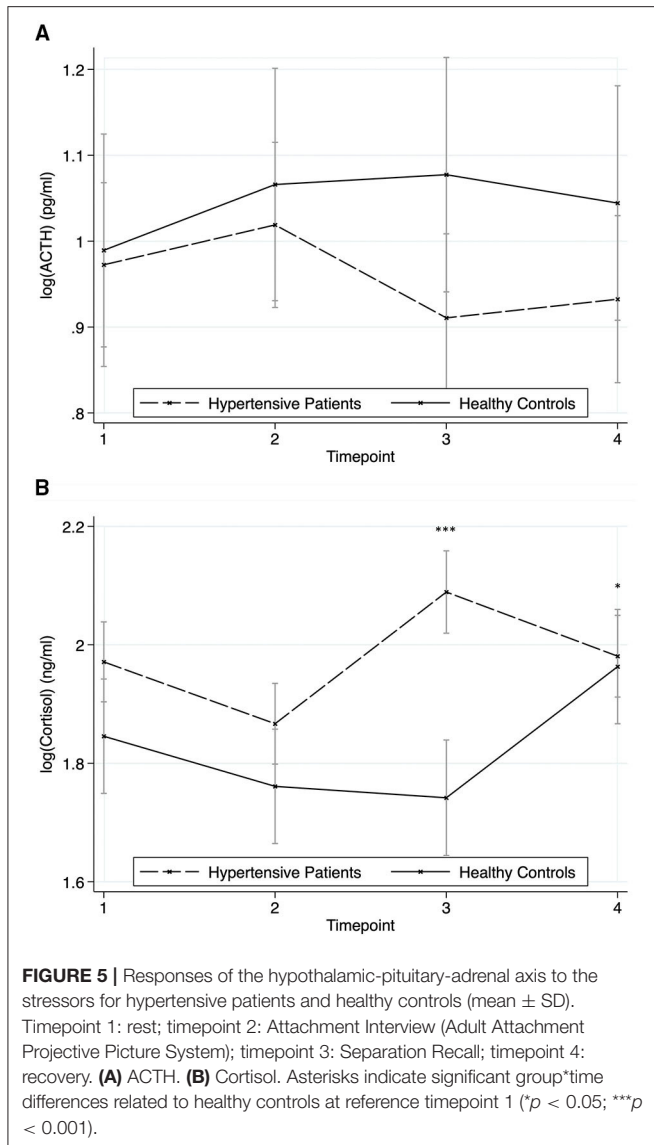
The attachment-related stressors AAP and SR provoked a significant response of the CV system (BP, HR), the ANS, norepinephrine, and the HPA axis (cortisol). For the SR, this has already been shown regarding HR and BP (19).

There were no significant differences for SBP and DBP between hypertensive and healthy subjects and no significant group effects for BP. Therefore, we conclude that our study population was well-treated with regard to resting BP.

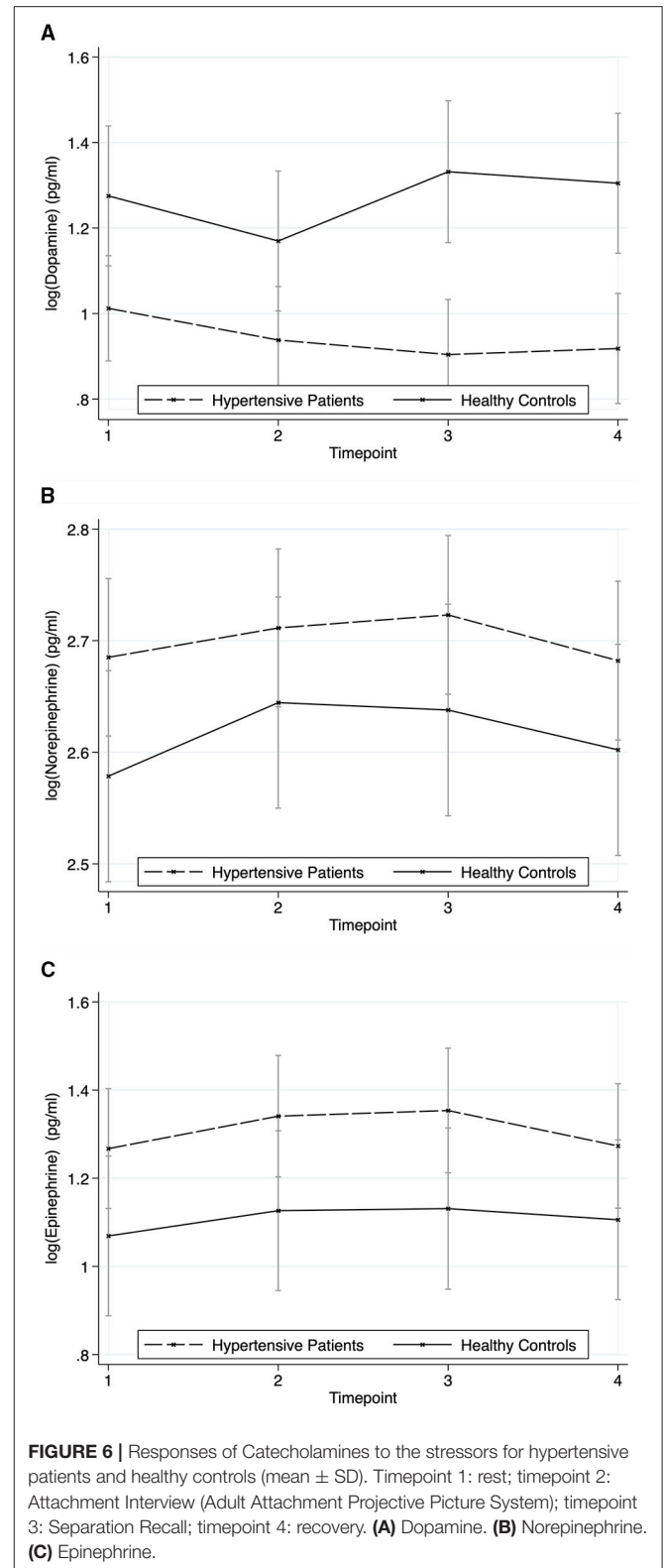
Still, hypertensives showed a steeper rise in blood pressure. We suppose that this is at least partly caused by a hyperreactive sympathetic nervous system (SNS) which we did not assess



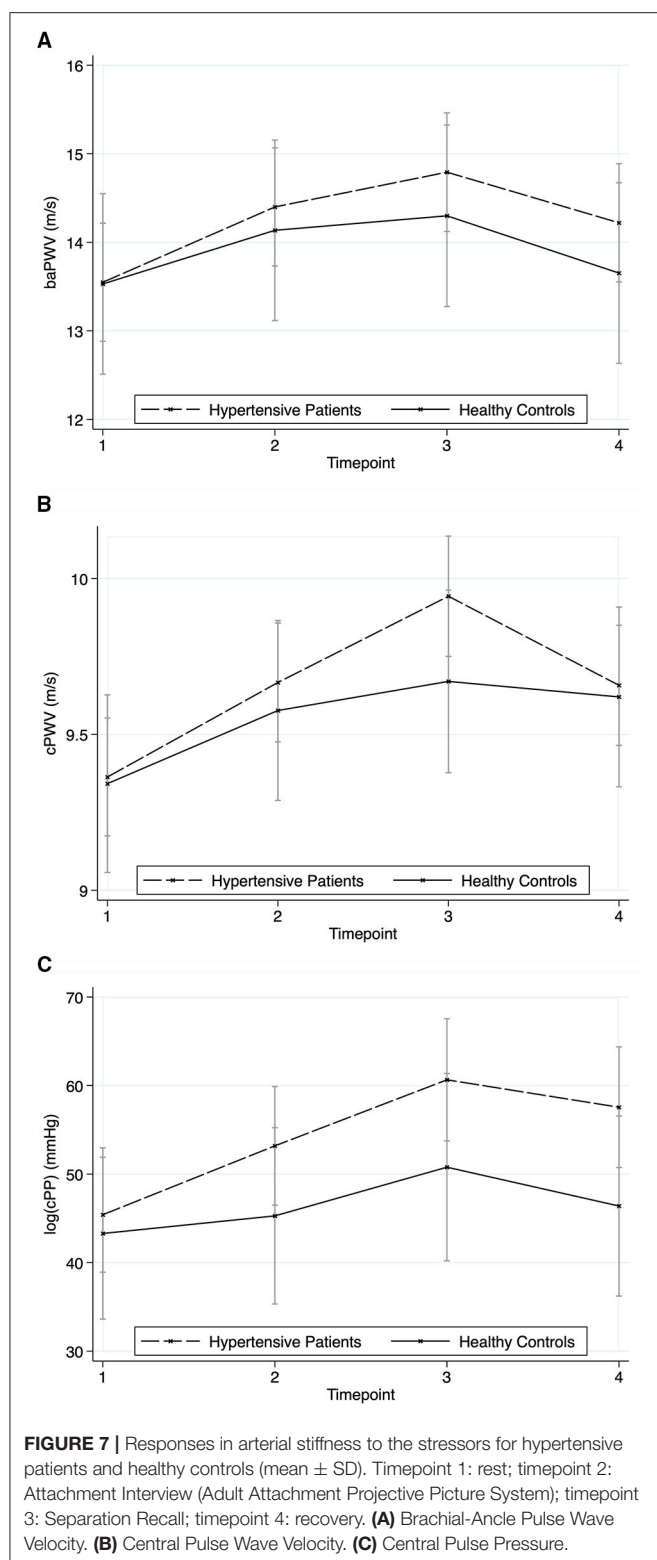
directly in our study but indirectly via HRV measurement. HRV represents the activity of the ANS and combines sympathetic and parasympathetic activity. Though there is no parameter



representing mainly SNS activity, RMSSD is supposed to represent mainly vagal activity. Our results show an enhanced SDNN decline in hypertensive subjects compared to healthy ones while no such differences can be found regarding RMSSD. Therefore, we conclude that SNS activation is a major part of the heightened SDNN response next to vagal withdrawal. This is not supported by the norepinephrine response which was not enhanced in hypertensive subjects. However, there is evidence that norepinephrine in plasma does not reliably reflect SNS activity in general and especially not regional (15). Still, epinephrine levels were higher in hypertensive patients than in controls, a finding also reflected in other studies (11), which might reflect a higher systemic SNS tone. Our finding that levels of Dopamine which has natriuretic and vasodilating effects (31) were lower in hypertensive subjects than in controls is in line with the proposed imbalance of factors regulating sodium retention and vascular tone in essential hypertension (32).



Our results show that BP response is enhanced in hypertensives while HR response does not differ. An explanation might be that beta-blocking medication taken by 78% of



the patients is effective in reducing HR and has a reducing, thus improving arterial stiffness (PWV) (33, 34), while BP response is still hyperreactive, i.e., this response is not blocked

effectively. This would be in line with the results of Rothwell et al., who showed a higher BP variability in patients treated with beta-blocker compared with calcium channel blocker, which correlated with stroke risk (4).

Cortisol showed a significant rise in response to the stressor, while the rise in ACTH was not significant. This is not surprising, as the translation from ACTH to cortisol is not linear. Diurnal rhythms show a 5-fold higher rise in Cortisol than in ACTH. This is due to signal enhancement of ACTH via a risen ACTH-receptor-sensitivity, which can be SNS-mediated, and via a diurnal intra-adrenal regulation of the activity of enzymes synthesizing cortisol. Sympathetic innervation of the adrenal medulla, for instance, via the splanchnic nerve is known to play a critical role in modulating the diurnal adrenocortical sensitivity to ACTH (35, 36). The cortisol response to the stressor in our sample differed between healthy and hypertensive participants. While healthy controls showed a small, non-significant rise of ACTH in response to the stressors with a consecutive, physiologically delayed rise in cortisol, hypertensive patients responded faster with a steeper rise of cortisol levels. While Hamer and Steptoe found a higher cortisol response in individuals that later developed hypertension to those who did not in response to a mental stressor (10), this was not shown by Nyklicek in a study of hypertensive vs. healthy individuals in salivary cortisol levels (12). Wirtz found differences between healthy and hypertensive patients in terms of an attenuated cortisol awakening response and a suppressed feedback sensitivity after dexamethasone suppression (37). An altered HPA axis in hypertension might substantially contribute to the development of atherosclerosis via inflammation (38). In rats, both candesartan and ramipril attenuate Cortisol and ACTH response to CRH-stimulation (14). This finding was replicated in humans with diabetes (39). Though almost all of the hypertensive subjects in our study were on an ACE-inhibitor or an AT1-antagonist and the ACTH response seemed to be lower in hypertensive subjects than in controls, the cortisol response was not. This needs further investigation.

Limitations

The study population might not be representative for subjects with hypertension in general as most of them already developed CV disease and took several antihypertensive drugs. Different kind of drugs have different effects on the physiological systems, and especially Dopamine and Epinephrine are affected by antihypertensive agents. However, due to small numbers and multiple combinations, we could not conduct separate analyses considering the different drugs. Therefore, the effects of some drugs may be masked. Also, we do not know the physiological response of the participants without taking drugs, so we do not know the net effect of the drugs. With consideration of the number of drugs and diagnoses, a cessation of drugs would not have been ethically justifiable. Further, we did not assess BP at home nor by a 24 h-measurement, so we can conclude adequacy of medication only by resting BP during the experiment.

The sample of hypertensive patients differed significantly from the healthy controls regarding age and BMI, both known risk factors for hypertension. We included them in our analyses as

covariates. However, a subsample of hypertensive patients of age and BMI comparable to the healthy controls showed similar results with no deviances regarding significant effects.

Regarding the stressor, we neither included a solely cognitive mental stressor like a mental arithmetic, nor did we include a physical stressor. Thus, we cannot compare the stress response between cognitive mental, attachment-related mental, and physical stress.

It would have been desirable to directly measure neural activity of the SNS. Unfortunately, this was exceeding our resources. Further, the Renin-Angiotensin-Aldosterone-system is also not included in our parameters, which emerges to be another important stress axis (40).

CONCLUSION

All in all, the response of the CV system, the ANS and the HPA axis is heightened in medicated subjects with hypertension in response to attachment-focused stressors compared to healthy subjects, though resting measurements do not differ between the groups. We suppose that the remaining hyper-reactivity even with sufficient antihypertensive medication still poses a substantial risk for affected patients. Sufficient antihypertensive treatment not only under ambulatory blood pressure control but by including stress-related measurements should be considered.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the corresponding author, EB, upon reasonable request without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by ethical review board of Ulm University. The

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

AUTHOR CONTRIBUTIONS

EB designed the study, supervised data acquisition and conduction of the experiments, interpreted the data, and drafted the manuscript. MJ performed the statistical analyses and interpreted the data. SR and DL performed the measurement of ACTH and cortisol and interpreted part of the data. AS-T and SE supervised the PWV and PP measurements and interpreted part of the data. HG contributed to the conception of the experimental setting and critically revised the manuscript for important intellectual content. AF, JK, and SC planned and conducted the experiments and data acquisition, interpreted the data, and critically revised the manuscript for important intellectual content. CW contributed to the conception of the experimental setting, supervised the research project, and critically revised the manuscript for important intellectual content. All authors contributed to the article and approved the submitted version.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: <https://www.frontiersin.org/articles/10.3389/fpsy.2021.718919/full#supplementary-material>

Supplementary Material 1 | Linear mixed-effects regression model for stress parameter reactivity: complete tables. Linear mixed-effects regression model with random intercepts. Covariates included in the models: age, body mass index. Time was level 1, the individual level (Persons) were on level 2. A two-way-interaction between group (Healthy vs. Hypertensive) and time (rest [1], AAP [2], SR [3], recovery [4]) was modeled using restricted maximum likelihood. Significance level: $p < 0.05$. df, degrees of freedom; bmi, body mass index; sbp, systolic blood pressure; dbp, diastolic blood pressure; HR, heart rate; n, normalized (with log-transformation); Cort, Cortisol; SDNN, standard deviation of normal to normal R-R intervals; RMSSD, root mean square of successive differences; ACTH, adreno-corticotrope hormone; baPWV, brachial-ankle pulse wave velocity; cPWV, central pulse wave velocity; cPP, central pulse pressure.

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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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Factors That Influence Adherence to Medication in Adults With Congenital Heart Disease (ACHD)

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Objective: Innovative operative and interventional procedures have improved survival in congenital heart disease (CHD), and today more than 90% of these children reach adulthood. Consequently, adherence and psychosocial issues are becoming increasingly important because non-adherence to treatment recommendations worsens morbidity and mortality. This study aimed to identify factors modifying adherence to medication in adult congenital heart disease (ACHD).

Methods: This cross-sectional study included 451 outpatients (female 47.9%, average age $\pm$ SD: 37.9 $\pm$ 12 years) from the ACHD department, who completed a questionnaire assessing medication non-adherence and individual barriers to treatment. Further assessments included psychological well-being (Hospital Anxiety and Depression scale; HADS), childhood traumatization, sociodemographic, and clinical data. Binary logistic regression analysis calculated the impact of these factors on drug adherence.

Results: Of the 451 patients 162 participants (35.9%) reported to be non-adherent. In univariate analysis non-adherence to treatment was associated with smoking ($P = < 0.001$) and internet addiction ($P = 0.005$). Further factors negatively influencing adherence were the presence of depressive symptoms ($P = 0.002$), anxiety ($P = 0.004$), and childhood traumatization ($p = 0.002$). Factors positively associated with adherence were older age ($P = 0.003$) and more advanced heart disease as indicated by NYHA class ($P = 0.01$), elevated NT-proBNP ($P = 0.02$), device therapy ($P = 0.002$) and intermittent arrhythmias ($P = 0.01$). In multivariate analysis especially psychopathological factors such as depression ($P = 0.009$), anxiety ($P = 0.032$) and childhood traumatization ($P = 0.006$) predicted non-adherence.

Conclusion: Adherence is a critical issue in the long-term management of ACHD. Identifying modifiable factors that worsen adherence offers the opportunity for targeted interventions. Depressive symptoms, anxiety, and adverse childhood experiences are amenable to psychosocial interventions, as well as cigarette smoking. Our study suggests that a multimodal and interdisciplinary treatment concept for the long-term

management of adults with congenital heart disease could be beneficial. Whether it will further improve morbidity and mortality, should be assessed in prospective interventions.

Keywords: adherence to medication, adult congenital heart disease (ACHD), depression, anxiety, childhood trauma

INTRODUCTION

With a prevalence of 9–10/1,000 livebirths, congenital heart disease (CHD) is the most common birth defect in new-borns worldwide (1–3). In recent decades, innovations in surgical and interventional procedures have resulted in over 90% of CHD patients now reaching adulthood (4, 5). For this aging population, there is an increased risk of worsening CHD and additional acquired cardiac and non-cardiac comorbidities requiring chronic drug treatment. Consequently, the spectrum of mortality shifted from high perioperative mortality to chronic heart failure as the leading cause of death (6, 7). Major cardiac comorbidities necessitating intensive drug treatment include heart failure and supraventricular arrhythmias (8, 9). In addition, the increasing frequency of acquired diseases such as diabetes or arterial hypertension also need strict pharmacological and non-pharmacological treatment (10–12). In general, in congenital heart disease medication non-adherence, as well as non-adherence to other therapeutic recommendations is associated with adverse outcome (13–16). Adherence to medication has already been examined in chronic diseases and cardiac diseases other than congenital heart disease. In these studies, non-adherence was predicted by disease severity, lower education, smoking, and psychiatric comorbidities such as depression and anxiety disorders (17–21). However, in adults with congenital heart disease, non-adherence to medication has not been evaluated before. This study aimed to identify modifiable and non-modifiable risk factors of non-adherence to medication treatment, in adults with congenital heart disease (ACHD). This might enable the identification of vulnerable patients, allowing preventive interventions, potentially improving outcome.

MATERIALS AND METHODS

Participants

Between August 2020 and February 2021, data were collected from the CHD outpatient clinic of the Department of Cardiology at Hannover Medical School. Inclusion criteria were: (a) a structural heart defect, (b) age ≥ 18 years and (c) the ability to read and answer the questionnaire in German. During the inclusion period, 747 patients visited the outpatient clinic. Pregnancy, language barriers, and intellectual disability led to the exclusion of 156 patients. Sixteen patients refused to participate. Of the 575 participants, 124 had to be excluded due to missing data in the adherence scale. The remaining 451 patients (female: 47.9%, mean age $\pm$ SD of: 37.9 ± 12 years, range from: 18 to 81) were included in this study (Figure 1).

Assessment of Adherence

To assess the adherence to medication regimens, the A14-adherence questionnaire (A14 scale) was used (22). The scale consists of 14 questions covering different characteristics of non-adherence. Non-adherence is divided into the categories: changes in medication schedule due to safety and efficacy reasons, practical barriers such as costs and time requirement of therapy, non-adherence due to a generally negative perception of pharmacological treatment, and unintentional missing of drug intake. The questions are answered in a 5-item Likert-scale with the range of 4 (“never”) to 0 (“very often”). With a total score of 50 to 56 points, patients are classified as adherent. Non-adherence is set to a score of < 50 points.

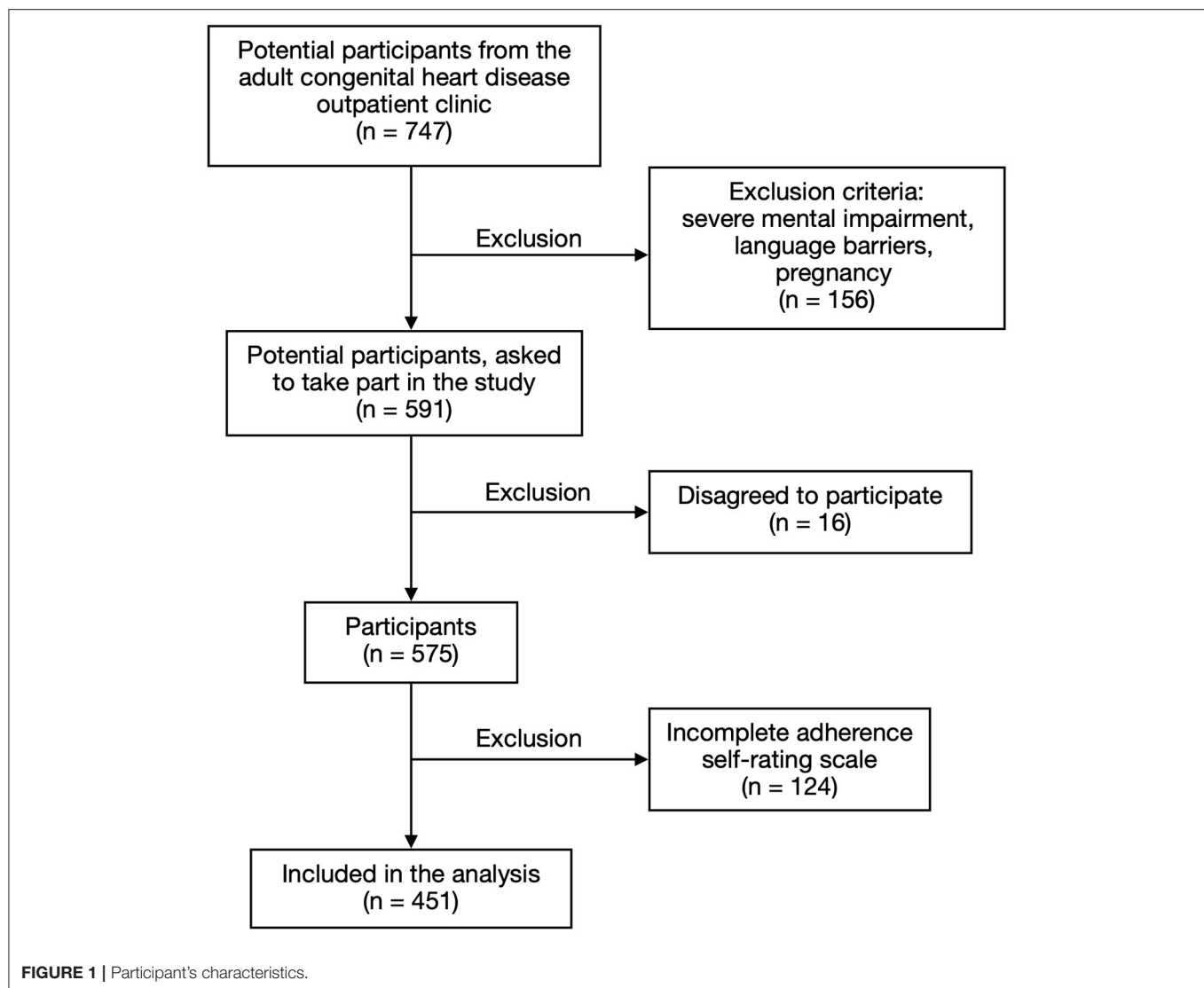
Assessment of Psychosocial Status

All participants answered questions about their lifestyle habits and social status including smoking habits (smoker: yes/no), relationship status (in a current relationship: yes/no), number of school years, and hours of sleep per night. Lifestyle was further assessed using the alcohol use disorders identification test (AUDIT) and the internet addiction scale (Internetsuchtskala, ISS-10), a German questionnaire to identify potential internet addiction. The ISS-10 consists of 10 questions, each answered in a 4-item Likert scale ranging from 1 (does not apply) to 4 (fully applies). The questions are based on the ICD-10 criteria for other addiction disorders. We compared the total ISS-10 score and ISS scores ≥ 25 , which indicates internet addiction.

To analyse depressive symptoms and symptoms of anxiety, the hospital anxiety and depression scale (HADS) was used. For our analysis we compared the total HADS score with the anxiety score of the HADS (HADS-A) and the depression score of the HADS (HADS-D), as well as a cut-off of ≥ 8 points for both sub-scores. Furthermore, the childhood trauma questionnaire (CTQ) was used to assess childhood traumatization. For comparison we calculated the total CTQ score including all sub-scores.

Assessment of Cardiac Disease

All participants receiving their routine check-up were examined by a senior cardiologist of the ACHD outpatient clinic. The functional status was assessed using the New York Heart Association classification (NYHA class). The complexity of the underlying heart disease was divided into “simple,” “moderate” and “complex” defects, using the Bethesda classification (23). Information about intermittent arrhythmias, device therapy including pacemaker and/or defibrillator and daily medications were extracted from medical records. Blood samples were taken during examination and laboratory data were collected.



Statistical Analysis

All data was analyzed using SPSS (IBM SPSS Statistics for Macintosh, Version 27). For group comparison (adherent/non-adherent) we used the *t*-Test for unpaired samples, Fisher's exact test or Mann-Whitney U-test as appropriate. All data are given as mean $\pm$ standard deviation (SD) or as n (%) out of the subgroups. A *P*-value < 0.05 was considered as statistically significant. For missing data in the HADS, CTQ, ISS-10, and AUDIT questionnaires, singular imputation method by calculating the mean of each question was performed. Missing data were found in 31 cases of the CTQ, 10 cases of the HADS and ISS-10 and 7 cases of the AUDIT questionnaire. Univariate binary regression analysis calculated single predictors associated with non-adherence. In multivariate analysis, all significant variables from the univariate calculation were included. In case of a close correlation between parameters ($r > 0.4$) the variable with the higher significance level in univariate analysis remained in the multivariate calculation. This led to the exclusion of

NT-proBNP (correlation with NYHA class, $r = 0.548$) and intermittent arrhythmias (correlation with device therapy, $r = 0.403$). The variables CTQ, total HADS, HADS-D and HADS-A, were closely interrelated ($r > 0.7$). Therefore, these parameters were calculated in different models. The raw data model included the variables age, smoking, internet addiction, NYHA class, device therapy, hypertension, and creatinine. All models were adjusted to age and sex.

RESULTS

Most of the participants presented with mild symptoms corresponding to NYHA classes I and II 419/451 (92.2%), while 32/451 (7.1%) had severe symptoms of chronic heart failure. The largest group were patients presenting with complex heart defects, according to the Bethesda classification: 249/451 (55.2%), followed by patients with moderate defects: 157/451 (34.8%). 45/451 (10%) had morphological simple defects. Intermittent

TABLE 1 | Demographic, lifestyle, psychiatric and cardiological data of adults with congenital heart disease (ACHD).

	All ACHD patients (N = 451)	Adherent ACHD patients (N = 289)	Non-adherent ACHD-patients (N = 162)	P value
Female, n (%)	216 (47.9%)	135 (46.7%)	81 (50%)	n.s
Age, mean y $\pm$ SD	37.9 $\pm$ 12	39.2 $\pm$ 12	35.6 $\pm$ 11.8	0.002
BMI, mean $\pm$ SD	26 $\pm$ 5	26.1 $\pm$ 4.8	25.8 $\pm$ 5.3	n.s.
Partnered, n (%)	297 (65.9%)	194 (68.1%)	103 (65.2%)	n.s.
School years, mean $\pm$ SD	11.7 $\pm$ 1.8	11.7 $\pm$ 1.8	11.7 $\pm$ 1.8	n.s.
Medicines, mean per day $\pm$ SD	2.6 $\pm$ 2.7	3 $\pm$ 2.8	1.8 $\pm$ 2.2	<0.001
Sleep, mean h/per night $\pm$ SD	6.8 $\pm$ 1.3	6.83 $\pm$ 1.3	6.69 $\pm$ 1.3	n.s
Smoking, n (%)	54 (12%)	21 (7.3%)	33 (20.4%)	<0.001
AUDIT-score, mean $\pm$ SD	2.9 $\pm$ 3.2	2.8 $\pm$ 3	3.0 $\pm$ 3.4	n.s.
AUDIT-score $\geq$ 7, n (%)	35 (7.8%)	22 (7.6%)	13 (8.0%)	n.s.
ISS10-score, mean $\pm$ SD	14.4 $\pm$ 4.1	14 $\pm$ 3.7	15.2 $\pm$ 4.8	0.011
ISS10-score $\geq$ 25, n (%)	15 (3.3%)	4 (1.4%)	11 (6.8%)	0.004
Total HADS score, mean $\pm$ SD	9.8 $\pm$ 6.4	9.0 $\pm$ 5.7	11.15 $\pm$ 7.3	0.002
HADS-D score, mean $\pm$ SD	3.8 $\pm$ 3.3	3.45 $\pm$ 3	4.48 $\pm$ 3.7	0.003
HADS-D score $\geq$ 8, n (%)	60 (13.3%)	26 (9.2%)	34 (21.3%)	<0.001
HADS-A score, mean $\pm$ SD	6 $\pm$ 3.8	5.61 $\pm$ 3.4	6.68 $\pm$ 4.3	0.004
HADS-A score $\geq$ 8, n (%)	132 (29.3%)	75 (26%)	57 (35.2%)	0.041
Total CTQ score, mean $\pm$ SD	32.7 $\pm$ 9.6	31.7 $\pm$ 8.1	34.6 $\pm$ 11.5	0.004
Emotional neglect, n (%)				
low/moderate or higher	143 (31.7%)	79 (27.3%)	64 (39.5%)	0.008
NYHA class, mean				0.01
I, n (%)	313 (69.4%)	189 (65.4%)	124 (76.5%)	
II, n (%)	106 (23.5%)	75 (26%)	31 (19.1%)	
III or IV, n (%)	32 (7.1%)	25 (8.7%)	7 (4.3%)	
Bethesda class				n.s.
Simple, n (%)	45 (10%)	25 (8.7%)	20 (12.3%)	
Moderate, n (%)	157 (34.8%)	96 (33.2%)	61 (37.7%)	
Severe, n (%)	249 (55.2%)	168 (58.1%)	81 (50%)	
Total devices, n (%)	57 (12.7%)	47 (16.3%)	10 (6.2%)	0.002
Intermittent arrhythmias, n (%)	75 (16.6%)	58 (20.1%)	17 (10.6%)	0.009
Hypertension, n (%)	103 (22.8%)	75 (26%)	28 (17.3%)	0.036
NT-proBNP mean ng/l $\pm$ SD	218 $\pm$ 372.4	250.9 $\pm$ 418.6	159.6 $\pm$ 263	0.005
CRP, mean mg/dl $\pm$ SD	2 $\pm$ 3	1.9 $\pm$ 2.6	2.2 $\pm$ 3.6	n.s.
LDL, mean mg/dl $\pm$ SD	105.3 $\pm$ 31.1	104.7 $\pm$ 29.5	106.24 $\pm$ 33.8	n.s.
HDL, mean mg/dl $\pm$ SD	53.7 $\pm$ 19	52.3 $\pm$ 16.5	56.2 $\pm$ 22.7	n.s.
HbA1c, mean $\pm$ SD	5.4 $\pm$ 1.4	5.36 $\pm$ 0.6	5.48 $\pm$ 2.2	n.s.
Creatinine (μ mol/l)	80.9 $\pm$ 21.2	82.9 $\pm$ 23.2	77.4 $\pm$ 16.5	0.008

AUDIT, alcohol use disorder identification test; ISS-10, internet addiction scale (German: Internetsuchtskala); Total-HADS, hospital anxiety and depression scale; HADS-D, depression score of HADS; HADS-A, anxiety score of HADS; NYHA, severity of chronic heart failure according to New York Heart Association; Total devices, pacemaker and/or defibrillator; NT-proBNP, N-terminal prohormone of brain natriuretic peptide; CRP, C-reactive protein; LDL, low density lipoprotein; HDL, high density lipoprotein; n.s., $P > 0.05$; SD, standard deviation.

arrhythmias were present in 75 (16.6%) of the patients and a total of 57 (12.7%) were fitted with a device (either pacemaker and/or defibrillator). Symptoms of anxiety (HADS-A score $\geq$ 8) were found in 132 (29.3%) of the participants, depressive symptoms (HADS-D score of $\geq$ 8) were present in 60 (13.3%). One hundred and forty three (31.7%) participants reported low to moderate/higher emotional neglect during childhood (Table 1). Non-adherence was reported by 162 (35.9%) of the participants. There was no drug specific difference in adherence detected.

Predictors of (Non)-adherence in Univariate Analysis

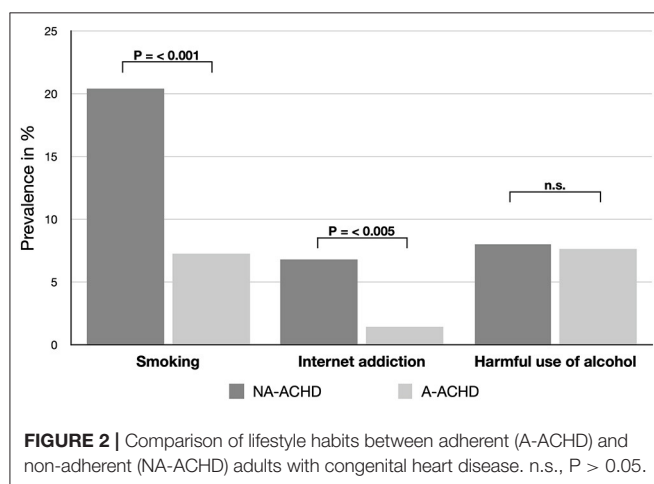
Lifestyle and Sociodemographic Factors

In univariate analysis, non-adherence was negatively associated with smoking [Hazard ratio (HR): 3.265, 95%-CI: 1.817–5.866, $P = < 0.001$] and internet addiction [(HR: 5.190, 95%-CI: 1.625–16.578), $P = 0.005$]. No significant difference was calculated for the participants sleeping routine, alcohol use, school education

TABLE 2 | Univariate predictors of (non)-adherence to medication.

	HR	95%-CI of HR	P-value
Age (y)	0.974	(0.957–0.991)	0.003
Smoking	3.265	(1.817–5.866)	<0.001
ISS-score ≥ 25	5.190	(1.625–16.578)	0.005
NYHA class	0.641	(0.458–0.898)	0.01
Total devices	0.339	(0.166–0.690)	0.003
Intermittent arrhythmias	0.468	(0.262–0.836)	0.01
Hypertension	0.596	(0.367–0.968)	0.037
NT-proBNP (ng/l)	0.999	(0.998–1.0)	0.02
Creatinine ($\mu\text{mol/l}$)	0.983	(0.971–0.995)	0.006
Total HADS score	1.051	(1.020–1.083)	0.001
HADS-D score	1.097	(1.035–1.163)	0.002
HADS-A score	1.078	(1.024–1.134)	0.004
Total CTQ score	1.032	(1.012–1.053)	0.002

ISS-10, internet addiction scale; NYHA, New York Heart association; NT-proBNP, N-terminal prohormone of brain natriuretic peptide; HADS, hospital anxiety and depression scale; HADS-D, depression score of HADS; HADS-A, anxiety score of HADS; CTQ, childhood trauma questionnaire; CI, confidence interval; HR, hazard ratio.



or relationship status. Older age was positive associated with adherence (HR: 0.974, 95%-CI: 0.957–0.991, $P = 0.003$) (Table 2; Figure 2).

Cardiac Status

NYHA class (HR: 0.641, 95%-CI: 0.458–0.898, $P = 0.01$) and NT-proBNP (HR: 0.999, 95%-CI: 0.998–1.0, $P = 0.02$) were higher in the adherent group (A-ACHD). Moreover, hypertension (HR: 0.596, 95%-CI: 0.367–0.968, $P = 0.037$), intermittent arrhythmias (HR: 0.468, 95%-CI: 0.262–0.836, $P = 0.01$) and device therapy (HR: 0.339, 95%-CI: 0.166–0.690, $P = 0.003$), suggesting a more advanced stage of disease, were related to a higher adherence (Table 2).

Psychiatric Diseases

Depressive symptoms were highly correlated with non-adherence ($P = 0.002$). Correspondingly, symptoms of anxiety

were also found to be negatively correlated with adherence ($P = 0.004$) as well as childhood traumatization, indicated by the total CTQ score ($P = 0.002$) (Table 2; Figure 3).

Predictors of (Non)-adherence in Multivariate Analysis

Because depression, anxiety disorder and childhood trauma were closely interrelated, in multivariate analysis each psychiatric condition was calculated in an individual model. Even after adjustment for sex and age, the psychiatric conditions remained significant single predictors of non-adherence: depressive symptoms ($P = 0.007$), anxiety calculated by the HADS-A score ($P = 0.032$), the total HADS score ($P = 0.009$), and childhood traumatization indicated by the total CTQ score ($P = 0.006$). In all models smoking remained a strong predictor of non-adherence (HR: 3). In contrast, older age ($P = 0.017$ – 0.031) and device therapy ($P = 0.005$ – 0.007) were associated with better adherence and remained significant in all models (Table 3).

DISCUSSION

To the best of our knowledge, this study is the first to assess adherence to medication in adults with congenital heart disease (ACHD). The main findings of our study are a high prevalence of self-reported non-adherence (35.9%) within the population of ACHD patients and that factors contributing to non-adherence are closely linked to underlying mental health problems and psychiatric comorbidities such as depressive symptoms, anxiety symptoms and childhood trauma. The prevalence of these comorbidities is high in ACHD patients. We found that 31.7% of the patients experienced mild to moderate emotional neglect, 29.3% had a HADS-A score ≥ 8 , pointing to the presence of an anxiety disorder and 13.3% had a HADS-D score of ≥ 8 , pointing to the presence of depression. Added to these factors were lifestyle factors such as smoking, as strong predictors of non-adherence. However, our study also revealed that those in older age or with implanted medical devices were more likely to adhere to their medication regimens.

Non-adherence to pharmacological treatment is not limited to ACHD and has been identified to emerge in many other chronic diseases (24). Adherence to medication has also been reported to be increased by frequent office follow-up visits (“white-coat adherence”) and non-attendance appears to be linked to non-adherence to medication (25, 26). Therefore, non-adherence might even be underestimated in our study since all patients scheduled their visits on a regular basis and those lost to follow were not sampled. Given that the number of ACHD patients requiring intensified drug treatment will continue to grow, the issue of treatment adherence will become increasingly important to avoid the risk of non-response and consequent adverse morbidity and mortality outcomes. The relevance of drug treatment for the outcome of ACHD patients is still poorly studied and will need further exploration, but the seriousness of the disease suggest that it might have major relevance.

The high prevalence of psychiatric comorbidities is coherent with previous studies describing elevated rates of mental

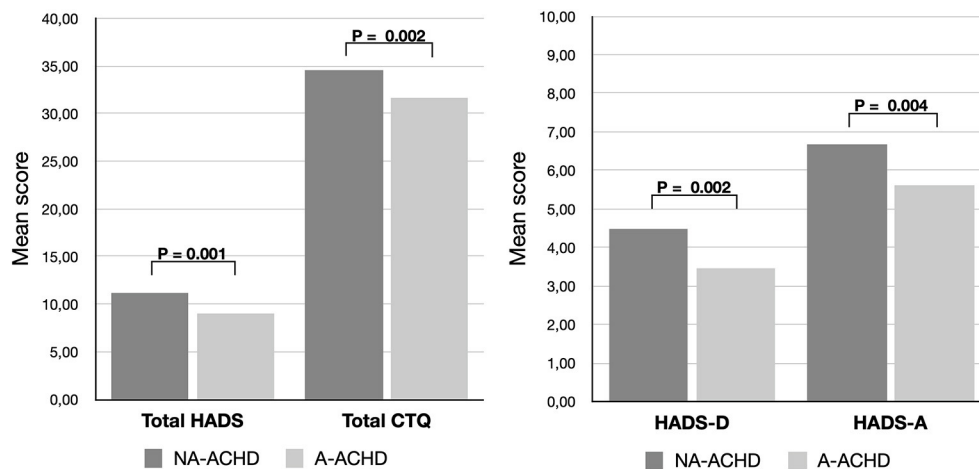


FIGURE 3 | Comparison of the mean score of the hospital anxiety and depression scale (total HADS score) and its sub-scores for depression (HADS-D) and anxiety (HADS-A) as well as the childhood trauma questionnaire (CTQ), showing significantly higher levels in non-adherent patients (NA-ACHD) compared to adherent patients (A-ACHD).

disorders in ACHD patients compared to the general population (27–29). A recent study also reported higher rates of childhood traumatization in ACHD patients compared to the general German population (30). These comorbidities are often underdiagnosed and untreated (27, 31). Our results further underline the importance of screening for psychiatric diseases in ACHD patients, as they were identified as risk factors associated with non-adherence to medication. Our findings are supported by the results of White et al., who showed that depression, anxiety, and cardiac denial were associated with lower adherence to cardiac care visits in ACHD patients (32). Depression, anxiety, and traumatization are modifiable risk factors that are amenable to guideline-based pharmacological and non-pharmacological treatments. However, even in specialized ACHD centers, psychological support is still underrepresented, although multidisciplinary treatment concepts are already recommended (33). Our study results strengthen the demand of psychological and psychiatric treatment concepts for ACHD. Ferguson and Kovacs previously demonstrated the benefit of specialized psychological care for ACHD patients, noting that they face a number of psychological challenges linked to their disease such as health-related and heart related anxiety, depressed mood, and difficulty coping with medical conditions (28). To identify ACHD patient in need of psychological support, the HADS-scale could be a useful screening instrument for depressions and anxiety disorders in the outpatient clinical setting. In a previous study of ACHD patients, the HADS-scale showed good results in detecting moderate and severe depressions but suggesting lower cut-off values (34).

A further relevant finding of our study was the correlation between smoking and associated non-adherence to medication. As previously described, tobacco smoking was linked to higher levels of depression in ACHD patients which may partly explain our results (35). However, smoking did not correlate with depressive symptoms in our study ($r = -0.09$), suggesting

TABLE 3 | Multivariate predictors of (non)-adherence to medication in adults congenital heart disease.

	HR (95%-CI)	95%-CI	P-value
Total HADS-score	1.043	(1.011–1.077)	0.009
-Smoking	3.0	(1.616–5.570)	0.001
-Age	0.978	(0.961–0.997)	0.02
-Device therapy	0.355	(0.170–0.743)	0.006
-Creatinine ($\mu\text{mol/L}$)	0.987	(0.974–1.0)	n.s.
HADS-D-score	1.088	(1.023–1.157)	0.007
-Smoking	2.996	(1.615–5.557)	0.001
-Age	0.978	(0.960–0.996)	0.017
-Device therapy	0.362	(0.173–0.758)	0.007
-Creatinine ($\mu\text{mol/L}$)	0.986	(0.973–0.999)	0.03
HADS-A-score	1.060	(1.005–1.119)	0.032
-Smoking	3.082	(1.665–5.702)	0.001
-Age	0.979	(0.961–0.997)	0.023
-Device therapy	0.348	(0.166–0.729)	0.005
-Creatinine ($\mu\text{mol/L}$)	0.987	(0.975–1.0)	n.s.
Total CTQ-score	1.031	(1.009–1.053)	0.006
-Smoking	2.990	(1.611–5.549)	0.001
-Age	0.979	(0.961–0.998)	0.031
-Device therapy	0.351	(0.166–0.741)	0.006
-Creatinine ($\mu\text{mol/L}$)	0.988	(0.975–1.001)	n.s.

CI, confidence interval; HADS, hospital anxiety and depression scale; HADS-D, depression score of HADS; HADS-A, anxiety score of HADS; CTQ, childhood trauma questionnaire; n.s., not significant.

that other effects also need to be considered. Smoking is associated with other unhealthy behaviors: a reduction in self-care and adherence to treatment (36–38). Our results may suggest that smoking cessation fosters medication adherence. Similarly, internet addiction was another contributory factor associated with non-adherence. As for other addiction disorders, internet

addiction is frequently concurrent with psychiatric diseases such as anxiety and depression (39, 40). Therefore, the presence of multiple collinearities in our data set may be one of the reasons that internet addiction did not yield significant values in our multivariate models. Addiction disorders can be treated, and therapeutic interventions may be improving drug adherence.

On the opposite, our results showed that older age and having an implanted device, either defibrillator or pacemaker, positively correlated with drug adherence. It should be taken into account, that older age in the ACHD population also implies a relatively good health status, which may be also supported by the patients adherence (13). In addition, it is recommended that patients fitted with a device go for check-ups every 3 to 6 months (41). More frequent controls in this group may therefore also have a positive impact on adherence. Univariate analysis suggested that adhering to treatment regimens might be associated with more advanced stages of disease, indicated by for example, NYHA class, NT-proBNP, device therapy, and common cardiac comorbidities such as hypertension and arrhythmias. This could not be verified in multivariate regression models, suggesting that disease severity potentially only accounts for some positive influence on medication adherence. We suggest that the impact of disease severity, specific health conditions and the effect of multimodal interventions on drug adherence should be investigated in further prospective studies, to become certain on their influence, potentially improving the outcome for ACHD patients.

Strength and Limitations

The main strength of our study is the large population of ACHD patient included and the usage of validated self-assessment questionnaires that can be easily applied in patients' clinical routine. Adherence to treatment is an important factor in the long-term management of CHD and can be assessed with self-rating instruments. We used the A-14 self-report questionnaire on medication adherence, which is an effective and inexpensive method that reveals a detailed picture of the various potential causes of treatment adherence. However, as with other self-assessment questionnaires, results may be biased by recall bias and social desirability. It has also to be mentioned, that some of the questionnaires have not been validated for ACHD. Further limitations are that the study only included patients from one center who were present for their routine check-ups and that data were collected during the period of the 2nd wave of COVID-19 in the end of 2020 with nationwide restrictions implemented, which could have led to selection bias within the study population. Therefore, we cannot rule out, that the elevated rates of depressive symptoms and anxiety detected by us, are partly explained by the COVID-19 pandemic. Moreover, the rate of non-adherence might be even higher, given that 296 patients were excluded from our study for various reasons.

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CONCLUSION

In summary, our study provides first insights into factors associated with medication non-adherence in ACHD and pointing to the potential importance of multimodal and multidisciplinary therapy concept, that include psychological and psychiatric treatment concepts in the long-term management of ACHD patients. Depression, anxiety, traumatization as well as smoking and other addiction disorders are modifiable risk factors. Their treatment might improve adherence and outcome in ACHD.

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 Ethics Committee - Medical School Hannover, Hannover, Germany. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

KK and MW-B are leading investigators in the PsychOnHeart study and have been involved in all aspects of this study. In particular, they were involved in (i) experiment design, (ii) experiment realization, (iii) data collection, (iv) data analysis, (v) data interpretation and (vi) manuscript writing. TH was involved in experiment design, data collection, data analysis, data interpretation and manuscript writing. SA was involved in experiment design, data collection, data analysis and data interpretation. FL was involved in data collection, data interpretation and revising the manuscript. AG, IH, WH, and JB were involved in data interpretation and revising the manuscript. All authors have materially participated in the research and/or manuscript preparation and have approved the final manuscript.

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Yohimbine-Induced Reactivity of Heart Rate Variability in Unmedicated Depressed Patients With and Without Adverse Childhood Experience

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Stressful life events play a role in the pathogenesis of major depressive disorder (MDD) and many patients with MDD were exposed to developmental stress due to adverse childhood experiences (ACE). Furthermore, dysregulation of the autonomic nervous system and higher incidence of cardiovascular disease are found in MDD. In MDD, and independently in individuals with ACE, abnormalities in heart rate variability (HRV) have been reported. While these are often confounded, we systematically investigated them with a study which included MDD patients with/without ACE as well as healthy individuals with/without ACE. With this study, we investigated the influence of noradrenergic stimulation on HRV reactivity in unmedicated participants in a randomized, double-blind, repeated measures design. Our sample consisted of men and women with MDD and ACE ($n = 25$), MDD without ACE ($n = 24$), healthy participants with ACE ($n = 27$), and without ACE ($n = 48$). Participants received a 10 mg single dose of the alpha-2 antagonist yohimbine that increases noradrenergic activity or placebo on 2 separate days, with ECG recordings before and after drug administration at defined intervals. We found lower basal HRV in MDD and ACE: patients with MDD had reduced RMSSD whereas participants with ACE had lower LF-HRV. Contrary to our hypothesis, there was no effect of yohimbine. With this study, we were able to replicate previous findings on HRV differences in MDD and ACE. From the null effect of yohimbine, we conclude that the yohimbine-induced sympathetic activation is not a significant driver of HRV in MDD and ACE.

Keywords: childhood trauma, early life maltreatment, adverse childhood experience, heart rate variability, major depressive disorder, yohimbine, norepinephrine, parasympathetic and sympathetic reactivity

INTRODUCTION

Major Depressive Disorder (MDD) is associated with a dysregulation of the autonomic nervous system (ANS), reflected in a disturbed balance between the sympathetic and parasympathetic branch of the ANS (1–3). Among several other adverse health effects, MDD increases the risk of developing cardiovascular disease and ultimately of cardiac mortality (4). Numerous studies have demonstrated that patients with MDD, and independent of comorbid cardiovascular disease, have

lower heart rate variability (HRV) when compared to healthy controls, both under resting condition and measured as reactivity after stress (5, 6). Heart rate variability describes the natural variation of the time interval between successive heartbeats and reflects the ability of the organism to constantly adapt the heart rate to current demands. Acute stress, physical exercise, or mental load require an increase in heart rate, which normally decreases again when the body is relieved of workload and relaxed. Lower variability of the heart rate can therefore be interpreted as an reduced adaptability of the organism, i.e., lower capacity to adjust to current demands (7). The organism adjusts the heart rate *via* autonomous physiological regulatory pathways. While it is established that high frequency changes in heart rate are mediated by the vagus nerve and therefore the parasympathetic nervous system, the hypo-reactivity found in MDD patients could as well be attributed to constant sympathetic dysregulation (8–10).

Along with adrenaline, noradrenaline (NA) is the main transmitter of the sympathetic nervous system and is also involved in numerous cognitive processes in the brain (11). Noradrenaline metabolism and the transmission processes based on this neurotransmitter are also disturbed in MDD (12). This involves both the concentration levels measured in patients' blood and receptor sensitivity, whereby the findings are inconsistent to some degree and numerous questions remain to be elucidated (13). In depressed patients, lower NA levels are found and antidepressant medication that increases the availability of NA is therapeutically effective (14, 15). Yet, after stress, the release of NA is extensively increased—and chronic stress is a major risk factor for the development of MDD, patients often report increased stress leading up to a depressive episode, an alleged contradiction which has even been termed “the noradrenergic paradox” (16). However, this paradox might be resolved by taking receptor level alterations into account. For instance, a higher density and sensitivity of alpha2- adrenergic receptor in the brains of MDD patients have been reported (17, 18). The alpha2-receptor essentially controls the autoregulation of NA release in the central nervous system, primarily *via* the Locus Coeruleus (LC) region in the brainstem. The increased release of NA after stress, in addition to an increased affinity of NA-binding auto-receptors in the LC, could lead to a subsequent reduction of transmitter levels and compensatory changes in the LC in MDD patients (12, 16).

Among patients with MDD, difficult, often traumatizing, experiences in childhood, and adolescence are frequently found, which are commonly referred to as adverse childhood experiences (ACE). These experiences are associated with chronic stress in important developmental stages and have a lasting influence on psychological and physiological processes in adulthood, potentially *via* epigenetic mechanisms (19). Different studies have shown increased stress reactivity of the sympathetic nervous system in adult subjects with traumatic experiences in childhood, accompanied by increased NA release (20, 21). Similar to MDD, increased alpha2 receptor sensitivity was reported in individuals with ACE (22). The autonomic

dysregulation described above should be most pronounced in the subpopulation of MDD patients whose biographies are influenced by ACE such as physical or sexual abuse.

Taken together, these findings indicate that persistent autonomic dysregulation is present in both patients with MDD and individuals with ACE, which may represent a causal mechanism for lower HRV. However, the two factors usually do not occur independently of each other: ACE represents one of the most important influences in the pathogenesis of MDD, and numerous patients report previous ACE (23). As with MDD, individuals with ACE show lower resting HRV (24), and also blunted HRV reactivity to stress (25, 26). The joint presence of both factors leads to a compounding effect: some studies have demonstrated the strongest HRV abnormalities in patients with MDD and early traumatic experiences, compared with MDD patients without them or healthy controls (27). Another study that examined the joint influence of MDD and ACE on stress-related HRV reactivity found that MDD patients with a trauma history exhibited the lowest HRV after stress exposure (28).

In this regard, numerous of the aforementioned studies have exclusively examined HRV parameters that reflect the activity of the parasympathetic branch of the ANS. Although this seems justified by the fact that the vagal control of these parameters is well-established, this represents only a part of the autonomic cascade. It could be shown that especially sympathetic, and not parasympathetic activation, mediates stress-related HRV reactivity in individuals with ACE (29), and sympathetic over-activation, alongside with vagal withdrawal, has been proposed as an explanatory mechanism for altered HRV stress reactivity in MDD (6).

With this study, we systematically investigated both MDD and ACE in a full factorial, fully crossed orthogonal design, which included MDD patients with/without ACE as well as healthy individuals with/without ACE. We specifically aimed to investigate the influence of sympathetic autonomic activation on HRV reactivity in these groups. For this purpose, the alpha2-adrenergic antagonist yohimbine was administered and ECG was recorded over 5 min periods once before and three times after administration at fixed intervals. Because our manipulation was targeted at direct and specific sympathetic activation, low frequency (LF)-HRV, that primarily reflects variations in cardiac sympathetic activity, served as our primary outcome measure (5). Since a complex interplay between the sympathetic and parasympathetic nervous systems can be assumed, we also report those well-established parameters that are primarily associated with the parasympathetic nervous system, i.e., the root mean square of successive differences (RMSSD) in the time domain and the high frequency (HF)-HRV for the frequency domain. RMSSD and HF-HRV reflect cardiac vagal activity and, in addition, RMSSD is comparatively free of respiratory influences (8). With the selection of these outcome measures, we also ensure comparability to previous studies in the same research area, which are predominantly based on these 3 parameters (5, 6, 24, 30).

Based on previous literature, we expected lower basal HRV across all parameters in patients with MDD and individuals with ACE. Both factors should interact, so that the lowest values

should be found in depressed patients with a history of ACE. However, we were agnostic about the relative contribution of the two group factors. After administration of yohimbine, we expected an increase in LF-HRV and a decrease in the vagally-mediated parameters RMSSD and HF-HRV across groups. This reduction should have been more pronounced in MDD and ACE due to the higher α_2 -adrenoceptor sensitivity. Again, we had expected a summative effect of both factors.

METHODS

Participants

We recruited patients with MDD and healthy participants through public announcements and from our special department for affective disorders at the Department of Psychiatry and Psychotherapy, Campus Benjamin Franklin, Charité Universitätsmedizin Berlin. Healthy participants and outpatients received monetary compensation (100 €) for their participation. The study was approved by the ethics committee of the Deutsche Gesellschaft für Psychologie (DGPs, German Society of Psychology) and carried out in accordance with the Declaration of Helsinki, all participants gave their written informed consent.

Patients with MDD were included if they met criteria for a current MDD episode as assessed by a trained psychologist using a German version of the Structured Clinical Interview for DSM-IV Axis I (SCID-I) to validate psychiatric diagnoses (31). In addition to the SCID-I interview, current depressive symptoms were assessed by a clinical rating scale and questionnaire, the Montgomery Asberg Depression Rating Scale (MADRS) (32, 33), and the Beck Depression Inventory (BDI) (34). Adverse childhood experiences were defined as repeated physical or sexual abuse at least once a month over duration of a year or more. These had to occur during childhood or adolescence, i.e., before age 18. Again, criteria were assessed by a semi-structured interview, the validated German version of the Early Trauma Inventory (35, 36). In addition, ACE was assessed with a German version of the Childhood Trauma Questionnaire (CTQ) (37, 38). In the MDD groups, schizophrenia, schizoaffective disorder, bipolar disorder, depressive disorder with psychotic features, dementia, alcohol or drug abuse, and panic disorder led to exclusion. Healthy participants had no current diagnosis of a mental disorder and no previous diagnosis of MDD. Additional exclusion criteria for all participants included CNS-related disorders, neurological disorders, severe somatic illness, type 1 and 2 diabetes, steroid disorders, hypertension, current infections, pregnancy, and use of psychotropic medications. Physical health criteria were assessed by physical examination, clinical interview, and blood test.

Of the participants who completed the measurement on both days, data from 12 participants were incomplete due to a technical or recording malfunction. Two participants were excluded from the analysis because the values in our dependent measures deviated abnormally (for this purpose, the average per participant per session was regarded; outliers were defined as deviation by more than three standard deviations from the mean of the total sample in at least two of the three parameters in both sessions). The final data set consisted of 124 participants: 25 MDD patients with ACE (MDD+/ACE+), 24

MDD patients without ACE (MDD+/ACE-), 27 participants with ACE but without current or lifetime MDD (MDD-/ACE+), and 48 participants without current or lifetime MDD and no ACE (MDD-/ACE-).

Procedure

Participants came for 3 separate sessions. During the first appointment, participants underwent a physical examination and blood sampling. Afterwards, diagnostics and assessment of MDD and ACE with questionnaires and structured interviews took place. Experimental testing was conducted on 2 separate days. On 1 day, the participants received 10 mg of oral yohimbine (Spiegel, DESMA), on the other day a placebo (p-Tabletten, Lichtenstein). Experimental order was counterbalanced across participants; drug administration was double blinded to participant and experimenter.

Experimental testing started at 9:30 h in the morning. Participants had to refrain from physical activity and caffeine consumption on these mornings and from eating, drinking and smoking 30 min prior to the start of the experiment. Participants were seated upright in a comfortable chair. Drug administration took place at 9:45, and the entire study lasted until 12:15. Participants were at rest, filled out questionnaires and were allowed to read for 1 h after drug administration. Multiple experimental psychological tests were part of the study, the results of which have been reported elsewhere (34, 39, 40). We conducted ECG recordings at four different times, for 5 min each: at 9:40, immediately before drug administration (baseline), at 10:35, 11:15, and 11:45.

Assessment of Heart Rate Variability

We recorded electrocardiogram (ECG) using Tyco Healthcare H34SG Ag/AgCl ECG electrodes and a Biopac MP150 amplifier system at 1 kHz sampling rate, with a hardware high-pass filter of 0.5 Hz. ECG data were analyzed in Kubios HRV version 2.2 software (41). Data were manually controlled for artifacts and beat-to-beat (R-R) intervals were calculated with Kubios' automated QRS detection.

We calculated the RMSSD as a time domain measure, LF power (0.04–0.15 Hz) and HF power (0.15–0.4 Hz) as frequency-domain measures of HRV using fast Fourier transformation and are expressed in ms^2 . In addition, we also conducted a Poincaré plot analysis (plotting the RR_n interval values against RR_{n+1}), and report the standard deviation (SD)1 and SD2 to quantify the shape of the plot. While SD2 describes the length of the long axis of the elliptical distribution and is assumed to reflect intermediate-term variability due to parasympathetic and sympathetic activity, SD1 describes the length of the transverse axis and is associated with short-term variability. Poincaré plot analysis was conducted for confirmatory purposes and results presented as **Supplementary Material**.

Statistics

Data analyses were carried out using SPSS 22.0 statistical software (IBM Inc., Chicago, IL, USA). Since HRV values were non-normally distributed (Kolmogorov–Smirnov $p < 0.05$), data were log-transformed using a natural logarithm. Because

we expected basal group differences, we initially calculated a univariate ANOVA 2×2 ("MDD $\times$ ACE"), with baseline HRV measurements averaged over both sessions as dependent variable. To adjust for those baseline differences and to have a measure of intervention-induced reactivity, we calculated change scores. For this purpose, we subtracted each participant's baseline value from the three respective post-intervention values. These derived change scores were analyzed with a mixed-measures analysis of variance (ANOVA) to investigate the effects of yohimbine on HRV reactivity, with the between-subjects factors "MDD" (MDD+ vs. MDD-) and "ACE" (ACE+ vs. ACE-) and the within-subjects factors "drug" (yohimbine vs. placebo) and "time" (+50, +90, and +120 min). Bonferroni corrected *post-hoc* tests were used to further analyze significant interaction effects. For testing of statistical significance, *p*-values smaller than 0.05 were considered to indicate significance. In case of violations of sphericity, reported *p*-values were Greenhouse-Geisser corrected.

RESULTS

Demographic Characteristics

Groups did not differ with regard to sex, age, educational status, and the intake of hormonal contraception (see **Table 1**). Patients with MDD had overall significantly lower MADRS and BDI scores, compared to the group without MDD and irrespective of ACE. Participants with ACE had overall lower ETI scores, compared to the group without ACE and irrespective of MDD. Also, participants with ACE had overall lower CTQ scores, however, this measure was qualified by MDD status: participants with ACE and MDD had lower scores than those with ACE and no MDD [for a detailed description of the sample, see Kuehl et al. (42)].

Heart Rate Variability

Basal Differences Between Groups

Analysis of baseline values before the intervention revealed differences between the groups that were specific to the parameter studied. Compared to participants without MDD, patients with MDD had lower HRV values for RMSSD [$F_{(1,119)} = 6.65$, $p = 0.01$, $\eta_p^2 = 0.06$]. The effect for ACE, i.e., participants with vs. without ACE [$F_{(1,119)} = 2.55$, $p = 0.11$, $\eta_p^2 = 0.02$] and the interaction between MDD and ACE [$F_{(1,119)} = 0.07$, $p = 0.79$, $\eta_p^2 < 0.01$] were not significant. In the HF frequency band, there were no significant differences (main effects and interaction) between the groups, yet the effect for MDD was slightly above the significance threshold [MDD: $F_{(1,119)} = 3.59$, $p = 0.06$, $\eta_p^2 = 0.03$, ACE: $F_{(1,119)} = 0.76$, $p = 0.39$, $\eta_p^2 = 0.01$, MDD $\times$ ACE: $F_{(1,119)} = 0.29$, $p = 0.63$, $\eta_p^2 < 0.01$]. In the LF frequency band, HRV was lower in participants with ACE compared to those without ACE [$F_{(1,119)} = 4.42$, $p = 0.04$, $\eta_p^2 = 0.04$]. The effect for MDD [$F_{(1,119)} = 2.35$, $p = 0.14$, $\eta_p^2 = 0.02$] and the interaction between MDD and ACE [$F_{(1,119)} = 0.11$, $p = 0.74$, $\eta_p^2 < 0.01$] were not significant (see **Figure 1**).

Reactivity to Yohimbine

Across all parameters, we found an increase in HRV over the factor "time" [RMSSD: $F_{(2,224)} = 15.61$, $p < 0.001$, $\eta_p^2 = 0.12$, HF: $F_{(2,224)} = 8.59$, $p < 0.001$, $\eta_p^2 = 0.07$, LF: $F_{(2,224)} = 24.58$, $p < 0.001$, $\eta_p^2 = 0.18$]; this effect was moderated by the between-subjects factor "time $\times$ MDD" [RMSSD: $F_{(2,224)} = 8.46$, $p < 0.001$, $\eta_p^2 = 0.07$, HF: $F_{(2,224)} = 5.67$, $p < 0.01$, $\eta_p^2 = 0.05$, LF: $F_{(2,224)} = 4.27$, $p = 0.02$, $\eta_p^2 = 0.04$]. To elucidate these interaction effects, *t*-tests were calculated to compare MDD+ vs. MDD- at each time interval: patients with MDD had a more pronounced increase in RMSSD at +90 min ($t_{(117)} = 2.62$, $p = 0.01$) and +120 min ($t_{(115)} = 2.58$, $p = 0.01$) and LF at +90 min ($t_{(117)} = 2.79$, $p < 0.01$). However, this change over time was independent of our experimental intervention and was found across both levels of the factor "drug" (see **Figure 2**). There were no significant main effects or interactions involving the factor "drug" (all $p > 0.05$).

DISCUSSION

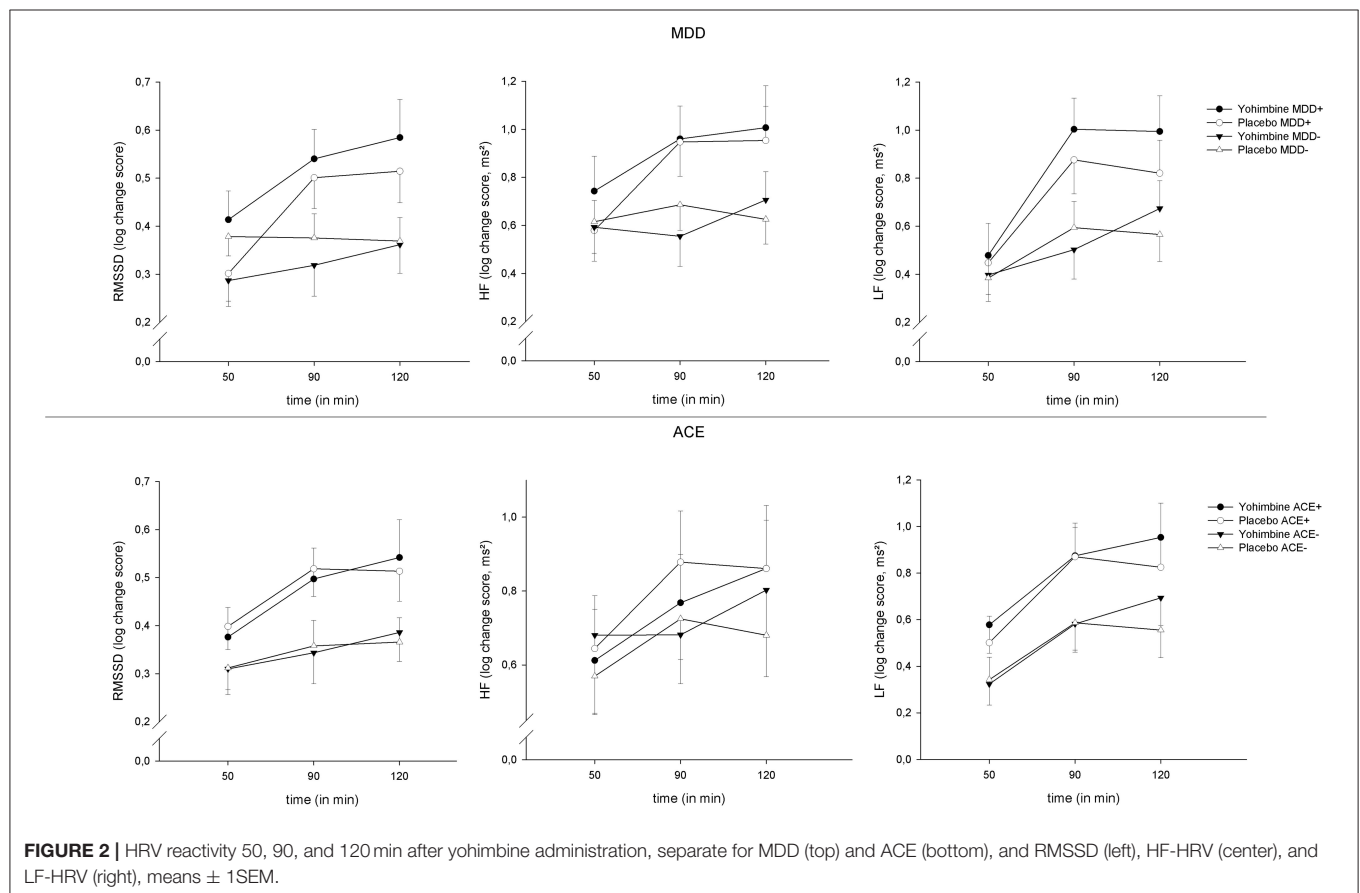
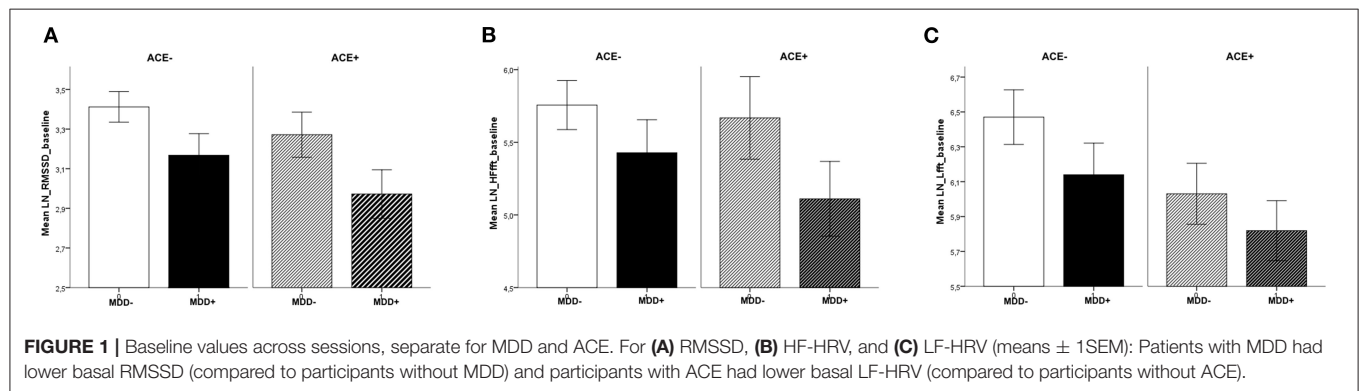
In this study, we investigated the influence of a single administration of the alpha2-antagonist yohimbine on the reactivity of HRV in a sample with/without MDD and with/without ACE. A baseline HRV measurement under rest was obtained before the experimental intervention, as well as 3 measurements after the intervention at defined time intervals. As expected and in line with our hypotheses, basal group differences were found: patients with MDD had lower values in the parameters HF-HRV (trend level significance) and RMSSD, both measures that primarily reflect parasympathetic vagal activity. We further found lower basal values for the parameter LF-HRV in subjects with ACE. LF-HRV represents a joint influence of sympathetic and parasympathetic nervous system. There were no statistically significant interactions between MDD and ACE. The main objective of the study was the influence of yohimbine in these groups; therefore the change over time was measured and compared to baseline. In contrast to our hypotheses, we found no effect of yohimbine on HRV, neither as a main effect nor in interaction with MDD or ACE, for any parameter.

The lower basal HRV in depressed patients is well in line with previous research and complements the literature (5). The finding is indicative of persistent autonomic dysregulation in MDD. That we found effects in indicators of parasympathetic activity suggests that this impaired HRV is due to reduced vagal activity, which is also in line with existing research (43). However, we had also expected higher sympathetic activation in the group of MDD patients (44), which would have been expressed in lower LF-HRV. Contrary to our expectations, there was no effect of MDD for this parameter. We can only speculate about the reasons for this, but would like to point out that previous large meta-analyses came to similarly discrepant findings: while Kemp et al. (45) found reduced HF-HRV and no evidence for LF-HRV deviations in MDD, Brown et al. (30) analyzed studies specifically in older adults and, in contrast, found lower LF-HRV in MDD, with no difference in HF-HRV. However, a very recent meta-analysis indicated a significant reductions in both

TABLE 1 | Sample characteristics of MDD patients with and without ACE and healthy participants with and without ACE.

	MDD+/ACE+ N = 25	MDD+/ACE- N = 24	MDD-/ACE+ N = 27	MDD-/ACE- N = 48	Statistics
Sex (f/m)	13/12	13/11	15/12	26/22	$p = 0.99$
Age (years; SD)	40.5 (11.2)	34.8 (10.9)	33.9 (10.6)	35.5 (10.3)	$p = 0.12$
Education (years; SD)	11.2 (1.5)	12.0 (1.4)	11.7 (1.5)	11.6 (1.6)	$p = 0.29$
Use of hormonal contraceptives (women, y/n)	4/9	3/10	5/10	5/21	$p = 0.72$

MDD, Major depressive disorder; ACE, Adverse childhood experiences.



HF- and LF-HRV (5). Of note, there has been controversy about whether and to what extent antidepressants contribute to the reduction in HRV (46, 47). Since the patients in our study were all unmedicated, it can be concluded that HRV is decreased independently of this factor.

Interestingly, we found an inverse pattern for ACE: significantly lower basal values in the parameter LF-HRV—more strongly associated with sympathetic activation—and no differences in RMSSD and HF-HRV. Likewise, a recent meta-analysis could demonstrate reduced HRV in individuals with ACE, however, because the focus of this work was on dysregulations in resting-state vagal activity, only the vagally mediated parameters HF-HRV and RMSSD were included as outcome measures in the analysis (24). Yet, another recent paper also described a significant relationship between ACE and LF-HRV (48). Using path analysis models, the authors found a mediation of the relationship between CTQ scores (as a measure of ACE) and LF-HRV *via* affective lability and beta EEG activity, related to alertness and anxiety.

We found a significant increase in HRV over the duration of the experiment (factor “time”), which was more pronounced for patients with MDD (who again had lower basal values). However, this change was independent of our experimental manipulation (“drug”) and probably due to the situation in the laboratory and the orthostatic posture (sitting in the chair). In contrast to our hypothesis and to existing research, we did not find effects of yohimbine on HRV. Yeragani et al. (49) reported an increase in midfrequency (MF—) HRV (0.07–0.15 Hz, which basically corresponds to LF-HRV by contemporary standards) after a single dose administration of yohimbine. However, that study found the effect in patients with panic disorder, whose response to yohimbine was supposedly more pronounced when compared to our sample. In a further study, single dose administration of yohimbine increased LF-HRV (50). However, that study had a distinctly different research subject and procedure: it included only healthy participants and investigated the effects of meal-stimulated glucagon-like peptide-1 release on autonomic nervous functions, alone and in combination with yohimbine. Yohimbine was administered as a bolus and HRV was assessed in a postprandial period after overnight fasting and subsequent oral nutrient infusion. This null effect of our treatment was unexpected in that yohimbine induces a state similar to the immediate stress response through increased release of catecholamines and activation of the sympathetic nervous system, and since effects of stress on HRV are well-known from the literature (51).

In answering the question why, contrary to the hypotheses, no effect of yohimbine was found, several explanations can be thought of. The effect of yohimbine on the availability of noradrenaline corresponds to a part of the initial stress response, which is characterized by vagal withdrawal and increased sympathetic activation. However, this shift in ANS activity is accompanied by numerous other changes as part of the stress response. In particular, complex interactions with the hormones of the hypothalamic-pituitary-adrenal axis are evident (52), and isolated sympathetic activation may not be sufficient to map the effects of stress on HRV. We administered 10 mg of oral

yohimbine, with dosages of 5–20 mg reported to affect cognitive processes in previous studies (53–56). However, this dosage may not have been sufficient to show effects on HRV; Bharucha et al. (50) found an effect on LF-HRV after an intravenous administration of 0.125 mg/kg over 10 min. Because of the specific effects of yohimbine on the sympathetic nervous system, we took LF-HRV as the dependent measure. This measure was originally used as a measure of sympathetic activation; however, this interpretation has become the subject of widespread controversy (57). While there is general consensus that high frequency (HF)-HRV is controlled by vagal activity and thus the parasympathetic nervous system, the neurophysiological, autonomic drivers influencing LF-HRV have been subject of recent debate (7). It can be considered certain that both branches of the ANS, sympathetic as well as parasympathetic, are reflected in LF-HRV (8). The relative proportion again depends on the recording conditions. The proportion of sympathetic influence is probably more pronounced during longer recordings. At short-term recordings such as the 5 min intervals in our study, LF-HRV is markedly influenced by feedback loops in the baroreflex system (7, 10). Potentially, an orthostatic challenge such as a standing posture as in Yeragani et al. (49) might have yielded different results. Again, while Yeragani et al. (49) reported their effect in patients with panic disorder, those were a population we specifically excluded. Future research could investigate these effects with higher doses of yohimbine, examining HRV over longer periods of time and under non-rest conditions.

Every single parameter of HRV measurement comes with its limitations. Problems with the interpretation of LF-HRV as a measure of sympathetic activity have already been discussed above. Normalization of LF-HRV and the use of normalized units (nu) have been proposed in the literature (58, 59). These are obtained by dividing LF power by the total power minus the (very low frequency) VLF power. While some authors proposed a closer conceptual correspondence between normalized LF-HRV and sympathetic activity, these claims have also been challenged. Data are distorted due to these mathematical transformation and the underlying assumption of autonomic reciprocity as well as the association between nu and LF (in absolute units) remain controversial (57). Furthermore, many studies of relevance to our research question have relied on (non-normalized) LF-HRV (5). Both RMSSD and HF-HRV reflect parasympathetic-vagal activation according to current research and are generally highly correlated. However, both have their specific advantages and disadvantages: compared to HF-HRV, RMSSD is less affected by respiratory influences (i.e., changes in breathing frequencies) and more robust to disturbances of the cardiac rhythm by ectopic beats, yet it is more dependent on basal heart period (42, 60–62). For these reasons, and for comparability to previous research findings of relevance to our topic, we included RMSSD, HF-HRV, and LF-HRV.

In conclusion, independent of MDD and ACE and potentially for the reasons mentioned above, no effect of yohimbine on HRV could be shown. However, we were able to demonstrate basal differences in HRV between the

psychiatric groups. These form an interesting pattern, with low values in the parameters HF-HRV and RMSSD in MDD and lower LF-HRV in ACE. From this pattern, one could assume—relatively speaking—a stronger mediation by vagal dysregulation in MDD and influences of the sympathetic nervous system in ACE. However, this interpretation should be viewed with caution, in light of partial contrary findings in the literature as well as the unclear mechanisms underlying LF-HRV.

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 German Psychological Society (Deutsche Gesellschaft für Psychologie). The patients/participants provided their written informed consent to participate in this study.

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CD, CO, KW, and LK conceptualized, planned, and designed the study. CD and LK conducted the study and analyzed the data. CD wrote the manuscript.

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Quality of Life After Myocardial Infarction as a Function of Temperamental Traits, Stress Coping Styles, and Posttraumatic Stress Disorder Symptoms

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The presented study aims to explore the relationship between quality of life after myocardial infarction and factors such as temperamental traits, stress coping, and posttraumatic stress disorder (PTSD) symptoms. Ninety-six participants, including 51 females and 45 males aged 24–85 years, who have survived ST-elevation myocardial infarction were asked to complete the Formal Characteristics of Behavior—Temperament Inventory, Coping Inventory for Stressful Situations, PTSD Inventory, and Quality of Life SF-36 questionnaire. According to the obtained results, a lower level of briskness and sensory sensitivity, as well as a higher level of perseverance and endurance, correlates with a higher level of emotion-oriented coping, whereas a higher level of perseverance, endurance, and activity correlates with a higher level of avoidant-distracted coping. Moreover, a higher level of briskness and activity is correlated with a higher level of avoidant-social coping. A higher level of emotion-oriented and avoidant-distracted coping is, in turn, associated with a higher intensity of PTSD symptoms, whereas a higher level of avoidant-social coping correlates with lower intensity of PTSD symptoms. Furthermore, a higher level of avoidant-distracted coping is correlated to a better physical quality of life, whereas higher levels of endurance and activity are associated with a better emotional quality of life. Also, the more severe the PTSD symptoms, the lower quality of life in general. Contrastingly, higher sensory sensitivity and briskness correlate with better quality of life. The meaning of other temperamental traits, however, is more ambiguous. Nevertheless, the findings support the model of psychological processes in which the subsequent stages are temperament, coping, PTSD, and quality of life.

Keywords: quality of life, myocardial infarction, temperamental traits, stress coping styles, PTSD

INTRODUCTION

As a result of medical advances, it is now possible to treat diseases that, such as cardiovascular diseases, were formerly considered fatal. People formerly considered terminally ill can survive with chronic diseases for many years. This phenomenon results in new problems, e.g., stress related to one's state of health, a necessity for both emotional and cognitive adaptation to the illness, its

psychological effects, and treatment. There are also some inevitable changes in the family and the social background of people with chronic diseases.

A systematic increase in the number of effectively treated patients can be observed. Therefore, it is essential to address and understand the matters of their emotional and spiritual condition and their professional, social, and family situation. A key aspect is an issue concerning adaptation to the challenges of the new circumstances resulting in a changed level of the quality of life.

To fulfill this demand, it is vital to abandon the unidimensional medical model in favor of the biopsychosocial one, which accentuates the physical, psychological, and social integrity of the human being.

The research presented in this paper aims to explore whether the quality of life after myocardial infarction (MI) and psychological variables, including temperamental characteristics, ways of coping with stress, and symptoms of posttraumatic stress disorder (PTSD), are actually related.

In fact, aside from being a medical phenomenon, MI comes as a highly distressing and unexpected event (1). The affected person would often be unaware of what is happening, experience excruciating chest pain and shortness of breath, become anxious, and fear death (2, 3). Such an experience may indeed be considered a traumatic event, and symptoms of PTSD may subsequently develop (4, 5).

In most cases, the period of hospitalization after MI is not long. However, afterward, patients may have to cope with restrictions in their physical functioning, i.e., they easily become tired and breathless, have to change their diet, and limit their working hours. Although, initially, they tend to be fearful of another heart attack, the level of their anxiety decreases over time (6).

Higher quality of life level along with the absence of posttraumatic symptoms can be recognized as an indicator of adaptation to the new reality of life with demands and limitation of one's state of health and effective psychological coping in a situation of the sudden collapse of one's capabilities and sense of security. On the other hand, a manifestation of PTSD symptoms and reduced quality of life may contribute to an increased risk of another heart attack and mortality (7, 8).

As defined by the World Health Organization (9), quality of life comprises an individual's assessment of physical health, emotional state, self-dependence, and interactions with the social environment. Meanwhile, chronic illness changes the functioning in all of these domains. The ability to adapt to new situations may be determined by a variety of factors such as temperamental characteristics and coping strategies (10).

The Regulatory Theory of Temperament by Strelau (11) is primarily focused on the formal characteristics of behavior involving energetic and temporal categories. Temperamental traits included in the energetic aspect are sensory sensitivity, emotional reactivity, endurance, and activity, whereas the temporal aspect covers briskness and perseverance. Sensory sensitivity refers to the ability to perceive even very subtle sensory stimuli. Emotional reactivity describes one's disposition to an intense response to emotionally charged stimuli. Endurance can be defined as the mental capacity to withstand prolonged

or exhausting conditions, whereas activity is the propensity to engage in behaviors under circumstances of high stimulation. Briskness is the ability to react swiftly and fluently move from one behavior to another. Lastly, perseverance refers to the tendency to recurrently experience particular emotional states in response to stimuli, even when those stimuli are not present anymore. The functional importance of temperamental traits proposed in the Regulatory Theory of Temperament has been the focus of multiple pieces of research, a number of which was conducted on survivors of cataclysms and calamities. Traits such as emotional reactivity, perseverance, and activity have been found to be important moderators of the psychological implications (e.g., PTSD) of the trauma they have experienced (12). Furthermore, some studies imply that lower emotional reactivity might itself have a protective effect against symptoms of cancer-related trauma in adults (13, 14).

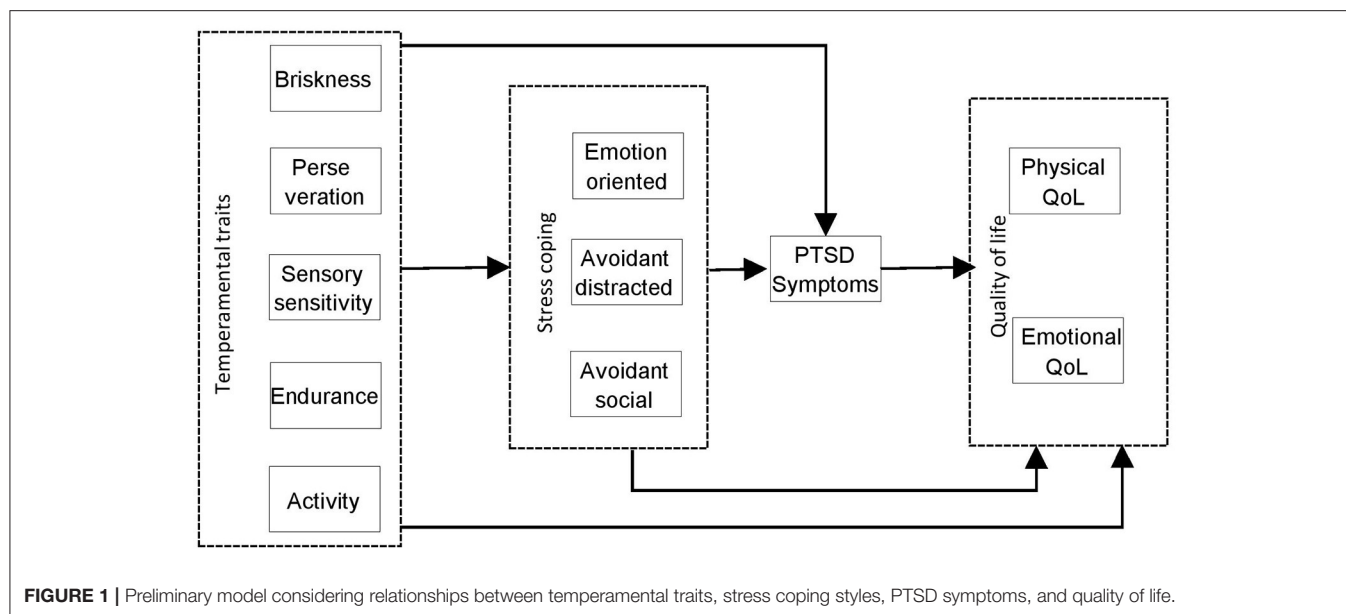
Thus, temperamental traits have the potential to function as moderators of the impact of life events by enhancing or reducing their stimulatory effect (15). Moreover, stress-related coping strategies might be influenced by them as well.

As already mentioned, after MI, patients are facing a number of different stress sources, primarily the disease itself but also mood swings, changes in their organisms and its capabilities, and those related to their personal, family, and professional life. So far, research indicates that quality of life is more influenced by the way one copes with stress than the stress itself (16). Indeed, individuals tend to vary in the range of coping strategies. Some are more likely to use a more task-oriented approach, whereas others would rather apply more emotion-oriented or avoidant strategies (17). It is worth noting that coping strategies, which may be regarded as ineffective in normal functioning, may yet prove beneficial under certain conditions. In fact, it has been reported that post-heart attack patients may actually feel better while adopting a more avoidant approach (18). However, further research is still needed in this area.

CURRENT STUDY

This paper aims to explore four different elements of coping with the circumstances after a heart attack, such as the trauma associated with a sudden breakdown in health and the changes required to promote recovery. Those elements comprise temperamental traits, stress coping styles, symptoms of PTSD, and quality of life. These are considered to be four consecutive phases in the psychological processes model. Based on this model, temperamental characteristics influence the way of coping with stress, which may appear more or less effective depending on the patient's situation. Subsequently, more or less adaptive strategies of coping with stress may either lead to the development of PTSD symptoms or adequate coping with the experienced trauma. As a result, quality of life is affected by one's ability to cope with a new situation. The subsequent stages of this process are temperamental characteristics, coping with stress, PTSD symptoms, and quality of life (see **Figure 1**).

Temperamental traits, which may directly or indirectly influence coping and all consecutive stages of the process, can



only undergo relatively slow changes throughout time. Thus, coping flexibility after MI is restricted to the degree to which temperamental traits determine coping with stress.

The objective of the presented study is to verify the following research hypotheses:

H1. Temperamental traits are in relation to coping styles, presence of PTSD symptoms, and quality of life after MI.

H2. Stress coping styles are in relation to the presence of PTSD symptoms and quality of life.

H3. PTSD symptoms are in relation to the quality of life.

METHODS

The study included 96 participants who had suffered a MI. Of these, there were 51 women and 45 men aged 24–85 years ($M = 52.27$; $SD = 12.29$). All participants were survivors of ST-elevation MI with no record of other chronic diseases. They were tested in the hospital from 6 to 12 months after the incident. Participation in the study was voluntary and anonymous; no compensation was paid to participants.

Seventy of the participants (72.9%) were known to have children. In **Table 1**, the frequency distribution is shown for a place of residence, education level, marital status, and illness duration. The most common place of residence was a large city with a population of more than 100,000. Secondary school was the most common level of education. The majority of the participants were married.

The local Research Ethics Committee of the Faculty of Psychology of the University of Warsaw approved the project of this study.

To assess temperamental traits, the Formal Characteristics of Behavior—Temperament Inventory (19) was used. There are six temperament traits measured by this questionnaire: briskness, perseverance, sensory sensitivity, emotional reactivity,

endurance, and activity. Overall, 120 items were included, 20 of them on each of the six scales. The range of points that can be obtained on each scale is from 0 to 20. Participants are asked to answer affirmatively or contradictorily to each of the questionnaire items. The psychometric characteristics of the Formal Characteristics of Behavior—Temperament Inventory are good. Depending on the scale, Cronbach's α reliability ranges from 0.72 to 0.86. In the presented research, reliability coefficient values ranged from 0.60 to 0.70.

To assess stress coping style, the Coping Inventory for Stressful Situations, developed by Endler and Parker (17), was used. It covers a total of 48 diagnostic positions. Three stress coping styles measured by this questionnaire are distinguished, i.e., emotion-oriented, task-oriented, and avoidant. The latter is two-dimensional, with distraction as the first dimension and social diversion as the second one. Cronbach's α reliability for the Polish adaptation ranges from 0.71 to 0.92. In the current study, reliability coefficient values ranged from 0.70 to 0.74 (20).

Furthermore, the PTSD Inventory created by Strelau et al. (21) was used to measure the intensity of PTSD symptoms. Using this questionnaire, PTSD symptoms can be quantitatively assessed based on the following dimension: intrusiveness/hyperactivity (I/H) (recurring thoughts related to the experienced trauma that cause increased arousal) and avoidance/numbness (A/N) (avoidance and impaired response to the stimuli associated with the traumatic event). A general scale of PTSD symptoms is included as well. The inventory consists of 30 items rated on a four-point scale from 1 (symptom never present) to 4 (symptom constantly present). Both the general scale and two subscales show good reliability, with Cronbach's α ranging from 0.90 to 0.97. In the present study, with the instruction referring to the endured disease as a traumatic experience, the reliability coefficient values were 0.70 for intrusiveness/hyperarousal and 0.75 for avoidance/numbness.

TABLE 1 | Frequency distribution—place of residence, educational level and marital status, and duration of illness.

Place of residence	<i>n</i>	%
City with number of inhabitants more than 100,000	47	49.0
City with number of inhabitants from 1,000 to 100,000	37	38.5
Small town with number of inhabitants <1,000	12	12.5
Level of education	<i>n</i>	%
Higher completed	22	22.9
Higher professional	6	6.3
Post-secondary	14	14.6
Secondary	39	40.6
Occupational	14	14.6
Elementary	1	1.0
Marital status	<i>n</i>	%
Married	71	74.0
Informal relationship	13	13.5
Single	12	12.5
Duration of illness	<i>n</i>	%
<1 year	48	50.0
1–2 years	30	31.3
Longer than 2 years	18	18.8

n, number of participants; %, percentage of sample.

As for measuring the quality of life, the 36-item Short Form Survey questionnaire in its Polish version (22) was applied. It consists of 36 positions referring to the state of health and reaction to illness. Two main dimensions of the quality of life are taken into account. The first one, namely physical quality of life, covers somatic aspects such as physical activities and pain and its impact on daily functioning, whereas the second one is an emotional quality, which includes issues such as social activity, the emotional consequences of health-related limitations, energy level, and fatigue. Furthermore, apart from these dimensions, the questionnaire also provides an overall measure of the quality of life. A five-point scale is used for the answers. In the Polish version of the questionnaire, the score is inversely proportional to the quality of life, which means that a higher score indicates a low quality of life, whereas a lower score corresponds to a high quality of life. The questionnaire is characterized by good reliability, with Cronbach's α ranging from 0.75 to 0.95. In the present study, the reliability coefficient values were 0.72 for physical quality of life and 0.86 for emotional quality of life.

DATA ANALYSIS

Statistical analysis was conducted using IBM SPSS 24, and IBM AMOS 24 statistical package was used (23).

At first, descriptive statistics were calculated for the demographic characteristics of the sample and the interval scales. Secondly, an analysis of the relationship between quality of life and the sample characteristics was conducted.

The main analysis consisted of two phases. In a first step, the dependencies between the consecutive concepts of the assumed model were examined using regression analysis, starting with the quality of life and moving backward to temperamental traits.

With the obtained regression coefficients, it became possible to build a model, subsequently tested by conducting a path analysis. In line with the results of the prior regression analysis, the input model comprised pathways that were found to be statistically significant.

RESULTS

Descriptive statistics of all interval scales, i.e., mean values, standard deviation, minimum and maximum values, are presented in **Table 2**.

No significant difference in the quality of life was observed between men and women. The Mann–Whitney *U*-test results were statistically insignificant for both physical quality of life, $U = 1,135.50$, $p > 0.05$, and emotional quality of life, $U = 890.50$, $p > 0.05$.

The Spearman rank correlation coefficient was applied to explore the correlations between quality of life, disease duration, and demographic variables, i.e., level of education and size of the place of residence.

Results indicate that physical quality of life correlates positively with illness duration, $\rho(n = 96) = 0.206$, $p < 0.05$. However, no significant correlation was observed either with place of residence $\rho(n = 96) = 0.009$, $p > 0.05$, or level of education, $\rho(n = 96) = -0.194$, $p > 0.05$.

The emotional quality of life, on the other hand, correlated negatively with size of place of residence $\rho(n = 96) = -0.247$, $p < 0.05$, and level of education, $\rho(n = 96) = -0.252$, $p < 0.05$, whereas no significant correlation was observed with illness duration, $\rho(n = 96) = 0.201$, $p > 0.05$.

Relationships between consecutive model stages were first analyzed using regression analysis. PTSD symptoms were

TABLE 2 | Descriptive statistics for interval scales.

Questionnaires	Variables	M	SD	min	max
FCB-TI	Briskness	11.24	3.48	1	19
	Perseverance	10.26	3.45	1	20
	Sensory sensitivity	10.43	3.52	3	20
	Emotional reactivity	10.55	3.23	3	18
	Endurance	8.18	3.46	0	16
	Activity	9.96	3.85	1	18
CISS	Task-oriented coping	50.48	7.17	37	72
	Emotion-oriented coping	46.47	7.32	23	69
	Avoidant coping	48.15	6.30	27	63
	Avoidant-distracted coping	23.43	4.21	10	30
	Avoidant-social coping	15.76	2.60	9	23
PTSD-C	Intrusion/arousal	34.45	5.30	15	44
	Avoidance/numbing	33.59	6.20	18	45
	PTSD-C Total score	68.04	10.62	33	82
SF-36	Physical QoI	54.86	11.14	24	84
	Emotional QoI	28.67	6.49	11	56
	Quality of life index	83.53	15.86	35	136

M, mean; SD, standard deviation; min, minimum; max, maximum.

analyzed as an explanatory variable for both physical and emotional quality of life, coping styles were analyzed as an explanatory variable for intrusion and avoidance PTSD symptoms, and temperamental traits were analyzed as an explanatory variable for coping styles. The variables used are of univariate distribution; thus, the assumption of normality of distribution is not met. Under these circumstances, the analysis was based on bootstrap samples. For the purpose of the study, 1,000 such samples were generated. Estimation of the model was carried out assuming a 95% confidence interval for the parameters. The obtained coefficients are presented in **Table 3**.

A significant association was observed between avoidance/numbing and physical quality of life. Higher scores on the 36-item Short Form Survey questionnaire were associated with higher levels of disability, whereas higher levels of avoidance/numbness were accompanied by stronger deterioration in physical quality of life.

However, the emotional quality of life was found not to be related to the level of PTSD symptoms, nor avoidance/numbness or intrusions/arousal. Therefore, in the subsequent regression analysis, coping styles were analyzed as explanatory variables.

It was found that higher levels of both avoidant-distracted and avoidant-social coping were related to a lower level of the emotional quality of life. Furthermore, it was also shown that both emotion-oriented and avoidant-distracted coping was positively related to avoidance/numbness. Contrastingly, a negative association was observed between avoidance/numbing and avoidant-social coping.

Moreover, higher perseverance and endurance and lower sensory sensitivity were found to be related to the more frequent application of emotion-oriented coping. On the other hand,

higher perseverance and endurance along with higher activity were shown to be predicates of a tendency to use avoidant-distracted coping more frequently. Finally, more frequent use of avoidant-social coping was found to be predicted by a higher level of briskness.

After that, in the second stage of statistical analysis, only statistically significant explanatory variables were included. A path analysis, also based on 1,000 bootstrap trials, was used to examine the final model. The results of this analysis are shown in **Figure 2**.

Based on modifying indicators with a threshold value of 4, paths were added between the physical quality of life and avoidant-distracted coping, between the emotional quality of life and avoidance/numbing, between the emotional quality of life and endurance, between the emotional quality of life and activity, between emotion-oriented coping and briskness, and between avoidant-social coping and activity. As the path between the emotional quality of life and avoidant-social coping after inclusion of endurance and activity appeared to be statistically insignificant, it was excluded from further analysis.

For more transparency, the regression coefficients between temperamental traits and stress coping styles are given in **Table 4**.

The final fit of the model proved to be satisfactory, $\chi^2(32, N = 96) = 39.34, p > 0.05, CFI = 0.97, TLI = 0.94, RMSEA = 0.05, [90\% CI = 0.01, 0.10]$.

It was shown that a lower level of briskness, higher level of perseverance, lower level of sensory sensitivity, and a higher level of endurance were associated with a tendency toward emotion-oriented coping. The latter, in turn, was found to correlate positively with avoidance/numbing.

A higher level of perseverance, endurance, and activity was, on the other hand, related to a higher level of avoidant-distracted

TABLE 3 | Estimates from regression models for subsequent stages.

Physical QoI	Beta	SE	95% CI	P-value
Intrusion/arousal	−0.13	0.18	−0.48, 0.23	0.485
Avoidance/numbing	0.43	0.15	0.15, 0.71	0.001
Emotional QoI	Beta	SE	95% CI	P-value
Intrusion/arousal	0.13	0.15	−0.15, 0.44	0.388
Avoidance/numbing	0.24	0.18	−0.12, 0.58	0.201
Avoidance/numbing	Beta	SE	95% CI	P-value
Task-oriented coping	−0.14	0.11	−0.34, 0.08	0.186
Emotion-oriented coping	0.33	0.11	0.10, 0.54	0.004
Avoidant-distracted coping	0.22	0.10	−0.01, 0.41	0.036
Avoidant-social coping	−0.21	0.10	−0.41, 0.01	0.046
Emotional QoI	Beta	SE	95% CI	P-value
Task-oriented coping	−0.12	0.14	−0.38, 0.15	0.399
Emotion-oriented coping	0.14	0.14	−0.16, 0.38	0.319
Avoidant-distracted coping	−0.23	0.11	−0.47, 0.03	0.042
Avoidant-social coping	−0.30	0.13	−0.56, 0.07	0.029
Emotion-oriented coping	Beta	SE	95% CI	P-value
Briskness	−0.22	0.15	−0.52, 0.05	0.168
Perseverance	0.34	0.13	0.07, 0.59	0.016
Sensory sensitivity	−0.29	0.12	−0.50, 0.05	0.020
Emotional reactivity	0.03	0.10	−0.20, 0.21	0.817
Endurance	0.32	0.11	0.10, 0.52	0.005
Activity	0.06	0.14	−0.21, 0.36	0.656
Avoidant-distracted coping	Beta	SE	95% CI	P-value
Briskness	−0.14	0.14	−0.43, 0.09	0.329
Perseverance	0.27	0.11	0.04, 0.49	0.024
Sensory sensitivity	−0.11	0.12	−0.32, 0.13	0.336
Emotional reactivity	−0.02	0.13	−0.27, 0.23	0.917
Endurance	0.25	0.11	0.04, 0.49	0.036
Activity	0.33	0.12	0.08, 0.55	0.009
Avoidant-social coping	Beta	SE	95% CI	P-value
Briskness	0.31	0.13	0.05, 0.58	0.026
Perseverance	0.22	0.11	0.02, 0.47	0.055
Sensory sensitivity	−0.02	0.12	−0.27, 0.22	0.875
Emotional reactivity	−0.05	0.11	−0.27, 0.16	0.651
Endurance	0.08	0.11	−0.11, 0.30	0.411
Activity	0.21	0.11	−0.02, 0.43	0.067

Beta, standardized regression coefficient; SE, standard error; 95% CI, bootstrap confidence interval.

coping, which was also shown to correlate positively with avoidance/numbing.

Furthermore, a higher level of briskness and activity appeared to be related to a more avoidant-social coping style, being in turn negatively correlated with avoidance/numbness level. Moreover, avoidance/numbing level was also negatively correlated with both the emotional and physical qualities of life. On the other hand, a higher level of avoidant-distracted coping was directly related to a better physical quality of life; meanwhile, a higher level of endurance and activity was associated with a better emotional quality of life.

DISCUSSION

Through the conducted analysis, a complex model was obtained showing multiple associations between the different psychological variables, hence the main conclusion that quality of life depends on a number of factors. Considering the temperamental profile, it can be stated that only two traits unambiguously explain a better quality of life. Namely, higher sensory sensitivity is related to a lower level of emotion-oriented coping, which in turn may lead to a reduction in PTSD symptoms and thus improved physical and emotional quality of life.

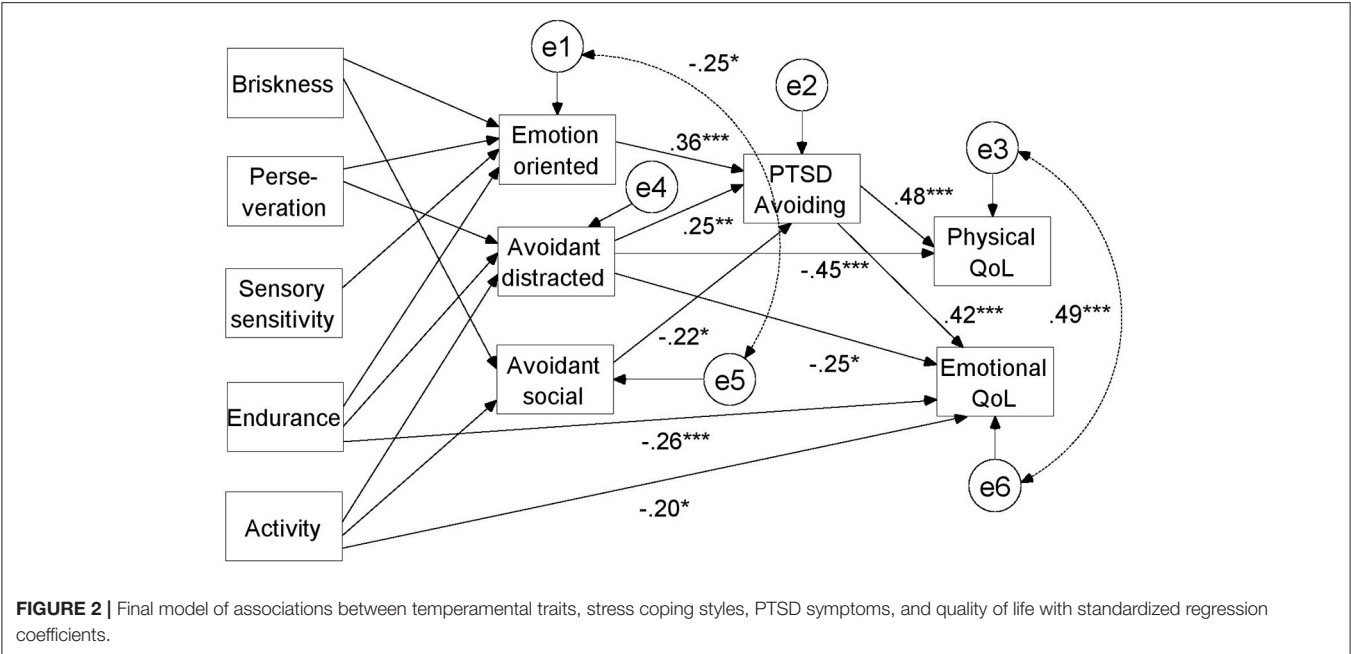


TABLE 4 | Regression weights between temperamental traits and stress coping styles acquired in path analysis.

Stress coping styles	Temperamental traits	Beta
Emotion-oriented coping	Perseverance	0.38***
Emotion-oriented coping	Sensory sensitivity	−0.29***
Emotion-oriented coping	Endurance	0.31***
Avoidant-distracted coping	Perseverance	0.22*
Avoidant-distracted coping	Endurance	0.20*
Avoidant-distracted coping	Activity	0.31***
Avoidant-social coping	Briskness	0.34***
Avoidant-social coping	Activity	0.22*
Emotion-oriented coping	Briskness	−0.21*

* $p < 0.05$; *** $p < 0.001$.

Furthermore, a higher level of briskness is associated with both a lower level of emotion-oriented coping and a higher level of avoidant-social coping, which is, in turn, explanatory for milder PTSD symptoms and consequently higher quality of life.

As previously outlined, high sensory sensitivity enables one to detect and perceive even low-level stimuli (11). As such, it has the potential to induce openness to experience and appreciation of small details in the environment, making emotional coping unnecessary and thus enhancing life satisfaction. Meanwhile, briskness is the foundation for increased adaptive capacity, potentially allowing for better adaptation to the disease-related limitations.

However, the relevance of other temperamental traits appears to be more ambiguous. In stress coping, both emotion-oriented and avoidant-social coping styles are clearly related to the higher level of PTSD symptoms, which in turn explain the lower physical and emotional quality of life. However, it is important to note

that avoidant-distracted coping is associated not only with better quality of life—both physical and emotional, but also with a higher level of PTSD symptoms, which, by contrast, are linked to lower quality of life. A possible explanation is that avoidance-distraction coping may be associated with a higher quality of life, provided that it is a strategy of coping with the disease and its consequences and not a strategy of coping with the trauma itself. Nevertheless, further research is still much needed on the subject, taking into account also other variables. According to a study by Ayers et al. (24), dysfunctional coping strategies were associated with PTSD after MI, whereas the findings presented by Marke and Bennett (25) indicated that problem- and emotion-focused coping styles were related to a lower likelihood of developing PTSD.

Moreover, higher perseverance and endurance are associated with a tendency to more emotion-oriented coping, thereby explaining the lower quality of life, and yet, at the same

time, higher perseverance is related to more intense avoidant-distracted coping, which may or may not be beneficial to the quality of life. Furthermore, higher activity is connected with more avoidant-social coping, linked to a better quality of life; however, it may also be associated with more avoidant-distracted coping. Although a higher level of activity, coming with a higher need for stimulation can be of some benefit; simultaneously, it may prove maladaptive while dealing with cardiovascular disease.

Besides, endurance and activity are also directly related to the emotional quality of life, as it appears that higher intensities of these characteristics are likely to result in a more positive impact. Due to their immunizing aspects, both of these characteristics may directly contribute to one's life satisfaction level.

According to the findings of several studies (26, 27), higher neuroticism has been shown to contribute to higher severity of PTSD symptoms after MI. Although temperamental traits taken into account in the described study are more specific with stricter definitions than neuroticism as a personality dimension, in theory, neuroticism is believed to be associated with high emotional reactivity, low endurance, and high perseverance. Such connections have also been demonstrated in empirical studies (28). Nevertheless, the findings of the current study failed to confirm a disadvantageous role of emotional reactivity. It is also important to note that, depending on which stress coping component is considered, perseverance and endurance may or may not prove to be of benefit.

With the findings of the current study, however, the significant influence of PTSD symptoms on quality of life is confirmed. In a number of previous studies, both retrospective and prospective, negative effects of PTSD symptoms have been reported (29–31). Similarly, the model presented in this paper highlights this negative relationship, although PTSD symptom level was analyzed as an implication of coping styles, i.e., emotion-oriented coping may be associated with an increased level of anxiety and tension, both being symptomatic of posttraumatic disorders. Consequently, suffering posttraumatic symptoms along with the underlying effects and limitations resulting from cardiovascular disease can substantially undermine one's ability to enjoy life.

Undoubtedly, the findings of the current study support a model of psychological processes where the consecutive stages are temperament, coping styles, PTSD, and quality of life. Nevertheless, there were certain limitations to this study. Presumably, the most significant was the lack of longitudinal data. Data obtained during the adaptation process with the controlled amount of time after infarction might have strengthened the conclusion. Moreover, it is important to note that there was no control group in this study. Thus, the obtained results apply only to the clinical group of patients after MI. Finally, one may also argue that there is a need to monitor health status variables in many aspects other than cardiovascular disease, including the healthcare standard along

with its implications, and similarly the social factors, e.g., the support provided to post-MI patients by their families and loved ones (10, 32).

CONCLUSIONS

In the presented research, relationships between four different aspects of coping with the situation of MI were analyzed. These aspects were temperamental traits, stress coping styles, presence of PTSD symptoms, and quality of life. Although the obtained model suggests that the quality of life after MI depends on many factors, the conducted analysis has shown several more significant correlations. Namely, emotion-oriented coping is correlated with sensory sensitivity, briskness (negatively), perseverance, endurance, and level of PTSD symptoms (positively). Avoidant-social coping is correlated with briskness, activity, and level of PTSD symptoms, whereas avoidant-distracted coping is correlated with perseverance and activity. Furthermore, it has been confirmed that PTSD symptoms may influence the quality of life. There were, however, certain limitations to this study, such as the lack of a control group or longitudinal data. It would be beneficial to include it in future research.

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 Ethical committee of the Faculty of Psychology, University of Warsaw. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

The idea of the research was developed jointly. The research was conducted by AB. MW supported the process of obtaining data as far as possible and made sure that all answers in the questionnaires were marked. In the event of missing responses, MW made an attempt to complete the missing responses and entered the results into the database and dealt with the preliminary statistics. AB wrote an article, made corrections, and made proofreading. Both authors contributed to the article and approved the submitted version.

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Anxiety, Mental Stress, and Sudden Cardiac Arrest: Epidemiology, Possible Mechanisms and Future Research

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Sudden cardiac arrest (SCA) is a leading cause of mortality and morbidity in affluent societies, which underscores the need to identify persons at risk. The etiology of SCA is however complex, with predisposing and precipitating factors interacting. Although anxiety and mental stress have been linked to SCA for decades, their precise role and impact remain unclear and the biological underpinnings are insufficiently understood. In this paper, we systematically reviewed various types of observational studies (total $n = 20$) examining the association between anxiety or mental stress and SCA. Multiple methodological considerations challenged the summarizing and interpretation of the findings. For anxiety, the overall picture suggests that it predisposes for SCA in physically healthy populations (unadjusted OR = 2.44; 95% CI: 1.06–5.59; $n = 3$). However, in populations at risk for SCA ($n = 4$), associations were heterogeneous but not significant. Anxiety may partly predispose to SCA by contributing to other risk factors such as cardiovascular disease and diabetes mellitus via mechanisms such as unhealthy lifestyle and metabolic abnormalities. Mental stress appears to precipitate SCA, presumably by more directly impacting on the cardiac ion channels that control the heart's electrical properties. This may lead to ventricular fibrillation, the arrhythmia that underlies SCA. To advance this field of research, experimental studies that unravel the underlying biological mechanisms are deemed important, and most easily designed for mental stress as a precipitating factor because of the short timeframe. These proof-of-concept studies should examine the whole pathway from the brain to the autonomic nervous system, and eventually to cardiac ion channels. Ultimately, such studies may facilitate the identification of persons at risk and the development of novel preventive strategies.

Keywords: sudden cardiac arrest (SCA), sudden cardiac death (SCD), anxiety, mental stress, biological mechanism, predisposing and precipitating risk factors

INTRODUCTION

Sudden cardiac arrest (SCA) refers to the sudden, unexpected cessation of the heart's pump function as a result of cardiac arrhythmia, most often ventricular fibrillation (VF). In VF, the electrical activation which initiates the heart's contractile function is uncoordinated and too rapid ($>300/\text{min}$), leading to the abolishment of a coordinated contraction. Consequently, blood circulation stops and unless a normal coordinated heart rhythm is restored, death will set in within minutes, called sudden cardiac death (SCD) (1).

Regarding the etiology of SCA, the a priori risk for SCA is elevated by various predisposing factors, because these factors result in morphological changes (e.g., scar tissue) and/or functional changes in the heart (e.g., downregulation or changes in the functional properties of cardiac ion channels that control the heart's electrical properties). In addition, precipitating factors result in dysfunction of the cardiac ion channels, thereby triggering the occurrence of VF and SCA. When the a priori risk is high, a small precipitating factor will be sufficient to elicit SCA, whereas a larger trigger is required when the a priori risk is lower. Among the most prevalent predisposing factors are cardiovascular disease (CVD) and diabetes mellitus (2). For example, in adults, the incidence of SCA is 6.0 per 1,000 person-years in those with CVD, vs. 0.8 per 1,000 person-years without CVD (3). Similarly, SCD risk is elevated up to 2.7-fold in patients with diabetes (4).

A precipitating factor disrupts cardiac ion channel function. The autonomic nervous system (ANS) controls the functional properties of these ion channels (5). Sympathetic activation triggers a pathway which eventually results in changes in cardiac ion channel function, i.e., increased calcium influx which sets the stage for delayed afterdepolarizations that may trigger VF in vulnerable people and hence SCA. Parasympathetic activation causes the opposite effects, i.e., reduced cardiac excitability. For instance, activation of acetylcholine-sensitive potassium channels in atrial cardiomyocytes causes hyperpolarization of the resting membrane potential, thereby counteracting atrial depolarization. This property is being investigated as a novel drug target for the treatment of atrial fibrillation (6). External factors impacting the ANS may thus influence cardiac ion channels. One of the best-known external factors is physical stress, causing sympathetic activation during which adrenaline binding to its receptor on muscle cells triggers the pathway mentioned above.

SCA is a major public health problem, causing 20% of total mortality in industrialized societies (7, 8). SCA most often occurs in the community (out-of-hospital cardiac arrest) where rescuers are most often too late to arrive, resulting in low survival rates, ranging from 4 to 27% across Europe (9). Moreover, those who survive may suffer significant and persistent disabilities due to long-lasting hypoperfusion of the heart and the brain (7, 10). In upcoming years, the incidence and burden of SCA are expected to rise, because predisposing factors such as CVD and diabetes will become more prevalent in the aging world population. Insight in risk factors for SCA facilitates identification of persons at risk and, moreover, might contribute to understanding biological

underpinnings, and thereby to the development of novel (secondary) preventive strategies.

For decades, anxiety symptoms and symptoms of mental stress have been linked to the occurrence of SCA (11). Whereas anxiety may be present without an external stressor, mental stress is regarded as a direct response to an external stressor (12). However, the distinction between these emotional responses is not always clear and symptom profiles are highly similar, including nervousness, difficulty sleeping and concentrating, fatigue, muscle tension, and irritability. The link between anxiety symptoms and symptoms of mental stress and SCA has been studied in various systematic reviews. For example, Strike and Steptoe concluded that mental stress caused by the experience of stressful public events such as earthquakes or emotionally challenging sporting occasions are probable triggers or precipitating factors for acute coronary syndromes, which in turn may lead to VF and subsequently to SCA and SCD (13). Likewise, in a previous meta-analysis, we have shown that anxiety symptoms are a predisposing factor for CVD mortality (including SCA), increasing the risk by 61% (14). However, these studies did not specifically examine SCA as the outcome measure. Overall, the possible role of mental stress or anxiety on the specific cardiac endpoint of SCA has received little attention.

As a result, the impact of anxiety or mental stress on SCA remains unclear. Moreover, the biological underpinnings are insufficiently understood. This article aims to expand on previous research by systematically searching the literature for studies examining the strength of the association between anxiety symptoms or mental stress symptoms and (non-)fatal SCA in the general population and patients with increased vulnerability for SCA. We thereby focus on studies with a long timeframe that are best suited to study predisposing risk factors, as well as on studies with a shorter timeframe which are more adequate to study direct triggers for SCA. In the discussion, we relate the findings concerning the predisposing and triggering role of anxiety/mental stress on SCA to the potential biological mechanisms and address the next steps in research. Ultimately, understanding whether and how anxiety and mental stress play a part in SCA may facilitate the development of (secondary) preventive strategies that are so dearly needed.

METHODS

To examine the association between anxiety or mental stress and SCA, a systematic search was performed in Embase, PubMed and APA PsycInfo of scientific literature in English dating up until May 21, 2021. Examining this association is complicated for various reasons, such as the difficulty to collect sufficient numbers of patients in whom SCA is ascertained, unclear biological mechanisms and consequently unclear timeframe, etc. We therefore aimed at gathering evidence from different angles, which has resulted in a broad search strategy. Eligible studies investigated the influence of anxiety or mental stress on the risk of SCA/SCD using a comparative, observational design. Studies on anxiety or mental stress were included independent of severity but had to use a psychiatric diagnosis of anxiety

disorders according to the DSM, or an anxiety or mental stress questionnaire. Studies using proxies for experienced mental stress were also included, such as earthquakes or the presence of stressful life events. Since the biological underpinnings are insufficiently understood, and appropriate timeframes for predisposing or triggering effects could thus not be defined, studies were selected independent of timeframes used. We qualitatively analyzed unadjusted and multivariable-adjusted risk estimates [risk ratio (RR), odds ratio (OR), hazard ratio (HR), or absolute numbers with details of statistical tests, as reported by the original studies] to estimate the association between anxiety or mental stress and fatal or non-fatal SCA. If possible, we meta-analyzed unadjusted ORs and 95% CIs, using the “admetan” module in Stata 17 (15). As the incidence of SCA is relatively low [0.5–1/1,000/year (16)], ORs or HRs were assumed to be accurately close to estimates of the RR. ORs were calculated and forest plots are shown, using original data on dichotomized exposure and outcome data (2×2 tables), for both healthy and populations at risk. If anxiety/mental stress was classified into more than two categories, the categories with higher exposure were compared with the category with lowest exposure. Pooled ORs were calculated using random-effects models, assuming that the true effects would vary across studies. Potential heterogeneity among studies was calculated using the I^2 statistic, which is a quantitative measure of inconsistency across studies. Studies were pooled irrespective of timeframe, considering the trade-off between inclusiveness vs. heterogeneity, and since the most appropriate timeframes to study predisposing or precipitating effects are unknown. See **Supplementary Material 1** for detailed methods, including the search strategy and flow chart.

RESULTS

Our search identified 1,580 unique records. After title or abstract screening and full-text assessment, 20 studies were included in the systematic review. The publications were subdivided into three types of observational studies (**Table 1**). In type I, researchers directly examined the association between the presence or severity of anxiety and subsequent SCA or SCD ($n = 7$ studies) (17–23). In type II, researchers compared the rates of SCA or SCD during or directly after a public event likely to be accompanied by mental stress (Covid-19 pandemic, earthquakes, terrorist attack, important football tournaments) with those during control periods ($n = 8$ studies) (24–31). In type III, researchers retrospectively examined the life events in the period before SCA described by SCA survivors or relatives of SCA victims as compared with control persons or periods ($n = 5$ studies) (32–36). These three types of observational studies substantially differed in the timeframes examined. Longer time intervals are required to study anxiety/mental stress as a predisposing factor, and short time intervals are appropriate to study anxiety/mental stress as a triggering factor. In type I studies, SCA in the general population was examined over time intervals of 2 years (23), 12 years (20), and 32 years (22), whereas studies in populations at risk generally used a shorter time interval (1–3 years) (17–19, 21). By contrast, type II studies assessed SCA

during or in the days or weeks following the emotionally charged event. Finally, type III studies used a timeframe of 1 month to up to 1 year prior to the SCA/SCD event. Of note, it appeared that studies with a longer timeframe examined anxiety symptoms (i.e., as predisposing factor), whereas studies with a shorter timeframe examined mental stress (i.e., as triggering factor).

Type I: Anxiety and Fatal or Non-fatal SCA

Seven studies examined the association between anxiety and SCA or SCD during follow-up, five of which used a prospective cohort design (18–21, 23), one used a retrospective cohort (17), and one a case-control (22) design. In one study, the exposure was based on pre-existing anxiety disorders (17), whereas most studies used severity of anxiety symptoms, i.e., the state portion of Spielberger’s State-Trait Anxiety Inventory (STAI-S) (18, 21), the phobic anxiety subscale of the Crown-Crisp experiential index (CCEI) (19, 20, 23), or anxiety symptoms based on the Cornell Medical Index (CMI) (22). Follow-up duration ranged from 1 to 32 years. Only three studies were based on participants free from CVD at baseline (20, 22, 23), whereas the remaining studies included patients who already had increased vulnerability for SCA. For more details on the individual studies, see **Supplementary Material 2**.

Physically Healthy Populations

All prospective cohort studies in physically healthy participants found an increased risk for SCD in those participants who were more anxious at baseline. Based on the Nurses’ Health Study data of 71,162 registered female nurses without CVD or cancer at baseline, both continuous (p-trend across quartiles of CCEI phobic anxiety) and dichotomized (highest vs. lowest CCEI quartile) anxiety symptoms at baseline were associated with SCD over the 12 years of follow-up (20). Associations remained statistically significant when adjusted for age and risk factors of coronary heart disease (CHD) but were attenuated after further adjustment for various comorbidities (hypertension, diabetes, hypercholesterolemia). Based on the Normative Aging Study data of 1,895 community-dwelling male veterans without chronic medical conditions at baseline, higher anxiety at baseline (CMI scores ≥ 1) was associated with increased odds of SCD over 32 years of follow-up, also after adjustment for CHD risk factors, although the small numbers resulted in imprecise risk estimations (SCD events per CMI category: 19/1,670, 5/171, 2/35) (22). Based on the Health Professionals Follow-up Study data of 33,858 male health professionals free of diagnosed CVD at baseline, higher anxiety at baseline (CCEI scores ≥ 2) was associated with increased odds of SCD over 2 years of follow-up, also after adjustment for CHD risk factors (significant p-trend across CCEI categories; the small numbers resulted in imprecise risk estimations of SCD events per CMI category: 5/23,259, 2/4,821, 7/3,485, 2/2,293) (23). Pooling the unadjusted associations between dichotomized anxiety symptoms at baseline (higher categories vs. lowest category) and incidences of SCD at follow-up in initially physically healthy populations resulted in significantly increased odds of SCD for highly anxious individuals (OR = 2.44, 95%CI 1.06–5.59; **Figure 1**).

TABLE 1 | Summary of included studies.

	References	Study design, sample <i>n</i>	Anxiety or mental stress measure	Findings
Type I	Li et al. (17)	Retrospective cohort with propensity score matching, <i>n</i> = 26,204	Pre-existing anxiety disorders	The incidence of in-hospital SCA was lower in the anxiety group than in the non-anxiety group of MI patients. This protective effect was only found in patients with non-ST segment elevation MI.
	Habibović et al. (18)	Prospective cohort, <i>n</i> = 1,012	STAI-S at time of ICD implantation	Anxiety increased the incidence of aborted SCD over 1-year follow-up. The associations remained significant after adjustment for multiple variables and were similar for men and women.
	Watkins et al. (19)	Prospective cohort, <i>n</i> = 947	CCEI phobic anxiety subscale	Overall, there was no association between anxiety and SCD. In women, however, anxiety increased the risk of SCD.
	Albert et al. (20)	Prospective cohort, <i>n</i> = 71,162	CCEI phobic anxiety subscale	Anxiety increased the risk of SCD in a sample of healthy women over a 32-year follow-up. The associations remained significant after adjustment for multiple variables but were attenuated after further adjustment for various comorbidities.
	Frasure-Smith et al. (21)	Prospective cohort, <i>n</i> = 222	STAI-S at time of post-MI hospital admission	Anxiety was not significantly associated with incident fatal or non-fatal SCA in the first year post-MI.
	Kawachi et al. (22)	Case-control in a prospective cohort, <i>n</i> = 1,895	Anxiety symptom scale out of 5 questions from the CMI	Anxiety increased the risk of SCD in a sample of healthy men over a 12-year follow-up, also after adjustment for several variables.
	Kawachi et al. (23)	Prospective cohort, <i>n</i> = 33,858	CCEI phobic anxiety subscale	Anxiety increased the risk of SCD in a sample of healthy men over a 2-year follow-up, also after adjustment for several variables.
Type II	Marijon et al. (24)	Cross-sectional database	Paris COVID-19 lockdown vs. control period	During the Paris lockdown, the maximal weekly SCA incidence was significantly higher than during control periods, and a rapid return to normal was seen in the final weeks.
	Simon et al. (25)	Cross-sectional database	Football tournaments (2012, 2016, 2018) vs. control periods.	There was no increased SCA incidence during the (combined) football tournament periods vs. control periods in Polish men.
	Niyama et al. (26)	Cross-sectional database	Great East Japan earthquake and tsunami 2011 vs. control periods	For the initial 4 weeks after the earthquake, the incidence of SCD in the Iwate prefecture was doubled as compared with control periods, after which it returned to baseline.
	Niederseer et al. (27)	Cross-sectional database	Football tournament days the German team played (2006) vs. control periods	There was no increased incidence of SCA hospital admissions during the football tournament vs. control periods in men and women in the German province of Bavaria.
	Aoki et al. (28)	Cross-sectional database	Great East Japan earthquake 2011 vs. control periods	The number of SCA ambulance transports was significantly increased in the week following the earthquake as compared with control periods; it peaked on day 2 followed by a gradual decline.
	Gold et al. (29)	Cross-sectional database	Nisqually earthquake 2001 and 9-11 terrorist attack 2001 (USA) vs. control periods	The incidence of SCD increased during the 48 h following the Nisqually earthquake, as compared with control periods. No increased SCD incidence was found during 1-week post-earthquake, nor during 48-h or 1 week after the 9-11 terrorist attack.
	Katz et al. (30)	Cross-sectional database	FIFA Football World Cup 2002 vs. control period	The incidence of SCD increased during the FIFA in both men and women.
	Leor et al. (31)	Cross-sectional database	Northridge (USA) earthquake 1994 vs. control periods	The incidence of SCD increased on the day of the Northridge earthquake as compared with control periods and afterwards returned to baseline level.
	Chang Liu et al. (32)	Case-control, <i>n</i> = 72	LCUs over 1 year before SCA, based on the SRSS, SSS, or RLCQ	SCA survivors did not significantly differ from matched controls with respect to stressful life events during the year before the SCA.

(Continued)

TABLE 1 | Continued

References	Study design, sample <i>n</i>	Anxiety or mental stress measure	Findings
Jeong et al. (33)	Case-control, <i>n</i> = 190	Major life events in 1 year before SCA or control periods based on family	SCA survivors had a higher number of major life events than matched controls.
Wicks et al. (34)	Case- crossover, <i>n</i> = 490	Major life events in 1 vs. 2–6 months before SCA, based on spouse interviews.	Major life events occurred more frequently during the 1 month before the SCA than during the control period.
Cottingham et al. (35)	Case-control, <i>n</i> = 162	Major life events in 6 months before SCD, based on interviews with spouses or next of kin.	SCD cases had experienced a similar number of life events (total, negative, unclassifiable) during 6 months before death as had neighborhood controls, however, they had experienced less positive life events and more often the death of a significant other.
Rahe and Lind (36)	Case- crossover, <i>n</i> = 39	LCUs over 3 years before SCD based on the Schedule of Recent Events questionnaire by spouses or next of kin.	LCUs were higher in the 6 months before SCD than during the control periods in both healthy subjects and those at risk (CHD history).

CCEI, Crown-Crisp experiential index; CHD, coronary heart disease; CMI, Cornell Medical index; ICD, implantable cardioverter defibrillator; LCUs, life change units. LVEF, left ventricular ejection fraction; MI, myocardial infarction; SCA, sudden cardiac arrest; SCD, sudden cardiac death; SRRS, Social Readjustment Rating Scale; SSS=Student Stress Scale; STAI-S, state portion of Spielberger's State-Trait Anxiety Inventory; RLCQ, Recent Life Changes Questionnaire.

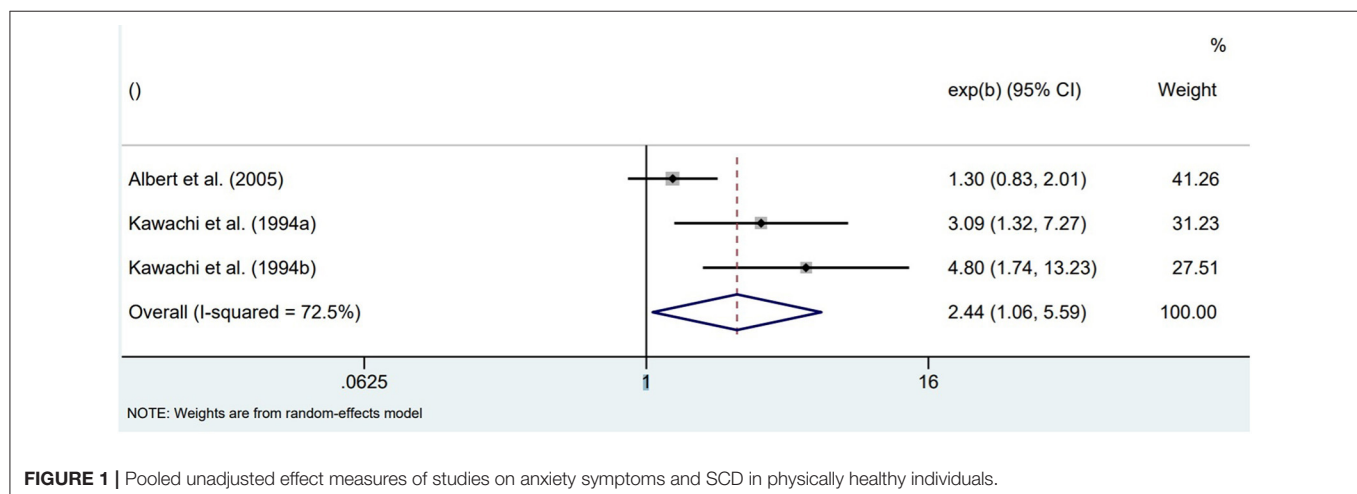


FIGURE 1 | Pooled unadjusted effect measures of studies on anxiety symptoms and SCD in physically healthy individuals.

Populations at Elevated Risk for SCA

The four included studies investigating populations at elevated risk for SCA show highly heterogeneous results. One prospective cohort study in patients with implantable cardioverter defibrillators (ICDs) found that patients with higher anxiety symptoms at ICD insertion (STAI-S) had a higher 1-year incidence of ventricular arrhythmias, also after adjustment for covariates (18). Two prospective cohort studies in patients with an acute MI or with angina admitted for diagnostic cardiac catheterization found that high anxiety at baseline was not associated with fatal or non-fatal SCA. High anxiety was defined as a STAI-S score of at least 40 measured 5–15 days post-MI (21), or as the highest quartile of the CCEI phobic anxiety scale measured 0–4 days post-catheterization (19). One of these studies (VAGUS cohort) also showed that, in contrast to men, highly-anxious women had a significantly increased risk of SCD over 3 years of follow-up (19). In the other study, however, it was mentioned that all cases of arrhythmic events over the

1-year follow-up period occurred in men (21). Finally, a large retrospective cohort using the 2016 National Inpatient Sample data of MI patients showed a protective effect of pre-existing anxiety disorders on the incidence of in-hospital SCA, but only in non-ST segment elevation MI patients (17). Pooling the unadjusted associations of these studies between baseline anxiety and incidence of SCA resulted in highly heterogeneous effect estimates, with the pooled odds for higher symptoms of anxiety not being significantly different from low symptoms of anxiety (OR = 1.15, 95%CI 0.69–1.91; Figure 2).

Type II: Emotionally Charged Public Events and Fatal or Non-fatal SCA

Eight studies compared the rates of SCA or SCD during or directly after an emotionally challenging public event (Covid-19 pandemic, earthquakes, terrorist attack, important football tournaments as proxies for mental stress) with those during control periods (24–31). These “natural experiment” studies are

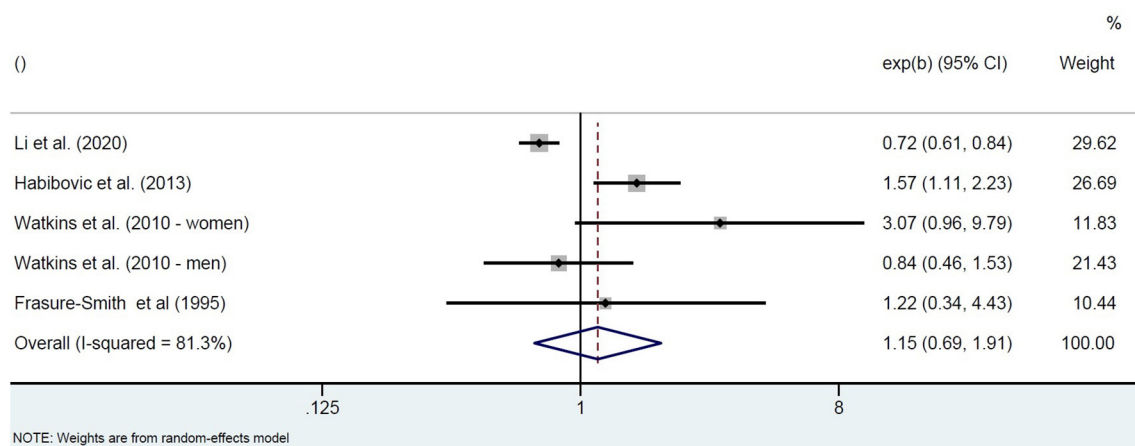


FIGURE 2 | Pooled unadjusted effect measures of studies on anxiety and SCA in individuals with elevated SCA risk.

based on records of insurance companies or the authorities of a certain catchment area. Due to the large heterogeneity in effect measures and standardization, results of type II studies have not been pooled. For more details of the individual studies, see **Supplementary Material 3**.

Humanitarian Disasters

Studies on the effects of four out of five selected humanitarian disasters were suggestive of a relative increase in (non)fatal SCA rates. For instance, the weekly incidence of SCA during the Paris COVID-19 lockdown was significantly higher than during control periods (24). Likewise, data on the Northridge earthquake 1994 and the Nisqually earthquake 2001 showed increased SCD rates in the affected countries as compared with the control periods (29, 31). Furthermore, data on the Great East Japan earthquake and tsunami 2011 also showed increased SCD or SCA rates in affected prefectures (26, 28). With respect to the timeframes, three of the earthquake studies reported that the incidence of (non)fatal SCA was particularly increased on either the day of or the day after the event (28, 29, 31). The 9–11 terrorist attack in 2001, however, gave no rise to SCD rates in King County (situated far away from the place of the terrorist attacks) (29).

Football Matches

The three studies on the effects of football tournament periods were less suggestive of an association between mental stress and (non)fatal SCA. Only one study found a significantly increased incidence of SCD in Swiss men and women during the FIFA World Cup 2002 as compared with the control period (30). Two other studies, covering four tournament periods, found no significant associations between football spectatorship and the incidence of SCA in Polish men (25) or German men and women in the province of Bavaria (27).

Type III: Stressful Life Events and Fatal or Non-fatal SCA

Five studies examined the experienced recent life events (as proxy for mental stress) described by SCA survivors or relatives of SCA victims as compared with control persons or

periods (32–36). For more details of the individual studies, see **Supplementary Material 4**. Three studies based on information of spouses or relatives found an association between major life events and fatal or non-fatal SCA. One case-crossover study showed that the total stress-generating potential of experienced life events (life change units, i.e., counting life-events and weighting these for stress-generating potential) in the 6-months prior to SCD in Swedish men was higher compared to the same period in two preceding control years (36). Likewise, another case-crossover study showed that the occurrence of a major life event involving family or friends was higher in the month before the SCA than in the control period of 2–6 months before the SCA (34). A case-control study also showed that SCA survivors had experienced a significantly higher number of major life events in the year prior to the SCA than had matched controls (33). In contrast, two other case-control studies found no association between life events and (non)fatal SCA. One study in a population with a broad age range found no significant differences between the SCA survivor group and matched controls with respect to the total stress-generating potential of experienced life events over the year prior to the SCA (32). Another study found that American women with SCD overall did not differ from the race, sex, and age-matched controls with respect to the total number of stressful life events in the 6 months prior to SCD, although they had experienced fewer positive life events and more often the death of a significant other (35).

DISCUSSION

Main Findings

We may conclude from this systematic literature research that the evidence for the relationship between anxiety or mental stress and SCA or SCD derived from various types of studies is mixed.

Anxiety

The pooled results of three prospective cohort studies (type I) in healthy populations suggest that people with high anxiety scores had a more than 2-fold higher chance to experience SCA (20, 22,

23). This suggests that the risk of SCA in people with more severe anxiety symptoms is of similar magnitude as the risk associated with established predisposing risk factors such as diabetes (5). However, pooling four studies (type I) in populations at risk for SCA resulted in a non-significant effect estimate. It should be noted that in both meta-analyses heterogeneity was substantial (I^2 higher than 70%).

Studies in healthy populations and in populations at risk both examined the effect of presence and severity of anxiety symptoms as a predisposing risk factor, but populations at risk in general had much shorter time intervals for follow-up measurements. It might be that anxiety symptoms indeed predispose to SCA by a process that requires time, which is thus better captured in studies with longer follow-up intervals. It might also be that the role of anxiety is primarily to contribute to a predisposition, and once the predisposition is present, its role is limited.

Mental Stress

Studies on the precipitating effect of symptoms of mental stress and SCA showed a mixed picture. Stress was only assessed indirectly by proxies, including natural disasters, football spectatorship, or by the experience of life events. It is likely that these sources of stress highly differ in intensity and in impact on disrupting life, which might explain the mixed results. Indeed, as would be expected, in type II studies, the evidence for an association with SCA was stronger for studies investigating natural disasters (particularly earthquakes) than for those on football spectatorship. Of the retrospective case-control and case-crossover studies on life events (type III studies), three studies found an association with SCA, whereas two studies did not.

Methodological Considerations

The main strength of this systematic review is its broad scope, including the overlapping aspects of both anxiety and mental stress, both physically healthy and at-risk populations, and varying timeframes. In addition, we included various types of observational studies, each with its own assets, for example the possibility of adjustment for covariates in type I, the large sample size in type II, and the detailed assessment of the period prior to the SCA in type III. This broad scope was deemed necessary to study a complex association of which so little is known. By focusing on SCA specifically as outcome, we addressed limitations of previous research on the cardiac risk associated with anxiety and mental stress. However, per definition, examinations of outcomes that are assumed to have a multifactorial etiology such as SCA will often be surrounded by uncertainties, and more so when outcomes are less frequent. On top of that, several limitations should be mentioned. First, the timeframe chosen in studies is highly relevant. In general, to study predisposing factors, longer follow-up periods are required as compared to precipitating factors directly triggering SCA. More specifically, the most appropriate timeframe depends on the assumed underlying biological mechanisms. Any mismatch between the follow-up period and the time required for the biological mechanism to act will have an impact on findings, i.e., too long follow-up periods will dilute associations, whereas too short follow-up periods will not show effects. If more studies

become available, it would be preferable to pool those with similar timeframes, which also could diminish the substantial heterogeneity found in the meta-analyses.

Second, in all three types of studies presented here, confounding factors may be substantial and are often not accounted for sufficiently. For example, increased rates of SCA during the COVID-19 pandemic might be due to fear and psychological stress due to the pandemic, but might also be due to other factors, such as COVID-19-related complications, temporarily limited access to the health care system (24, 37), or lifestyle changes during lockdown. Likewise, although persons with anxiety may use selective serotonin reuptake inhibitors (SSRIs), some of which have proarrhythmic effects (38), analyses were not adjusted for medication use. Moreover, only baseline assessments of time-dependent confounding variables (such as cardiovascular status) were used in the analyses. An individual patient data meta-analysis would shed the clearest light on the influence of (time-dependent) confounding factors at an individual level.

Third, the assessment of anxiety and mental stress is suboptimal. It appeared that anxiety was examined only as a predisposing factor precluding evidence for its potential triggering role. Likewise, mental stress only was examined as a triggering factor. The predisposing potential of (chronic) mental stress therefore remains unknown. Furthermore, in type I studies, the assessment of anxiety took place only once, at baseline, thereby neglecting the fact that anxiety may vary over time, especially over periods of multiple years. In both cases of anxiety symptoms either disappearing or developing after baseline, the effect estimates will have been biased toward zero. In addition, most type I studies assessed anxiety symptoms rather than disorders and the proportion of “clinically significant anxiety” (39, 40) was limited. As some studies reported a dose-response relationship, it is possible that assessing clinically significant anxiety only would have resulted in higher effect sizes. In type II and type III studies, mental stress was assessed indirectly by means of experienced life events, disasters, or emotionally challenging public events. In other words: no rating scale on presence or severity of stress was used. Such indirect assessments have various limitations. For example, we do not know exactly which emotions are triggered. We pragmatically labeled them as “mental stress,” thereby ignoring that, while positive life events may also trigger positive emotions, negative life events may trigger anxiety or mourning, and football matches may trigger emotions depending on the outcome of the match (41). Thus, “mental stress” is likely to encompass various emotions which might have a differential impact on the development of SCA. Moreover, measuring events rather than the emotions themselves assumes that these events are emotionally challenging for all people. This assumption is not likely to be true. For example, people not interested in football will not experience any emotions, thereby introducing a bias toward zero. Also, stress due to the 9–11 terrorist attacks is likely to be higher in places near the terrorist attacks than in distant places. Furthermore, the impact of unforeseeable events (e.g., earthquakes) might differ from that of foreseeable events (e.g., football matches).

Finally, retrospective assessments are prone to bias inflating effects, i.e., people and relatives are more prone to remember life events when followed by SCA in an attempt to understand the occurrence of the cardiac event (42). Finally, data obtained from relatives is indirect, thereby hampering reliability.

In sum, the findings of the present meta-analysis and systematic review are surrounded by uncertainties due to methodological aspects. Overall, the estimated risk for SCA associated with anxiety/mental stress is modest, suggesting that other factors play a role and may even modify the effect of anxiety and mental stress.

Potential Biological Pathways

Predisposing to SCA

Findings of type I studies that were conducted in the general population and mainly had long follow-up intervals suggest that anxiety symptoms increase the risk for SCA by more than 2-fold. Anxiety thus seems to predispose individuals to SCA by processes requiring time. This may also explain why findings in populations at risk for SCA were less clear, i.e., follow-up periods were restricted to 1 or at most 3 years which may be short. In the general population studies, the risk estimate of anxiety decreased when analyses were adjusted for known risk factors for SCA such as CVD and diabetes. Hence, the presence of anxiety symptoms partly increases the *a priori* risk for SCA by associations with CVD and diabetes. Indeed, we previously reported that anxiety symptoms are associated with the onset of CVD (14). The underlying biological mechanisms may range from the association of anxiety disorders with unhealthy lifestyle factors (i.e., smoking, lower physical activity, and poor diet) to metabolic abnormalities (i.e., hypercholesterolemia, immune dysregulations, hypercoagulability). These may promote atherosclerosis and subsequently result in the onset of CVD (14). Likewise, anxiety is associated with the onset of diabetes mellitus (43). Though the biological underpinnings of this association need to be unraveled, inflammation and also cardiometabolic abnormalities might play a role (43).

When analyses were adjusted for multiple lifestyle and biological measures, the risk remained present. This suggests that anxiety symptoms not only impact SCA via their influence on other predisposing factors mentioned above. The increased risk estimate might be due to other, yet unknown, biological pathways which also require time. Moreover, as anxiety often runs a chronic course, it may also be that anxiety at baseline is associated with (peaks of) anxiety years later, and that such later (peaks of) anxiety trigger the direct onset of SCA.

Precipitating SCA

In most type II studies, emotionally challenging humanitarian disasters led to higher rates of SCA, and the risk was highest directly following the disaster, returning to normal levels fast (24, 26, 28, 29, 31). This suggests that stressful or emotional situations may acutely elicit SCA when stress levels are highest. Likewise, we have found the risk was less clear or absent in football matches, or for disasters happening relatively far away (29), suggesting that the amount of mental stress impacts on SCA, which is in line with Hill's criterion of biological gradient (44).

Type III studies, examining the impact of life events on SCA, used a timeframe of 1 month until 1 year prior to the SCA/SCD event. Due to this design, the time relationship between the highest stress level and occurrence of SCA is less clear in these studies.

It is hypothesized that the underlying biological mechanism by which mental stress elicits SCA involves cardiac ion channels, as these ion channels directly control the heart's electrical properties. The normal cardiac cycle is composed of a depolarization (activation) phase, a repolarization phase, and a resting phase between heartbeats. Ion channel dysfunction causing VF may occur in sodium and calcium ion channels important in the depolarization phase, or in various potassium channels, important in the repolarization phase. The functional properties of these ion channels are controlled by a balanced system of sympathetic and parasympathetic regulators of the ANS (5), which respond in turn to the central control of the brain. In various inherited or common acquired conditions, sympathetic stimulation is associated with cardiac arrhythmias underlying SCA. The inherited arrhythmia syndromes most strongly associated with mental stress-induced arrhythmias and SCA are long QT syndrome type 2 (LQTS2) (45), catecholaminergic ventricular tachycardia (CPVT) (46) and an idiopathic VF syndrome linked to a risk haplotype that contains the DPP6 gene (5). Arrhythmogenic right ventricular dysplasia/cardiomyopathy (47, 48) and LQTS type 1 (45) are also strongly triggered by sympathetic stimulation, particularly following physical stress. In common acquired conditions, the clearest example of cardiac arrhythmia evoked by mental stress-induced sympathetic stimulation is electrical storm. Following acute management of this cardiac emergency (49), psychiatric treatment may play a role in its long-term treatment (50).

Dysfunction of ion channels due to mental stress may primarily occur during the cardiac repolarization phase. This notion derives from documentation of changes in the ST-T segment of the electrocardiogram (ECG) during mental stress (51–53), reflecting changes in cardiac repolarization. Moreover, LQTS2 predisposes to SCA by gene mutations in the KCNH2 gene, which encodes the potassium ion channels at play during repolarization (52).

Next Steps in Research

Our review of observational studies underpins the idea that anxiety and mental stress influence the occurrence of SCA. However, due to the multiple methodological limitations of observational studies as mentioned above, the causality of this relationship will be difficult to prove, if not impossible. This hampers the development of preventive strategies. To advance research on the cardiac effects of stress, experimental studies unraveling the underlying biological mechanisms are required. Due to the short timeframe, such studies are easier to design for precipitating factors as opposed to predisposing factors. Findings from these studies might support the causality criteria of plausibility and coherence as formulated by Hill (44).

So far, most studies have focused on peripheral effects, i.e., effects of neurotransmitters (mostly catecholamines) on the heart and its constituent ion channels. Therapies based on these insights have limited applicability, either because they are

only partly effective in SCD prevention (e.g., β -adrenoceptor blockers), or because they involve a high risk for side-effects and are therefore used in highly selected patients only (e.g., stelletomy). Emerging evidence suggests a role for central control of cardiac function by specific brain regions, such as the ventromedial prefrontal cortex, insular cortex, amygdala, bed nucleus of the stria terminalis, hypothalamus and periaqueductal gray (54, 55).

In our opinion, the scope of experimental studies to examine the precipitating role of mental stress for SCA should therefore not be limited to peripheral effects. Rather, proof-of-concept studies should be extended to the whole pathway from the brain to the cardiac ion channel function. The amygdala should be of particular interest, since it is crucial in processing mental stress, and its activity has already been related to the occurrence of cardiovascular events (56). The hypothalamus-pituitary-adrenal (HPA) axis projects onto the hypothalamus through the most prevalent inhibitory (gamma-amino butyric acid; GABA) and excitatory (glutamate) neurotransmitters in the hippocampus, amygdala and prefrontal cortex (57, 58). Moreover, rat studies found a significant imbalance between GABA and glutamate after exposure to acute and chronic stress (59, 60). Not many studies have investigated the influence of acute stress on the human glutamate and GABA concentrations. One magnetic resonance spectroscopy (MRS) study investigating stress using a psychosocial stressor found no changes in the prefrontal cortex (61). In contrast, two other MRS studies reported imbalance between GABA and glutamate after chemically induced panic or threat of shock, either by increased glutamate (62) or decreased GABA (63) concentrations in the prefrontal cortex. Results on metabolite changes induced by acute stress are still scarce, but it has been suggested that the direction of GABA concentration changes after acute stress is stressor dependent, both in the hippocampus (64) and in the frontal cortex (65, 66).

The priority therefore lies with studies investigating whether (different kind of) stress-induced changes in brain functioning and alterations in GABA and glutamate are indeed associated with changes in ECG markers of SCA risk. Consequently, if mental stress indeed reduces GABA concentrations in the amygdala and changes cardiac electrophysiology, future studies should investigate whether an altered SCA risk is associated with changes in GABA-ergic metabolism based on medication use or a particular genetic profile. Based on these findings, pharmacological treatment and development could then be advanced to reduce SCA risk (i.e., GABA-ergic pharmacotherapy of cardiac arrhythmias). In view of the addictive properties of most GABA-ergic drugs, we would also like to advocate more studies into the efficacy of behavioral therapy to prevent cardiac arrhythmias. This could involve learning a more adaptive stress response using functional Magnetic Resonance Imaging (fMRI) neurofeedback or cardiac physiology output-based training of bodily stress regulation (biofeedback).

Thus, studying stress-induced changes in the brain and cardiac electrophysiology will help to unravel the underlying biological mechanisms by which stress increases SCA risk. These

insights may be used to identify individuals at risk and to develop preventive interventions to reduce SCA rates. For example, structural or functional changes in particular brain regions or certain molecular signaling pathways could serve as a biomarker. Likewise, these identified molecular signaling pathways could aid the development of novel (drug) treatments.

CONCLUSION

By summarizing observational studies this review supports the prevailing idea that anxiety and mental stress may increase SCA risk. Anxiety predisposes (particularly physically healthy persons) to SCA by processes requiring time, partly by contributing to other risk factors for SCA. Mental stress may elicit SCA, presumably by impacting upon cardiac ion channels. To advance the field, experimental studies examining the precipitating role of mental stress for SCA are required to complement observational studies. These should encompass the whole pathway from the brain to cardiac ion channel dysfunction.

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NB, OH, LR, and HT: study design. AS and AB: data collection and analysis. All authors: interpretation of findings, drafting manuscript, critical revision, and approval of final version of the manuscript.

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SUPPLEMENTARY MATERIAL

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Impact of Pulmonary Arterial Hypertension on Employment, Work Productivity, and Quality of Life - Results of a Cross-Sectional Multi-Center Study

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Introduction: Data on burden of pulmonary arterial hypertension (PAH) are mostly limited to physical and clinical endpoints as well as quality of life. Research on employment, work productivity, and educational background is scarce. The aim of this study was to assess the impact of PAH on employment status and work productivity in Germany.

Materials and Methods: In a multicenter cross-sectional survey, patients with PAH were surveyed in two large pulmonary hypertension referral centers in Germany. The survey contained questions on education, employment, work productivity and impairment (WPAI, also at the time of diagnosis), quality of life, and socioeconomic status. Additional data was assessed using clinical research database for 6-min walk distance (6MWD), WHO functional class, and N-terminal fragment of pro-brain natriuretic peptide. All patients provided written informed consent, and the institutional review board approved this study.

Results: In total, 212 patients were surveyed (72% female; median, 57 years) approximately 6 years after initial PAH diagnosis. A total of 76% had an idiopathic PAH followed by hereditary and associated PAH (10% each). Employment at the time of diagnosis was 48% (34% full-time, 14% part-time), with productivity measured by a WPAI score of 6 points and decreased to 29% (21% full-time, 8% part-time) at the time of the survey (with a WPAI score of 2 points, $p < 0.001$). Logistic regression showed education and 6MWD as predictors for employment. Patients in moderate or high educational category had a 3.6- or 5.6-fold chance, respectively, of being employed ($p = 0.025$ and $p = 0.019$), and per 50-m increase of 6MWD, the odds of being employed were 1.2, $p = 0.042$.

Conclusion: Patients with PAH had a reduced employment rate, which was influenced by education and 6MWD. There was a considerable loss of employment over the course

of the disease. Employment should be one possible treatment goal in patients with PAH to provide social participation to this patient group.

Keywords: employment status, work productivity, work productivity activity impairment questionnaire, pulmonary arterial hypertension, quality of life, social participation, education

INTRODUCTION

Pulmonary arterial hypertension (PAH) is a rare pulmonary disease marked by debilitating symptoms, such as exertional dyspnea, syncope, and clinical signs of heart failure (1). PAH is characterized by pulmonary vascular remodeling, leading to increased pulmonary vascular resistance. Despite successful therapeutic strategies, PAH is frequently fatal, with right heart failure being the leading cause of death (2, 3). Patients with PAH experience impaired physical activity and quality of life (QoL) (4). Sociodemographic data on PAH patients is scarce. To our knowledge, no study addressed the factors influencing the status of employment in patients with PAH so far.

The impact on work productivity of numerous diseases, including asthma, irritable bowel syndrome, and rheumatoid arthritis, has been widely studied (5, 6). Research included missed time from work, reduced performance, and reduced routine working hours. Reilly et al. developed the work productivity and impairment (WPAI) questionnaire to assess the effect of health and symptom severity on work productivity (7).

While the burden of PAH with its limitations on physical capability and QoL is widely recognized, employment, work productivity, and educational background remain underrepresented (8). There are few studies exclusively discussing the employment status of patients with PAH. Taichman et al. suggest that better physical QoL is associated with active employment and found an employment rate of 35% (1). Another study demonstrated the symptoms of PAH to impair the ability to perform at work and maintain a full-time work schedule and lead to feelings of loss of independence and purpose (9). In the US, Matura et al. found a diminished rate of employment in PAH patients and the educational status to be a strong predictor for overall QoL (10). The European Pulmonary Hypertension Association surveyed 326 patients and found that employment and work are main issues for at least 85% of patients with PAH, resulting in a relevant loss of income (11). So far, no data exist on work productivity or employment status for patients with PAH in Germany. However, there is some data on employment and QoL in patients with left heart failure. With high rates of retired patients, just 9 to 15% of the patients were employed. The employed patients reported 29% impaired work productivity (12, 13).

The aim of this study was to assess the impact of PAH on employment over the course of the disease as part of social participation. Factors associated with not being able to work were analyzed. The secondary outcomes were QoL in relation to employment, work productivity, and clinical status of PAH patients.

MATERIALS AND METHODS

In this cross-sectional, observational, multicenter study, patients with a confirmed diagnosis of PAH at two participating pulmonary hypertension (PH) referral centers (Hannover Medical School and University of Giessen, both in Germany) were surveyed. This study was conducted between November 2018 and October 2019 in routine outpatient care using a paper-based self-administered questionnaire. The study was approved by the local institutional review board (no. 8115_BO-K_2018), and all patients gave written informed consent for the use of their data.

Patient Setting and Clinical Parameters

All patients in both centers with a confirmed diagnosis of PAH according to current European Society of Cardiology/European Respiratory Society (ESC/ERS) Guidelines (2) and with age ≥ 18 years were invited to complete a questionnaire as part of their routine outpatient visit. For clinical characterization, hemodynamics from right heart catheterization at time of diagnosis were assessed. The study visit included WHO functional class (FC), 6-min walk distance (6MWD), serum levels of N-terminal fragment of pro-brain natriuretic peptide (NT-proBNP), anthropometry (body weight, height, and body mass index), and pulmonary function testing (PFT). PFT included forced expiratory volume in 1 s (FEV1) and diffusing capacity of the lung for carbon monoxide (DLCO). The ERS/ESC risk score assessment for our cohort was based on three variables (FC, 6MWD, and BNP/NT-proBNP) as previously described (14, 15). Each variable was graded with a number from 1 to 3, representing low risk = 1, intermediate risk = 2, and high risk = 3. The average risk was calculated by dividing the sum of the grades by the number of available variables and rounding to the next integer.

Abbreviations: 6MWD, 6-min walk distance; APAH, associated PAH; AUDIT-C, Alcohol Use Disorder Identification Test; BMI, body mass index; BNP, brain natriuretic peptide; DLCO, diffusing capacity of the lung for carbon monoxide; ERS, European Respiratory Society; ESC, European Society of Cardiology; FC, World Health Organization functional class; FEV1, forced expiratory volume in 1 s; HADS, Hospital Anxiety and Depression Scale; HPAH, hereditary PAH;

HRQoL, quality of life; IPAH, idiopathic PAH; NT-proBNP, N-terminal fragment of probrain natriuretic peptide; OR, odds ratio; PAH, pulmonary arterial hypertension; PCH, pulmonary capillary hemangiomatosis; PFT, pulmonary function testing; PH, pulmonary hypertension; PVOD, pulmonary veno-occlusive disease; QoL, quality of life; SD, standard deviation; VAS, Visual Analog Scale; WPAI, work productivity and impairment.

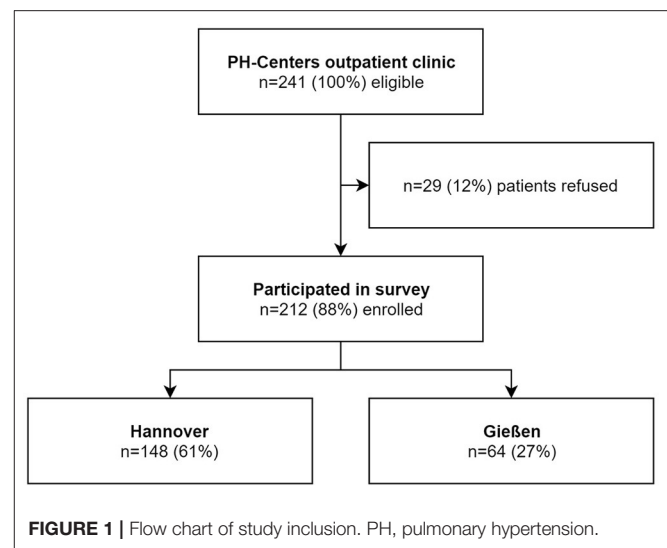
Assessment of Socioeconomic Status, Lifestyle Factors, Work Productivity, and HRQoL

We assessed socioeconomic status (employment and education) as well as work productivity and health-related quality of life. Employment status and work productivity were assessed both for the time of diagnosis (retrospectively) and at study visit (current status). The sociodemographic standards of the German Federal Statistical Office (Destatis) (16) were used to assess employment as well as general and professional education. Educational status was further categorized in low, moderate, and high education as follows: no education (low), non-academic education (moderate), and academic education (high). Education was compared to the German population using the German population census “Mikrozensus 2018,” and retirement types (due to age or due to disability) were compared using data from the German retirement agency (Deutsche Rentenversicherung Bund) (17, 18). Work productivity was assessed using the WPAI instrument (7). Focusing on question #5 of WPAI, the patients were asked by how much their productivity, while working during the past 7 days, was affected by PAH-derived health problems. The patients were asked to encircle a number between zero and 10, ranging from health problems had no effect on work productivity to health problems completely prevented the patient from working. The patients were asked to omit this question in case they were not employed.

At study visit, QoL, family status, degree of disability, smoking status, and alcohol use were assessed. QoL was assessed using the EuroQoL EQ-5D sub-scored in EQ-5D-3L and EQ-VAS (19) and emPHasis-10 (20). Details for the instruments used are found in **Supplementary Table 1**. The EQ-5D-3L has five dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression). Higher scores indicate a better quality of life. The EQ-VAS is a scale with a range from 0 (the worst health you can imagine) to 10 (the best health you can imagine). The emPHasis-10 is a PH-specific QoL questionnaire. The emPHasis-10 score ranges from 0 to 50, with higher scores indicating a worse QoL. The degree of disablement in Germany is a score between 20 and 100 points, characterizing the extent of disability of a patient, with a higher score indicating a greater disability. The patients were asked to state their smoking status (active smoker, former smoker, or never a smoker) as well as the duration of smoking and the mean number of cigarettes per day to calculate the number of packyears (21).

Statistical Analysis

IBM SPSS Statistics (version 27.0, IBM Corp., Armonk, NY, USA) and Stata 13.0 (State Corp LP, College Station, TX, USA) statistical software programs were used for statistical analysis. Categorical data were presented as counts with percentages. Continuous variables were presented as median with the first and third quartile (Q1 and Q3) or as mean and standard deviation (SD), depending on the distribution. For group comparisons, chi-square test, Fisher's exact test, or McNemar–Bowker test, in case of paired comparison, was used as appropriate. Continuous parameters were compared using paired *t*-test, or Wilcoxon test



was used as appropriate. To assess the impact on employment in patients who were eligible of being employed (using the official German retirement age of 67 years as the cutoff), simple and multiple logistic regression analysis was conducted (forward-stepwise conditional) and odds ratios (OR) were calculated. Significant variables of the simple model were included in the multiple model, and variables with $p < 0.10$ remained in the multiple model. To visualize change in categories over time, Sankey–Chart diagrams were created. All tests were two-sided, with $p < 0.05$ considered to be statistically significant.

RESULTS

A total of 212 from 241 (88%) patients agreed to participate and returned their questionnaires; 148 (70%) were from Hannover and 64 (30%) were from Gießen (see **Figure 1**). Female sex comprised 72%, and the majority of the patients (76%) had a group 1.1 idiopathic PAH, followed by hereditary PAH, and associated PAH (10% each; see **Table 1**). The median age at study visit was 57 (43–66) years, and the study visit occurred 6 (2–11) years after the diagnosis of PAH.

Most patients were in WHO FC II or III (85%) and in low-risk ESC/ERS category (55%), and 44% were capable to climb a maximum of one flight of stairs. PFT showed a slight reduction in FEV₁ (78% predicted) and a moderate reduction in DLCO (60% predicted). The NT-proBNP was 221 ng/L (92–611), and 6MWD was 448 m (338–540). Fifty percent of the patients had a history of smoking, with a median of 13 (6–26) packyears, of whom 15% were active smokers.

Education, Employment, Work Productivity, and HRQoL

Most patients were classified as moderately educated (63%), followed by higher education of 18% and a lower educational status in 17% of the patients (**Table 1**). This is in line with data from the population census from Germany 2018. Here 57%

TABLE 1 | Patient characteristics at study visit.

	Demographics, <i>n</i> = 212 patients
Age in years, median (IQR)	57 (43–66)
Sex, <i>n</i> (%)	
Female	2%
Male	59 (28%)
Diagnosis, <i>n</i> (%)	
IPAH—group 1.1	(6%)
HPAH—group 1.2	(10%)
DPAH—group 1.3	(2%)
APAH—group 1.4	(10%)
PVOD/PCH—group 1.6	3 (1%)
Age at diagnosis in years, median (IQR)	48 (34–60)
Time since diagnosis in years, median (IQR)	6 (2–11)
Hemodynamic at diagnosis, median (IQR)	
mPAP (mmHg)	50 (42–57)
PVR (dyn s cm ⁻⁵)	767 (543–1,031)
Cardiac index (L/min/m ²)	2.3 (1.9–2.7)
WHO FC, <i>n</i> (%)	
I	22 (10%)
II	(37%)
III	(8%)
IV	10 (5%)
PAH medication, <i>n</i> (%)	
Monotherapy	(28%)
Double combination therapy	(45%)
Triple combination therapy	55 (26%)
NT-proBNP (ng/L), median (IQR)	221 (92–611)
ESC/ERS risk score	<i>n</i> = 169, 43 missing values (20%)
Low	(55%)
Intermediate	(41%)
High	6 (4%)
Pulmonary function test, median (IQR)	
FEV ₁ (% of predicted)	(65–90)
D _{LCO} (% of predicted)	60 (49–71)
6MWD, median (IQR)	
Walk distance (m)	462 (369–546)
Flights of stairs, <i>n</i> (%)	<i>n</i> = 204, 8 missing values (4%)
None	25 (12%)
One flight	89 (44%)
Two flights or more	90 (44%)
BMI (kg/m²), median (IQR)	26 (23–31)
Smoking status, <i>n</i> (%)	<i>n</i> = 207, 5 missing values (2%)
Active smoker	30 (15%)
Former smoker	73 (35%)
Never a smoker	104 (50%)
Packyears, median (IQR)	13 (6–26)
Education, <i>n</i> (%)	<i>n</i> = 206, 6 missing values (3%)

(Continued)

TABLE 1 | Continued

	Demographics, <i>n</i> = 212 patients
Low education	35 (17%)
Moderate education	134 (63%)
Higher education	37 (18%)
HRQoL scores	
EQ-5D-3L, median (IQR)	7 (6–9)
EQ-VAS, median (IQR)	5.5 (3.5–7.5)
emPHasis-10, median (IQR)	18 (13–27)

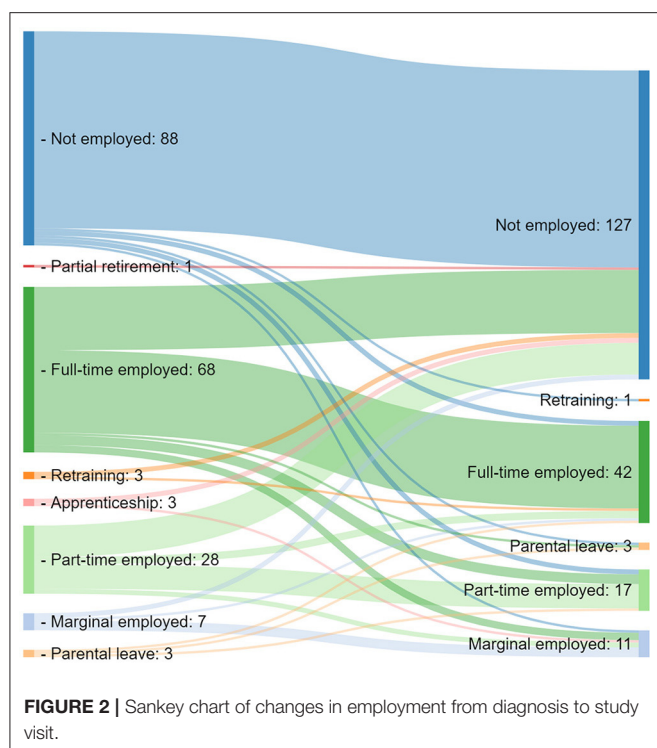
IQR, interquartile range; PH, pulmonary hypertension; IPAH, idiopathic pulmonary hypertension; HPAH, hereditary pulmonary hypertension; APAH, associated pulmonary hypertension; DPAH, drug- and toxin-induced pulmonary hypertension; PVOD, pulmonary veno-occlusive disease; PCH, pulmonary capillary hemangiomatosis; BMI, body mass index; MPAP, mean pulmonary arterial pressure; PVR, pulmonary vascular resistance; WHO-FC, World Health Organization functional class; NT-proBNP, N-terminal fragment of probrain natriuretic peptide; ESC, European Society of Cardiology; ERS, European Respiratory Society; FEV₁, forced expiratory volume in 1 s; DLCO, diffusing capacity of the lung for carbon monoxide; 6MWD, 6-min walk distance; AUDIT-C, Alcohol Use Disorder Identification Test; VAS, Visual Analogue Scale.

TABLE 2 | Change of employment and work productivity from diagnosis to study visit.

	Diagnosis	Study visit
Item	<i>n</i> = 201, 11 missing values (5%)	
Unemployed	88 (44%)	(3%)
○ Retired	(59%)	77 (61%)
• Old age pension	(33%)	50 (39%)
• Disability pension	(26%)	27 (21%)
○ Disability	12 (14%)	27 (21%)
○ Homekeeper	10 (11%)	9 (7%)
○ Unoccupied	4 (5%)	11 (9%)
○ Others	4 (5%)	1 (1%)
○ College/university students	4 (5%)	1 (1%)
○ Students	2 (2%)	1 (1%)
Full-time employed	68 (34%)	21%
Part-time employed	28 (14%)	(8%)
Marginal employed	7 (3%)	(5%)
Retraining	3 (1%)	(1%)
Apprenticeship	3 (1%)	(0%)
Parental leave	3 (1%)	(1%)
Partial retirement	1 (1%)	0 (0%)
WPAl, median (IQR)	6 (3–8)	2 (0–7) – <i>p</i> = 0.001

IQR, interquartile range; WPAl, work productivity and impairment.

were moderately educated, followed by 25% with a lower and 18% with a higher educational status, respectively. At the time of diagnosis, 44% of the patients were unemployed, 34% were employed fulltime, and 14% were employed part-time. At study visit, unemployment was determined in 63% of the patients (+19%), fulltime employment in 21% (–13%), and 8% were employed part-time (–6%) (*p* < 0.001, see **Table 2** and **Figure 2**). Retirement was due to age (*n* = 50, 65%) or disability (*n* = 27,



35%). Compared to the German population with 6.2% of adult citizens retired due to disability, PAH patients had a significantly higher rate of retirement due to disability ($p < 0.001$). The WPAI score of employed patients at diagnosis was 6 (3–8) points, and it was 2 (0–7) points at study visit ($p = 0.001$). The WPAI score at diagnosis was available for 96 employed patients, and at study visit, $n = 57$ patients who were employed stated a WPAI score (-39 patients).

The EQ-5D-3L score was 7 (6–9), EQ-VAS was 5.5 (3.5–7.5), and emPHasis-10 was 18 (13–27) points at study visit. The EQ-5D-3L as well as emPHasis-10 showed more problems in physical sub-scores. In the dimension mobility of EQ-5D-3L, 55% had some or extreme problems; in the dimension pain/discomfort, 80% had moderate or extreme problems, while 39% had some or extreme problems in the dimension anxiety/depression. The sub-scores of emPHasis-10 showed the most problems in sub-score 6 (breathlessness in walking up a flight of stairs), with a median of 3 (1–4) points, and in sub-score 5 (having lots of energy), with a median of 3 (2–4) points. Least problems in emPHasis-10 were found in sub-score 2 (interrupting conversations due to breathlessness), with a median of 1 (0–2) points, and sub-score 7 (confidence in public places), with a median of 1 (0–3) points. In EQ-5D-3L, least problems were found in the dimension self-care, with 70% of the patients stating no problems.

Comparing the QoL for employed vs. unemployed patients at study visit, the EQ-5D-3L score was 9 (8–10) vs. 6 (5–8) points ($p < 0.001$), EQ-VAS was 7.5 (5–8.5) vs. 4.5 (3–6) points ($p < 0.001$), and emphasis-10 was 15 (8–24) vs. 21 (14–29) points ($p = 0.001$), respectively. In the EQ-5D-3L dimension mobility, 24% of employed patients had no problems vs. 71% of unemployed

patients ($p < 0.001$). In the dimension anxiety/depression, 23% of employed patients stated problems, while 49% of patients who were not employed had problems in this dimension ($p < 0.001$).

Impact on Employment Status

This analysis included 162 patients eligible of being employed (age at study visit, < 67 years). Univariate models were calculated using the following predictors of being employed: education (low, moderate, and high), female sex, smoking (never a smoker, former smoker, and active smoker), flight of stairs, WHO FC, PFT (FEV₁ and DLCO), Audit-C, ESC/ERS risk score, EQ-VAS, EQ-5D-3L, emPHasis-10, and degree of disability on the odds of being employed. The significant covariates education (low, moderate, and high), formerly smoking, flight of stairs, WHO FC, 6MWD per 50-m increase (22), PFT (FEV₁ and DLCO), Audit-C, ESC/ERS-Risk, NT-proBNP as ≥ 300 ng/L (23), EQ-VAS, EQ-5D-3L, and emPHasis-10 were included in the multivariate regression model. Moderate (vs. low) education had an OR of 3.6 (1.2–11.3), $p = 0.025$ being employed, and high education had an OR of 5.6 (1.3–23.4), $p = 0.019$ of being employed. In addition, 6MWD was associated with being employed, with an OR of 1.2 (1.0–1.3), $p = 0.042$ per 50-m increase (see **Table 3**).

DISCUSSION

This present study examined the impact of PAH on employment status and quality of life. We demonstrated (i) the influence of educational status and 6MWD on employment status, (ii) good work productivity in long-term-employed patients, and (iii) a considerable loss of employment with associated limited social participation and subsequent unfavorable QoL in patients with PAH patients.

In the present study, we demonstrated the impact of educational status and 6MWD on employment status in patients with PAH. Long-term-employed patients had good work productivity, whereas impaired work productivity and employment rates were associated with limited social participation and, subsequently, worse QoL.

Overall, the employment rates in our study were in line with a study from Matura et al. (10), whereas in subgroup analyses they revealed higher rates of retirement due to disability compared to our study. These differences may be partly related to disparities in the US and German healthcare systems. In Germany, the legal retirement age is stepwise increasing from 65 to 67 years. In addition, after a certain age-adjusted time on disability leave, people enter retirement plans. In this study, the rate of retirement due to disability in patients with PAH was substantially higher than in the general German population, which is not an unexpected finding in a debilitating disease.

Factors Influencing Employment

To our knowledge, the impact of PAH on employment and its influencing factors have not been investigated in Germany to date. Our study found that, compared to patients with lower education, patients with non-academic education (moderate education category) had a 3.6-fold higher chance of being employed, whereas patients with academic education (high

TABLE 3 | Influencing factors on employment in pulmonary arterial hypertension patients.

Parameter	Univariate		Multivariate	
	OR (95% CI)	<i>p</i>	OR (95% CI)	<i>p</i>
Education				
Low	1 (reference)	<0.001	1 (reference)	0.042
Moderate	3.7 (1.6–8.9)	0.003	3.6 (1.2–11.3)	0.025
High	10.4 (3.4–32)	<0.001	5.6 (1.3–23.4)	0.019
Female sex	0.8 (0.4–1.5)	0.481		
Age at diagnosis per 5 years increase	0.8 (0.7–0.9)	<0.001		
Smoking				
Never a smoker	1 (reference)			
Former smoker	2.6 (1.4–4.9)	0.004		
Active smoker	1.4 (0.6–3.3)	0.385		
Stair climbing (flights of stairs)	2.0 (1.4–2.8)	<0.001		
WHO FC	0.4 (0.3–0.6)	<0.001		
6MWD _{50min} increase	1.5 (1.2–1.7)	<0.001	1.2 (1.0–1.3)	0.042
Number of PH medications	1.1 (0.7–1.6)	0.816		
FEV ₁ %	1.0 (1.0–1.0)	0.016		
D _{LCO} %	1.0 (1.0–1.1)	<0.001		
ESC/ERS risk score	0.4 (0.2–0.6)	<0.001		
NT-proBNP, ≥300 ng/L	0.74 (0.37–1.48)	0.394		
EQ-VAS	1.3 (1.1–1.4)	0.001		
EQ-5D-3L	2.3 (1.7–3.0)	<0.001		
Mobility dimension	8.0 (3.9–16.7)	<0.001		
Self-care dimension	6.1 (2.4–15.4)	<0.001		
Usual activities dimension	8.1 (3.9–16.7)	<0.001		
Pain/discomfort dimension	6.9 (2.9–16.3)	<0.001		
Anxiety/depression dimension	2.4 (1.3–4.5)	0.007		
emPHasis-10	1.2 (1.0–1.4)	0.022		
Degree of disablement	1.2 (0.6–2.2)	0.579		

OR, odds ratio; CI, confidence interval; WHO-FC, World Health Organization functional class; FEV₁, forced expiratory volume in 1 s; DLCO, diffusing capacity of the lung for carbon monoxide; AUDIT-C, Alcohol Use Disorder Identification Test; ESC, European Society of Cardiology; ERS, European Respiratory Society; NT-proBNP, N-terminal fragment of probrain natriuretic peptide; 6MWD, 6-min walk distance; VAS, Visual Analogue Scale.

education category) had a 5.6-fold chance of being employed. This might be explained by the association of physical labor and lower education. Accordingly, highly educated individuals in white-collar jobs are less likely to experience manual labor (7), and this might contribute to a higher likelihood of employment for PAH patients with a higher educational status despite the burden of the disease. However, we cannot rule out that education might have an impact on employment itself, and further studies are needed to answer this question.

The severity of PAH related to physical impairment is, in part, described by 6MWD (24, 25). In our study, we found that a higher 6MWD was associated with employment status. Inversely, we can conclude that physical impairment is a major risk factor for unemployment. No other disease severity parameter was included in the multivariate model, and we presume that this was due to the multicollinearity of disease severity parameters (WHO FC, NT-proBNP, and ESC/ERS risk status).

Matura et al. demonstrated that education and physical status influence the QoL in PAH (10). In our study, we assessed associations of employment using education and QoL as

independent factors. In the univariate analysis, a higher QoL was associated with employment, which is in line with the findings of Matura et al. Furthermore, Helgeson et al. found in a study regarding the psychosocial and financial burden of therapy in the USA that 53% of initially working patients were no longer employed (26). Compared to the 61% loss in full- or part-time employment in our study, the differences might be explained by the different social security systems in the US and Germany.

Cascino et al. revealed associations between socioeconomic status and the perceived need for exercise rehabilitation in patients with PAH (27). Patients with a lower socioeconomic status had a significant lack of perceived need for rehabilitation, were less informed about the existence of exercise therapy, and preferred to take care of their health alone. We acknowledge the need to explore interventions to promote referral especially among low-educational-status patients to improve their exercise capacity as we see such a clear impact on employment.

In our study, there were strong associations between QoL, education, employment status, and physical condition. Furthermore, we showed that the employed patients had a

significantly better QoL in EQ-5D-3L, EQ-VAS, and emphasis-10 in contrast to unemployed patients. Olsson et al. described a high prevalence of mental disorders in 38% of PAH patients, with a negative impact on QoL (28). We showed similar results with 39% of PAH patients having an impaired EQ-5D-3L dimension anxiety/depression. Undoubtedly, PAH has a direct impact on physical impairment and, *via* this pathway, on mental disorders like anxiety or depression, resulting in reduced QoL, employment rate, and work productivity in this patient group.

PAH remains a partly “invisible” disease as Kingman et al. described the perspective of patients to feelings of insecurity and isolation (29). This was mainly driven by the lack of understanding of the disease and symptoms among family, friends, and the general public. Kingsman et al. found that different coping strategies played a major role. Patients who sought solutions tried to maintain a social life. With more independence, they were, in many cases, able to work at least part-time. Furthermore, these authors proposed a greater psychological impact of PH on the QoL of patients, emphasizing the importance of healthcare providers and physicians to educate the patients on disease progression, symptoms, and effects on QoL. In our work, we did not assess the coping strategy of patients, but the impact of the coping strategies should be addressed in further research. In this and previous studies (Olsson et al.), we did see associations between QoL and mental health, leading us to believe that encouraging participation in support groups, PH associations, and counseling should be an aspect addressed in the healthcare provider and patient relationship.

Limitations

Our study had several limitations, including the cross-sectional design and the participation of two study sites. Prospective studies with a structured follow-up are needed to assess the impact of the disease over time. Paper-based questionnaires led to missing data in some cases. Data on physical/manual labor or job descriptions, to assess the assumed surrogate effect of educational status, were missing. Although we assessed mental disorders as part of the EQ-5D-3L, future research should consider utilizing dedicated mental health questionnaires, e.g., the Hospital Anxiety and Depression Scale, as suggested by Olsson et al. (28). The strengths of our study were the high number of surveyed patients and the important but understudied issue of social participation of PAH patients.

CONCLUSION

Employment and work productivity in patients with PAH were impaired, and there was a considerable loss of employment during the course of the disease. Education and 6MWD were the relevant factors associated with employment in patients

with PAH. The employed patients had a significantly better QoL than the unemployed patients. Patients in physical or manual labor were more likely to be unemployed. Loss of employment had a major impact on the life and mental health of patients. Re-education strategies are needed for patients who are eligible to work and should be an aspect of empowerment from their treating physicians. Employment can provide patients with more independence and thus a more favorable QoL and social participation.

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 Ethikkommission der Medizinischen Hochschule Hannover. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

JF was responsible for study design, implementation of the study, data collection, statistical analysis, data interpretation, and drafting the manuscript. DHP was responsible for implementation of the study, data collection, statistical analysis, data interpretation, and drafting the manuscript. TvL was responsible for study design, data interpretation, and critically revising the manuscript. HGa, MR, and HGH were responsible for implementation of the study, data collection, and revising the manuscript. JK was responsible for data interpretation and revising the manuscript. MH was responsible for study design, implementation of the study, data interpretation, and critically revising the manuscript. KO was responsible for study design, implementation of the study, data interpretation, and critically revising the manuscript. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: <https://www.frontiersin.org/articles/10.3389/fpsy.2021.781532/full#supplementary-material>

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Childhood Trauma in Patients With PAH—Prevalence, Impact on QoL, and Mental Health—A Preliminary Report

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Background/Objective: Child maltreatment is associated with increased risk of psychological consequences, contributes to morbidity and has long lasting effects on mental health and quality of life. Child maltreatment has not been assessed in patients with pulmonary arterial hypertension (PAH). We examined the prevalence of child maltreatment and determined their impact on disease severity in patients with PAH.

Methods: A cross-sectional observational multicenter study at two PH centers in Germany was conducted. Patients with a confirmed diagnosis of PAH were given a self-administered questionnaire. Child maltreatment using the Childhood Trauma Questionnaire (CTQ), quality of life (QoL), anxiety, depression, and lifestyle factors were assessed and enhanced by clinical parameters 6-min walk distance (6MWD), WHO functional class (WHO FC), and serum levels of N-terminal fragment of pro-brain natriuretic peptide (NT-proBNP). Prevalence rates of child maltreatment were compared to the general population and impact of child maltreatment on disease severity was calculated by logistic regression analysis.

Results: Two-hundred and seventeen patients, 71% female and a median age of 56 years were enrolled in this study. Patients with PAH had higher rates of emotional abuse and lower rates of physical neglect compared to the German population while rates of emotional neglect, physical abuse, and sexual abuse did not differ between patients and German population. Patients with any form of child maltreatment were more likely to be active smokers, had a worse QoL and more anxiety or depression. Moderate associations between child maltreatment, mental health, QoL, lifestyle factors and clinical parameters could be observed. Logistic regression analysis showed a significant impact of CTQ-total score on disease severity with an OR of 1.022 (95%-CI: 1.001–1.042, $p = 0.035$).

Conclusion: We found a higher rate of child maltreatment in patients with PAH in comparison to the German population. Correlations suggest moderate associations

between CTQ-scores and mental health as well as QoL. Child maltreatment had significant impact on disease severity. However, effects were moderate. We conclude that child maltreatment has effects on mental health and quality of life in patients with PAH and may have limited effect on disease severity.

Keywords: pulmonary arterial hypertension, child maltreatment, mental health, quality of life, prevalence, pulmonary hypertension

INTRODUCTION

Pulmonary arterial hypertension (PAH) is progressive pulmonary vascular disease. Characterized by remodeling of pulmonary vasculature it leads to increased pulmonary vascular resistance (1, 2). Patients with PAH are experiencing symptoms such as dyspnea on exertion, fatigue and with disease progression potentially clinical signs of heart failure. These debilitating symptoms impair physical activities and quality of life (QoL) (3, 4). While the disease remains fatal as none of the currently available drugs are curative, improvement of therapeutic options, clinical outcomes and life expectancy have put questions of patient's quality of life, mental health, emotional, and social burden are on the forefront of current research (5–8). Data on prevalence of psychiatric disorders in PAH patients (9, 10) is still scarce. Olsson et al. demonstrated a higher prevalence of anxiety and depression disorders with negative impact on QoL in PAH compared to levels in the German population (11, 12). Child maltreatment may pose an additional risk factor associated with lower QoL and mental disorders in patients with PAH. Several studies have identified child maltreatment as an important contributing factor to the incidence and severity of depressive disorders (13). Child maltreatment is defined as the abuse and neglect against a child under the age of 18 by a parent or other caregivers. It includes all types of physical and/or emotional ill-treatment, sexual abuse and neglect which results in actual or potential harm to the child's health, survival, development, or dignity in the context of a relationship of responsibility, trust, or power (14). It has been associated with poorer overall health, greater physical, and emotional functional disability and higher degree of health risk behavior. Patients with multiple types of maltreatment showed greatest worsening of self-reported health symptoms (15). Child maltreatment is associated with various diseases such as the development of cardiovascular diseases, type 2 diabetes or chronic obstructive pulmonary diseases leading to higher mortality (16–18). Proskynitopoulos et al. (19) found increased prevalence of child maltreatment in adults with congenital heart disease compared to the general German population. Higher total Child trauma questionnaire (CTQ) scores correlated with

decreased quality of life, higher rates of anxiety, and depression and contributed to the prediction of New York Heart Association (NYHA) scores (19). The present study aimed to assess the (i) prevalence of child maltreatment in patients with PAH and (ii) to compare this with the prevalence in the German general public as well as (iii) to assess the impact, differences and associations of child maltreatment on disease severity, lifestyle factors, mental health, and QoL in patients with PAH.

METHODS

This cross-sectional observational multicentre study included patients with a confirmed diagnosis of PAH at two participating PH referral centers (Hannover Medical School and University of Giessen and Marburg, both in Germany). The study concept was developed in cooperation with patient organizations as suggested during the latest Pulmonary Hypertension World Symposium in 2018 (20). All patients gave written informed consent. The study was approved by local institutional review boards (Nr. 8540_BO_K_2019 for Hannover and Nr. 21119 for Giessen and Marburg). Patients were contacted between September 2019 and March 2020. This study was conducted by a self-administrated questionnaire.

Patient Setting and Clinical Parameters

Patients were selected based on diagnosis of PAH according to current criteria (1) and age ≥ 18 years. Assessment included hemodynamics from right heart catheterization at time of diagnosis, 6-minute walk distance (6MWD), WHO functional class (FC), and serum levels of N-terminal fragment of pro-brain natriuretic peptide (NT-proBNP). Risk assessment for our cohort was based on three variables FC, 6MWD, and BNP/NT-proBNP as previously described (21, 22). Each variable was graded with a number as low risk (1), intermediate risk (2), and high risk (3). The average risk was calculated by dividing the sum of the grades by the number of available variables and rounding to the next integer (23).

Assessment of Child Maltreatment

Child maltreatment was assessed using the German version of the Childhood Trauma Questionnaire CTQ (24). The CTQ consists of a 28-item self-rating scale divided in five subscales inquiring five areas: emotional abuse, physical abuse, sexual abuse, emotional neglect, and physical neglect. The items are rated from 1 (never true) to 5 (very often true). The subscale scores range from 5 to 25 with an overall score from 25 to 125 points. Several studies have supported the reliability and validity of reported childhood trauma obtained with this instrument,

Abbreviations: 6MWD, 6-minute walk distance; BNP, brain natriuretic peptide; CTQ, child trauma questionnaire; FC, World Health Organization functional class; HADS, Hospital Anxiety and Depression Scale; NT-proBNP, N-terminal fragment of pro-brain natriuretic peptide; NYHA, New York Heart Association; PAH, Pulmonary arterial hypertension; PEPPAH, Psychische Einschränkungen bei Patienten mit pulmonal arterieller Hypertonie (Prevalence of mental disorders and impact on quality of life in patients with pulmonary arterial hypertension); QoL, quality of life; SD, Standard Deviation.

discriminant validity with structured trauma interviews and corroboration with independent data (24). Thresholds presented by Walker et al. (15) were used to construct groups with either form of maltreatment or no maltreatment. Child maltreatment was classified when threshold scores for emotional abuse (10), emotional neglect (15), physical abuse (8), physical neglect (8), and sexual abuse (8) were met. The CTQ-derived prevalence rates and mean-values of child maltreatment were compared to the German general population described by Iffland et al. (25).

Assessment of Symptoms of Anxiety and Depression and Quality of Life

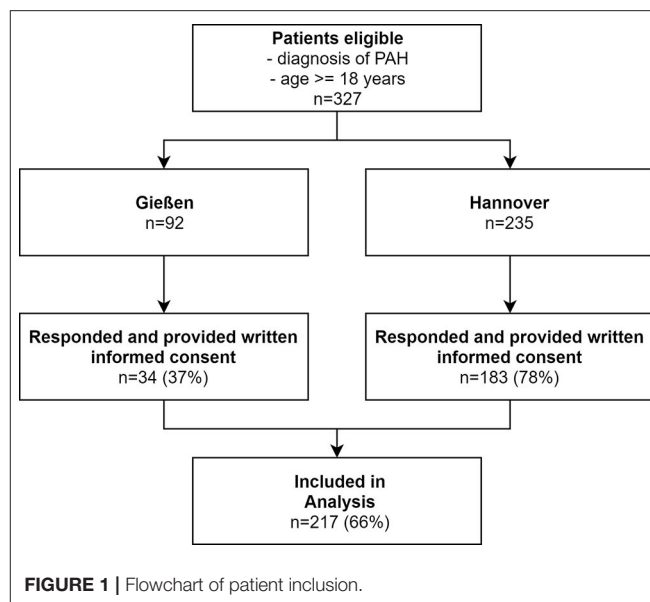
Symptoms of anxiety and depression were assessed with participants completing the Hospital Anxiety and Depression Scale (HADS) (26). The HADS questionnaire is divided into subscales for anxiety (HADS-A) and depression (HADS-D), each containing seven questions for a maximum of 21 points per subscale. The higher score indicating a more severe anxiety or depression. Zigmond et al. (26) proposed a score >11 per subscale to be associated with significant anxiety or depression. A cut-off score of 8 or above for both HADS-A and HADS-D was validated, showing probable signs of anxiety or depression (27, 28). The World Health Organization Quality of Life [WHO-QoL-BREF (29)] was used to assess quality of life.

Statistical Analysis

IBM SPSS Statistics (version 28.0, IBM Corp., Armonk, New York) and Stata 13.0 (State Corp LP, College Station, Texas, USA) statistical software programs were used for statistical analysis. Continuous parameters are presented as median and interquartile range (Q_{25} - Q_{75}) or as mean and standard deviation (SD). Categorical variables are presented as number (n) and percent (%). Comparisons of continuous parameters were conducted using t -test or Mann-Whitney U -test (if not normally distributed or ordinal scaled) and comparison of categorical parameters by using Chi-square-test or Fisher's exact test, unless indicated otherwise. Correlations of continuous and ordinal parameters were assessed using Pearson correlation coefficient. Parameters were CTQ-scores, lifestyle factors (exercise, drinks per week, and smoking intensity) and clinical parameters such as BMI, HADS-scores, QoL, 6MWD, and WHO FC. Logistic regression analysis was conducted to assess impact of CTQ-score on clinical outcome parameter WHO FC as surrogate for disease severity (WHO FC I and II vs. WHO FC III and IV was used as binary outcome). Further univariate logistic regression was conducted to assess impact of child maltreatment (any positive CTQ-subscore) on anxiety or depression disorder. Nagelkerke's R^2 was determined to assess model quality. All tests were two-sided, $p < 0.05$ were considered statistically significant. P -values of multiple correlations were adjusted using the Benjamini-Hochberg-procedure.

RESULTS

This patient cohort was previously described in the PEPPAH-study (12). A total of 327 patients were approached in this



study. Two hundred and seventeen patients (66%) agreed to participate and returned the questionnaires (Figure 1). Patient characteristics are shown in Table 1. The majority of patients were female ($n = 155$, 71%); median age was 56 (49-67) years. All patients were treated with PAH medications, most of them (47%) with dual combination therapy. Nearly all patients (96%) fell in the low or intermediate ERS risk score category. Patients with any form of child maltreatment were more likely to be active smokers, had a worse overall QoL and more anxiety and depression. Trends could be observed in 6MWD with more than 30m difference in patients with or without any form of child maltreatment (Table 1). Disease severity indicated by ERS risk status, WHO FC and NTproBNP, hemodynamics at time of diagnosis, and PAH treatment did not differ between groups.

Prevalence of Child Maltreatment in Patients With PAH

In this study, child maltreatment with a least one subgroup above threshold was detected in fifty percent of the patients (Table 1). Emotional abuse and emotional neglect were about 2 times more frequent in patients with PAH than in the general population (Table 1; Figure 2). Patients with PAH had a significantly higher total CTQ score ($p < 0.001$), while physical neglect was more prevalent in the general German population (48.4 vs. 36.4%, $p = 0.041$) and physical abuse did not significantly differ between both groups (14.3 vs. 12.0%, $p = 0.458$). Sexual abuse was reported under 10% in both patients with PAH and the general population (Table 2).

Correlation of CTQ Subscores on Quality of Life, Mental Health, Lifestyle, and Clinical Parameters

Moderate associations between CTQ-scores, mental health, QoL, lifestyle factors, and clinical parameters could be observed (see

TABLE 1 | Patient characteristics.

	All patients <i>n</i> = 217	Patients with any CTQ positive subscore <i>n</i> = 108 (50%)	Patients without any CTQ positive subscore <i>n</i> = 109 (50%)	<i>p</i> -value of group comparison
Age—years	56 (49–67)	55 (41–65)	57 (45–66)	0.422
Sex—female (%)	155 (71%)	74 (69%)	81 (74%)	0.345
BMI (kg/m ²)	26 (23–31)	26 (23–31)	26 (23–31)	0.813
Time since PAH diagnosis (years)	6 (3–11)	6 (2–11)	7 (4–13)	0.062
Diagnosis—<i>n</i> (%)				
- 1.1 IPAH	122 (56%)	66 (61%)	56 (51%)	0.233 ^c
- 1.2 HPAH	25 (12%)	13 (12%)	12 (11%)	
- 1.4 Associated PAH	70 (32%)	29 (27%)	41 (38%)	
WHO FC				
- I, <i>n</i> (%)	20 (9%)	7 (7%)	13 (12%)	0.439 ^c
- II, <i>n</i> (%)	92 (43%)	45 (42%)	47 (44%)	
- III, <i>n</i> (%)	93 (43%)	51 (47%)	42 (39%)	
- IV, <i>n</i> (%)	10 (5%)	5 (5%)	5 (5%)	
ESC/ERS risk status—<i>n</i> (%)				
- Low	107 (50%)	52 (49%)	55 (52%)	0.799 ^c
- Intermediate	97 (46%)	51 (53%)	46 (47%)	
- High	9 (4%)	4 (44%)	5 (56%)	
6MWD	439 (353–521)	423 (339–502)	454 (371–539)	0.061
NT-proBNP (ng/l), <i>n</i> = 192	184 (88–517)	169 (74–419)	207 (104–586)	0.961
DLCO (% pred.), <i>n</i> = 138	62 (47–74)	64 (42–73)	61 (48–74)	0.844
paO ₂ , mmHg	67 (60–75)	67 (60–76)	67 (61–75)	0.788
Hemodynamics at diagnosis				
- mPAP (mmHg)	48 (41–57)	48 (41–58)	49 (41–58)	0.651
- PAWP (mmHg)	9 (6–12)	9 (6–12)	9 (6–12)	0.794
- CI (l/min/m ²)	2.4 (2.0–2.9)	2.4 (2.0–3.0)	2.4 (2.0–2.7)	0.284
- PVR (dyn·s·cm ⁻⁵)	707 (501–947)	689 (505–951)	752 (498–927)	0.914
PH-therapy—<i>n</i> (%)				
- Monotherapy	44 (20%)	21 (19%)	23 (21%)	0.673 ^c
- Double combination therapy	102 (47%)	54 (50%)	48 (44%)	
- Triple combination therapy	71 (33%)	33 (31%)	38 (35%)	
Smoking status				
- Active, <i>n</i> (%)	24 (11%)	17 (16%)	7 (6%)	0.021 ^c
- Former, <i>n</i> (%)	31 (14%)	19 (18%)	12 (11%)	
- Never, <i>n</i> (%)	162 (75%)	72 (67%)	90 (83%)	
- Packyears	14 (5–25)	15 (6–23)	9 (4–33)	0.495
Alcohol drinking (drinks per week)	0.8 ± 2.0	0.9 ± 2.5	0.8 ± 1.1	0.772 ^a
Exercise score (points)	3 (2–4)	3 (2–3)	3 (2–4)	0.906 ^b
HADS-A (points)	6 (2–9)	7 (3–10)	5 (2–9)	0.034
HADS-D (points)	5 (2–8)	6 (3–9)	4 (2–7)	0.002
QoL-overall (points)	50 (38–75)	50 (38–63)	63 (44–75)	0.026
QoL-psych (points)	71 (58–79)	63 (50–79)	71 (63–83)	0.020
QoL-physical (points)	57 (45–75)	57 (43–71)	64 (50–75)	<0.001
QoL-social (points)	67 (58–83)	67 (58–83)	67 (50–75)	0.009
QoL-environment (points)	78 (69–88)	75 (63–84)	78 (70–88)	0.012

Continuous variables are stated as median and interquartile ranges (IQR) and categorical variables are stated as *n* and percent (%), unless indicated otherwise. All *p*-values were derived using *t*-test, unless indicated otherwise.

^aMean and SD because of distribution of the data.

^bNon-parametric Mann–Whitney *U*-test because of ordinal scale of the variable.

^cChi²-test because of the categorical scale of the variable.

BMI, body mass index; QoL, quality of life; HADS-A, Hospital Anxiety and Depression Scale—anxiety; HADS-D, Hospital Anxiety and Depression Scale—Depression; I/HPAH, idiopathic or heritable pulmonary arterial hypertension; WHO FC, World Health Organization Functional Class; 6MWD, 6-min walking distance; NT-proBNP, N-terminal fragment of pro-brain natriuretic peptide; DLCO, diffusion capacity of the lung for carbon monoxide; paO₂, mmHg, arterial pO₂; mPAP, mean pulmonary arterial pressure; PAWP, pulmonary artery wedge pressure; CI, cardiac index; PVR, pulmonary vascular resistance; IQR, interquartile range. Statistically significant values as bold.

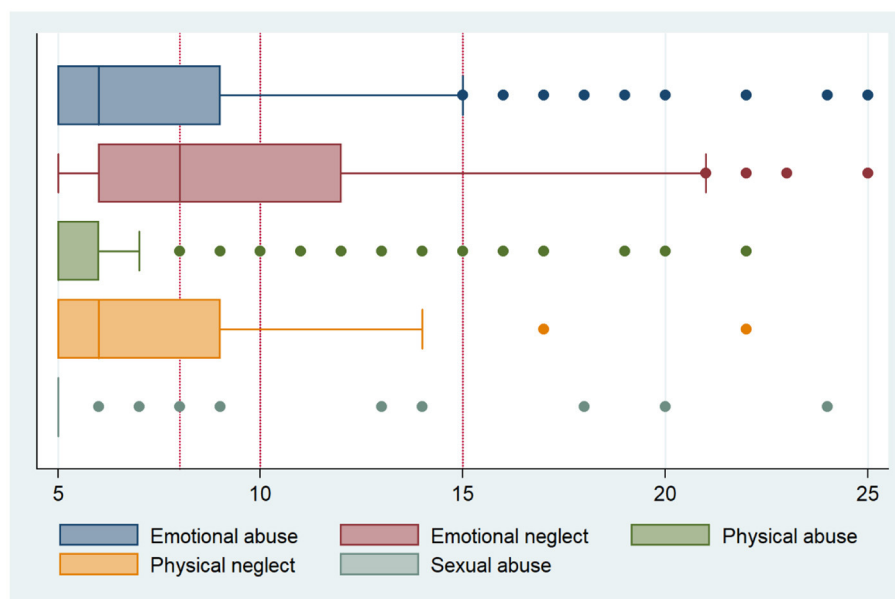


FIGURE 2 | Subscores of childhood trauma questionnaire of patients with pulmonary arterial hypertension.

TABLE 2 | Scores and prevalence of child maltreatment in patients with PAH compared to German population.

Item	PAH <i>n</i> = 217	German population (25) <i>n</i> = 2,500	<i>p</i>
Comparison of CTQ-scores, Mean (SD)			
- CTQ-total score	41.84 ± 14.43	35.99 ± 10.48	<0.001
- CTQ-emotional abuse	7.68 ± 4.00	6.51 ± 2.60	<0.001
- CTQ-emotional neglect	9.58 ± 4.88	10.09 ± 4.23	0.093
- CTQ-physical abuse	6.19 ± 2.83	5.88 ± 2.17	0.049
- CTQ-physical neglect	7.18 ± 2.75	8.15 ± 3.02	<0.001
- CTQ-sexual abuse	5.54 ± 2.24	5.45 ± 1.66	0.458
Comparison of CTQ-categories, <i>n</i> (%)			
- CTQ-emotional abuse	43 (19.8%)	254 (10.2%)	<0.001
- CTQ-emotional neglect	42 (19.4%)	348 (13.9%)	0.078
- CTQ-physical abuse	31 (14.3%)	301 (12.0%)	0.458
- CTQ-physical neglect	79 (36.4%)	1,210 (48.4%)	0.041
- CTQ-sexual abuse	14 (6.5%)	156 (6.2%)	0.920

Continuous variables are stated as mean and standard deviation and categorical variables are stated as *n* and percent (%).

CTQ, childhood trauma questionnaire; PAH, pulmonary arterial hypertension; SD, standard deviation; Statistically significant values as bold.

Table 3). Higher CTQ emotional-, physical, or total scores were correlated with higher HADS depression and anxiety scores ($r = 0.201$ – 0.401 , $p < 0.001$) while being negatively correlated with QoL ($r = -0.200$ to -0.315 , $p < 0.001$). History of smoking and WHO FC were positively correlated with emotional and physical CTQ-scores ($r = 0.113$ – 0.216). Total CTQ-scores were negatively correlated to 6MWD ($r = -0.145$ to $r = -0.204$, $p < 0.005$) whereas exercise and drinks per week were not significantly related. There were no significant association between CTQ-sexual abuse and any evaluated parameter.

Impact of CTQ on Disease Severity and Mental Health

Univariate logistic regression analysis on disease severity (WHO FC I+II vs. WHO FC III+IV) revealed a significant impact of CTQ-total score with an OR of 1.022 (95%-CI: 1.001–1.042, $p = 0.035$) while the model describes 2.9% of the independent variable. Further univariate regression analysis showed that patients with reported emotional neglect had a 6.8% higher chance (95%-CI: 1.009–1.131, $p = 0.023$) of being in WHO FC III or IV per CTQ point increase. Model accuracy was 3.3%. Impact of any positive CTQ-subscore on anxiety had an OR of 1.678

TABLE 3 | Correlations of CTQ-scores in PAH with HADS, QoL, Lifestyle and 6MWD, and WHO FC.

	HADS-D	HADS-A	QoL	BMI	Exercise	Drinks	Smoking	WHO FC	6MWD
CTQ-total score	0.368**	0.351**	-0.315**	0.158*	-0.068	-0.071	0.188*	0.186*	-0.192*
CTQ-emotional abuse	0.388**	0.401**	-0.302**	0.126	-0.039	-0.027	0.181**	0.125	-0.174*
CTQ-emotional neglect	0.316**	0.255**	-0.308**	0.121	-0.056	-0.082	0.113	0.210*	-0.145*
CTQ-physical abuse	0.262**	0.268**	-0.200*	0.139*	-0.081	-0.066	0.157*	0.118*	-0.146*
CTQ-physical neglect	0.251**	0.204*	-0.269*	0.131	-0.041	-0.088	0.216*	0.192*	-0.204*
CTQ-sexual abuse	0.112	0.106	-0.056	0.123	-0.033	0.001	0.021	0.049	-0.097

Pearson correlation coefficient. Statistically significant values are marked using asterisk, ** $p < 0.001$; * $p < 0.05$.

BMI, body mass index; CTQ, childhood trauma questionnaire; QoL, quality of life; HADS-A, Hospital Anxiety and Depression Scale—anxiety; HADS-D, Hospital Anxiety and Depression Scale—Depression; PAH, pulmonary arterial hypertension; WHO FC, World Health Organization Functional Class; 6MWD, 6-min walking distance.

(95%-CI: 0.788–3.574, $p = 0.179$) while impact on depression showed an OR of 2.761 (95%-CI: 1.369–5.209, $p = 0.004$) while model accuracy was 1.5 and 6%, respectively.

DISCUSSION

To the best of our knowledge this is the first study to assess the prevalence of child maltreatment in patients with PAH. Patients with PAH had a higher overall CTQ-score with fifty percent of our patients exceeding the threshold for any subscore of child maltreatment. In these patients, moderate associations between CTQ-scores and QoL, anxiety and depression, WHO FC, and 6MWD could be detected. Higher prevalence of CTQ-scores were mainly driven by higher subscores in emotional abuse or physical abuse. This is in line with previous observations from patients with congenital heart disease (19). While absolute scores were higher in patients with PAH, both groups reported only moderately elevated scores on the scale of 5–25 points per subscore (as seen in **Figure 2**). Inversely physical neglect was comparatively more frequent in the general population than in patients with PAH. It has been discussed that elderly who experienced privation of (post-)war year were more likely to report physical neglect (25). With comparatively weak psychometric properties and weak internal consistency, comparisons for the physical neglect subscale discussion on impact can only be held cautiously.

Several severe long-term consequences of child maltreatment have been studied and suggested. Ranging from mentioned physical health, psychological to behavioral, and societal consequences. Most children who experienced child maltreatment are often affected by many other adversities such as domestic violence, poverty, and parental substance abuse (30).

Child maltreatment poses a higher risk on the development of mental disorders such as depression (31–34). Olsson et al. have recently demonstrated a higher prevalence of mental disorders in patients with PAH. Our findings indicate a correlation between higher CTQ scores and higher HADS depression and anxiety scores. Gamble et al. (35) in as early as 2006 had described the correlation between childhood trauma and severity of anxiety and depression. Similarly, we demonstrated impact of child maltreatment on the diagnosis of depression, which is in line

with these previous studies. Several studies examining impact of child maltreatment on disease outcomes saw attenuation of the relationship between child maltreatment and disease when adjusting for mental disorder (36). Our data supports existing evidence in indicating that child maltreatment is a risk factor for mental disorders which themselves may be mediators for disease severity of PAH (36).

QoL contributes to the evaluation of emerging PAH treatments as well as disease course. QoL in patients with PAH is severely impaired by clinical symptoms as well as emotional domains (20, 37). Mathai et al. (38) have found QoL to be a predictor of outcomes in PAH and thus a target for therapeutic interventions. Child maltreatment in patients with PAH correlate with worse QoL. This is in line previous studies such as Corso et al. who demonstrated significant and sustained losses of QoL in adulthood of persons who experienced child maltreatment (39, 40).

Several studies have demonstrated association between child maltreatment and cardiometabolic diseases such as systemic hypertension, ischemic heart disease, and chronic heart disease (41, 42). Many authors examined child maltreatment as a composite measure of adversity and reported a dose-response relationship between number of childhood adversities and heightened risk for cardiometabolic diseases. Overall, CTQ scores were associated with disease severity measured by WHO FC. In a subscore analysis of our study, we found that patients with higher scores in emotional neglect had a significantly higher chance of being in a higher WHO FC per CTQ point increase. While this impact might suggest negative influence on disease course, morbidity, and mortality model accuracy is comparatively low. Clinical signs of right heart failure, 6MWD, NT-proBNP/BNP, and WHO FC are strong indicators of disease severity and risk status in patients with PAH (23). Arguably these somatic factors play a more prominent role on disease severity with a minor role of child maltreatment and by association mental disorders.

Limitations

Our paper has strength and limitations. Data for childhood maltreatment, mental health and QoL were derived using a self-administered, paper-based questionnaire. Reliable measurements of prevalence and severity of child maltreatment have yet relied

on self-reports, showing discrepancies of rates compared to reports of child-protection agencies (43, 44). Median global prevalence rates differ substantially by maltreatment type, gender and by continent with varying number of studies and available data (45). Only two German PH-centers were involved in this study which might cause selection bias. This study was carried out between September 2019 and March 2020. In January, the Corona virus pandemic hit Germany and this study didn't control for any possible impact on mental disease during this time. Of note, Park et al. (46) have studied effects on first waves of corona virus pandemic on a subsample of this cohort and found minor changes in mental health due to the corona virus pandemic. However, a strength is relatively large sample size of PAH patients given that PAH is a rare disease as both participating centers are large university-based tertiary-level referral centers.

CONCLUSION

In the present study, child maltreatment, in particular, subscores for emotional abuse and physical abuse was more prevalent in patients with PAH than in the general population. The presence of child maltreatment was associated with a higher likelihood of anxiety and depression and reduction in QoL. Child maltreatment in patients with PAH might play a role in disease severity. With wide ranges of long-term consequences of child maltreatment, screening for a history of child maltreatment can help physicians in assessment of patients' needs and treatment options. This should be taken into consideration in addition to more widely acknowledged impact of mental disorders and QoL on PAH. Psychosocial interventions as a treatment approach have been proven effective in patients with a history of child maltreatment (47–49). Integrating past experiences and psychological problems in the care and treatment of patients with PAH is recommended. The lasting consequences of child maltreatment warrant further investigation.

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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 Hannover Medical School and University of Giessen and Marburg. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

DHP was responsible for study design, implementation of the study, data collection, data interpretation, and drafting the manuscript. TM was responsible for data collection and revising the manuscript. KK was responsible for study design, data interpretation, and revising the manuscript. JK was responsible for data interpretation and revising the manuscript. MR, HG, and HAG were responsible for implementation of the study and critically revising the manuscript. MH was responsible for implementation of the study, data interpretation, and critically revising the manuscript. KO was responsible for study design, implementation of the study, data interpretation, and critically revising the manuscript. JF was responsible for study design, implementation of the study, data collection, statistical analysis, data interpretation, and drafting the manuscript. All authors contributed to the article and approved the submitted version.

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Child and Parent Physical Activity, Sleep, and Screen Time During COVID-19 and Associations With Mental Health: Implications for Future Psycho-Cardiological Disease?

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The COVID-19 pandemic has afforded the opportunity for some to improve lifestyle behaviours, while for others it has presented key challenges. Adverse changes in global lifestyle behaviours, including physical activity, sleep, and screen time can affect proximal mental health and in turn distal cardiovascular outcomes. We investigated differences in physical activity, sleep, and screen time in parents and children during early stages of the COVID-19 pandemic in Australia compared to pre-COVID-19 national data; and estimated associations between these movement behaviours with parent and child mental health. Cross-sectional baseline data from the COVID-19 Pandemic Adjustment Study (CPAS; $N = 2,365$) were compared to nationally representative pre-pandemic data from the Longitudinal Study of Australian Children (LSAC; $N = 9,438$). Participants were parents of children aged ≤ 18 years, residing in Australia. Parents provided self-report measures of mental health, physical activity and sleep quality, and reported on child mental health, physical activity and screen time. Children in CPAS had significantly more sleep problems and more weekend screen time. Their parents had significantly poorer sleep quality, despite increased weekly physical activity. Children's sleep problems were significantly associated with increased mental health problems, after accounting for socioeconomic status, physical activity, and screen time. Poorer parent sleep quality and lower levels of physical activity were significantly associated with poorer mental

health. Monitoring this cohort over time will be important to examine whether changes in movement behaviour are enduring or naturally improve with the easing of restrictions; and whether these changes have lasting effects on either parent or child mental health, and in turn, future risk for CVD.

Keywords: psychiatry, physical activity, children, adults, depression, anxiety, sleep, screen time

INTRODUCTION

COVID-19, a disease caused by the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-Cov-2), was classified as a pandemic by the World Health Organization on March 11, 2020 (1). In an attempt to stop the spread of COVID-19, strict quarantine, lockdown, and social distancing measures were implemented around the world, including in Australia, where Federal and State governments introduced Stage three lockdown (2) in April 2020 to reduce the rate of infection. Measures to prevent the spread of COVID-19, such as home confinement, school closures, restriction on the gathering of groups of people, and the shutdown of community services and facilities (e.g., organised sports, playgrounds, pools, and gyms) are likely to have an impact on a number of important health promoting global movement behaviours [e.g., physical activity, screen time and sleep; (3, 4)]. These behaviours are closely related to both mental health and risk for cardiovascular disease (CVD). Given that the childhood origins of mental health disorders and CVD are increasingly recognised (5), and there are known links between depression, stress and risk for CVD (6–8), there is potential that adversity associated with the COVID-19 pandemic may have long-term effects on the development of psycho-cardiologic diseases. This is plausible due to the shared risk pathways that have been shown to link a range of mental health indicators (e.g., depression, psychosocial stress, lack of social support and negative emotions) with CVD, including both intermediary markers of CVD risk (9, 10) and established CVD [(11); for a review of shared pathways see (12)].

Emerging evidence on how COVID-19 related restrictions may be affecting people's physical activity, sleep quality and screen time has been mixed (13–16) but it is not difficult to see how such restrictions may have a negative impact across these domains. For example, the closure of parks, beaches and sports facilities, a lesser need for active transport as people are urged to stay home and increases in screen use related to working and schooling from home, are likely to reduce the time that children and parents spend in environments associated with physical activity. This may be offset at least in part by physical activity being one of a very small number of permitted activities. Similarly, increased time at home may disrupt normal routines, with increased access to screens and potential changes to bedtime routines. In addition, pre-pandemic research has shown that, on unstructured and non-school days (i.e., similar to COVID-19-related home confinement), children are less physically active and more sedentary (17), engage in more recreational screen time (18) and have less regularity in sleep patterns (19). To-date, there has been minimal evidence considering the impact of home

confinement on physical activity, sleep and screen time for both children and parents within households, meaning that the overall family burden of changes in movement related behaviours is not well-understood. A family systems perspective on the impact of COVID-19 on movement behaviours may be a novel and conceptual approach, particularly in relation to understanding mental health within families.

Decreased physical activity and increased sedentary behaviour may be a risk factor not only for more proximal indicators of mental health but in turn, for more distal risk of CVD among both children and their parents (20, 21). For example, poor sleep is closely linked with symptoms of depression and anxiety in children (22) as well as in adults (23, 24). Similarly, lower levels of physical activity and greater amounts of time spent in sedentary activities are linked to poorer mental health outcomes among children, including anxiety and depressive symptoms (25, 26) and irritability (27). A similar picture presents itself in adults, where reductions in physical activity are related to increases in mental health symptoms (28, 29) and a greater likelihood of a clinical diagnosis, such as major depressive disorder (30, 31). Furthermore, any negative change to movement behaviours, brought about by COVID-19 restrictions, may be further compounded by COVID-19 stressors, including educational (school disruption), environmental (e.g., loss of employment, housing) and biopsychosocial (e.g., COVID-19 diagnosis, loss of social support) stressors. Within families, these have the potential to directly impact child health through adverse impacts on parent health. Given that poor mental health is also a known risk factor for CVD, alongside these lifestyle risk factors, gaining a clear understanding of the mental health burden of the COVID-19 pandemic among families and its relationship to global movement behaviours can inform targeted public health efforts for effective prevention and/or intervention.

The aim of the current study was to investigate levels of physical activity, screen time, and sleep during the early stages of COVID-19 social restrictions in Australia, and compare it to pre-COVID-19 national data. Further, we sought to estimate the association between these movement behaviours and a range of mental health indicators among both parents and children. Specific aims were to:

- Compare levels of child screen time, sleep problems and regular bedtime routine during the early stages of the COVID-19 social restrictions to Australian pre-pandemic national data.
- Compare levels of parent sleep quality and physical activity during the early stages of the COVID-19 pandemic to Australian pre-pandemic national data.

- Investigate the associations between child physical activity, sleep and screen time with child indicators of mental health, including depression symptoms (in children aged 2–18 years), anxiety symptoms (in children aged 2–18 years) and irritability (in children aged 0–18 years), and whether these associations were moderated by COVID-19 related stressors.
- Investigate the association between parent physical activity and sleep quality with parent depression, anxiety, stress, emotion regulation and positive affect, and whether these associations were moderated by COVID related stressors.

METHODS

The COVID-19 Pandemic Adjustment Survey (CPAS)

This study uses cross-sectional baseline data from the COVID-19 Pandemic Adjustment Survey (CPAS) (32), which aims to investigate the mental health impacts of the COVID-19 crisis in a sample of Australian parents using regular (longitudinal) online surveys. Participants were recruited via paid and unpaid social media advertisements using a range of methods to increase the representativeness of the sample (e.g., targeting demographic factors/postcodes). Recruitment occurred from 8 to 28th April, 2020, which coincided with the Australian federal and state governments introducing increasingly strict social distancing measures to slow the rate of infection. Participants were 2,365 Australian parents. Parents were eligible to participate if they resided in Australia and were aged ≥ 18 years, English speaking and a current parent of a child aged 0–18 years. The current study was approved by the Deakin University Human Ethics Advisory Group (HEAG-H 52_2020).

The Longitudinal Study of Australian Children (LSAC)

As a means of pre-pandemic comparison, we drew on national data from the Longitudinal Study of Australian Children (LSAC), a nationally-representative prospective cohort study of Australian children and their families (33). Participating children were randomly selected in a two-stage cluster sampling design using Australian postcodes and the Medicare universal healthcare database (34). We used biennial parent-report data (99% mothers) from three waves of the Baby cohort ($N = 5,107$), covering child ages 0–1 (Wave 1, collected in 2004), 2–3, and 4–5 years; and from five waves of the Kindergarten cohort (4,656), covering child ages 6–7 (Wave 2, collected in 2006), 8–9, 10–11, 12–13, and 14–15 years.

Measures

Table 1 provides a summary of the socio-demographic, parent, child and COVID-19 risk measures from CPAS and LSAC used in the current analysis.

Population Weighting

Post-stratification weights in the CPAS dataset were derived to compensate for differences between the final sample and the national population of parents. Post-stratification weights for CPAS were produced through a raking approach (42), using six

demographic factors: (1) geographic location (major city, inner and outer regional areas, and remote areas); (2) child age groups (0–4, 5–9, 10–12, 13–14, and 15–18 years); (3) parent gender (male, female); (4) family structure (single parent, couple family); (5) parent education (did not complete high school, high school completion; and (6) pre-pandemic parent employment status (employed, unemployed). The CPAS dataset was weighted to be equivalent to a subpopulation of Australian adults (i.e., parents of a child 0–18 years), with an estimated total population size of 8.4 million parents. LSAC population weights were also applied in weighted analyses.

Statistical Analysis

Analyses were conducted in Stata version 16. Item level missing data in the CPAS study ranged from 0 to 8% on individual variables; and up to 29% in the LSAC study. Missing data were therefore replaced using multivariate multiple imputation by chained equations for each study separately. All variables from the final analytic models and weights were included in the multiple imputation model to create 50 imputed datasets. All reported results are from the multiply imputed datasets.

To address Aims 1 and 2, proportions and 95% confidence intervals were calculated for LSAC data using all available time-points for each measure. Two sets of CPAS estimates were calculated; firstly, for the full available sample; and secondly, for an age-matched subsample consistent with LSAC age ranges to allow comparison with the LSAC national data. LSAC estimates were averaged across available waves within each imputation model, and then combined across the Baby and Kindergarten cohorts using a meta-analysis process based on metaphor in R (43, 44). For CPAS and LSAC, both unweighted and weighted data are presented to ensure reported outcomes are as close to population representation as possible. However, given that our datasets varied from population statistics on several population indicators (see **Table 2**), we primarily focused on unweighted results. We conducted a series of independent samples *t*-tests to assess unweighted differences between samples/groups.

To address Aims 3 and 4, a series of unadjusted linear regression models, using unweighted CPAS data, were conducted to determine the association between movement behaviours and indicators of mental health in the CPAS sample. Next, adjusted models were conducted to assess the unique contribution of each movement behaviour to each indicator of mental health, while accounting for the contribution of the other concomitant variables in the model. In regression models assessing adult data, adjustments were made for age, gender, deprivation, education, Aboriginal and Torres Strait Islander Peoples status and language other than English (LOTE) spoken at home, and for data related to child factors, adjustments were made for child age, child gender, parent age, parent gender, partner status, deprivation, and parent education. Final adjusted models were derived by including concomitant variables where there was evidence for an unadjusted association with the outcome ($p < 0.1$). Interaction terms were added to assess whether COVID related stressors moderated relationships between the movement behaviours and mental health indicators.

TABLE 1 | Study measures.

Construct	Measure (items)	CPAS	LSAC
Demographics	Parent age, gender, country of birth, Aboriginal and Torres Strait Islander status, whether a language other than English was spoken at home, highest level of education, relationship status, whether they were living with their partner, number of children in the household, geographic location and whether they had a mental health or physical health condition. Demographic information prior to COVID-19 included employment and study status, household income, source of income and shortage of money. Parents also reported on their child's age, gender and whether their child had a neurodevelopmental condition (attention-deficit/hyperactivity disorder, autism spectrum disorder).	•	
COVID-19 psychological stressors	4 items adapted from the CoRoNaVirus Health Impact Survey (CRISIS) V0.1. (35). Two items asked about participants' feelings about the likelihood catching COVID-19, and COVID-19 being a serious health risk for the participant (both rated on a 7-point Likert scale ranging from 1 = Strongly Disagree to 7 = Strongly Agree) and two items asked about the extent to which they experience certain negative feelings (worry, fear) when thinking about their ability to deal with COVID-19 (both items rated on a 4-point scale from "not at all" to "a great deal"). These items were averaged to form a total score (range, 3–18), with higher scores reflecting greater COVID-19 related psychological stress ($\alpha = 0.69$).	•	
COVID-19 environmental stressors	The following binary coded stressors (presence/absence of stressor) were summed to form a count variable (range, 0–6). Housing insecurity, financial insecurity; job loss, new job, reduction or increases in work hours, or changes ("redeployment") in employment; food shortages; and COVID-19 illness (contracting the COVID-19 virus, hospitalisation of themselves or a family member due to infection, and death of a family member due to the virus).	•	
Parent measures			
Mental health	Depression Anxiety Stress Scale (DASS) - Symptoms of depression, anxiety and stress in the last week were assessed using the widely used and well-validated Depression Anxiety Stress Scale-21 [DASS-21; (36–38)]. The scale comprises three 7-item subscales to measure depression ($\alpha = 0.89$), anxiety ($\alpha = 0.82$), and stress ($\alpha = 0.87$), with items rated on a 4-point Likert scale (0 = Did not apply to me at all to 3 = Applied to me very much, or most of the time). Higher scores indicate greater symptom severity.	•	
Emotion regulation	Difficulties in Emotion Regulation Scale-16 Item Version - Used to assess emotion regulation in parents ($\alpha = 0.95$). Each item is rated on a 5-point Likert scale ranging from 1 = Almost never to 5 = Almost always (no time frame specified). Higher scores indicate greater emotion regulation difficulties.	•	
Positive affect	Positive and Negative Affect Schedule Short Form - A valid and reliable (39) 5-item measure whereby participants rated on a 5-point Likert scale (1 = Very Slightly or Not at All to 5 = Extremely) whether each affective state applies to them in the present moment ($\alpha = 0.80$). Higher scores indicate greater positive affect.	•	
Physical activity	Parent physical activity was assessed using the LSAC physical activity item, "About how many days each week do you do at least 30 min of moderate or vigorous physical activity (like walking briskly, riding a bike, gardening, tennis, swimming, running, etc.?)", rated from 1 to 7 days.	•	•
Sleep	Parent sleep quality was assessed using the LSAC item, "During the past month, how would you rate your sleep quality overall?" Rated on a 4-point scale from "very good" to "very bad". Item responses were then dichotomised, where response options 1–2 were coded 1 (very good/good) and 3–4 were coded 2 (very bad/bad).	•	•
Child measures			
Depression ^a	Short Mood and Feelings Questionnaire (SMFQ) – 13-item measure of child depression symptoms with items rated on a 3-point Likert scale (1 = Not true to 3 = True) (overall $\alpha = 0.87$; children 6 years and above, $\alpha = 0.88$; children <6 years, $\alpha = 0.79$). Higher scores indicate greater depression symptoms.	•	
Anxiety ^a	Modified Brief Spence Children's Anxiety Scale – 4-items assessing symptoms of anxiety ($\alpha = 0.77$). Parents rated on a 4-point Likert scale ("never" to "always") how frequently their child had experienced symptoms in the last 2 weeks. Higher scores indicate greater anxiety symptoms.	•	
Irritability	1 item, adapted from the CoRoNaVirus Health Impact Survey (CRISIS) (35), which asked, "During the past 2 weeks, how irritable or easily angered has your child been?" Parents rated this item on a 5-point Likert scale, ranging from "Not at all" to "Extremely," with higher scores indicating greater child irritability.	•	
Physical activity	Assessed via 1 item, adapted from LSAC, which asked parents, "About how many days each week did your child do at least 30 min of moderate or vigorous physical activity (like walking briskly, riding a bike, gardening, tennis, swimming, running, etc.?)" Parents provided a rating ranging from 0 to 7 days.	•	•
Sleep	Sleep pattern was assessed using the LSAC item, "How much is your child's sleeping pattern or habits a problem for you?" rated on a 4-point scale ("not at all a problem" to "a large problem"). Responses dichotomised, where response options 1–2 were coded 1 (not a problem/small problem) and response options 3–4 were coded 2 (moderate problem/large problem) as per previous research (40, 41). Child sleep regularity was assessed using the LSAC item, "Does the study child go to bed at regular times?" Parents rated this item on a 5-point scale, ranging from "never" to "always." Item responses were then dichotomised, where response options 1–3 (never/rarely/sometimes) were coded 1 and response options 4–5 (usually/always) were coded 2, with higher scores representing a more regular bedtime.	•	•
Screen time	Two items from LSAC, which asked how many hours on a typical (item 1) weekday and (item 2) weekend day did their child use media devices at home for non-educational purposes. Each item was rated on a sliding scale from 1 to 24 hours and provided a measure of weekday screen time and weekend day screen time (hours per day).	•	•

CPAS, COVID-19 Pandemic Adjustment Survey; LSAC, Longitudinal Study of Australian Children.

^aMeasured only in children aged ≥ 2 years of age.

TABLE 2 | Participant characteristics in the COVID-19 Pandemic Adjustment Survey ($N = 2365$, child aged 0–18 years) and the Longitudinal Study of Australian Children Baby Cohort (Wave 1, $N = 5,107$) and Kindergarten Cohort (Wave 3, $N = 4,331$).

Participant characteristic ^a	CPAS (Time 1, 2020)	LSAC-B (Wave 1, 2004)	LSAC-K (Wave 3, 2008)
Parent age, m(sd)	38.30 (7.07)	31.0 (5.51)	39.1 (5.40)
Child age, m(sd)	8.66 (5.14)		8.26 (0.44)
Parent gender			
Cisgender men	19.2%	1.5%	4.3%
Cisgender women	80.7%	98.6%	95.8%
Transgender or non-binary	<1.00%	NA	NA
Child gender			
Cisgender boy	50.9%	51.1%	51.1%
Cisgender girl	48.7%	48.9%	49.0%
Transgender or non-binary	<1.0%	NA	NA
Aboriginal or Torres Strait Islander	2.1%	NA	NA
Language other than English	4.5%	14.4%	13.7%
Parent born overseas	17.9%	18.6%	20.4%
Low household income ^b	14.0%	NA	NA
Receiving government benefit	5.8%	NA	NA
Did not complete high school	9.4%	33.3%	39.1%
Single parent household	10.9%	9.5%	29.3%
Geographic location			
Major cities of Australia	69.8%	NA	NA
Inner regional Australia	23.2%	NA	NA
Outer regional Australia	6.1%	NA	NA
Remote Australia	1.0%	4.3%	3.7%
Number of children			
1 child	28.4%	39.5%	8.2%
2 children	46.1%	36.7%	44.2%
3 children	18.2%	16.1%	31.3%
4 or more children	5.3%	7.6%	16.4%
Parent mental or physical health condition	56.1%	NA	NA
Child neurodevelopmental condition			
Attention-deficit/hyperactivity disorder	7.3%	NA	NA
Autism spectrum disorder	8.6%	NA	NA
COVID-19 related factors			
Deprivation index, m(sd)	0.38 (0.95)	NA	NA
Child home while working	49.64%	NA	NA
Parent reported CVD	0.9%	NA	NA

m(sd), Mean (standard deviation), data are unweighted; NA, not applicable.

^aData collected 8th–28th April 2020, data are multiply imputed and thus n cannot be presented for each characteristic.

^b\$52,000 or less per year.

RESULTS

Participant Characteristics

Participant characteristics are presented in **Table 2**. CPAS parents had a mean age of 38 years ($SD = 7.07$), were primarily female (81%), resided in a major city (70%) and had two children (46%) who were on average 9 years old ($SD = 5.14$). Single parent households were a minority (11%), and half of the sample had a child at home while working (50%). Twelve percent of parents

reported that their child had an attention-deficit/hyperactivity disorder (ADHD) and/or autism spectrum disorder (ASD) and more than half of parents indicated that they themselves had either a physical or mental health condition. In contrast, LSAC parents in both cohorts were almost all female, but there were similar proportions of LSAC parents born overseas or from single parent families, compared to CPAS parents. A greater proportion of LSAC parents spoke a language other than English and did not complete high school.

TABLE 3 | Parent and child physical activity, sleep, and screen time compared to Australian normative data (LSAC).

	Unweighted						Weighted					
	CPAS			LSAC			CPAS			LSAC		
	%	LL	UL	%	LL	UL	%	LL	UL	%	LL	UL
Child sleep problem												
Full CPAS sample	17.7	15.9	19.4				16.4	13.6	19.2			
Matched: children 0–13 years	17.4	15.5	19.3	8.9	8.6	9.3	16.9	13.6	20.2	9.6	9.1	10.0
Child no regular bedtime												
Full CPAS sample	20.1	18.3	21.8				21.5	18.2	24.9			
Matched: Children 0–13 years	13.1	11.4	14.8	2.8	2.5	3.0	15.0	11.3	18.7	3.1	2.7	3.4
Parent poor sleep quality												
Full sample	56.0	53.9	58.1				58.3	54.4	62.2			
Matched: Children 0–13 years	56.7	54.3	59.0	21.0	20.4	21.6	59.1	54.6	63.5	21.6	21.0	22.3
	M (se)	LL	UL	M (se)	LL	UL	M (se)	LL	UL	M (se)	LL	UL
Screen-time (weekday)												
Full CPAS sample	3.19 (0.07)	3.05	3.33				3.56 (0.13)	3.31	3.82			
Matched: Children 4–13 years	2.84 (0.07)	2.70	2.99	2.98 (0.01)	2.97	2.99	3.14 (0.13)	2.89	3.39	3.02 (0.01)	3.01	3.04
Screen-time (weekend)												
Full CPAS sample	4.33 (0.08)	4.18	4.48				4.84 (0.14)	4.56	5.11			
Matched: Children 4–13 years	3.98 (0.08)	3.82	4.13	3.35 (0.01)	3.34	3.37	4.45 (0.17)	4.12	4.79	3.36 (0.01)	3.34	3.38
Child physical activity												
CPAS: Children 1–18 years	4.93 (0.05)	4.84	5.02				4.91 (0.08)	4.75	5.07			
Parent physical activity												
Full CPAS sample	3.88 (0.04)	3.80	3.97				4.03 (0.09)	3.85	4.22			
Matched: Children 0–13 years	3.86 (0.05)	3.77	3.96	2.85 (0.01)	2.82	2.88	4.04 (0.11)	3.82	4.25	2.85 (0.02)	2.81	2.88

"Full CPAS sample" refers to children aged 0–18 years. "Matched" samples refer to CPAS participants that match the child age range available for LSAC normed data. LL/UL refer to the lower limit (LL) and upper limit (UL) estimates from 95% confidence intervals. se, standard error.

Physical Activity, Screen Time, and Sleep During COVID-19 Compared to National Data

Table 3 presents parent and child physical activity, sleep, and screen time for CPAS compared to LSAC data.

Child

During the pandemic, ~1 in 6 parents reported that their child's sleep was a problem, in both the full CPAS sample (i.e., children 0–18 years) and the matched CPAS sample (children 0–13 years). This rate was close to double the rates reported by LSAC parents of children 0–13 years [17.4 vs. 8.9%, $X^2_{(1,11,621)} = 109.23$, $p < 0.001$]. Although 1 in 5 parents reported their child had no regular bedtime in the full CPAS sample, this was less frequent in the age-matched sample, where approximately 1 in 8 children did not have a regular bedtime. However, this rate was still much higher than the LSAC national data [13.1 vs. 2.8%, $X^2_{(1,11,621)} = 79.49$, $p < 0.001$].

In the CPAS full sample, children spent on average just over 3 and 4 h per day, respectively, engaged in weekday, and weekend day recreational screen time. These times were lower in the CPAS age-matched sample (i.e., aged 4–13 years), and there was evidence that CPAS parents reported their child spent less time engaged in recreational screen time on weekdays [$t_{(11,183)}$

$= 4.31$, $p < 0.001$, $d = 0.12$] but more time on weekend days [$t_{(11,619)} = -16.72$, $p < 0.001$, $d = -0.42$] compared to the LSAC national data.

Parents

On average, parents participated in at least 30 min of physical activity up to 4 days per week, in both the full and matched CPAS samples, which was higher than the average rates reported in the LSAC national data [$t_{(11,620)} = -24.96$, $p < 0.001$, $d = -0.63$]. Over half of parents reported poor sleep quality in both the full and matched CPAS samples, which was more than double the average rates reported in LSAC national data [56.7 vs. 21%, $X^2_{(1,11,621)} = 1147.12$].

Sensitivity Analysis

Given the high proportion of CPAS parents who reported having a child with ADHD and/or ASD, and the known links between the movement behaviours and mental health outcomes among these children and parents (45–47), a sensitivity analysis was run removing parents who reported having a child with these conditions to determine the effect on our findings ($n = 15\%$). No differences were found in our findings comparing CPAS age-matched sample with and without ADHD/ASD children compared to LSAC national data, indicating this

TABLE 4 | Associations between child movement behaviours (physical activity, screen time, sleep problems, and sleep routine) and mental health outcomes.

	Unadjusted				Adjusted			
	Coefficient	LL	UL	p	Coefficient	LL	UL	p
Child depression^a								
Physical activity	−0.22	−0.32	−0.12	0.000	−0.05	−0.15	0.06	0.362
Screen time (weekday)	0.26	0.20	0.32	0.000	0.08	−0.02	0.18	0.123
Screen time (weekend)	0.25	0.19	0.31	0.000	0.13	0.03	0.23	0.009
Sleep problems	2.68	2.18	3.18	0.000	2.35	1.83	2.88	0.000
No regular bedtime	1.40	0.90	1.90	0.000	−0.08	−0.64	0.48	0.776
Child anxiety^b								
Physical activity	0.03	−0.03	0.09	0.298	0.05	−0.01	0.11	0.090
Screen time (weekday)	0.02	−0.02	0.05	0.382	−0.02	−0.07	0.03	0.455
Screen time (weekend)	0.02	−0.02	0.05	0.312	0.05	−0.01	0.10	0.078
Sleep problems	1.40	1.11	1.68	0.000	1.36	1.06	1.65	0.000
No regular bedtime	0.08	−0.18	0.34	0.562	−0.30	−0.59	−0.01	0.042
Child Irritability^c								
Physical activity	0.03	0.01	0.05	0.010	0.04	0.02	0.06	0.001
Screen time (weekday)	0.01	−0.01	0.02	0.229	0.01	−0.02	0.03	0.654
Screen time (weekend)	0.01	−0.01	0.02	0.375	0.02	0.00	0.05	0.057
Sleep problems	0.34	0.22	0.46	0.000	0.33	0.20	0.45	0.000
No regular bedtime	0.01	−0.10	0.13	0.809	−0.01	−0.14	0.12	0.862

^aAdjusted for child age, parent gender, no partner and other movement behaviours.

^bAdjusted for child age, parent gender, deprivation, no partner, education and other movement behaviours.

^cAdjusted for child age, parent age, parent gender and other movement behaviours.

over-representation did not change the interpretation of the findings reported.

Association Between Movement Behaviours and Mental Health Outcomes Child

Unadjusted and adjusted models investigating the association between movement behaviours and mental health outcomes for children in the CPAS cohort are presented in **Table 4**. In unadjusted models, participating in at least 30 min of moderate or vigorous physical activity per day on fewer days ($B = -0.22$, 95% $CI [-0.32 \text{ to } -0.12]$, $p < 0.001$), spending more hours per day engaged in weekday ($B = 0.26$, 95% $CI [0.20-0.32]$, $p < 0.001$) and weekend day ($B = 0.25$, 95% $CI [0.19-0.31]$, $p < 0.001$) recreational screen time, having no regular bedtime ($B = 1.40$, 95% $CI [0.90-1.90]$, $p < 0.001$) and greater sleep problems ($B = 2.68$, 95% $CI [2.18-3.18]$, $p < 0.001$) were associated with greater depressive symptoms. These associations remained significant in adjusted models for weekend screen time and sleep problems (both $p < 0.001$).

In unadjusted models, more disrupted sleeping patterns in the CPAS cohort were associated with greater child anxiety symptoms ($B = 1.40$, 95% $CI [1.11-1.68]$, $p < 0.001$) but no associations were found for having no bedtime routine, weekday or weekend screen time or physical activity (all $p > 0.05$). In adjusted models, the association remained for sleep problems ($B = 1.30$, 95% $CI [1.01-1.60]$, $p < 0.001$) and having no regular bedtime became significantly associated with anxiety symptoms ($B = -0.30$, 95% $CI [-0.59 \text{ to } -0.01]$, $p = 0.042$). Higher levels

of physical activity ($B = 0.04$, 95% $CI [0.02-0.06]$, $p = 0.001$) and greater sleep problems ($B = 0.33$, 95% $CI [0.20-0.45]$, $p < 0.001$) were both associated with child irritability in adjusted models. There was no significant moderating effect of COVID-19 environmental stressors or COVID-19 psychological stressors on the associations between movement behaviours and child mental health outcomes (all $p > 0.05$).

Sensitivity Analysis

Given some measures have not yet been validated in a younger sample (e.g., our measure of depression and anxiety have been validated for children as young as 6 years, yet we investigated associations in children as young as 2 years in our full CPAS sample), we undertook a sensitivity analysis, including only children aged 6 years and above. While for the most part our finding remained unchanged, when limiting the sample to 6 years and above, having an irregular bedtime was not associated with anxiety ($p = 0.181$) and weekend screen time was not associated with depression ($p = 0.111$).

Parent

Unadjusted and adjusted models examining the association between movement behaviours and mental health outcomes for CPAS parents during the pandemic are summarised in **Table 5**. In adjusted models, lower levels of physical activity and poorer sleep quality were associated with greater parent depressive symptoms. Lower levels of physical activity and poorer sleep quality were also associated with parent anxiety and stress symptoms. Similarly, less physical activity and poorer sleep quality were associated with greater difficulties regulating emotions. More physical

TABLE 5 | Associations between parent movement behaviours (physical activity and sleep quality) and mental health outcomes.

	Unadjusted				Adjusted			
	Coefficient	LL	UL	p	Coefficient	LL	UL	p
Depressive symptoms^a								
Physical activity	−0.40	−0.48	−0.31	0.000	−0.28	−0.36	−0.20	0.000
Poor sleep quality	2.63	2.29	2.98	0.000	2.16	1.82	2.51	0.000
Anxiety symptoms^b								
Physical activity	−0.23	−0.30	−0.17	0.000	−0.13	−0.19	−0.07	0.000
Poor sleep quality	1.97	1.69	2.25	0.000	1.59	1.31	1.87	0.000
Stress^c								
Physical activity	−0.29	−0.38	−0.21	0.000	−0.14	−0.22	−0.06	0.001
Poor sleep quality	3.56	3.21	3.91	0.000	3.18	2.83	3.53	0.000
Emotion regulation^d								
Physical activity	−0.89	−1.13	−0.65	0.000	−0.56	−0.80	−0.33	0.000
Poor sleep quality	6.60	5.57	7.62	0.000	5.44	4.42	6.46	0.000
Positive affect^e								
Physical activity	0.57	0.50	0.64	0.000	0.49	0.42	0.56	0.000
Poor sleep quality	−1.98	−2.29	−1.68	0.000	−1.59	−1.88	−1.29	0.000

^aAdjusted for parent age, deprivation, parent education, and other movement behaviours.

^bAdjusted for parent age, parent gender, deprivation, parent education, parent ATSI status, and other movement behaviours.

^cAdjusted for parent age, parent gender, deprivation, language other than English spoken at home and other movement behaviours.

^dAdjusted for parent age, deprivation, parent education, and other movement behaviours.

^eAdjusted for parent age, parent gender, parent Aboriginal, and Torres Strait Islander Peoples status and other movement behaviours.

activity and greater sleep quality was associated with greater positive affect. COVID-19 environmental stressors moderated the association between sleep quality and depression ($B = 0.31$, 95% $CI [0.02-0.60]$, $p = 0.034$), and moderated the association between sleep quality and difficulties with emotion regulation ($B = 0.96$, 95% $CI [0.09-1.84]$, $p = 0.031$), where parents reporting both high COVID-19 stressors and poor sleep quality reported the highest levels of emotion regulation difficulties and depression (see **Tables 1, 2**). There was no significant moderating effect of COVID-19 psychological stressors on the associations between movement behaviours and parent mental health (all $p > 0.05$).

DISCUSSION

This study investigated differences in a set of movement behaviours, namely physical activity, sleep and screen time, in parents and children during early stages of the COVID-19 pandemic in Australia compared to pre-COVID-19 national data; and estimated associations between these movement behaviours with parent and child mental health. Given the growing body of research establishing the mental health impacts of COVID-19 (48, 49), and the known association between movement behaviours with proximal indicators of mental health and more distal risk for CVD, identifying modifiable factors that can be targeted to improve both mental health and risk for CVD, is a priority. Here we show that children and parents under lockdown restrictions report substantially higher rates of sleep problems compared to pre-pandemic rates, with parents also reporting their child had greater levels of recreation screen time on weekends. Children who participated in lower levels of

physical activity, had higher levels of recreational screen time and had greater sleep problems also experienced greater depressive symptoms. Greater disruptions to child sleep patterns was also associated with elevated anxiety and irritability symptoms, after accounting for physical activity and screen time. Similarly, poorer parent sleep quality and lower levels of physical activity were associated with poorer parent mental health, increased emotion regulation difficulties, and reduced positive affect. Given the association between the movement behaviours and indicators of mental health for both children and parents during the early stage of COVID-19; coupled with the finding of mostly unfavourable differences in these behaviours compared to pre-pandemic rates, there is potential that adversity associated with the COVID-19 pandemic may have long-term effects on the development of psycho-cardiologic diseases. While longitudinal investigations of this cohort are needed to confirm this hypothesis, at the very least, this study identifies a number of potential modifiable levers that may reduce both risk for more proximal mental health problems and more distal CVD risk.

Australian movement behaviour guidelines recommend that adults be active on most, and preferably all, days of the week, and that children should accumulate 60 min or more of moderate to vigorous physical activity per day, involving mainly aerobic activities (3). During the pandemic, children were engaging in 5 days of at least 30 min of moderate or vigorous physical activity, slightly below recommended levels. This finding is somewhat consistent with recent Canadian online survey showing that only 18% of children were adhering to physical activity recommendations (50). Results are also consistent with Moore et al. who reported in their online survey that children experienced a significant decline in all

physical activities compared to pre-pandemic rates, with the most dramatic decline seen in outdoor physical activity and sport (16). Whether the lower rates of child physical activity during the early stages of COVID-19 in the current cohort compared to pre-pandemic rates is maintained beyond the initial lockdown restrictions will be important to determine. Physical activity is a known primordial risk factor for later CVD development (51), therefore, any maintenance of low levels of physical activity among our cohort would be of concern. Targeted public health interventions, sympathetic to the COVID-19 context may be required to re-engage children in daily physical activity to achieve pre-pandemic participation rates.

Although parents in the current sample appear to have high levels of physical activity compared to national data, this was still lower than recommended guidelines. Even so, this increase compared to pre-pandemic national data is somewhat heartening, given lower levels of physical activity were associated with poorer mental health across all indicators, even when accounting for sleep quality. Prioritising regular physical activity may be an important strategy for improving parents' mental health, and with COVID-19 related restrictions, it may be that parents are finding more time to engage in physical activity, which may come from greater flexibility in employment conditions or commute time. These higher rates of physical activity among parents are also heartening in terms of the more distal risk for later CVD development, given insufficient levels of physical activity is considered a primordial risk for later CVD (51). Further investigation into the contributing factors that may explain these trends among parents would be worthwhile for public health efforts aiming to improve physical activity levels among the general population, which may in turn improve proximal indicators of mental health indicators but also more distal risk for CVD. However, given the cross-sectional nature of the data, the reverse association cannot be ruled out—that instead, poor mental health contributes to lower physical activity. Regardless of the direction of associations, a key issue however, is that this increase in physical activity did not translate to increases in child physical activity behaviour. Surprisingly, increased physical activity in children was associated with higher levels of irritability. It may be that parents of children with high irritability may be prioritising exercise as an outlet to manage difficult child behaviour.

A growing body of research has demonstrated an increase in sleep problems in the general population as a result of the COVID pandemic (52–56), however, these studies have not systematically compared rates of sleep problems to pre-pandemic levels and/or have not focused on parents and children specifically. The higher levels of child sleep problems and irregular bedtime reported by parents in the CPAS cohort, and the connexion between child sleep problems and indicators of poorer mental health, suggest that sleep has the potential to be an important modifiable factor to improve children's functioning during the COVID-19 pandemic. Consistent with this notion, pre-pandemic studies have connected poorer sleep to increased mental health difficulties in children (57). Even though it may be tempting to relax the rules around children's bedtime during lockdown restrictions, our data suggest that sleep problems during the

pandemic continue to be associated with worse mental health in children. Parents in the current study also had substantially higher rates of sleep problems compared to national data, which is consistent with findings from a cross-sectional study of 1,005 adults in France (52). It is notable that over half of parents rated their sleep quality as problematic. Moreover, sleep problems were associated with poorer parent mental health across multiple domains, even when accounting for physical activity levels. This is consistent with the findings of Stanton et al. (55) in their general Australian sample of adults, however, we extend these findings by considering parents specifically, and simultaneously accounting for physical activity levels.

We found mixed evidence concerning screen time. Children had lower levels of recreational screen use during weekdays but higher levels on weekends compared to pre-pandemic national data. It is important to note that parents reported on their child's screen time related to “non-educational purposes.” It may be that our findings are affected by variability in the context of schooling across participants. For example, a portion of children are likely to have been on school holidays between late March and late April (varying by State/Territory), overlapping with our data collection period (8th–28th April 2020). Further, about half the sample were juggling work from home while supervising children, and a portion of these children were engaged in remote learning (“home-schooling”) at the time of data collection; which is likely to bear an increased screen time load compared to on-campus school learning. It may be that parents restricted non-educational screen time for children already spending much of their day on screens for educational purposes.

In unadjusted analyses, increased weekday and weekend screen time was associated with child depression symptoms but this association was attenuated for weekday screen time when accounting for sleep problems, physical activity and other covariates. Similarly, associations between weekend screen time and child depression symptoms were attenuated when restricting analyses to those aged 6 years and above. Global movement behaviour guidelines for children and adolescents (4) recommend that young children aged 3–4 years engage in no more than 1 h of sedentary screen time, and that older children and adolescents 5–17 years engage in no more than 2 h of sedentary recreational screen time. On average, children in our study were engaging in 3 h of screen time on weekdays and 4 h on weekends, above recommended guidelines.

It is important to note that children may be using screens to maintain social connexions and this likely has many positive benefits, particularly in the context of limited opportunities for in-person interactions given COVID-19 restrictions. It is also difficult to tease apart the use of screens for educational and non-educational purposes. Overall, the lack of association between screen time and poor child mental health is reassuring for parents. Further, it may not be realistic to reduce child screen time during COVID-19 social distancing restrictions. Instead, family media plans can be used to manage screen time at home and parents should also consider the quality of the content that children are accessing during screen time (58). Fading (graduated extinction) approaches can gradually reduce non-educational screen time to recommended levels. Overall, it will be important

to monitor screen time in this cohort to see whether screen time naturally reduces once restrictions have lifted.

Surprisingly, we found little evidence that COVID-19 related environmental or psychological stressors moderated associations between movement behaviours and mental health outcomes in children. However, for adults, COVID-19 environmental stressors moderated the association of sleep quality with both depression and emotion regulation. This is consistent with emerging research linking COVID-19 related risk factors to increased sleep difficulties (53). Prevention and intervention efforts that support parents to navigate environmental stressors related to the pandemic need to move beyond helping individuals cope. Focussing on the broader policy levers that may alleviate such stressors, including policies related to financial aid, secure housing and employment, access to COVID-19 safe childcare and school environments, and gendered division of labour will likely have a greater impact on alleviating COVID-19 related stressors and in turn improve parent sleep and mental health. Future research would benefit from focussing on these systemic, policy-based interventions.

Taken together, our findings linking disrupted sleep, low levels of physical activity and weekend screen time to a range of mental health indicators may have important implications for later psycho-cardiological disease. An emerging body of evidence in children and adolescents suggests that early experiences and environments (59, 60) in general may influence the course of health and chronic illness. COVID-19 related stressors and the experience of early depression and other emotional distress in children may be particularly relevant to the course of chronic disease development (60, 61). A compelling body of evidence has linked both stress and depression to a range of CVD risks and diseases (8, 62–68). Understanding the trajectory and prevailing nature of the COVID-19 related stressors and mental health problems reported by parents in the current study has particular importance when considering risk for later CVD. It has previously been suggested that persistent adversity and ongoing chronic stress may result in the greatest risk to CVD and that this increased “wear and tear” on the cardiovascular system over time, induced by stressful experiences that over use and dysregulate stress response pathways that is most problematic (66, 68). In addition, better quality sleep and higher levels of physical activity are also associated with a lower risk for developing CVD and better prognosis among those with established CVD (12, 69). It is through continuing longitudinal studies such as the CPAS study, and others around the world that the clinical significance of COVID-19 related stressors both in terms of proximal mental health problems and in terms of risk for more distal CVD will be better understood.

Our study has several strengths. The samples are relatively large, and included both children and parents. Our study is comprehensive in that we examine multiple domains of mental health and movement behaviours. We were further able to compare movement behaviours to nationally representative pre-pandemic data. However, several limitations should be considered. First, our sample was recruited online and appears to be more vulnerable than the general population. One example is that the rates of ADHD and ASD are much higher than

would be expected in the general population. To address this, we applied sample weighting and conducted a sensitivity analysis indicating that our results are robust, both with and without the higher-risk ADHD/ASD children. Second, given that this is a cross-sectional study directionality and causality cannot be inferred and it is possible that the investigated associations are in fact, bidirectional, whereby poor mental health influences sleep, screen time and physical activity. However, population-based longitudinal research has shown that sleep difficulties appear to precede internalising difficulties in childhood, while there is more evidence of a bi-directional association between sleep and behavioural difficulties (57). Longitudinal examination of this cohort will enable further understanding of the directionality between movement behaviours and mental health. Finally, the role other important risk factors for both mental health and CVD risk, including diet and alcohol use, could not be considered as no data was collected on these constructs.

In summary, children in the current study had higher rates of sleep problems and increased weekend screen time compared to national pre-pandemic data. Parents had higher levels of sleep problems compared with pre-pandemic data, while physical activity also appeared to be higher. Poor sleep in both parents and children, and lower levels of physical activity and higher levels of weekend recreational screen time were associated with poorer mental health outcomes. Monitoring this cohort over time will be important to examine whether changes in movement behaviour are enduring or naturally improve with the easing of restrictions and whether these changes have enduring effects on either parent or child mental health, and in turn, more distal risk for psycho-cardiological disease.

CODE AVAILABILITY

CPAS code is shared on the Open Science Framework.

DATA AVAILABILITY STATEMENT

Data from CPAS participants who consented to data sharing (91.21%) will be available through the Australian Data Archive (currently under review) for research projects that are related to CPAS. Please direct enquires to the corresponding author, lisa.olive@deakin.edu.au.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Deakin University Human Ethics Advisory Group (Project No: HEAG-H 52_2020). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

LO conceived the current study, while EW conceived the larger CPAS study. LO, EW, and ES drafted the initial manuscript. EH and TB were responsible for data management. LO, EW, TB, EH,

and RT completed the statistical analysis. All authors contributed to and provided feedback on the final draft.

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Health Disparities and Differences in Health-Care-Utilization in Patients With Pulmonary Arterial Hypertension

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Introduction: Mental disorders are common in patients with pulmonary arterial hypertension (PAH) and contribute to impaired quality of life (QoL). The impact of mental disorders on access to health care, differences in clinical parameters and treatment in patients with PAH is unclear. In this study we sought to assess the impact of mental disorders and other health disparities on health-care-utilization in patients with PAH.

Methods: In a cross-sectional observational study of patients with PAH, mental disorders were characterized using a structured clinical interview. In addition, patients completed a self-administered questionnaire to assess QoL, symptoms of anxiety and depression, lifestyle-factors and educational status. Number of outpatient visits and communication events per year were calculated as a surrogate for health-care-utilization and were compared by the presence of mental disorder. Linear regression analysis was conducted to assess the impact on health-care-utilization.

Results: 117 patients with PAH participated in this study (70% female, median age 59 (interquartile range, 49–70) years). Significant differences between patients with or without mental disorders were found in anxiety, depression and QoL. There were no significant differences in clinical parameters. Patients with mental disorders had higher rates of outpatient visits and communication events than patients without mental disorders. Linear regression revealed a gain of 2.2 communication events per year in the presence of any mental disorders.

Conclusion: Mental disorders in patients with PAH are common and significantly affect health-care-utilization. This higher demand in patients with mental disorder needs to be addressed by physicians, psychiatrists and specialized nurses offering therapeutic strategies.

Keywords: pulmonary arterial hypertension, mental health, quality of life, health disparities, health-care-utilization

INTRODUCTION

Pulmonary arterial hypertension (PAH) is a rare disease characterized by increased pulmonary vascular resistance due to remodeling of pulmonary vasculature (1, 2). Symptoms of PAH include clinical signs of heart failure, dyspnea on exertion, syncope leading to impaired physical activities and a reduced quality of life (QoL) (3). Therapy of PAH has greatly advanced over the last decades improving clinical outcomes and survival of PAH patients. However, PAH remains a fatal illness with right heart failure being the primary cause of death (4).

Mental disorders such as major depression disorder (MDD) or panic disorder (PD) are common in patients with PAH, and patient's quality of life, mental health, and access to medical care have been addressed in recent studies (5–10). The prevalence of anxiety, depression and adjustment disorders in patients with PAH correlate with disease progression, intensity of symptoms as well as functional impairment (11, 12). Mental disorders such as major depression disorder, panic disorder or adjustment disorder are common in patients with PAH (13).

Health disparities are defined as significant differences in health or outcomes with correlation to greater obstacles to healthcare based on ethnicity, sex, age, socioeconomic status, occupation, mental health, cognitive or physical disability (14). Health disparities can impact quality of life, disease treatment and outcomes (15, 16). With only few studies addressing health disparities in patients with PAH, the American Thoracic Society encouraged further research to achieve more equitable care, improve advocacy efforts and public health policy for patients with PAH (8). Health disparities, in particular mental disorders may contribute to differences in clinical parameters, treatment and survival in patients with PAH. Thus, in this study, we sought to assess possible implications of mental disorders in patients with PAH leading to differences in PAH treatment and healthcare utilization.

METHODS

This cross-sectional observational study included patients with a confirmed diagnosis of PAH from one PH referral center (Hannover Medical School in Germany). This patient cohort is a subsample of a larger cohort that was originally described by Olsson et al. (13). All patients gave written informed consent and the study was approved by the local institutional review board (Nr. 8540_BO_K_2019). Patients were contacted and interviewed between September 2019 and March 2020 to perform a structured clinical interview. This study further comprised self-administrated questionnaires and data was enriched using a clinical research database.

Abbreviations: 6MWD, 6-minute walk distance; DLCO, diffusing capacity of the lung for carbon monoxide; DSM-V, Diagnostic and Statistical Manual of Mental Disorders V; FC, World Health Organization Functional Class; HADS, Hospital Anxiety and Depression Scale; NT-proBNP, N-terminal fragment of probrain natriuretic peptide; PAH, pulmonary arterial hypertension; QoL, quality of life; SCID, structured clinical interview for DSM-V, Structured Clinical Interview; SD, standard deviation.

Patient Setting and Clinical Parameters

Patients were selected from a clinical research database based on diagnosis of PAH according to current criteria (1) and age ≥ 18 years. Assessment included hemodynamics from right heart catheterization at time of diagnosis, 6-minute walk distance (6MWD), serum levels of N-terminal fragment of pro-brain natriuretic peptide (NT-proBNP), WHO functional class (FC) and diffusing capacity of the lung for carbon monoxide (DLCO). Lifestyle factors included smoking status (active smoker, former smoker or never-smoker), duration of smoking and mean number of cigarettes per day to calculate the number of packyears (17) as well as alcohol abuse as drinks per week.

Assessment of Mental Disorders, Quality of Life and Educational Status

Psychiatric characterization was performed using the Structured Clinical Interview (SCID) for Diagnostic and Statistical Manual of Mental Disorders, fifth Edition (DSM-V) by a medical student carefully trained and under the supervision of a senior physician to determine the presence of MDD and PD and covered the past 4 weeks prior to the interview (18). The Hospital Anxiety and Depression Scale (HADS) was used to assess symptoms of anxiety and depression (19). The HADS questionnaire comprises two subscales for anxiety (HADS-A) and depression (HADS-D), each containing 7 questions for a maximum of 21 points per subscale. Higher scores indicating a more severe anxiety or depression. A score > 11 per subscale was proposed by Bjelland et al. and Lowe to be associated with significant anxiety or depression while a cut-off score of > 8 for both subscores showing probable signs of anxiety or depression (20, 21). The World Health Organization Quality of Life [WHO-QoL-BREF (22)] questionnaire was used to assess quality of life. To assess patients educational status, the sociodemographic standards of the German Federal Statistical Office (destatis) (23) were applied. Further educational status was categorized in low (no education), moderate (non-academic education) and high (academic education) educational status.

Assessment of Outpatient Visits and Patient Communication

Total number of outpatient visits and patient communication datasets were derived from a clinical research database as well as the date from first and last outpatient visit or communication event respectively. Patient communication is defined as any kind of unscheduled communication event (e.g., e-mail, mail, phone calls or other correspondence) documented in the clinical research database by a physician or a specialized nurse. Time-variables comprising the time in years between first and last date of outpatient visit or communication event were calculated and set into relation to the number of visits and communications. This allowed us to calculate outpatient visits and communication events per year for each patient.

Statistical Analysis

IBM SPSS Statistics (version 28.0, IBM Corp., Armonk, New York) and Stata 13.0 (State Corp LP, College Station, Texas, USA) statistical software programs were used for statistical analysis. Continuous parameters are presented as median and

TABLE 1 | Characteristics of the patients at baseline.

	All patients <i>n</i> = 117	Patients with depression or panic disorder <i>n</i> = 31 (27%)	Patients without depression or panic disorder <i>n</i> = 86 (74%)	<i>p</i> -value
Age (years)	59 (49–70)	51 (40–60)	61 (50–70)	0.010
Female sex (%)	82 (70%)	22 (71%)	60 (70%)	0.900
BMI (kg/m ²)	25 (22–31)	25 (23–33)	25 (22–30)	0.369
Diagnosis				
→ IPAH, <i>n</i> (%)	58 (50%)	13 (42%)	45 (52%)	0.248 ^a
→ HPAH, <i>n</i> (%)	8 (7%)	4 (13%)	4 (5%)	
→ Associated PAH, <i>n</i> (%)	51 (44%)	14 (45%)	37 (43%)	
Time since PAH diagnosis (years)	5 (2–10)	6 (2–9)	5 (3–10)	0.395
WHO FC				
→ I/II, <i>n</i> (%)	58 (50%)	12 (38%)	46 (53%)	0.469 ^a
→ III, <i>n</i> (%)	53 (45%)	17 (55%)	36 (42%)	
→ IV, <i>n</i> (%)	6 (5%)	2 (7%)	4 (5%)	
6MWD (m)	429 (340–503)	429 (335–500)	431 (345–505)	0.700
NT-proBNP (ng/l), <i>n</i> = 105	236 (101–691)	248 (67–1128)	228 (105–505)	0.222
DLCO (% pred.), <i>n</i> = 75	62 (45–74)	65 (50–73)	58 (39–74)	0.263
paO ₂ , mmHg	67 (60–77)	68 (61–76)	66 (57–78)	0.342
Hemodynamics at diagnosis				
→ mPAP (mmHg)	45 (37–55)	45 (41–55)	46 (37–55)	0.945
→ PAWP (mmHg)	9 (6–12)	8 (6–11)	9 (6–12)	0.175
→ CI (l/min/m ²)	2.4 (2.1–2.9)	2.5 (2.2–3.0)	2.4 (2.0–2.9)	0.552
→ PVR (dyn·s·cm ⁻⁵)	652 (464–830)	642 (481–891)	652 (448–824)	0.819
PAH medication				
→ Monotherapy	32 (27%)	7 (23%)	25 (29%)	0.082 ^a
→ Double combination therapy	63 (54%)	14 (45%)	49 (57%)	
→ Triple combination therapy	22 (19%)	10 (32%)	12 (14%)	
Smoking Status				
→ Active, <i>n</i> (%)	17 (15%)	7 (23%)	10 (12%)	0.267 ^a
→ Former, <i>n</i> (%)	9 (8%)	3 (10%)	6 (7%)	
→ Never, <i>n</i> (%)	91 (78%)	21 (68%)	70 (81%)	
→ Packyears	15 (10–25)	12 (9–20)	20 (10–40)	0.161
Sociodemographic Items				
→ Drinking (drinks per week) ^b	0.74 ±1.31	0.71 ±1.22	0.74 ±1.35	0.901
→ Exercise Score (points)	3 (2–4)	2 (2–3)	3 (2–4)	0.126 ^c
→ HADS-A (points)	6 (3–9)	9 (7–12)	5 (2–7)	< 0.001
→ HADS-D (points)	5 (2–7)	8 (5–13)	4 (2–6)	< 0.001
→ QoL-overall (points)	50 (38–75)	38 (25–63)	63 (50–75)	< 0.001
→ QoL-psych (points)	67 (58–79)	54 (46–67)	75 (63–88)	< 0.001
→ QoL-physical (points)	57 (41–75)	43 (32–64)	66 (50–75)	< 0.001
Education				
→ Low	19 (16%)	3 (10%)	16 (19%)	0.347 ^a
→ Moderate	82 (70%)	22 (71%)	60 (70%)	
→ High	14 (14%)	6 (19%)	10 (12%)	

Significant *p*-values are presented in bold.

Continuous variables are stated as median and interquartile ranges (IQR) and categorical variables are stated as *n* and percent (%), unless indicated otherwise.

^aChi²-test.

^bMean and standard deviation (SD) because of distribution of the data.

^cNon-parametric Mann-Whitney-U-Test because of ordinal scale of the variable.

BMI, body mass index; QoL, quality of life; HADS-A, hospital anxiety and depression scale – anxiety; HADS-D, hospital anxiety and depression scale – depression; I/HPAH, idiopathic or heritable pulmonary arterial hypertension; WHO FC, World Health Organization Functional Class; 6MWD, six-minute walking distance; BNP, brain natriuretic peptide; NT-proBNP, N-terminal fragment of pro-brain natriuretic peptide; DLCO, diffusion capacity of the lung for carbon monoxide; paO₂, mmHg, arterial pO₂; mPAP, mean pulmonary arterial pressure; PAWP, pulmonary artery wedge pressure; CI, cardiac index; PVR, pulmonary vascular resistance; SD, standard deviation; IQR, inter quartile range.

TABLE 2 | Comparison of patient contacts and communication events by mental disorders.

Item	All PAH <i>n</i> = 117	Patients with depression or panic disorder <i>n</i> = 31 (27%)	Patients without depression or panic disorder <i>n</i> = 86 (74%)	<i>p</i> -value
Patient contacts				
→ Outpatient visits	2.2 (1.8–2.6)	2.4 (1.8–3.0)	2.2 (1.8–2.4)	0.022
→ Communication events	1.8 (1.0–3.6)	2.8 (1.8–6.2)	1.5 (1.0–2.9)	0.001

Significant *p*-values are presented in bold.

Continuous variables are stated as median and interquartile ranges (IQR) and categorical variables are stated as *n* and percent (%). All *p*-values were derived using *t*-test.

PAH, pulmonary arterial hypertension; IQR, inter quartile range.

interquartile range (Q₂₅–Q₇₅) or as mean and standard deviation (SD). Categorical variables are presented as number (*n*) and percent (%). Comparisons of continuous parameters were conducted using *t*-test or Mann-Whitney *U* test and comparison of categorical parameters by using Chi-square-test or Fisher's exact test, unless indicated otherwise. Linear regression models calculated on dependent variables outpatient visits per year and correspondences per year in a stepwise forward setting. Independent variables were age, sex, packyears, HADS-A and HADS-D scores, QoL, education, WHO FC, 6MWD and the diagnosis of any MDD or PD. All tests were two-sided, *p*-values < 0.05 were considered statistically significant.

RESULTS

A total of 117 patients were enrolled in this study. Patient characteristics are shown in **Table 1**. The majority of patients were female (*n*=82, 70%); median age was 59 (interquartile range, 49–70) years. Twenty six patients presented with MDD and 10 patients with PD resulting in 31 (27%) patients (five patients had a combination of MDD or PD). All patients were treated with PAH medications, most of them (73%) with combination therapy. Disease severity indicated by WHO FC, 6MWD, NT-proBNP, DLCO, hemodynamics at time of diagnosis as well as PAH treatment did not differ between patients with or without mental disorders (**Table 1**). In addition, there were no differences in drinking habits or exercise scores but patients with any form of mental disorder were nearly two-times more likely to be active smokers (23 vs. 12%). Patients with MDD or PD had significantly worse HADS-A and HADS-D scores. Psychological and physical QoL was worse in patients with MDD or PD (all *p* < 0.001).

Outpatient Visits and Communication of Patients With or Without MDD or PD

Detailed results are stated in **Table 2**. Grouped together, the patients had a median number of 2.2 outpatient visits and 1.8 communication events per year. Comparison of visits and communication revealed significant differences between patients with and without MDD or PD. Patients with MDD or PD had significantly more outpatient visits per year compared to patients without MDD or PD (2.4 vs. 2.2 visits per year, *p* = 0.022, **Figure 1A**). The number of communication events also differed significantly (**Figure 1B**), with 2.8 (interquartile range, 1.8–6.2) communication events per year in patients with MDD or PD

compared to 2.1 (interquartile range, 1.0–2.9) communication events in patients without MDD or PD (*p* = 0.001).

Impact on Number of Outpatient Visits and Communication Events

Impact on number of outpatient visits and communication events was tested using clinical parameters, the presence of MDD or PD, QoL and lifestyle factors. Linear regression analysis showed a significant impact of age and 6MWD on the number of visits per year. Per 10 years of patients age there was a loss of 0.2 visits per year (*p* = 0.003) and per 50 m 6MWD there was a loss of 0.1 visits per year (*p* = 0.007). Impact on communication events per year was only determined by the presence of MDD or PD. If a patient had any current MDD or PD, correspondence increased by 2.2 communication events per year (*p* = 0.001) with the linear regression analysis stating a constant of 2.4 communication events per year. This results in a near two-fold number of communication events in the presence of MDD or PD. The other covariates sex, packyears, HADS-A and HADS-D scores, QoL, education and WHO FC had no significant impact on the number of outpatient visits or communication events per year.

DISCUSSION

The main finding of this study can be summarized as follows: patients with MDD or PD have a higher need for patient care with a higher demand for extracurricular communication. The presence of MDD or PD was the only factor significantly influencing the rate of communication events. Patients with MDD or PD had worse QoL and HADS-scores while no differences in PAH medication or lifestyle factors were found. Education had no impact on number of outpatient visits or communication events nor were there any differences in education between patients with or without MDD or PD.

Impact on outpatient visits was determined by age and 6MWD while communication events were impacted by the presence of MDD or PD. While the association of age and 6MWD on outpatient visits was significant, absolute differences in number of outpatient visits were small suggesting only limited impact on clinical practice. Overall, the difference of 0.2 or 0.1 visits per year respectively might not result in an impaired health-care-utilization for patients with MDD or PD.

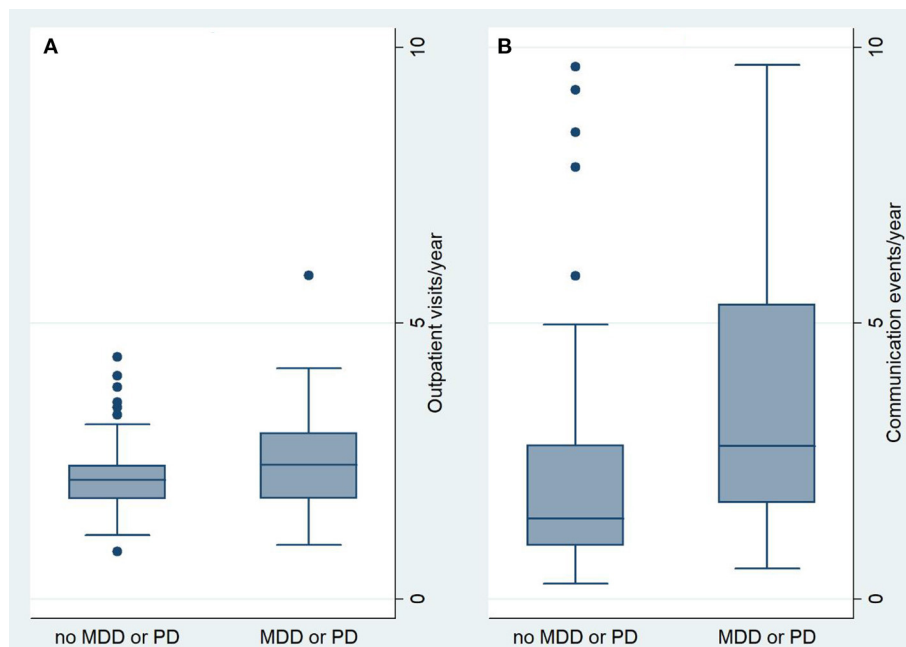


FIGURE 1 | Comparison of Outpatient visits/year **(A)** and communication events/year **(B)**. MDD, major depressive disorder; PD, panic disorder.

The only determinant for an increased number of communication events was the presence of MDD or PD. These patients had an almost two-fold increase in communication events while there were no differences in therapy strategies or disease severity (Table 1). This is in line with previous studies showing that the presence of a mental health disorder is associated with significantly higher health care resource utilization and costs independent of disease severity (24, 25).

Communication events beyond outpatient visits seem to be a valuable instrument for patients with mental disorders to facilitate health-care-utilization. Recent data have shown that the use of telecommunications such as video consultations reduced the need for onsite outpatients visits with increased use during the COVID-19 pandemic (26). While established patients had no worsening of mental disorders during the Covid-19 pandemic (27), health care utilization in form of diagnostic delay and increased time to referral in patients with PAH was impaired (28). Thus, future strategies and technologies are needed to fulfill patient's health-care-needs.

Our findings raise questions about optimizing the management of patients with PAH especially in the setting of mental disorders. First, mental disorders such as major depressive disorders or panic disorders need to be assessed in routine care. However, a SCID maybe not be feasible for screening purposes. The HADS was recently proven to detect anxiety and depression in patients with PAH (13) but also other tools such as the Hamilton Anxiety- or Depression Scale (HAM-A or HAM-D) might be feasible. Further, studies have shown that poor access to coordinated mental health care had impact on acute health-care-utilization. Different models of care such as a multidisciplinary approach with the integration of medical

and psychiatric health care have been described in primary as well as specialty care such as is PAH care (29). Recent studies have shown a higher prevalence of adjustment disorders among mental disorders in patients with PAH (13). Metacognitive treatment, a cognitive behavioral therapy, has been successfully applied to a patient with newly diagnosed PAH suffering from severe adjustment disorder (30, 31). With only limited data on psychiatric treatment options in patients with PAH, further studies are needed. This preliminary report on health disparities and health care utilization raises the question of improved patient care for patients with PAH. Knowledge, deeper understanding, and education of psychiatric disorders is key to prevent further stigma, increase awareness for patients challenges and needs and improve QoL beyond the physical burden of PAH. We suggest a specialized approach to address the needs of patients with MDD or PD through available treatment programs. PAH patients with MDD or PD have an increased need for assistance of social workers, physiotherapist and occupational therapist which should be a valuable asset in PAH patient's care. Further the availability of fast-track psychiatric consultations and acute crisis management should be of importance. In summery we suggest a comprehensive multidisciplinary psychiatric medical care for patients with MDD or PD and conclude that further research is needed to inform clinicians on the differences in health care utilization in the presence of psychiatric disorders.

Limitations

This study has limitations and strength. One limitation is the monocentric cross-sectional design of the study and the use of outpatients visits and another that communication events per year as a surrogate for health-care-utilization has

not been validated. Further no economical evaluation has been conducted. However, for a rare disease the analyzed sample size is high and the SCID-derived diagnosis of mental disorders is considered the gold standard of psychiatric assessment.

CONCLUSION

Compared to PAH patients without mental disorders, patients with MDD or PD are more likely to seek communication with their health care provider and health care systems should address the higher need of patients with MDD or PD. These findings were independent of disease severity or therapy. Future studies are needed to inform clinicians, psychiatrists and specialized nurses on differences in health care utilization as well as patients' individual needs.

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 Hannover Medical School. The patients/participants

provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

DHP was responsible for study design, implementation of the study, data collection, data interpretation and drafting the manuscript. TM was responsible for data collection and revising the manuscript. KK was responsible for study design, data interpretation, and revising the manuscript. JK was responsible for data interpretation and revising the manuscript. MR was responsible for implementation of the study and critically revising the manuscript. MH was responsible for implementation of the study, data interpretation, and critically revising the manuscript. KO was responsible for study design, implementation of the study, data interpretation, and critically revising the manuscript. JF was responsible for study design, implementation of the study, data collection, statistical analysis, data interpretation, and drafting the manuscript. All authors contributed to the article and approved the submitted version.

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Childhood Maltreatment, Mental Well-Being, and Healthy Lifestyle in Patients With Chronic Thromboembolic Pulmonary Hypertension

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Introduction: Chronic thromboembolic pulmonary hypertension (CTEPH) is a potentially life-threatening condition associated with high morbidity and mortality. However, advances in medical, surgical and interventional treatment have markedly improved the outcome of patients with CTEPH. Additional factors potentially influencing quality of life (QoL) and outcome in CTEPH are yet to be defined. Child maltreatment is a major risk factor for unfavorable behavioral, mental as well as physical health outcomes and has been associated with decreased QoL. To date, no study assessed the impact of childhood trauma in patients with CTEPH.

Methods: Patients with CTEPH were invited to complete the Childhood Trauma Questionnaire (CTQ). Data were compared to prevalence data from the German population. Mental well-being was assessed using the Hospital Anxiety and Depression Scale (HADS) and quality of life was measured using the WHO Quality of Life Questionnaire (WHOQOL). Furthermore, lifestyle factors and physical health parameters were studied.

Logistic regression analysis was used to investigate a possible impact of child maltreatment on markers of disease severity.

Results: One-hundred and seven patients with CTEPH completed the CTQ. These patients reported higher rates of emotional abuse and physical abuse and emotional neglect compared to the German population while rates of physical neglect and sexual abuse did not differ between patients and German population with prevalence of 20.6% for emotional abuse, 20% for physical abuse, 22% for emotional neglect, 46% for physical neglect, and 6% for sexual abuse in patients with CTEPH. Higher CTQ scores

were associated with anxiety symptoms as well as negatively associated with QoL. No direct impact of childhood trauma on CTEPH severity was found.

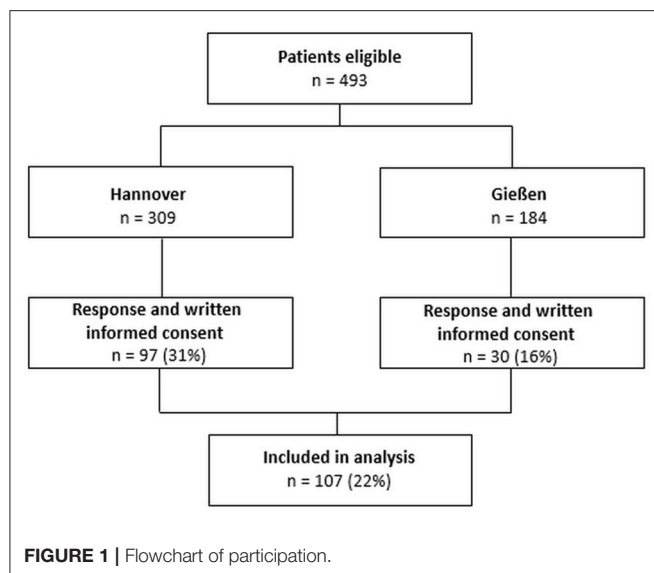
Conclusion: We found a higher rate of child maltreatment in patients with CTEPH in comparison to the German population. Correlations suggest moderate associations between CTQ scores and mental health and QoL. Child maltreatment had no significant impact on disease severity. Further investigation on proper interventions to support affected patients is needed.

Keywords: chronic thromboembolic pulmonary hypertension, pulmonary hypertension, childhood maltreatment, childhood trauma questionnaire, CTQ, CTEPH, quality of life

INTRODUCTION

Chronic thromboembolic pulmonary hypertension (CTEPH) is a chronic disease occurring as a possible complication after pulmonary embolism. There are several entities of pulmonary hypertension (PH), categorized into five groups by the World Health Organization (WHO). Of these, CTEPH is designated as WHO group 4.1 (1). In CTEPH, unresolved thromboembolic material leads to the occlusion of pulmonary arteries and progressive pulmonary vascular remodeling resulting in elevated pressure and resistance in the pulmonary vascular bed (2). As a consequence, patients are initially experiencing rather unspecific symptoms like progressive dyspnea on exertion and fatigue as well as syncope and signs of right heart failure in advanced disease (3). With pulmonary endarterectomy (PEA) as surgical treatment, CTEPH became a potentially curable disease for operable patients. The 3-year survival rate increased from estimated 40–90% in patients who underwent surgery. While the majority of operable patients can be cured or achieve functional improvement, residual or recurrent CTEPH might be present (4, 5). Further on, about one half of patients with CTEPH is considered inoperable and therefore receiving lifelong medical treatment and interventional therapy if possible (6, 7). Despite improvements in treatment and increased life expectancy, quality of life is impaired in comparison to the general population (8, 9), and concomitant mental disorders have shown to be associated with impaired physical health (10). Taking these results into account, other factors, increasing the risk of impaired quality of life, physical health and developing mental disorders, are of scientific interest. One of the factors potentially associated with disease coping and QoL is child maltreatment, which is associated with a various number of negative outcomes in adulthood. Child maltreatment is defined as abuse and neglect experienced by children through their parents or other caretakers potentially causing them harm. It is divided into five subtypes of sexual abuse, physical abuse, and neglect as well as emotional abuse and neglect (11). Global prevalence rates for subtypes of child maltreatment are being reported as 12.7% for sexual abuse, 22.6% for physical abuse, 36.3% for emotional abuse, 16.3% for physical neglect, and 18.4% for emotional neglect (12) as well as about one third of a German representative population sample experiencing at least one type of child maltreatment (13). The impact of

child maltreatment on developing mental health issues was considered by various studies. Experiencing one or multiple types of child maltreatment is associated with a higher risk for developing depression (14–16), anxiety and eating disorders (14) as well as personality disorders (17–19). In particular, the association between borderline personality disorder and childhood maltreatment is reported in current literature (20), for instance the earlier onset of the disorder in adults who experienced maltreatment through childhood in comparison to those who did not report maltreatment experiences (21). Furthermore, Marchetti et al. (22) were able to identify two personality profiles mediating the association between childhood maltreatment and borderline personality disorder. With one profile being characterized by a high tendency of self-criticism and the other of self-criticism in combination with dependency, they were able to suggest therapy addressing the specific traits, for example cognitive behavioral therapy, compassion focused therapy and schema therapy. Different forms of general health risk factors were found to be associated as well. Experiencing child maltreatment increases the risk for obesity, smoking, and risky sexual behavior (14, 23, 24) as well as alcohol abuse (16). While all of the subtypes are associated with negative health outcomes, a dose-response relationship was shown in more severe health outcomes through co-occurrence of different subtypes (15, 18, 23, 25). In addition to the aforementioned impacted factors, child maltreatment increases the risk of developing physical health issues. The experience of child maltreatment is associated with a higher risk of developing type 2 diabetes (26) with its association being partly mediated by obesity, smoking and high blood pressure (27, 28). It is related with a higher risk of developing chronic obstructive pulmonary disease (COPD) as well (26, 29) and with respiratory diseases in general (30, 31). Furthermore, a higher risk of developing cardiovascular disease is described (32) with higher risk of heart failure (25) and mortality in general (33). Decreased quality of life, higher ratings for anxiety and depression, and a lower cardiac function were found in patients with congenital heart disease who had experienced child maltreatment (34). To the best of our knowledge, this is the first study assessing child maltreatment in patients with CTEPH and the association of its intensity with measures of CTEPH severity, mental well-being and quality of life. Additionally, we assessed the prevalence of child maltreatment using the Childhood Trauma Questionnaire



(CTQ) and compared it with the prevalence of the general German population.

METHODS

This cross-sectional observational study enrolled patients diagnosed with CTEPH in two German pulmonary hypertension referral centers (Hannover Medical School and University of Gießen and Marburg). Local institutional boards (Nr. 8540_BO_K_2019 for Hannover and Nr. 21119 for Giessen and Marburg) approved the study. Inclusion criteria were a diagnosis of CTEPH (WHO Group 4.1) (1, 35), age ≥ 18 years, and mental as well as physical capability of completing all questionnaires in German. Participants were excluded if they did not answer all questionnaires. A current or lifetime psychiatric diagnosis was not considered an exclusion criterion. Four hundred and ninety-three patients (309 from Hannover, 184 from Gießen) were contacted by mail after being identified for meeting the criteria from the databases of both referral centers. Recruitment took place from December 2019 until May 2021. One hundred and seven participants were recruited. All participants provided written informed consent (see **Figure 1**). The results presented here are part of a larger examining psychosocial factors in patients with CTEPH. We here focused on adverse childhood experiences and its impact on mental well-being and healthy lifestyle.

Childhood Trauma Questionnaire

The Childhood Trauma Questionnaire (CTQ) (36) is a screening instrument retrospectively assessing experiences of child maltreatment including the subscales sexual abuse, physical abuse, emotional abuse, physical neglect and emotional neglect. In this study, the German short version (37, 38) was used, consisting of 28 items rated on a Likert-scale from 1 (never true) to 5 (very often true). Besides the five aforementioned subscales being measured by five items each, there are

three additionally items measuring the tendency to minimize experienced maltreatment. Wingenfeld et al. (38) reported high internal consistency for emotional abuse, emotional neglect, physical abuse and sexual abuse (Cronbachs $\alpha \geq 0.89$) but not for physical neglect (Cronbachs $\alpha = 0.62$). In order to measure the prevalence of each subtype, thresholds based on Walker et al. (39) were used, which were used in the prevalence study of the general German population as well (13). In accordance with Walker et al. (39), we utilized a threshold score of 10 for emotional abuse, of 15 for emotional neglect, of 8 for physical abuse, of 9 for physical neglect and of 8 for sexual abuse.

Mental Well-Being, Quality of Life, and Lifestyle Factors

In order to measure the participants' mental well-being, the Hospital Anxiety and Depression scale (HADS) (40) was used assessing symptoms of anxiety and depression. The German version shows high internal consistency for both scales (Cronbachs $\alpha = 0.8$) (41). Quality of life was investigated with the short version of the WHO Quality of Life Questionnaire (WHOQOL-BREF) (42). Internal consistency (Cronbachs Alpha) for the subscales of the German version range between $\alpha = 0.59$ and $\alpha = 0.91$ (43). Furthermore, anthropometric data (age, weight, height, and body mass index) as well as lifestyle factors (alcohol consumption, exercise, and smoking) and socio-demographic information (education, employment) were assessed. Exercise was defined on a scale from 1 (no sport exercise at all) to 6 (sport exercise more than three times a week). Alcohol consumption was measured in drinks per week.

Structured Clinical Interview for DSM-5

The participants were interviewed by a trained interviewer using the structured clinical interview for DSM-5 (SCID-5; German translation) (44). The interview was conducted either face to face or *via* telephone depending on the preferences of the participants. The SCID-5 consists of a semi structured interview using questions based on the diagnostic criteria for psychiatric disorders of the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) (45). The results of these interviews were used for a psychiatric characterization of the participants as reported elsewhere (46) and to control for possible confounders.

Clinical Assessments

Body mass index (BMI), lung function tests including WHO functional class (WHO-FC), serum levels of the N-terminal fragment of pro brain natriuretic peptide (NT-proBNP), 6-min walk distance (6MWD) and the diffusion capacity of the lungs for carbon monoxide (DLCO) were used for the clinical assessments. These parameters were assessed at the time of the study while the hemodynamic parameters were assessed at time of the diagnosis.

Statistical Analysis

In this study both, IBM SPSS Statistics 28.0 (IBM Corp., Armonk, NY, USA) and STATA 13.0 (StataCorp LP, College Station, Texas, USA) statistical software, were used for data-analysis. Depending

on its appropriation, either mean and standard deviation (SD) or median and interquartile range (IQR) were used for showing continuous variables. Furthermore, and unless indicated otherwise, *n* and percent (%) are used for categorical variables. Chi-square tests were used in order to compare prevalence rates of the different types of child maltreatment in CTEPH patients and a general German population presented by Iffland and colleagues (13). Associations between general child maltreatment (total CTQ score), the child maltreatment subtypes (CTQ sub scores), mental well-being (HADS and WHOQOL), and the aforementioned lifestyle factors were analyzed performing partial correlation adjusted for age and gender. The relationship between child maltreatment (total CTQ score) and physical functioning of CTEPH patients (WHO-Functioning class) was assessed through logistic regression analysis. Mildly symptomatic patients (WHO-FC I/II) and patients with more severe symptoms (WHO-FC III/IV) were compared. $P < 0.05$ were considered statistically significant.

RESULTS

Participant Characteristics

The final sample of this study consisted of 107 patients with mean age of 65 ± 14 years (range, 31–86). There was no significant sex difference between participants who experienced child maltreatment and who did not. None of the participants had current symptoms or a diagnosis of a post-traumatic stress disorder. Most patients (56%) were classified as WHO FC I/II and only 3% as WHO FC IV. For further characteristics (see **Table 1**).

Prevalence of Child Maltreatment in CTEPH

Fifty-seven percent of the participants had experienced at least one type of child maltreatment. 20.6% reported to have experienced emotional abuse. Furthermore, 19.6% reported physical abuse, 21.5% emotional neglect, 45.8% physical neglect, and 5.6% sexual abuse. Significantly higher rates of emotional abuse [$p \leq 0.001$] physical abuse [$p = 0.020$] and emotional neglect [$p = 0.028$] were found compared to the general German population (13). Prevalence rates of physical neglect [$p = 0.598$] and sexual abuse did not differ [$p = 0.791$] (see **Table 2**).

Association of Child Maltreatment and Mental Well-Being, Quality of Life, and Lifestyle Factors (Adjusted for age and Gender)

The total CTQ-score was correlated with anxiety symptoms of patients with CTEPH. It was negatively correlated with overall QoL and physical QoL. Emotional abuse was negatively correlated with overall QoL. Emotional neglect correlated with anxiety symptoms and showed negative correlation with physical QoL.

Physical abuse was not correlated with any aspects. Physical neglect correlated with anxiety symptoms and was negatively correlated with physical QoL. Sexual abuse was negatively correlated with overall QoL as well as physical QoL (see **Table 3**).

Differences in the Severity of CTEPH in Association With Child Maltreatment

Using a logistic regression model to evaluate the association between child maltreatment and the severity of CTEPH at the time of the study, we defined WHO FC as depended variable with WHO FC I and II being considered asymptomatic and WHO FC III and IV being considered symptomatic. CTQ total score was defined as the independent variable. The model was statistically not significant [$p = 0.650$]. Therefore, the CTQ total score was not associated with the severity of CTEPH defined by WHO FC class.

DISCUSSION

In this study, we investigated the prevalence of childhood maltreatment and its association with mental well-being, quality of life, and physical health in patients with CTEPH. More than half of the patients with CTEPH had experienced at least one subtype of childhood maltreatment with physical neglect being the most frequent subtype followed by emotional neglect and emotional abuse. While the prevalence of sexual abuse and physical neglect did not differ from prevalence rates in the general German population, the prevalence of emotional abuse, emotional neglect, and physical abuse were higher in patients with CTEPH. The relatively high rates of different kinds of childhood maltreatment in CTEPH could possibly be explained by changing parenting patterns during past decades. Parenting behavior, which is now considered abusive, was considered acceptable earlier on (47). Our patients had a mean age of 65 years, were born during the 1950s and educated by parents who themselves were survivors of the second world war. Being traumatized after experiencing a war was described to contribute to the next generations' childhood trauma (48, 49). In addition to that, parenting behavior was associated with being passed on from one generation to the other referred to as intergenerational transmission, increasing the likelihood of experiencing childhood maltreatment from former maltreated parents (47). Therefore, the experienced parental trauma and the parenting behavior based on old standards may have contributed to the higher prevalence rates of child maltreatment in this cohort. The high but not significantly different prevalence of physical neglect is reported to be especially apparent in the older German population due to growing up after the Second World War and suffering from privation (50).

Overall childhood maltreatment had a negative impact on general and physical QoL and was positively associated with anxiety symptoms. Furthermore, the subtypes emotional neglect and physical neglect were positively associated with anxiety symptoms as well. Emotional abuse and sexual abuse had a negative impact on overall QoL. Emotional neglect, physical neglect, and sexual abuse had a negative impact on physical QoL. A relationship between child maltreatment and the degree of physical impairment could not be identified.

The reported negative association between childhood maltreatment and overall and physical QoL is in line with other studies (51–53). Mechanistically, it has been suggested

TABLE 1 | Characteristics of the patients at baseline.

	All patients (<i>n</i> = 107)	Patients with any CTQ positive category (<i>n</i> = 61)	Patients without any CTQ positive category (<i>n</i> = 46)	<i>p</i> -value
Age (years)	69 (56–76)	70 (58–77)	65 (53–76)	0.066
Female sex (%)	55 (51%)	32 (53%)	23 (50%)	0.801 ^a
BMI (kg/m ²)	26 (24–31)	27 (24–32)	26 (24–30)	0.383
Diagnosis				
History of VTE, <i>N</i> (%)	63 (79%)	39 (87%)	24 (69%)	0.05 ^a
Time since CTEPH diagnosis (years)	4 (3–7)	4 (3–8)	4 (2–7)	0.423
WHO FC				
I/II, <i>N</i> (%)	56 (56%)	30 (52%)	26 (60%)	0.491 ^a
III, <i>N</i> (%)	42 (33%)	26 (45%)	16 (37%)	
IV, <i>N</i> (%)	3 (3%)	2 (3%)	1 (2%)	
6MWD (m)	449 (337–533)	449 (338–510)	459 (330–545)	0.462
NT-proBNP (ng/l), <i>N</i> = 86	168 (69–414)	174 (70–459)	167 (62–334)	0.728
DLCO (% pred.)	62 (53–74)	63 (51–77)	62 (55–71)	0.546
paO ₂ , mmHg	62 (58–70)	64 (59–71)	61 (58–66)	0.131
Hemodynamics at diagnosis				
mPAP (mmHg)	42 (33–50)	41 (31–48)	42 (34–52)	0.470
PAWP (mmHg)	9 (6–12)	9 (6–11)	9 (6–12)	0.642
CI (l/min/m ²)	2.4 (2–2.8)	2.2 (2–2.7)	2.4 (1.9–2.9)	0.602
PVR (dyn·s·cm ⁻⁵)	506 (339–743)	480 (333–744)	509 (361–766)	0.789
CTEPH medication*				
No therapy	22 (28%)	8 (18%)	14 (40%)	0.07 ^a
Monotherapy	47 (59%)	29 (64%)	18 (51%)	
Double combination therapy, <i>n</i> (%)	11 (14%)	8 (18%)	3 (9%)	
OAC, <i>n</i> (%)	101 (94%)	58 (95%)	43 (94%)	0.721 ^a
CTEPH interventions				
PEA, <i>n</i> (%)	27 (25%)	15 (25%)	12 (26%)	0.860 ^a
BPA, <i>n</i> (%)	37 (35%)	23 (38%)	14 (30%)	0.434 ^a
BPA Sessions	2 (0–5)	2 (0–5)	2 (0–5)	0.869
Smoking status				
Active, <i>n</i> (%)	2 (2%)	1 (2%)	1 (2%)	0.941 ^a
Former, <i>n</i> (%)	45 (42%)	25 (41%)	20 (44%)	
Never, <i>n</i> (%)	60 (56%)	35 (57%)	25 (54%)	
Packyears	12 (8–26)	9 (5–26)	18 (11–29)	0.523
Sociodemographic items				
Drinking (drinks per week)	0 (0–2)	0 (0–2)	0 (0–2)	0.753
Exercise Score (points)	3 (2–4)	3 (2–4)	3 (2–4)	0.509 ^b
HADS-A (points)	5 (2–9)	5 (3–9)	4 (2–7)	0.190
HADS-D (points)	5 (2–8)	6 (4–9)	4 (1–6)	0.007
QoL-overall (points)	72 (65–85)	70 (63–78)	81 (69–92)	0.002
QoL-psych (points)	71 (58–79)	63 (50–79)	75 (59–86)	0.024
QoL-physical (points)	64 (53–79)	61 (50–73)	71 (59–82)	0.011

Continuous variables are stated as median and interquartile ranges (IQR) and categorical variables are stated as *n* and percent (%), unless indicated otherwise. Mean and SD used because of distribution of the data. ^aNon-parametric Pearson's chi-squared test used because of nominal scale of the variable. ^bNon-parametric Mann-Whitney-U-Test used because of ordinal scale of the variable. *There were no cases for triple combination therapy. Statistically significant values are shown as bold.

CM, child maltreatment; BMI, body mass index; QoL, quality of life; HADS-A, hospital anxiety and depression scale—anxiety; HADS-D, hospital anxiety and depression scale—depression; WHO FC, World Health Organization Functional Class; 6MWD, six-minute walking distance; BNP, brain natriuretic peptide; NT-proBNP, N-terminal fragment of pro-brain natriuretic peptide; DLCO, diffusion capacity of the lung for carbon monoxide; paO₂, mmHg, arterial pO₂; mPAP, mean pulmonary arterial pressure; PAWP, pulmonary artery wedge pressure; CI, cardiac index; PVR, pulmonary vascular resistance; IQR, inter quartile range.

TABLE 2 | Prevalence of child maltreatment and its subtypes of CTEPH in comparison to data from the general German population.

	CTEPH (n = 107)	General German population (Iffland et al., 2013) n = 2,500	p-value
Emotional abuse	22 (20.6%)	254 (10.2%)	<0.001
Physical abuse	21 (19.6%)	301 (12.0%)	0.020
Emotional neglect	23 (21.5%)	348 (13.9%)	0.028
Physical neglect	49 (45.8%)	1,210 (48.4%)	0.598
Sexual abuse	6 (5.6%)	156 (6.2%)	0.791

Child maltreatment prevalence rates per group stated as percent (%), CTEPH, chronic thromboembolic pulmonary hypertension; n, total number of participants. Statistically significant values are shown as bold.

TABLE 3 | Partial correlation (Spearman's *r*) of CTQ-Scores in CTEPH with HADS, QoL, Lifestyle, and WHO FC adjusted for age and gender.

	HADS-D	HADS-A	QoL	Phys. QoL	Psych. QoL	BMI	Exercise	Drinks	Smoking	WHO FC
CTQ-TS	0.240	0.369**	−0.324*	−0.383**	−0.250	0.130	−0.211	−0.002	0.060	0.157
CTQ-EA	0.253	0.248	−0.277*	−0.242	−0.253	0.201	−0.196	0.015	0.103	0.126
CTQ-EN	0.234	0.276*	−0.262	−0.348**	−0.179	0.033	−0.197	−0.024	0.143	0.146
CTQ-PA	0.206	0.266	−0.233	−0.241	−0.265	0.155	−0.117	0.043	−0.072	0.008
CTQ-PN	0.129	0.299*	−0.241	−0.298*	−0.184	0.161	−0.204	−0.014	−0.040	0.204
CTQ-SA	0.234	0.245	−0.359**	−0.363**	−0.266	0.067	−0.041	−0.081	−0.155	0.001

CTQ-TS, childhood trauma questionnaire total score; CTQ-EA, childhood trauma questionnaire emotional abuse; CTQ-EN, childhood trauma questionnaire emotional neglect; CTQ-PA, childhood trauma questionnaire physical abuse; CTQ-PN, childhood trauma questionnaire physical neglect; CTQ-SA, childhood trauma questionnaire sexual abuse; HADS-D, hospital anxiety and depression scale—depression; HADS-A, hospital anxiety and depression scale—anxiety; QoL, WHO Quality of Life Questionnaire—total score; Phys. QoL, WHO Quality of Life Questionnaire—physical score; Psych. QoL, WHO Quality of Life Questionnaire—psychological score; BMI, body mass index; WHO FC, World Health Organization Functional Class.

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

that child maltreatment leads to biological and behavioral maladaptation, which interfere with the development of necessary skills to cope with obstacles later in life (54). The behavioral changes are associated with the development of maladaptive schemas in reaction to child maltreatment (55, 56). These schemas are hypothesized to negatively impact the way of dealing with wearing situations in adulthood, with little or no improvement over time (57). In addition to the maladaptive schemas, childhood maltreatment is characterized as increasing the risk of the disrupted ability to recognize and verbalize one's emotions, called alexithymia, increasing the risk of psychopathology (19, 58, 59). Furthermore, emotional dysregulation in general is associated with the experience of childhood maltreatment (60, 61) affecting the psychological well-being negatively by maladaptive coping with obstacles (62). The latter is explained with the need of a primary caretaker as role model in order to learn adequate emotion regulation and problem oriented coping strategies, which children, who experience childhood maltreatment, most likely do not have (63). In contrast maltreatment increases the probability of learning emotional coping strategies through the maltreating caretaker, characterized as avoidance of stressful situations as well as the suppression of emotions in general and the expression of negative emotions already during childhood and adolescence (61, 64) and later in adulthood with increased risk of engaging in substance use (65). The possible presence of maladaptive schemas, the lack of functional coping strategies with stressful events and the resulting impact on self-esteem and interaction might be responsible for the negative association between childhood maltreatment and QoL (54, 55). The association between

child maltreatment and anxiety symptoms in this cohort is supported by previous research (14, 34, 66, 67). The likelihood of developing anxiety after experiencing child maltreatment might be explained through an altered stress response. Changes in stress related systems [e.g., hypothalamus-pituitary-adrenal (HPA) axis, autonomic nervous system, serotonin transporter gene] tend to increase the anxiety sensitivity (68, 69). As CTEPH is a potentially life-threatening disease and debilitating symptoms as dyspnea are present, the increased anxiety sensitivity might be considered as a reason for the associations found in this study.

We did not find an association between child maltreatment of any kind and depressive symptoms as well as with other health risk factors such as BMI, smoking, low exercise and alcohol consumption. The result contrasts with the high prevalence rates of maltreatment found in this cohort and the strong association described between the aforementioned factors and child maltreatment in other cohorts (14, 16, 23, 54, 70). Additionally, we did not find an association between physical abuse and QoL, which is in contrast to other studies pointing out the influence of physical abuse on QoL (54). The lacking associations might be explained by the low number of participants in our study, masking the effects of childhood maltreatment on psychological and behavioral factors. A further possible explanation could be resilience as it was reported to lower the risk of developing depression after the experience of child maltreatment (71). Resilience is defined as adaptation to adverse experiences, showing at least average functioning in various domains and an absence of pathology (72). It is viewed as a dynamic process which therefore does not exclude the possibility of functioning in some domains while not in

others (73). The absence of the association with common health risk factors and depressive symptoms in this study might be explainable by enough protective factors within the participants to cope in a functional way with the experienced trauma instead of engaging in maladaptive behavior as smoking, low exercise, and alcohol consumption. Further investigation on the effect of childhood maltreatment and resilience simultaneously might help to further elucidate the mechanism between resilience on the one hand and maladaptation on the other hand.

Moreover, the absence of a direct impact of child maltreatment on the severity of CTEPH might be explainable with resilience as well as the underlying mechanisms and risk factors for developing CTEPH. Wegman and Stetler (31) described the association of child maltreatment with cardiovascular and respiratory diseases with a greater risk to engage in health risking behavior as smoking and consuming alcohol. Other studies described this mediating effect as well (25, 26) which could be missing in this cohort due to the lack of association between childhood maltreatment and the aforementioned health risk behaviors. Another reason for the missing impact of childhood maltreatment on CTEPH severity might refer to the dose-response relationship. Studies who investigated on the mental and physical health outcome of participants who experienced child maltreatment reported an increased risk especially in association with the co-occurrence of different subtypes (15, 23, 25, 26). In contrast to that, more than half of the participants who reported child maltreatment in this study, had experienced not more than one subtype, and less than one third had experienced three or more subtypes. Further studies with a larger sample might be needed to further investigate on the relationship between child maltreatment and severity of CTEPH.

In comparison to the general German population, three out of five maltreatment subtypes were present with higher prevalence in our CTEPH cohort. This implies the question whether childhood maltreatment might be associated with the development of CTEPH later in life. A possible link between childhood maltreatment and thromboembolic events might be seen *via* alterations of the inflammatory response. In fact, inflammation is linked to the development of CTEPH besides other risk factors such as acute pulmonary embolism, medical interventions (e.g., splenectomy and ventriculoarterial shunt) and plasmatic factors (74). Inflammatory markers like the C-reactive protein (CRP) were shown to be increased in comparison to healthy controls (75). As CRP was found to be associated with childhood trauma as well (76), changes in the inflammatory response could mediate the effect between child maltreatment and developing CTEPH. Molecular changes in maltreated individuals are associated with epigenetic changes in response to the experienced trauma. Alterations in DNA methylation are associated with altered gene expression, influencing for example the stress response and inflammatory processes (77, 78). Further studies on the mediating effect of epigenetic alterations due to child maltreatment associating it with CTEPH patients may be needed to clarify the exact relationship.

Regarding the conception of this study, limitations have to be acknowledged. Child maltreatment was assessed with the CTQ, which is based on self-report and retrospection making a recall bias possible (13, 79). Furthermore, out of the contacted

CTEPH patients, only 22% responded and were included into the assessment. Hence, the sample size was low in comparison to other studies focusing on the consequences of childhood maltreatment [e.g., (25, 33)]. One contributor to the low response rate may have been the higher age of our patient population compared to other studies. Furthermore, the motivation to participate might have been limited as many of the patients were no longer followed at their PH center (especially those who had undergone successful PEA surgery). In addition, the questionnaires had been sent out without personal advance notice from their PH physicians.

In conclusion, more than half of our patients with CTEPH had experienced at least one type of child maltreatment. A history of child maltreatment had a negative impact on QoL and was associated with anxiety symptoms. In order to improve the treatment of patients with CTEPH, the presence of experienced childhood maltreatment should be considered. Further studies are needed to assess tools that may help patients to cope better with the consequences of CTEPH.

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 Ethics Committee, Hannover Medical School, Hannover Germany and Ethics Committee, University Medical Center Gießen und Marburg, Marburg, Germany. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

NL, JE, MH, KK, KO, and M-RD were responsible for study design, implementation of the study, statistical analysis, data interpretation, and drafting the manuscript. NL and M-RD were responsible for conducting the interviews. NL, JE, and M-RD did data collection. JK, MR, and HGa implementation of the study. IH, D-HP, HGh, DE, JK, MR, HGa, TM, and H-DK were responsible for study design, data interpretation, and revising the manuscript. All authors contributed to the article and approved the submitted version.

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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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Prevalence of Mental Disorders in Patients With Chronic Thromboembolic Pulmonary Hypertension

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Objective: Pulmonary hypertension (PH) is a chronic and progressive pulmonary vascular disease resulting in symptoms such as shortness of breath and fatigue and leading to death from right heart failure if not adequately treated. Chronic thromboembolic pulmonary hypertension (CTEPH) is a subgroup of PH characterized by obstruction or occlusion of pulmonary arteries by post-embolic fibrotic material. To date, few studies examined symptoms of depression and anxiety in patients with CTEPH, showing depression levels as high as 37.5%. However, none of the former studies used structured expert interviews.

Methods: Mental disorders were diagnosed using the Structured Clinical Interview for DSM-5 (SCID). The prevalence of mental disorders in patients with CTEPH were compared to the prevalence in patients with pulmonary arterial hypertension (PAH) and the general German population. Quality of life (QoL) was measured with World Health Organization (WHO) Quality of Life questionnaire (short form). Factors associated with QoL were analyzed with linear regression and the diagnostic value of the Hospital Anxiety and Depression Scale (HADS) was evaluated using receiver operating characteristics (ROC) curve analysis.

Results: Hundred and seven patients with CTEPH were included. Almost one-third of the patients (31.8%) had current psychological disorders. Panic disorder (8.4%), specific phobia (8.4%), and major depressive disorder (6.5%) were the most prevalent mental illnesses. The prevalence of panic disorders was higher in CTEPH compared to the German population while major depressive disorder was fewer in CTEPH compared to PAH. The presence of mental disorders had a major impact on QoL. Hospital Anxiety and Depression Scale discriminated depression and panic disorder reliably.

Conclusion: Mental disorders are common in patients with CTEPH and associated with an impaired QoL. The HADS may be a useful screening tool for panic and depression disorders in patients with CTEPH. Further research on therapeutic strategies targeting mental disorders in patients with CTEPH is needed.

Keywords: chronic thromboembolic pulmonary hypertension, pulmonary hypertension, mental disorder, quality of life, depression disorder, panic disorder, CTEPH

INTRODUCTION

Chronic thromboembolic pulmonary hypertension (CTEPH) is characterized by non-resolving clots following pulmonary embolism resulting in elevated pulmonary arterial pressure and increased pulmonary vascular resistance (PVR) leading to right heart failure and death if not adequately treated (1). It is categorized as World Health Organization (WHO) Group 4 PH and a debilitating disease with exertional dyspnea and impaired exercise tolerance being the leading symptoms. As in other forms of pulmonary hypertension (PH), patients are prone to develop signs of right-sided heart failure, which is also the leading cause of death in these patients (2–4). The diagnostic and therapeutic options have increased during the last years (5–7). In operable patients, pulmonary endarterectomy (PEA) is the treatment of choice and may be curative whereas inoperable patients can experience symptom relieve by drug therapy and pulmonary balloon angioplasty (BPA) (8, 9).

The diagnosis of CTEPH might impact patients' life beyond the somatic disabilities. The physical impairment might mean a potential inability to participate in everyday life and to continue working, which may result in financial as well as social limitations. In addition, the patients are faced with the outlook of having to undergo invasive procedures and/or suffering from a chronic, life-threatening disease. As a consequence, patients might be at risk of developing concomitant mental disorders.

Previous studies on the prevalence of mental disorders in patients with CTEPH almost exclusively focused on depression and anxiety (10–15). The prevalence of these disorders ranged from 14.3 to 56.5% for depression and 4.1 to 43.5% for anxiety disorders. In a mixed sample of patients with CTEPH and pulmonary arterial hypertension (PAH) evaluated by Zhou et al., the prevalence of depression and/or anxiety was even higher (66.3%) (12). Whereas, all listed studies found impaired quality of life (QoL) in the presence of a mental disorder, the prevalence rates of mental disorders differed substantially and not all studies focused on CTEPH exclusively. Additionally, most studies almost exclusively used self-rating questionnaires rather than structured clinical interviews to determine the presence of mental disorders.

In the present study, we examined the prevalence of current mental disorders, especially depression and anxiety disorders, in patients with CTEPH compared to PAH and the normal population using structured clinical interviews (structured clinical interview for DSM-5, SCID) (16). Additionally, this study aimed to analyze the association between current mental disorders and QoL in CTEPH.

To the best of our knowledge, there has been no comparable study-design for patients with CTEPH yet.

METHODS

Design and Study Setting

In this observational cross-sectional multicenter study patients ≥ 18 years with a confirmed diagnosis of CTEPH according to current diagnosis criteria (3, 4, 17–19), who were mentally and physically capable and willing to complete all questionnaires and participate in an interview in German language, were included. The patients were recruited in two large German PH referral centers (Hannover Medical School and University of Gießen and Marburg). Approval of the study was given by the local institutional review boards (Nr. 8540_BO_K_2019 for Hannover and Nr. 21119 for Giessen and Marburg). Written informed consent was given by all included patients. The results presented here are part of a larger examining psychosocial factors in patients with CTEPH. This study focused on the prevalence of mental disorders and its impact on QoL.

Recruitment

Databases in both centers were searched for active patients with CTEPH.

Contact was established by mail. Written informed consent was obtained from all participants before other study-related procedures were performed.

The structured clinical interviews for DSM-5 were performed by psychologists either face to face or by telephone interview. The decision whether interviews were conducted face to face or by telephone was made depending on pending appointments in the outpatient clinics and the patients' preferences.

Questionnaires and SCID

All self-rated questionnaires included anthropometric data (age, weight, height, body mass index), lifestyle factors such as sports, smoking habits and current alcohol consumption (drinks per week). The sport score was defined by a 6-point-scale (1 = no sports; 2 = occasionally; 3 = less than one time a week; 4 = one time a week; 5 = more than one time a week; 6 = more than three times a week).

The psychiatric characterization was conducted using the SCID (German translation) for both current and past axis-I psychiatric disorders. It included a structured set of questions based on diagnostic criteria. Answers given by the interviewed person were rated by the trained interviewer regarding the presence and clinical impact of the symptom. Only current disorders were reported.

The Hospital Anxiety and Depression Scale (HADS) (20) was used to compare diagnostic validity of this frequently used self-rating instrument with the results of expert interviews (SCID). The HADS consists of the two dimensions “anxiety” (HADS-A) and “depression” (HADS-D). Both dimensions contain seven items each that are rated on four-point scales (0–3 points). Results are reported as sum per dimensions. Higher values in this screening tool mean a higher probability of clinically relevant depressive or anxiety disorder.

Quality of life was measured with the WHO QoL questionnaire in short form (WHOQOL-BREF) (21, 22). The WHOQOL-BREF consists of a total of 26 items, each rated on a five-point scale (1–5 points). The questionnaire consists of the scales “physical” (seven items), “psychological” (six items), “social” (three items), and “environment” (eight items). The first two items of the questionnaire are only considered in the calculation of the global health status. The respective scale scores are shown as mean values of the given items. The global health status is shown as the mean value of all items. All scales are converted from 1 to 5 points to 0 to 100 points to ensure comparability with the WHOQOL (23). Higher values in the given scales can be interpreted as higher QoL. We reported four dimensions of the WHOQOL-BREF, i.e., overall, psychological, physical, and social QoL.

The licenses for the German version of the SCID, HADS, and WHOQOL-BREF were acquired. The self-rated questionnaire including anthropometric data and lifestyle factors was self-created.

Psychiatric Diagnosis

The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) was used to define mental disorders (24).

Clinical Assessments

Clinical assessments included WHO functional class (WHO FC), 6-min walk distance (6MWD), blood gas analysis, lung function tests including diffusion capacity of the lungs for carbon monoxide (DLCO), serum levels of the N-terminal fragment of pro brain natriuretic peptide (NT-proBNP), and body mass index (BMI) at the time of this study. Hemodynamic parameters were documented at diagnosis. All data concerning CTEPH related therapies (medication, BPA, PEA) from diagnosis until psychiatric assessment were collected.

Patients who underwent PEA with no signs of residual PH and no need for medical CTEPH-therapy thereafter were categorized as curatively treated.

Comparison With Population of Patients With PAH and General Population

The comparison of the prevalence of mental disorders in patients with CTEPH with the prevalence of mental disorders in patients with PAH was conducted using a sample of 217 PAH-patients aged 44–66 years recently described by Olsson et al. (25). Additionally, baseline demographics of the PAH sample were used to compare with those of the CTEPH sample. Data from a sample aged 18–79 years of the mental health module of the German Health Interview and Examination Survey for

Adults (DEGS1-MH; $n = 5,381$) (26) were used to compare the prevalence of mental disorders in patients with CTEPH with the prevalence of mental disorders in the general population.

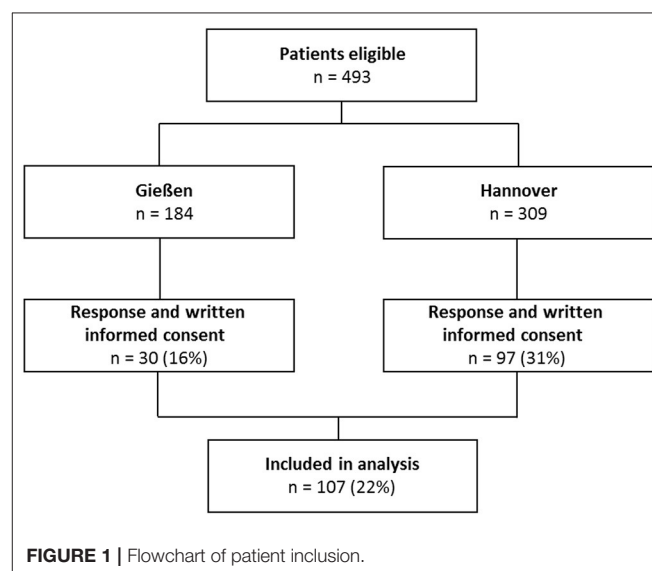
Statistical Analysis

The analysis of the data was done with the statistical software IBM SPSS Statistics 28.0 (IBM Corp, Armonk, NY, USA) and STATA 13.0 (StataCorp LP, College Station, Texas, USA). Unless indicated otherwise, categorical variables are displayed as n and percent (%). Continuous variables are shown as mean and standard deviation (SD) or median and interquartile range (IQR). t -Test, Mann-Whitney U-test, or χ^2 -test were used to compare groups, as appropriate. For the comparison of prevalence rates of mental disorders in CTEPH, PAH and a representative German population (DEGS1-MH), χ^2 -tests were used, respectively. Differences between the three populations and point estimates with 95% CIs were calculated. Differences in the prevalence of mental disorders between curatively treated CTEPH patients and non-curatively treated CTEPH patients were analyzed using χ^2 -test. The impact of mental disorders on QoL was examined with linear regression models. Determinants on QoL were calculated with psychological, physical, and overall QoL as dependent variables. The best cut-off values of HADS-A (anxiety) and HADS-D (depression) were calculated using receiver operating characteristics (ROC) curve analysis with calculation of the area under the curve (AUC) and corresponding sensitivity and specificity on the outcomes panic disorder and major depressive disorder derived from the structured clinical interview. All tests were two-sided, statistical significance was considered for p -values < 0.05 .

RESULTS

Participant Characteristics

All patients were approached and interviewed between December 2019 and May 2021. A total of 493 patients were contacted and



107 patients (22%) finally took part in the interview (**Figure 1**). Patient's characteristics are shown in **Table 1A**. Overall, patients with a current mental disorder were younger. In comparison with patients with PAH, the CTEPH sample was significantly older and included more male participants (**Table 1B**). Time since diagnoses was shorter in patients with CTEPH. Additionally, WHO FC, DLCO, mPAP, PVR, and the number of therapies differed between the groups. There were less active smokers in the CTEPH sample. Also exercise score as well as overall and psychological QoL differed between patients with CTEPH and patients with PAH.

Prevalence of Mental Disorders in CTEPH

Almost one-third of the patients showed current mental disorders (31.8%). Panic disorder and specific phobia (both 8.4%) were the most frequent disorders, followed by major depressive disorder (6.5%) (**Table 2A**). The prevalence of major depressive disorder was significantly lower in CTEPH compared to PAH ($p < 0.001$) while there was no difference to the general population. Compared to the general population, the prevalence of panic disorder was significantly increased in CTEPH, $p < 0.001$. The prevalence of mental disorders was independent of the CTEPH therapy, i.e. surgical, interventional, or medical therapy (**Table 1A**). There were no cases of alcohol dependence, schizophrenia, bipolar disorder, agoraphobia without panic disorder, PTSD, anorexia nervosa, and bulimia nervosa in this cohort at all. In addition, there were no differences between male and female patients concerning the prevalence of mental disorders.

Prevalence of Mental Disorders in Curatively vs. Non-curatively Treated CTEPH Patients

In total, 33% ($n = 9$) of all curatively treated patients and 32% ($n = 25$) of all non-curatively treated CTEPH patients were diagnosed with any current mental disorder. Detailed information is provided in **Table 2B**. Of note, none of the reported findings were significant.

Diagnostic Value of the Hospital Anxiety and Depression Scale in CTEPH

The ROC curve analysis of the HADS-D (Depression) showed an AUC of 80.4% (95% CI 63.5–97.3%, $p = 0.007$) and a cut-off value of ≥ 11 points for the detection of major depressive disorder. Sensitivity was 57.1% and specificity was 91.8% (**Figure 2B**).

For the HADS-A the ROC curve analysis showed an AUC of 79.7% (95% CI 66.1–93.3%, $p = 0.003$) for the detection of panic disorder at a cut-off value of ≥ 11 points with a sensitivity of 57.1% and specificity of 90.9% (**Figure 2A**).

Quality of Life in CTEPH

For all patients with CTEPH, the overall QoL assessed by the WOHQOL-BREF tool was 72 (65–85) points. Differentiated by presence of mental disorder, the overall QoL for patients with any current mental disorder was significantly lower with 69 (60–79) points compared to patients without any current mental disorder having 78 (66–90) points, $p = 0.002$. Both psychological and physical QoL were significantly lower in patients with any current

mental disorder while there were no differences in the severity of CTEPH in the somatic assessment (WHO FC, 6MWD, NT-proBNP) at the time of the psychiatric assessment (**Table 1A**). The social QoL did not differ between the groups.

Determinants of QoL in CTEPH

A linear regression analysis distinguished sports score, mental disorder and number of therapies as significant determinants of overall QoL ($r^2 = 31.1\%$), see **Table 3**. For the sports score, each point-raise was associated with a four-point increase in the overall QoL. Any current mental disorder was associated with a nine-point and each further therapy with a five-point decline in overall QoL. Sports score, current mental disorder and drinks per week were detected as significant determinants for psychological QoL ($r^2 = 20.4\%$). Each increase in sports score was associated with a three-point increase in the psychological QoL. A current mental disorder was associated with a 13-point decrease and drinks per week with a one-point decrease per drink in psychological QoL. World Health Organization functional class was the only significant determinant for physical QoL ($r^2 = 31.3\%$) which was associated with an 11-point decline per each WHO FC increase.

DISCUSSION

In summary, one third of the patients with CTEPH in our cohort had a current mental disorder, similar to what has been reported in the general population or patients with PAH. In patients with CTEPH, the most frequent mental disorders were panic disorder and specific phobia followed by major depression. The presence of any mental disorder had a major negative impact on overall and psychological QoL. Moreover, the HADS was identified as a possible screening tool for the identification of possibly present panic disorder and major depressive disorder in patients with CTEPH.

The prevalence of panic disorder in this study was comparable to previous findings in patients with other forms of PH (10–12, 14). One reason for the significantly increased prevalence of panic disorders in patients with CTEPH compared to the general population might be that symptoms of dyspnea can be perceived as threatening, cause anxiety, and potentially leading to avoidance of potentially dyspnea evoking activities (27). If this is linked to the actual perceived threatening experience of dyspnea connected to CTEPH in those patients, this could ensure that the mere appearance of the symptom leads to a negative evaluation which in turn triggers anxiety. Rumination due to breathlessness has already been described in CTEPH and has been associated with psychological distress (13).

Compared to PAH, the prevalence of panic disorder in CTEPH tended to be lower although this difference did not reach statistical significance. Most previous studies concerning anxiety disorders in CTEPH compared to PAH have yielded different results (10, 11, 14). Lower rates of anxiety disorders in patients with CTEPH compared to patients with PAH might be explained by the availability of more effective, sometimes even curative, therapeutic options for CTEPH such as PEA surgery and balloon pulmonary angioplasty (17, 28–30). At the same time there is

TABLE 1A | Characteristics of the patients at baseline.

	All patients <i>n</i> = 107	Any current mental disorders <i>n</i> = 35 (33%)	Patients without any current mental disorder <i>n</i> = 72 (67%)	<i>P</i> -value
Age (years)	69 (56–76)	59 (45–71)	72 (59–77)	0.001
Female sex (%)	55 (51%)	18 (51%)	37 (51%)	0.997 ^b
BMI (kg/m ²)	26 (24–31)	26 (24–32)	27 (24–30)	0.348
Diagnosis				
History of VTE, <i>n</i> (%)	63 (59%)	20 (57%)	43 (60%)	0.854 ^b
Time since CTEPH diagnosis (years) ^a	5.4 ± 0.5	4.6 ± 0.8	5.8 ± 0.6	0.208
WHO FC				
I, <i>n</i> (%)	23 (23%)	7 (21%)	16 (24%)	0.101 ^b
II, <i>n</i> (%)	33 (31%)	10 (30%)	23 (35%)	
III, <i>n</i> (%)	42 (39%)	13 (40%)	27 (41%)	
IV, <i>n</i> (%)	3 (3%)	3 (9%)	0 (0%)	
6MWD (m), <i>n</i> = 79	449 (337–533)	443 (227–546)	449 (340–519)	0.287
NT-proBNP (ng/l), <i>n</i> = 86	168 (69–414)	167 (78–439)	167 (58–421)	0.553
DLCO (% pred.), <i>n</i> = 85	62 (53–74)	66 (60–86)	61 (50–71)	0.052
paO ₂ , mmHg, <i>n</i> = 89	62 (58–70)	63 (60–70)	61 (58–66)	0.285
Hemodynamics at diagnosis				
mPAP (mmHg)	42 (33–50)	42 (27–47)	41 (33–52)	0.369
PAWP (mmHg)	9 (6–12)	10 (7–12)	9 (6–12)	0.242
CI (l/min/m ²)	2.4 (2–2.8)	2.1 (1.8–2.8)	2.4 (2.2–2.8)	0.265
PVR (dyn·s·cm ⁻⁵)	506 (339–743)	485 (316–830)	518 (376–731)	0.873
CTEPH medication*				
No therapy, <i>n</i> (%)	22 (28%)	9 (36%)	13 (24%)	0.517 ^b
Monotherapy, <i>n</i> (%)	47 (59%)	13 (52%)	34 (62%)	
Double combination therapy, <i>n</i> (%)	11 (14%)	3 (12%)	8 (15%)	
OAC, <i>n</i> (%)	101 (94%)	32 (94%)	67 (94%)	0.959 ^b
CTEPH interventions				
PEA, <i>n</i> (%)	27 (25%)	9 (27%)	18 (25%)	0.902 ^b
Time since PEA (month)	2 (1–19)	2 (1–6)	2 (1–27)	0.306
BPA, <i>n</i> (%)	37 (35%)	14 (42%)	23 (32%)	0.320 ^b
BPA sessions	2 (0–5)	2 (0–5)	2 (0–5)	0.932
Smoking status				
Active, <i>n</i> (%)	2 (2%)	0 (0%)	2 (3%)	0.558 ^b
Former, <i>n</i> (%)	45 (42%)	14 (40%)	31 (43%)	
Never, <i>n</i> (%)	60 (56%)	21 (60%)	39 (54%)	
Packyears	13 (8–26)	12 (8–28)	20 (8–26)	0.805
Sociodemographic items				
Drinking (drinks per week) ^a	1.6 ± 0.4	2.6 ± 1.0	1.1 ± 0.3	0.067
Exercise score (points)	3 (2–4)	3 (3–4)	3 (2–4)	0.845 ^c
HADS-A (points)	5 (2–9)	8 (4–11)	4 (2–7)	<0.001
HADS-D (points)	5 (2–8)	7 (4–10)	4 (1–7)	0.002
QoL-overall (points)	72 (65–85)	68 (60–79)	78 (66–90)	0.002
QoL-psych (points)	71 (58–79)	58 (46–75)	75 (59–83)	0.001
QoL-physical (points)	64 (53–79)	57 (46–71)	71 (55–82)	0.002
QoL-social (points)	71 (54–83)	67 (42–83)	75 (58–83)	0.110

BMI, body mass index; VTE, venous thromboembolism; CTEPH, chronic thromboembolic pulmonary hypertension; WHO FC, World Health Organization Functional Class; 6MWD, six-min walking distance; BNP, brain natriuretic peptide; NT-proBNP, N-terminal fragment of pro-brain natriuretic peptide; DLCO, diffusion capacity of the lung for carbon monoxide; paO₂, mmHg, arterial pO₂; mPAP, mean pulmonary arterial pressure; PAWP, pulmonary artery wedge pressure; CI, cardiac index; PVR, pulmonary vascular resistance; OAC, oral anticoagulation; PEA, pulmonary endarterectomy; BPA, pulmonary balloon angioplasty; HADS-A, hospital anxiety and depression scale-anxiety; HADS-D, hospital anxiety and depression scale-depression; QoL, quality of life; psych, psychological; SD, standard deviation; IQR, inter quartile range. Continuous variables are stated as median and interquartile ranges (IQR) and categorical variables are stated as *n* and percent (%), unless indicated otherwise.

^aMean and SD were used because of distribution of the data.

^bNon-parametric Pearson's chi-squared test was used because of nominal scale of the variable.

^cNon-parametric Mann-Whitney U-test was used because of ordinal scale of the variable.

*No cases for triple combination therapy.

Statistically significant values are shown as bold.

TABLE 1B | Comparison of the characteristics of the CTEPH and PAH patients at baseline.

	CTEPH <i>n</i> = 107	PAH <i>n</i> = 217	<i>P</i> -value
Age (years)	69 (56–76)	56 (44–66)	<0.001
Female sex (%)	55 (51%)	155 (71%)	<0.001
BMI (kg/m ²)	26 (24–31)	26 (23–31)	0.308
Diagnosis			
Time since diagnosis (years) ^a	5.4 ± 0.5	8.1 ± 4.1	0.002
WHO FC			
I, <i>n</i> (%)	23 (23%)	112 (52%)	0.012
II, <i>n</i> (%)	33 (31%)		
III, <i>n</i> (%)	42 (39%)	93 (43%)	
IV, <i>n</i> (%)	3 (3%)	10 (5%)	
6MWD (m)	449 (337–533)	439 (353–521)	0.856
NT-proBNP (ng/l)	168 (69–414)	184 (88–517)	0.854
DLCO (% pred.)	62 (53–74)	62 (47–74)	0.031
paO ₂ , mmHg	62 (58–70)	67 (60–75)	0.079
Hemodynamics at diagnosis			
mPAP (mmHg)	42 (33–50)	48 (41–57)	<0.001
PAWP (mmHg)	9 (6–12)	9 (6–12)	0.766
CI (l/min/m ²)	2.4 (2–2.8)	2.4 (2.0–2.9)	0.435
PVR (dyn·s·cm ⁻⁵)	506 (339–743)	707 (501–947)	<0.001
Medication			
No therapy, <i>n</i> (%)	22 (28%)	–	<0.001
Monotherapy, <i>n</i> (%)	47 (59%)	44 (20%)	
Double combination therapy, <i>n</i> (%)	11 (14%)	102 (47%)	
Triple combination therapy, <i>n</i> (%)	–	71 (33%)	
OAC, <i>n</i> (%)	101 (94%)	–	
Smoking status			
Active, <i>n</i> (%)	2 (2%)	24 (11%)	<0.001
Former, <i>n</i> (%)	45 (42%)	31 (14%)	
Never, <i>n</i> (%)	60 (56%)	162 (75%)	
Packyears	13 (8–26)	14 (5–25)	0.804
Sociodemographic items			
Drinking (drinks per week) ^a	1.6 ± 0.4	0.8 ± 2.0	0.589
Exercise Score (points)	3 (2–4)	3 (2–4)	0.021
HADS-A (points)	5 (2–9)	6 (2–9)	0.147
HADS-D (points)	5 (2–8)	5 (2–8)	0.708
QoL-overall (points)	72 (65–85)	50 (38–75)	<0.001
QoL-psych (points)	71 (58–79)	71 (58–79)	0.003
QoL-physical (points)	64 (53–79)	57 (45–75)	0.553

CTEPH, chronic thromboembolic pulmonary hypertension; PAH, pulmonary arterial hypertension; BMI, body mass index; WHO FC, World Health Organization Functional Class; 6MWD, six-min walking distance; BNP, brain natriuretic peptide; NT-proBNP, N-terminal fragment of pro-brain natriuretic peptide; DLCO, diffusion capacity of the lung for carbon monoxide; paO₂, mmHg, arterial pO₂; mPAP, mean pulmonary arterial pressure; PAWP, pulmonary artery wedge pressure; CI, cardiac index; PVR, pulmonary vascular resistance; OAC, oral anticoagulation; HADS-A, hospital anxiety and depression scale-anxiety; HADS-D, hospital anxiety and depression scale-depression; QoL, quality of life; psych, psychological; SD, standard deviation; IQR, inter quartile range. Continuous variables are stated as median and interquartile ranges (IQR) and categorical variables are stated as *n* and percent (%), unless indicated otherwise.

^aMean and SD were used because of distribution of the data.

Statistically significant values are shown as bold.

no comparable curative treatment available for patients with PAH except lung transplantation and survival is worse despite emerging therapies (19, 31).

The prevalence of specific phobia (anxiety disorder characterized by severe, unreasonable and irrational fear with a specific situation or object) (24, 32) in CTEPH did not differ from the prevalence in the general population or in patients with PAH. This result is consistent with the assumption that specific phobias have a moderate heritability (33). The presence of a chronic disease might therefore have a rather small impact on its prevalence.

In contrast to most previous studies, major depression was less frequent compared to patients with PAH and comparable to the general population (10–12, 14, 15). As in anxiety disorders, we assume that the better treatment opportunities and better prognosis in CTEPH might explain these findings. Additionally, the most commonly used questionnaire in the above mentioned studies (11–13) was the Patient Health Questionnaire 9 (PHQ-9) (34), which has already been found to overestimate the prevalence of major depression compared to SCID (35). Another explanation may be that in two studies in which the HADS was used, the cut-off value for depressive disorders was eight points (10, 14). In our study, a cut-off value of 11 points was used, which was calculated as described. Nevertheless, the high prevalence of major depression in previous studies is of importance given the strong negative impact of CTEPH on mental wellbeing.

Examining the prevalence of mental illnesses in “curatively treated patients” vs. non-curatively treated CTEPH patients, a numerically higher proportion of major depressive disorder, panic disorder, generalized anxiety disorder, and social phobia was found in the latter, whereas the prevalence of specific phobia and obsessive-compulsive disorder tended to be higher in curatively treated patients. Although none of these differences were statistically significant and based on small sample sizes, these observations might be of importance for further research specifically addressing the prevalence of mental disorders in curatively vs. non-curatively treated CTEPH patients.

The practical implications of our study need to be further investigated. Since the presence of any mental disorder had a substantial impact on overall and psychological QoL there is a need for screening tools as most PH physicians are not trained in detecting mental disorders. The HADS may be useful for cardiologists and pneumologists to detect hints of panic or major depressive disorder. The comparably high cut-off value for depression in this study is not in line with previously used cut-off values in general medical patients (HADS-A and HADS-D) (36) or adults with congenital heart disease, as another chronic disease (HADS-D) (37) but contributes to a higher specificity. To further examine whether patients with CTEPH who meet the cut-off values in the HADS truly suffer from mental disorders, streamlined access to psychological evaluation and counseling is needed. Psychological counseling might also be of help in decision making especially for CTEPH patients facing surgical therapy. As the presence of a mental disorder may also be associated with worse exercise tolerance and outcome in patients with CTEPH, it would be justified to provide integrated

TABLE 2A | Prevalence of common mental disorders of CTEPH in comparison to data from PAH and the general German population (DEGS1-MH).

	CTEPH <i>n</i> = 107	PAH <i>n</i> = 217	DEGS1-MH <i>n</i> = 5,318	<i>P</i> -value CTEPH vs. PAH	<i>P</i> -value CTEPH vs. DEGS1-MH
Any current mental disorder	31.8% (23.7–41.1)	38.2 (32.0–44.9)	27.7% (26.3–29.2)	0.254	0.351
Alcohol abuse	1.9% (0.1–0.7)	0.4% (0.08–2)	1.8% (1.4–2.3)	— ^a	— ^a
Alcohol dependence	0% (0–0.3)	1.3% (0.4–3)	3.0% (2.5–3.6)	— ^a	— ^a
Schizophrenia	0% (0–0.3)	0.4% (0.08–2)	2.6% (2.1–3.2)	— ^a	— ^a
Major depressive disorder	6.5% (2.9–13.5)	23% (17–29)	7.7% (6.9–8.6)	< 0.001	0.659
Bipolar 1 disorder	0% (0–0.3)	0.4% (0.08–2)	1.0% (0.7–1.4)	— ^a	— ^a
Panic disorder	8.4% (4.5–15.2)	15.2% (11–20)	2.0% (1.6–2.5)	0.087	< 0.001
Agoraphobia	0% (0–0.3)	5.9% (3.5–9.9)	4.0% (3.4–4.7)	— ^a	— ^a
Social phobia	3.7% (1.5–9.2)	3.6% (1.8–7.1)	2.7% (2.2–3.4)	0.974	0.366
Generalized anxiety disorder	3.7% (1.5–9.2)	2.7% (1.2–5.8)	2.2% (1.8–2.8)	0.500	0.138
Specific phobia	8.4% (4.5–15.2)	10.6% (7.1–15.4)	10.3% (9.3–11.3)	0.535	0.465
PTSD	0% (0–0.3)	4.1% (2.2–7.7)	2.3% (1.8–2.8)	— ^a	— ^a
Obsessive compulsive disorder	0.9% (0.1–5.1)	5.9% (3.5–9.9)	3.6% (3.1–4.4)	— ^a	— ^a
Anorexia nervosa	0% (0–0.3)	0% (0–1.7)	0.7% (0.5–1.1)	— ^a	— ^a
Bulimia nervosa	0% (0–0.3)	0.4% (0.1–2)	0.2% (0.1–0.3)	— ^a	— ^a

CI, confidence interval; PTSD, posttraumatic stress disorder; CTEPH, chronic thromboembolic pulmonary hypertension; PAH, pulmonary arterial hypertension; DEGS1-MH, Studie zur Gesundheit Erwachsener in Deutschland (German study of health status in adults)-Mental Health. Psychological disorder prevalence rates per group stated as percent (%) and 95% confidence intervals (CI) and risk ratios.

^aSamples do not satisfy the standard binomial requirement.

Statistically significant values are shown as bold.

TABLE 2B | Prevalence of current mental disorders in curatively treated in comparison to non-curatively treated CTEPH patients.

	Curatively treated <i>n</i> = 27	Non-curatively treated <i>n</i> = 80	<i>P</i> -value
Any current mental disorder	33% (0.2–0.5)	32% (0.2–0.4)	0.902
Alcohol abuse	4% (0–0.2)	1% (0–0.1)	0.416
Major depressive disorder	4% (0–0.2)	8% (0–0.2)	0.482
Panic disorder	4% (0–0.2)	10% (0.1–0.2)	0.308
Social phobia	0 (0–0.1)	5% (0–0.1)	0.236
Generalized anxiety disorder	0 (0–0.1)	5% (0–0.1)	0.236
Specific phobia	15% (0.1–0.3)	6% (0–0.1)	0.166
Obsessive compulsive disorder	4% (0–0.2)	0 (0–0.1)	0.084

CI, confidence interval; PEA, pulmonary endarterectomy; PH, pulmonary hypertension; CTEPH, chronic thromboembolic pulmonary hypertension; PTSD, posttraumatic stress disorder. Psychological disorder prevalence rates per group stated as percent (%) and 95% confidence intervals (CI). Curative treatment was defined for patients who underwent PEA with no residual PH and no need for medical CTEPH-therapy. There were no cases detected for alcohol abuse, schizophrenia, bipolar disorder, agoraphobia, PTSD, anorexia nervosa, and bulimia nervosa.

support (38). Overall, an integrative low-threshold treatment could possibly be of benefit for patients with CTEPH.

Besides current mental disorders, an increasing number of CTEPH therapies, increasing WHO FC and drinks per week had a negative impact on QoL. An increase in the frequency of sport was associated with an increase in QoL. Since all of those factors are modifiers of any mental disorder, mutual support (e.g., providing psychological or psychosomatic counseling) could increase the QoL of patients with CTEPH.

There are strengths and limitations to this study. This study focused specifically on patients with CTEPH and used structured face-to-face or telephonic interviews to identify mental disorders. The main limitations are the inclusion of data from only two German referral centers, a possible confounding lack of selected clinical data, and a lack of detailed information on mental status pre-therapy. The most important limitations are probably the relatively small sample size and the response rate of only 22% of the approached patients. Several reasons might have contributed to the low response rate: (1) Lack of general possibility to be personally contacted by their attending PH physician before receiving the questionnaires, (2) a relatively high age in the CTEPH population, (3) the fact that many patients had undergone surgery at the referring centers with follow-up by their local PH physicians and those patients might have been less motivated to participate in our study. The sample therefore might be biased by selecting a subset of patients with inoperable CTEPH or persistent symptomatic PH after surgery, potentially leading to a higher prevalence of mental disorders due to more severe physical disease. It is possible that this bias might have led to an overestimation of current mental disorders in the present study.

Future studies should include the prevalence of mental disorders before the diagnosis of CTEPH. The investigation of social support and physical comorbidities as influencing variables could also be of interest in further studies. The latter was not included in this study while social support was assessed with the WHOQOL-BREF subscale “social” and did not differ between the groups. A more detailed survey of social support could therefore be of benefit. Generally, future studies addressing diagnostic tools and therapeutic interventions are needed to further improve the treatment of patients with CTEPH.

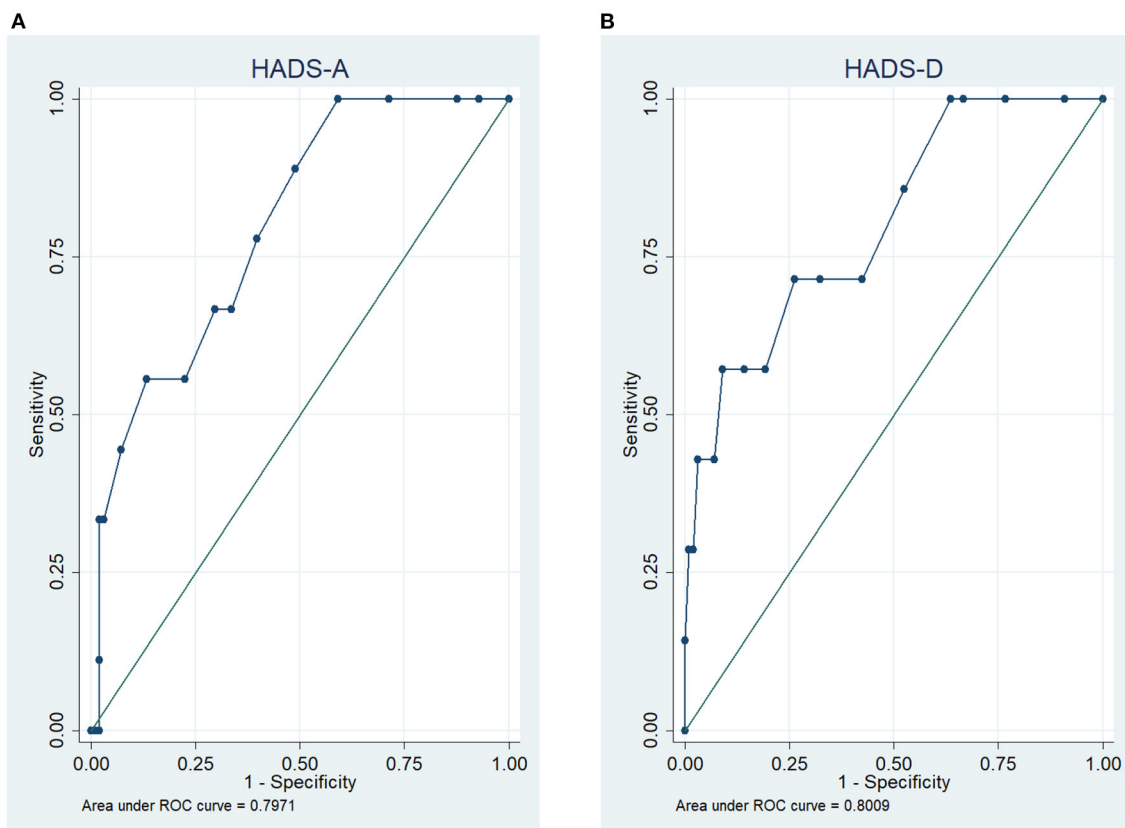


FIGURE 2 | Receiver operating characteristic (ROC) curves of the Hospital Anxiety and Depression Scale (HADS) for the detection of panic disorder **(A)** and depression **(B)**.

TABLE 3 | Results of the linear regression analysis for determinants of quality of life.

	Coefficient	P-value	95% CI
Impact on overall QoL			
Constant	73	<0.001	63.6 to 82.6
Sport score	4	0.001	1.5 to 5.8
Mental disorder	-9	0.003	-15.2 to -3.3
Number of therapies	-5	0.013	-9.7 to -1.2
Impact on psychological QoL			
Constant	64	<0.001	53.6 to 73.6
Mental disorder	-13	0.001	-20.8 to -5.5
Sport score	3	0.036	0.2 to 5.9
Drinks per Week	-1	0.040	-2.5 to -0.1
Impact on physical QoL			
Constant	91	<0.001	78.2 to 100
WHO FC	-11	<0.001	-15.9 to -6.4
Mental disorder	-11	0.009	-19.2 to -2.9

CI, confidence interval; QoL, quality of life; WHO FC, World Health Organization Functional Classification. Coefficients are stated as point values in the associated scales of the World Health Organization Quality of Life Assessment. Statistically significant values are shown as bold.

In conclusion, our study showed that almost one third of patients with CTEPH suffer from mental disorders. Panic disorders, specific phobia, and major depression were the most

frequent disorders. The presence of any current mental disorder contributed to a decrease of QoL. The HADS seemed to be a useful screening tool for detection of panic disorders and major depressive disorders.

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 Ethic Committee, Hannover Medical School, Hannover, Germany and Ethic Committee, University Medical Center Gießen and Marburg, Marburg, Germany. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

M-RD and NL were responsible for study design, implementation of the study, data collection, conducting the interviews, statistical

analysis, data interpretation, and drafting the manuscript. JF was responsible for study design, implementation of the study, data collection, statistical analysis, data interpretation, and drafting the manuscript. TM, IH, D-HP, HAG, DE, and H-DK were responsible for study design, data interpretation, and revising the manuscript. MH, KK, and KO were responsible for study design, implementation of the study, statistical analysis, data interpretation, and drafting the manuscript. JK, MR, and HG were responsible for study design, implementation of the study,

data interpretation, and revising the manuscript. All authors contributed to the article and approved the submitted version.

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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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Psychological and Psychopharmacological Interventions in Psychocardiology

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Patients with mental disorders have an increased risk to develop cardiovascular disease (CVD), and CVD are frequently comorbid with especially adjustment, anxiety and depressive disorders. Therefore, clinicians need to be aware of effective and safe psychological and pharmacological treatment strategies for patients with comorbid CVD and mental disorders. Cognitive behavioral therapy and third-wave of cognitive-behavioral therapy are effective for patients with CVD and mental disorders. Internet-based psychological treatments may also be considered. In more severe cases, psychopharmacological drugs are frequently used. Although generally well tolerated and efficacious, drug- and dose-dependent side effects require consideration. Among antidepressants, selective serotonin reuptake inhibitors, selective serotonin and noradrenalin reuptake inhibitors, and newer antidepressants, such as mirtazapine, bupropion, agomelatine, and vortioxetine, can be considered, while tricyclic antidepressants should be avoided due to their cardiac side effects. Mood stabilizers have been associated with arrhythmias, and some first- and second-generation antipsychotics can increase QTc and metabolic side effects, although substantial differences exist between drugs. Benzodiazepines are generally safe in patients with CVD when administered short-term, and may mitigate symptoms of acute coronary syndrome. Laboratory and ECG monitoring is always recommended in psychopharmacological drug-treated patients with CVD. Presence of a heart disease should not exclude patients from necessary interventions, but may require careful risk-benefit evaluations. Effectively and safely addressing mental disorders in patients with CVD helps to improve both conditions. Since CVD increase the risk for mental disorders and vice versa, care providers need to screen for these common comorbidities to comprehensively address the patients' needs.

Keywords: psychocardiology, psychological intervention, psychopharmacological intervention, cardiovascular disease, antidepressant, antipsychotic, psychotherapy

INTRODUCTION

Severe mental disorders, such as major depressive disorder (MDD), pose a higher risk for the development of cardiovascular disease (CVD), and vice versa (1, 2). In particular, adjustment disorder, anxiety disorders and MDD are more frequent in CVD patients compared to the general population (3, 4). The comorbidity of CVD and mental disorders is associated with worse treatment

outcomes and decreased quality of life (3, 5–10). The high prevalence of comorbid severe mental diseases and CVD has been attributed to several contributing factors. In this regard, dysregulation of biological systems as well as adverse health behaviors and insufficient economic and social support have been implied (11–15). Overall, severe mental diseases were found to be associated with pathological alterations in stress response systems, with systemic low-grade inflammation, with abnormalities in heart rate variability, and with reduced baroreflex sensitivity (16–18), and of note similar processes were found to profoundly impact metabolic pathways and subsequent development and progression of CVD (19, 20). Additionally, tobacco and alcohol consumption, a sedentary lifestyle, and poor diet, factors known for their contribution to the onset and progression of CVD, are common in patients with severe mental disorders (11, 12). Finally, patients suffering from mental disorders appear less likely to adhere to treatment regimens and were frequently found to have insufficient access to physical health care (21, 22).

Given the significant impact of mental disorders on the outcome of CVD patients, treatment interventions for comorbid patients are clinically important.

According to national and international guidelines, (23, 24) mental disorders within and without the context of an underlying physical illness can be treated using psychological and psychopharmacological interventions. However, iatrogenic effects of psychotropic medications have been described (1, 25). In this regard, the safety and efficacy of psychotropic medications in patients with CVD varies greatly, depending on drug- as well as disease type (26, 27). Consequently, precise knowledge regarding potential adverse effects of frequently used psychotropic medications, i.e., antipsychotics, antidepressants, and mood stabilizers, on parameters of physical health are indispensable in the treatment of comorbid mental disorders and CVD.

METHODS

Narrative review of practical clinical considerations when treating patients with cardiovascular and mental disorders pharmacologically and psychologically for their mental disorders.

RESULTS

Psychopharmacological Interventions Selective Serotonin Reuptake Inhibitors

National and international guidelines recommend the use of selective serotonin reuptake inhibitors (SSRIs) for the treatment of MDD and anxiety disorders (23, 24, 28–30). SSRIs are well tolerated in general, and beneficial effects of SSRI treatment in patients with depression following acute coronary syndrome regarding re-hospitalization rates have been shown in a dedicated meta-analysis (31). However, SSRIs pose the risk of cardiovascular side effects in a dose- and substance dependent manner. In principle, all SSRIs can lead to some QTc prolongation. However, especially citalopram (and to a much

lesser degree, its enantiomer *es*-citalopram) pose a relatively higher risk compared to other SSRIs (i.e., fluoxetine, fluvoxamine, paroxetine, sertraline). A meta-analysis revealed that SSRIs as a class increase QTc interval for an average of 6 ms (32). Although on average, this is not clinically relevant, subgroups of patients may experience clinically relevant QTc prolongation. Along with QTc prolongation, the risk for the development of ventricular arrhythmia and Torsades-de-Pointes (TdP) is increased (33–37). Most cases of SSRI-induced QTc interval prolongation and subsequent arrhythmia were observed in older patients above 65 years of age. Further risk factors comprise low potassium levels, female sex, polypharmacy, pre-existing cardiovascular disorders, pre-existing liver and/or kidney disease, and high doses of SSRIs (33, 38, 39). As mentioned above, among the SSRIs, this risk is highest for citalopram and *es*-citalopram. The United States Food and Drug Administration (FDA) as well as the European Medicines Agency (EMA) accordingly gave a safety warning, recommending doses not higher than 40 mg/day for citalopram and 20 mg/day for *es*-citalopram (40, 41). The relative risk of QTc prolongation with frequently used antidepressant drugs is summarized in **Table 1**.

Additionally, among different classes of antidepressants, SSRI treatment was found to be associated with the highest risk for hyponatraemia, brought forward by a drug-induced syndrome of inappropriate antidiuretic hormone (ADH) secretion (SIADH) (42). While conclusive evidence for differences of individual SSRIs regarding SIADH risk are lacking (43), two larger studies reported lower risks for paroxetine and sertraline compared to other SSRIs including fluoxetine, citalopram, and *es*-citalopram (44–47). Moreover, elevated SIADH risk under SSRI treatment has been found in the geriatric population and especially in concomitant (thiazide) diuretics (42, 48).

Further side effects of SSRIs with possible cardiovascular relevance are orthostatic hypotension, primarily in elderly patients (49–52), and impaired platelet activation and aggregation, possibly leading to an increased risk for intracerebral hemorrhages (45, 53–56). Therefore, SSRI treatment should be given carefully in patients with underlying hemostatic abnormalities and on anticoagulation treatment; additionally, non-steroidal anti-inflammatory drugs (NSAID) should not be given in SSRI treated patients (32, 57–59).

Serotonin Norepinephrine Reuptake Inhibitors

Serotonin norepinephrine reuptake inhibitors (SNRIs), particularly venlafaxine, can increase heart rate and blood

TABLE 1 | Relative risk of QTc prolongation with frequently used antidepressant drugs.

Substance	Risk of QTc prolongation
citalopram, <i>es</i> -citalopram, TCAs (particularly amitriptyline)	+
fluoxetine, fluvoxamine, mirtazapine, sertraline, venlafaxine	(+)
agomelatine, bupropion, duloxetine, milnacipran, paroxetine, reboxetine, vortioxetine	(±)

+, *existent*; (+), *low*; (±), *very low*.

pressure due to their noradrenergic effects (60–65). Among the SNRIs, venlafaxine and duloxetine may be associated with a possible risk of QTc prolongation, particularly in overdose situations (66, 67). Milnacipran, levomilnacipran and reboxetine have sometimes been associated with hypotension, particularly when administered at higher dosages (68–70). Albeit less frequent compared to SSRIs, SNRI treatment can lead to electrolyte disturbances, particularly hyponatremia (25, 42, 44, 71).

Tricyclic Antidepressants

Strong cardiovascular side effects are described with tricyclic antidepressants (TCAs) due to their anticholinergic and cholinergic-like properties. In particular, cardiac conduction abnormalities, such as atrioventricular block, QTc prolongation, atrial fibrillation, and ventricular tachycardia, have been described (72–75). Further, the use of TCAs has been associated with acute myocardial infarction and a higher risk of stroke compared to SSRIs (75).

Other Frequently Used Antidepressants

Agomelatine

Agomelatine is a melatonin agonist with antidepressant properties. To date, no evidence of cardiovascular risk has been reported (76). Of note, liver enzymes should be controlled frequently due to its dose-dependent liver toxic properties.

Mirtazapine

Mirtazapine acts as specific serotonergic and noradrenergic antidepressant drug, with a relatively favorable cardiovascular side effect profile (73). However, significant weight gain and sedation have been frequently, and orthostatic hypotension has also sometimes been described (25, 77). A prospective multicenter study including 2,177 patients with myocardial infarction and depression found no significant effect of mirtazapine on cardiac event rate at 18 months (78).

Vortioxetine

Vortioxetine, a multimodal antidepressant and serotonin transporter inhibitor, seems to have a favorable cardiovascular side effect profile (79, 80). Besides antidepressant efficacy, pro-cognitive and anti-inflammatory properties have been described (81).

Bupropion

Bupropion at therapeutic dosages has not been associated with adverse effects on heart rate, blood pressure, and other cardiovascular parameters (82). In patients with CVD, bupropion was found to have a favorable effect on depressive symptoms (83), and was also observed to be safe in the post-myocardial infarction period when given at therapeutic dosages (84). Although hypertension and tachycardia have been described (85), bupropion does not appear to induce severe cardiovascular events, even in overdose.

Recommendations

A substantial body of evidence indicates that the cardiovascular safety profile of newer-generation antidepressants is significantly improved compared to TCAs (76). Nevertheless, regular

monitoring concerning blood pressure, heart rate, ECG, body weight, and routine laboratory parameters (such as potassium levels) is generally recommended.

Selective serotonin reuptake inhibitors and SNRIs are generally considered safe in the treatment of patients with comorbid CVD when given within therapeutic limits. Due to the potential to increase the QTc interval (SSRIs and SNRIs) and heart rate/blood pressure (SNRIs), regular ECG and blood pressure monitoring is recommended. A combination of SSRIs with drugs that prolong QTc interval or that are associated with an increased bleeding risk (i.e., NSAIDs) should be avoided.

Newer antidepressant drugs (agomelatine, vortioxetine, mirtazapine, and bupropion) are generally considered safe when given within therapeutic dose limits. Albeit literature appears limited, the risk of QTc prolongation was found to be low for the majority of newer antidepressants (66). Weight monitoring (especially with mirtazapine) and blood pressure monitoring (especially with venlafaxine, duloxetine and bupropion) are recommended. For agomelatine, liver enzyme monitoring is recommended due to its propensity to significantly increase liver enzymes in up to 0.8% of treated patients.

Although substance- and dose-dependent, TCAs should be avoided in patients comorbid with CVD and mental disorders due to their potentially strong cardiovascular side effects.

First-Generation (Typical) and Second-Generation (Atypical) Antipsychotic Drugs

First- and second-generation antipsychotic drugs are used to treat patients with psychotic disorders, particularly schizophrenia (86, 87), and patients with bipolar disorders (88–90). Furthermore, several second-generation antipsychotics are recommended as augmentation strategy in treatment-resistant depression (91).

The increased cardiovascular morbidity and mortality observed in patients that receive antipsychotic drugs has been attributed to several factors, including an increased rate of unhealthy lifestyle (smoking, physical inactivity, and unhealthy eating habits), suboptimal screening and secondary preventive medical measures, and direct and indirect effects of antipsychotic medications (1, 92–94).

First-generation and, especially, second-generation antipsychotics have been associated with QTc prolongation and/or TdP (93, 95–109), as well as sudden cardiac death due to cardiac arrhythmia (95–97, 110, 111). More specifically, QTc prolongation has been reported for some first-generation antipsychotics (i.e., pimozide, IV haloperidol) and some low-potency phenothiazines (especially thioridazine, melperone), which were found to be associated with the greatest risk (112–114). Similarly, some second-generation antipsychotics (i.e., sertindole, iloperidone, amisulpride, ziprasidone) have been associated with QTc interval prolongation. Although a direct risk comparison is complicated by differences in study methodologies (96), especially ziprasidone appears to carry a higher risk for clinically meaningful increases in QTc interval (86, 114, 115). A summary regarding the relative risk of QTc prolongation with frequently used antipsychotic drugs is provided in **Table 2**. As with QTc prolongation with antidepressant drugs, further risk factors have to be considered,

TABLE 2 | Relative risk of QTc prolongation with frequently used antipsychotic drugs [modified according to Refs. (132, 86)].

Substance	Risk of QTc prolongation
Thioridazine, pimozide, sertindole, haloperidol (i.m., IV, high dose), iloperidone, melperone, amisulpride, ziprasidone	+++
Chlorpromazine, levomepromazine, quetiapine, sulpiride	++
Haloperidol (p.o.), fluphenazine, perphenazine, promethazine, pipamperone, chlorprothixene, olanzapine, risperidone, asenapine, clozapine	+
Aripiprazole, brexpiprazole, cariprazine, lurasidone, paliperidone, lumateperone	±

+++; high (>20 ms); ++, moderate (10–20 ms); +, low (<10 ms); ±, very low (< 10 ms, potentially not higher than placebo).

such as female sex, hypopotassemia, hypomagnesemia, higher age, and pre-existent cardiac diseases (116). Polypharmacy and the combination of drugs with the potential to alter cardiac conduction also enhance the risk of QTc prolongation compared to antipsychotic monotherapy (105). Some first- and second-generation antipsychotics are associated with an increased risk for cortical venous thrombosis or pulmonary embolism (117–131). Overall, the risk for hospitalization appears higher for second-generation antipsychotics: quetiapine (hazard ratio 2.68) > risperidone (1.98) > olanzapine (1.87) = clozapine (1.87) > phenothiazines (1.03) or other first-generation agents (0.98) (117).

Metabolic Syndrome and Type-2 Diabetes Mellitus

Increased blood lipid and glucose levels have been reported with several second-generation and some low-potency first-generation antipsychotics (93, 94, 133–135). Among these, clozapine and olanzapine as well as chlorpromazine and thioridazine have been associated with an increased risk for metabolic disturbances such as glucose disturbance, lipid changes, and in some cases with acute ketoacidosis (93, 94, 133, 136). Further, second-generation antipsychotics have been reported to increase body weight, with clozapine and olanzapine bearing the greatest risk (93). According to a systematic review of randomized, placebo-controlled studies, the risk of weight gain was reported as follows: clozapine and olanzapine > risperidone > quetiapine > aripiprazole > ziprasidone (93).

Increased blood pressure and orthostatic hypotension have been reported in the context of antipsychotic treatment. Concerning blood pressure, around one third of patients with a psychotic disorder presents with elevated blood pressure; however, it is unclear whether this effect is due to antipsychotic medication or to formerly undetected metabolic syndrome and its components (136).

Orthostatic hypotension, most frequently observed in response to treatment with first-generation antipsychotics, such as phenothiazine, chlorpromazine, and thioridazine, is mostly attributed to their antagonistic action on adrenergic receptors (137).

Recommendations

The use of antipsychotic medications is in general safe in patients with comorbid CVD and mental disorder, although caution is necessary concerning direct (ECG alterations) and indirect (cardiometabolic and thromboembolic) side effects

of certain drugs. For most psychiatric diseases, second-generation antipsychotics are currently recommended, rather than first-generation antipsychotics. Within the group of second-generation antipsychotics, the risk for cardiometabolic side effects (i.e., weight gain, hyperlipidemia, insulin resistance) differs substantially between drugs and is highest with the use of clozapine and olanzapine. In patients that present with, or display an increased risk for metabolic syndrome, drugs with lower metabolic side effects (i.e., aripiprazole, brexpiprazole, cariprazine, lurasidone, or lumateperone) should be considered.

Patients should be monitored closely for metabolic side effects, particularly in the first year of treatment. ECG monitoring should take place before and during antipsychotic treatment in patients with clinical risk factors for cardiac arrhythmias, i.e., family history of early cardiac death (<55 years old), personal history of structural heart defects, dizziness and, especially, syncope upon exertion, palpitations at rest (138). In CVD patients treated with clozapine, particular attention should be paid to anticholinergic side effects and the risk for myocarditis (139).

According to recommendations detailed in a consensus document by the American Diabetes Association (ADA) and American Psychiatric Association (APA), weight should be monitored monthly for the first three months and then quarterly, fasting blood glucose levels should be assessed at baseline, after 3 months, and then annually. A fasting lipid profile should be obtained at baseline, after 3 months, and then every 5th year (140), although the latter recommendation has been amended since, in that lipid levels ought to be monitored at the same time intervals as fasting glucose levels and that HbA1C should also be monitored, as increases occur several years before fasting glucose is elevated, signaling prediabetes or diabetes earlier (94).

Benzodiazepines

Benzodiazepines (BZDs) are frequently being prescribed for anxiety disorders, insomnia, and alcohol withdrawal and agitation (141–143). Due to their potential for abuse and their addictive properties, short-term use is recommended (144). Of note, some patients may have paradoxical effects of BZD medication, leading to confusion and an increase in agitation and delirium (145). In the context of CVD, BZDs may play a particular role in calming patients quickly who suffer from chest pain and acute myocardial infarction, reducing cardiac stress (146, 147). The addition of BZDs to standard cardiac medication in patients post myocardial infarction was associated with lower rates of re-infarction (148).

Recommendations

Benzodiazepines are generally considered safe in patients comorbid with CVD and mental disorders, when given as short-term acute treatment to relieve anxiety and agitation. Long-term use should be avoided due to inherent risks for iatrogenic BZD addiction, and caution should be given to elderly patients who are at greater risk of falls.

Mood Stabilizers

Mood stabilizers are given in the context of bipolar disorders to prevent further depressive/manic episodes (88–90), and in MDD as augmentation (91, 149) and, possibly prophylactic treatment (particularly lithium) (150). Lithium has been associated with sinus bradycardia, sinus node dysfunction, atrioventricular lock and ventricular irritability, and sick sinus syndrome is considered a cardiac contraindication for its use (151, 152). Valproic acid is a frequently given drug in epilepsy, and in bipolar disorders. Valproic acid is associated with thrombocytopenia, abnormal platelet function, bleeding risk, and with severe fetal abnormalities, restricting its use in female patients (153–157).

Lamotrigine is an anticonvulsant used in the treatment of bipolar disorder. Lamotrigine is known to bear the risk for toxic epidermal necrolysis (158), which is titration-speed dependent, but is considered safe concerning cardiac complications.

Recommendations

Mood stabilizers are generally considered safe concerning cardiovascular side effects in the absence of cardiac conduction delay. Lithium should be avoided in cases of atrioventricular block and sick sinus syndrome.

Psychological Interventions

Psychotherapy, in particular cognitive behavioral therapy (CBT), is established in the treatment of most major mental disorders, and is also applied to treat patients with mental disorders in the context of an underlying physical disease as well as in cardiometabolic disorders themselves (90, 159–163). In particular, adjustment disorder, anxiety and depressive disorders are frequent comorbidities in CVD, leading to decreased quality of life and in part worsen the disease course of the underlying physical illness (164–166).

Adjustment disorder represents an abnormal stress response to a stressor, such as acute myocardial infarction or chronic heart failure, and is reported to be common in primary care with rates ranging from 1% to 18% (167, 168). MDD also has been associated with a significant bidirectional comorbidity with CVD (169). Compared to MDD, adjustment disorder is almost three times more common in physically ill patients (13% versus 5%) (170) and is also frequently present in conjunction with chronic and potentially life-threatening diseases such as cancer (171). In the context of CVD, rates as high 38% have been reported, particular in acute and potentially life-threatening diseases such as peripartum cardiomyopathy and pulmonary artery hypertension (165, 166).

Different psychological treatments, such as CBT, low intensity psychological interventions, mindfulness-based techniques, metacognitive therapy (172) and e-mental health interventions,

have been proposed for the treatment of adjustment disorder. Common components of these treatment strategies are the enabling of patients to reduce or remove the stressor, interventions to improve stress coping, and stress reduction strategies (173). Although there is limited empirical evidence, CBT and CBT-derived strategies are promising treatment interventions in patients with CVD and adjustment disorders (172, 173) and for CVD disorders *per se* (160, 161).

Major depressive disorder and anxiety disorders (particularly panic disorders) are more frequent in patients with CVD compared to the general population (3, 4, 165, 166, 169). Different psychotherapeutic methods are available to treat these disorders including CBT, “third wave” CBT [such as Acceptance and Commitment Treatment (174)] or psychodynamic psychotherapy. CBT is based on the principles established by Aaron T. Beck (175), focusing on dysfunctional beliefs, maladaptive schemes, and avoidance behavior to counteract mental disorders. Recent meta-analyses revealed that CBT presents an effective treatment to reduce depression and anxiety in patients with CVD (176) and acute coronary syndrome (177).

CBT as a treatment option is often limited by its accessibility. For example, in Germany the time period until a first visit with a psychotherapist takes place lasts up to 3 months, and the duration to the start of psychotherapy may be as long as 6–9 months (178). Therefore, internet-based self-help programs and internet-based psychotherapy have been developed during the last two decades, and efficacy has been proven in the context of anxiety and depressive disorders. These programs are most often based on CBT strategies, and are frequently offered as blended treatments, meaning that a real-life psychotherapist supports the program on demand. A recent meta-analysis demonstrated that internet-based self-help/psychotherapeutic programs have a similar efficacy as face-to-face psychotherapy, although their use has been limited to mild to moderate disease severity (179). Less research has been done for the treatment of patients comorbid with anxiety/depression and CVD. Recently, an internet-based CBT treatment adapted to persons with heart failure was compared to a web-based discussion forum, demonstrating small effects of internet-based CBT (180). In a secondary analysis of the data, improvement of depressive symptoms was demonstrated to be associated with improved autonomous-based self-care (181).

Recommendations

Face-to-face CBT and “third wave CBT” interventions have been proven effective in frequent mental disorders that are associated with cardiovascular diseases, and should be considered as treatment options. Due to the mere quantity of CVD patients in need for psychotherapy, and the limited number of psychotherapists, internet-based psychotherapeutic interventions may become a field of growing interest.

CLINICAL SUMMARY

Due to the bidirectional association between cardiac and mental diseases, knowledge about treatment interventions and their

limitations is important. According to recent research, adjustment disorder, anxiety disorder and MDD are the most frequent mental disorders in patients with CVD; all of them are addressable by psychotherapeutic interventions. Therefore, particularly CBT and its related “third wave CBT” are recommended in patients with CVD and mental disorders of mild to moderate severity. Furthermore, CBT can be recommended in patients with CVD and severe mental disorder as an augmentation of psychopharmacological treatment. If CBT is not accessible, internet-based psychological interventions may also be considered, although more research is needed to prove the effectiveness of internet-based psychotherapy in this population.

In more severe cases, psychopharmacological drugs can be recommended. Although well tolerated and efficacious in general, drug- and dose-dependent side effects have to be considered. Among antidepressants, SSRIs, SNRIs, and newer antidepressants, such as mirtazapine, bupropion, agomelatine and vortioxetine, can be recommended, while TCAs should be avoided due to their cardiac side effects. Mood stabilizers have been associated with arrhythmias, and some first- and second-generation antipsychotic drugs can increase the risk of QTc prolongation and metabolic side effects, although substantial differences exist between individual drugs. BDZs are generally

considered safe in CVD when administered short-term. Of note, laboratory and ECG monitoring is always recommended in patients with CVD who are treated with psychopharmacological drugs, starting before the beginning of a drug treatment, and continuing on a regular basis.

Knowledge about effective psychological and safer pharmacological treatment options for mental disorders that are frequently comorbid with CVD can help clinicians optimize the biopsychosocial outcome of patients suffering from both mental and cardiovascular disorders. Importantly, since CVD increases the risk for mental disorders and vice versa, both physical and mental health care providers need to screen for the presence of the common comorbidity to consider the patient in their somato-psychiatric totality, which can help improve overall outcomes.

AUTHOR CONTRIBUTIONS

KK: conceptualization, investigation, writing—original draft, and supervision. BS: writing—review and editing. CC: investigation and writing—original draft. All authors contributed to the article and approved the submitted version.

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Impact of COVID-19 on Medical Supply in Adults With Congenital Heart Disease

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Introduction: In March 2020, the World Health organization declared COVID-19 a global pandemic. One year later, the direct and indirect burden of the COVID-19 pandemic become more visible. In this context, there is concern about the allocation of medical resources and medical treatment of other diseases than COVID-19. Particularly, patients with chronic diseases need constant medical and pharmacological treatment. Therefore, we evaluated a large cohort of patients with adult congenital heart disease (ACHD) regarding postponed medical appointments and their possibilities to receive medical treatment during the COVID-19 pandemic.

Methods: This cross-sectional study included 559 patients with ACHD (mean age 37.32 ± 11.98; 47% female). Clinical characteristics, answers to questionnaires concerning lifestyle, psychological well-being, addictive behavior and adherence were related to postponed medical appointments and limited access to medical care.

Results: One hundred and nine patients (19.5%) reported problems getting necessary medical treatment or visiting a physician. Higher anxiety levels ($p = 0.004$) emerged as the main factor associated with medical undertreatment. The main risk factors for postponement of least one medical appointment ($n = 91$) were higher depression ($p = 0.013$) and anxiety ($p = 0.05$) symptoms as well as female sex ($p \leq 0.0001$) and documented arrhythmias ($p = 0.007$) indicating a particular risk group of cardiovascular complications. In contrast, frequent physical activity identified patients at lower risk.

Conclusion: In ACHD anxiety and depressive symptoms handicap patients to receive medical care. Postponement of medical appointments additionally relates to female sex and documented arrhythmias. The latter indicates that patients at high risk of adverse cardiac outcome avoid routine medical care. Our data may lead policy makers to develop strategies for the provision of medical services to particular vulnerable patient groups, and to optimize management of both future pandemics and daily routine.

Keywords: adult congenital heart disease (ACHD), COVID-19, depression and anxiety disorders, adherence, medical care

INTRODUCTION

Physical and social distancing during the pandemic challenged the whole humankind and resulted in poorer mental health levels (1). Even though, there are chronic diseases, where compared to controls no changes in mental health during the COVID-19 pandemic or even less mental health illnesses were reported (2), notably in particularly vulnerable groups (3, 4) limitations in medical treatment (5, 6), acute care (7–10), screening examinations (11, 12) and higher levels of mental health issues were observed.

In addition to their physical limitations, ACHD patients are burdened by a huge variety of mental diseases, including depression and anxiety disorders as the most common mental illnesses (13–15) that affect about one third to one-half of this patient population (15, 16).

These patients appear to be particularly challenged by the stressor of the global pandemic associated with the fear of contracting COVID-19, resulting in concerns about seeking medical care (17). Postponement of essential medical appointments and interventions might lead to avoidable complications, potentially associated with an adverse outcome.

The aim of this study was to evaluate factors contributing to limited access to medical care and the postponement of medical appointments in ACHD patients during the Covid-19 pandemic.

METHODS

Study Design

This single center cross-sectional study evaluated the impact of life-style factors, health behavior and mental disorders on medical care during the COVID-19 pandemic. Participants were recruited from the outpatient clinic of the Adult Congenital

Heart Disease Centre at Hannover Medical School between August 2020 and March 2021. The local ethics committee approved this study. All patients gave written informed consent. This study is part of the collaboration of the Department of Cardiology and Angiology and the Department of Psychiatry to evaluate the burden of mental illness in cardiovascular diseases (PsyConHeart).

Exclusion criteria were pregnancy, intellectual disability, and inability to read and/or to answer the questionnaire. A total number of 591 patients were contacted. Sixteen patients denied participating (2.7%). In addition, 16 patients did not finish the questionnaire, resulting in a dropout rate of 5.4% (Figure 1).

Data Collection

The remaining 559 patients completed the Hospital Anxiety and Depression Scale (HADS), self-assessment of unhealthy alcohol use (AUDIT), nicotine abuse (Fagerstroem) and internet addiction questionnaire (ISS10). Participants also reported their extent of physical exercise. Further included parameters were self-reported physical limitations using the NYHA-class, the latter differentiated between patients with heart disease without physical limitations in class I, and those with symptoms at rest in class IV. Heart disease complexity was assessed according to the Warnes classification (18). In addition, anthropometric factors, biomarkers, current medication and comorbid physical disorders were included in the analysis. Arrhythmias were classified according to documented episodes of non-sustained supraventricular or ventricular arrhythmias and palpitations, independent from arrhythmia documentation. Patients training at least twice a week were defined as physically active. Details are provided in Table 1.

We focused on the question whether during the COVID-19 pandemic patients afflicted with congenital heart disease might

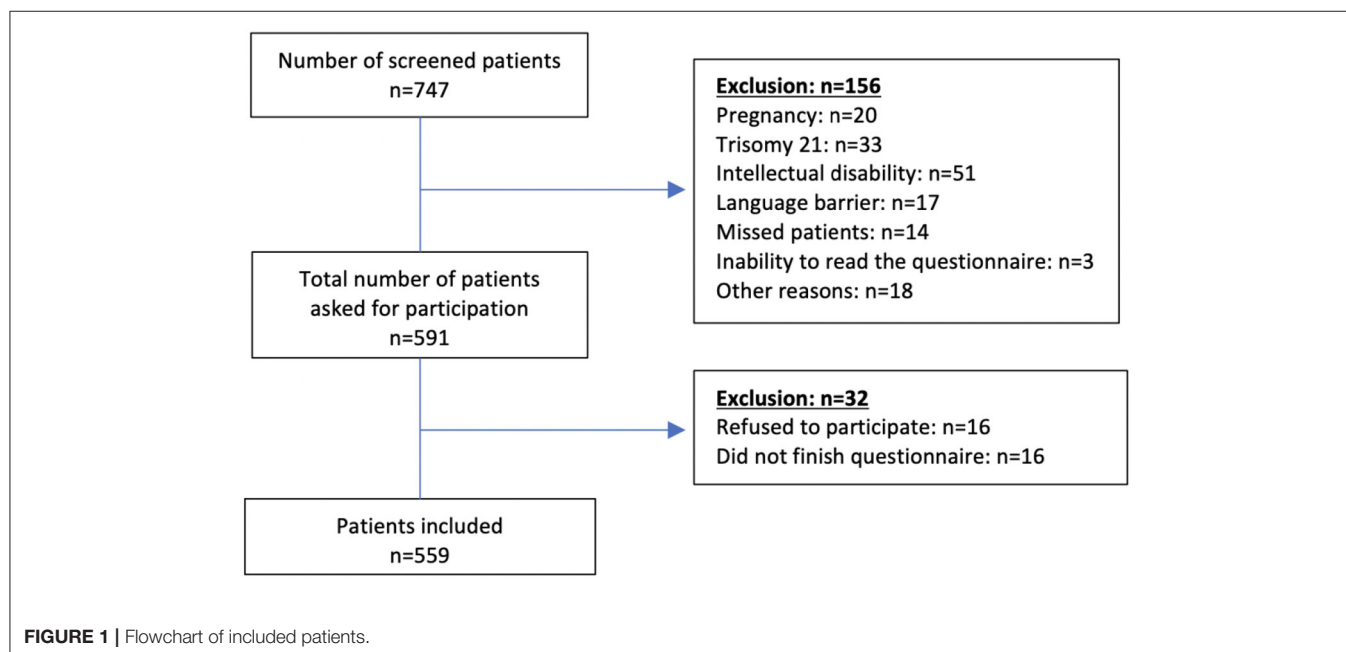


TABLE 1 | Demographic, psychiatric, lifestyle and clinical characteristics of total cohort.

Parameter	Total cohort (n = 559)
Age (years)	37.32 ± 11.98
Male sex (n/%)	296/53
Body Mass Index (kg/m ²)	25.81 ± 5.06
Bethesda-classification (I/II/III) ^a	59/201/299
NYHA-Class I/II/ (II/IV) (%) ^b	396/127/34/2
Diabetes (%)	3.2
Hypertension (%)	21.2
Pulmonary arterial hypertension (%)	3.7
Obstructive lung disease (%)	6.8
Oxygen-saturation (%)	97.81 ± 2.49
Hs-CRP (mg/l) ^c	1.94 ± 2.88
Creatinine (μmol/l)	81.85 ± 28.79
GGT (U/l) ^d	36.72 ± 37.82
GPT (U/l) ^e	27.69 ± 16.53
GOT (U/l) ^f	26.3 ± 15.76
GDF15 (ng/l) ^g	541.74 ± 845.27
NT-proBNP (ng/l) ^h	201.23 ± 347.24
HBA1c (%) ⁱ	5.39 ± 1.3
Hemoglobin	14.5 ± 1.72
QRS (ms)	123.1 ± 85.11
QTc (ms)	438.37 ± 43.65
Intermittent arrhythmias (n/%)	79/14.2
Palpitations (n/%)	50/8.94
ICD (n/%) ^{a0}	20/3.6
Pacemaker (n/%)	49/8.7
Limited medical care (n/%)	168/30.1
Perceived limitations in medical treatment (n/%)	109/19.5
Missed medical appointment (n/%)	91/16.3
Insufficient medical treatment (n/%)	63/11.3
Limited drug access (n/%)	59/10.6
AUDIT ^k	2.91 ± 3.04
Smoker (n/%)	65/11.6
ISS 10 ^l	14.48 ± 4.22
Non-Adherence (A-14) ^m n=444	49.57 ± 7.28
Regular Physical activity (n/%)	348/65.2
HADS-A ⁿ	5.84 ± 3.71
HADS-D ^o	3.77 ± 3.25

^aClassification of heart defect severity, ^bNYHA: Severity of chronic heart failure according to New York Heart Association, ^chigh sensitivity C-reactive protein, ^dGamma-Glutamyltransferase, ^eGlutamat-Pyruvat-Transaminase, ^fGlutamat-Oxalacetat-Transaminase, ^gGrowth-Differentiation Factor, ^hN-terminal prohormone of brain natriuretic peptide, ⁱHemoglobin A_{1c}, ^jImplantable Cardioverter Defibrillator, ^kalcohol use disorder identification test, ^lInternet addiction scale, ^mquestionnaire for assessment of adherence and individual barriers, ⁿHospital anxiety scale, ^oHospital depression scale.

have concerns about getting in contact with the medical health system and the ability to receive necessary drug treatment. In order to characterize patients with limited access to medical care or postponed medical appointments we dichotomized according to their answers to the following questions:

- (1) Did you postpone a medical appointment?
- (2) Did you have limited access to medical treatment and/or delivery of pharmaceuticals?

Statistical Analysis

Baseline characteristics of the total cohort and the evaluated subgroups are presented in **Table 1**. Continuous variables are provided as mean and standard deviation, categorical variables as absolute numbers or relative proportions.

We calculated group differences between participants with/without postponed appointments and limited access to medical care and/or necessary medication.

Unpaired *t*-test, Chi-Square-test and the Man-Whitney-*U*-Test calculated group differences. Binary regression analysis estimated the association between the reported medical care limitations during the COVID-19 pandemic and their explanatory variables.

Logistic regression analysis estimated dependent variables. All single parameters were calculated in univariate analysis, variables with *p* < 0.05 were included in multivariate calculation. The influence of depression and anxiety as measured with the Hospital Anxiety and Depression Scale (HADS) were calculated in different models, due to a close interrelationship of the depression and anxiety subscales (*r* = 0.66). These models also were adjusted for age, sex and BMI to evaluate their potential impact on independent variables.

Statistics was performed with IBM SPSS Statistics® 26.0.

RESULTS

Prevalence of Reported Limited Access to Medical Supply

A total of 559 patients (average age: 37.32 ± 11.98, female sex: 47%) participated in our study (**Figure 2**). The cohort reporting limited access to either pharmaceuticals (*n* = 59) and/or medical treatment (*n* = 63) consisted of 109 participants (19.5%). Moreover, 91 patients (16.28%) reported postponed appointments, varying between 1 and 10 in number. Of 559 participants, 168 (30.1%) patients reported at least one of these factors.

Differences in Patients With and Without Limited Access to Medical Treatment/Delivery of Pharmaceuticals

Patients with reported limited access to medical care and/or delivery of pharmaceuticals showed significantly higher self-reported depression (4.41 ± 3.47 vs. 3.62 ± 3.18, *p* = 0.026) and anxiety levels (6.92 ± 3.94 vs. 5.58 ± 3.61, *p* = 0.001) according to the HADS scales. In addition they reported less physical activity (49.54 vs. 65.33%, *p* = 0.001). Supplementary high sensitivity C-reactive proteine (hs-CRP) was significantly higher in this group (2.46 ± 3.26 vs. 1.82 ± 2.77, *p* = 0.037; **Table 2**).

Differences in Patients With/Without Postponed Medical Appointments

Female sex turned out to be the main influencing factor of postponed medical appointments (68.13 vs. 43.04%, *p* ≤ 0.0001), significantly higher depression (4.47 vs. 3.61, *p* = 0.02) and anxiety scores (6.73 vs. 5.65, *p* = 0.01), less physical activity (51.69 vs. 67.79%, *p* = 0.005) and less reported alcohol

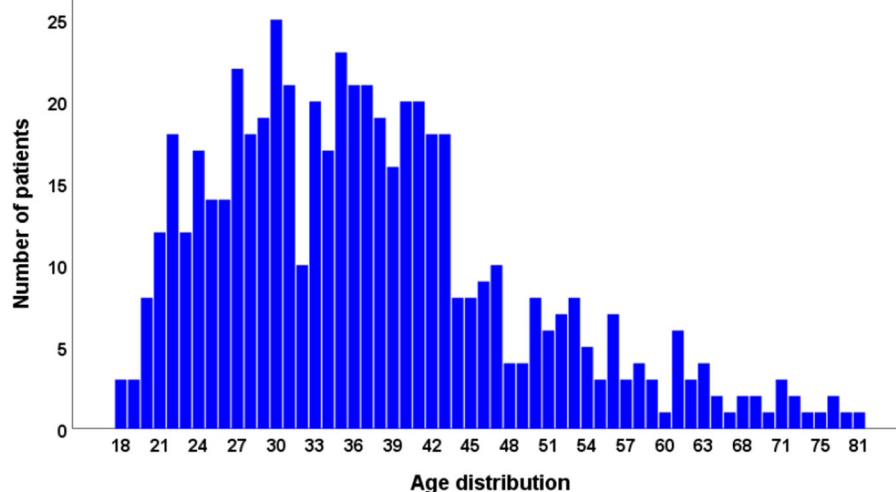


FIGURE 2 | Age distribution.

consumption (2.27 vs. 3.04, $p = 0.01$). However, in all subgroups the reported amount of drinking alcohol reflected a low-risk consumption according to World Health Organization (WHO) guidelines (<7).

Furthermore, we exhibited higher NYHA class ($p = 0.003$), more documented intermittent arrhythmias (24.18 vs. 12.23%, $p = 0.005$) and reported palpitations (15.38 vs. 7.71%, $p = 0.026$). In addition, a lower creatinine level (75.72 vs. 82.92, $p = 0.03$) accompanied postponed appointments, which can be explained by the physiologically lower creatinine observed in female (Table 3).

Univariate and Multivariate Analysis Predicting Limited Access to Medical Supply

The univariate analysis for limited access to medical treatment/delivery of pharmaceuticals identified higher HADS-D (HR: 1.073, 95%-CI: 1.008–1.142, $p = 0.027$) and HADS-A levels (HR: 1.096, 95%-CI: 1.037–1.159; $p = 0.001$) as well as increased hs-CRP (HR: 1.069, 95%-CI: 1.002–1.139; $p = 0.042$) as risk factors. Drinking more alcohol (HR: 0.917, 95%-CI: 0.842–0.999; $p = 0.048$) and doing more sports (HR: 0.486, 95%-CI: 0.315–0.75; $p = 0.001$) came up as protective factors, minimizing the risk of a perceived limited access to medical treatment.

In the univariate analysis, risk factors for postponed medical appointments were higher HADS-D (HR: 1.078, 95%-CI: 1.01–1.151; $p = 0.023$) and HADS-A levels (HR: 1.077, 95%-CI: 1.015–1.143; $p = 0.014$), female sex (HR: 2.829, 95%-CI: 1.755–4.561; $p \leq 0.0001$), higher NYHA class (HR: 1.555, 95%-CI: 1.119–2.163; $p = 0.009$), intermittent arrhythmias (HR: 2.288, 95%-CI: 1.315–3.982; $p = 0.0039$) and palpitations (HR: 2.177, 95%-CI: 1.22–4.225; $p = 0.0229$). In contrast, more physical activity (HR: 0.508, 95%-CI: 0.321–0.806, $p = 0.004$), more alcohol

consumption (HR: 0.896, 95%-CI: 0.812–0.988, $p = 0.028$) and higher creatinine levels (HR: 0.976, 95%-CI: 0.961–0.992, $p = 0.003$) acted as protective factors.

Multivariate analysis identified independent predictors of the evaluated subgroups. Due to the close interrelationship of HADS-A and HADS-D ($r = 0.66$) we calculated different models, either including or excluding HADS-D or HADS-A together with all other significant parameters as derived from the univariate analysis.

In unadjusted analysis single predictors for postponed medical appointments were female sex ($p < 0.0001$; 0.001), more documented intermittent arrhythmias ($p = 0.007$; 0.01) and higher HADS-A ($p = 0.05$) or HADS-D levels ($p = 0.013$). In particular higher levels of physical activity ($p = 0.02$ –0.46) acted as a protective factor.

The age and BMI adjusted analysis did not show any differences, regardless of whether the calculation was carried out with HADS-D or HADS-A as a variable. In contrast, including HADS-A in the calculation, adjustment for age and sex identified documented arrhythmias ($p = 0.005$), HADS-A score ($p = 0.30$), and physical activity ($p = 0.012$) as independent variables. Palpitations ($p = 0.052$) and creatinine levels ($p = 0.051$) missed significance level.

The age and sex adjusted analysis of the multivariate model including HADS-D and all other estimated significant univariate parameters computed HADS-D ($p = 0.033$), documented arrhythmias ($p = 0.012$), creatinine ($p = 0.008$) and physical activity ($p = 0.012$) as independent predictors of postponed medical appointments. The observed differences in creatinine levels can be interpreted as a physiological finding, as men have higher creatinine levels.

The analysis regarding limited access to medical supply only partially retrieved similar results. Multivariate analysis of raw data did not identify depression and sex as single predictors, whereas higher anxiety levels ($p = 0.004$) and slightly elevated

TABLE 2 | Displays the differences in demographic, psychiatric, lifestyle and laboratory data stratified according to limited or unlimited access to medical treatment.

Parameter	Limited medical treatment (n = 109)	No limited medical treatment (n = 450)	p-value
Age (years)	38.59 ± 13.09	37.01 ± 11.69	0.22
Male sex (n/%)	50/45.87	246/54.67	0.11
Body Mass Index (kg/m ²)	26.52 ± 4.99	25.64 ± 5.07	0.1
Bethesda-classification (I/II/III) ^a	11/38/60	48/163/239	0.72
NYHA-Class I/II/ (II/IV) (n)	73/27/9/0	323/100/25/2	0.30
Diabetes (n)	103/6	438/12	0.17
Hypertension (n)	89/20	351/99	0.44
Pulmonary arterial hypertension (n)	106/3	432/18	0.78
Obstructive lung disease (n)	99/10	422/28	0.29
Oxygen-saturation (%)	97.99 ± 1.37	97.76 ± 2.71	0.43
Hs-CRP (mg/l) ^c	2.46 ± 3.26	1.82 ± 2.77	0.037
Creatinine (μmol/l)	79.28 ± 16.15	82.47 ± 31.1	0.14
GGT (U/l) ^d	38.61 ± 37.71	36.26 ± 37.87	0.56
GGT (U/l) ^d	28.7 ± 15.91	27.44 ± 16.68	0.46
GPT (U/l) ^e	26.5 ± 8.88	26.25 ± 17.03	0.83
GOT (U/l) ^f	613.31 ± 596.92	524.13 ± 895.56	0.22
NT-proBNP (ng/l) ^h	190.62 ± 312.76	203.86 ± 355.53	0.7
HBA1c (%) ^j	5.46 ± 0.65	5.37 ± 1.41	0.36
Hemoglobin	14.4 ± 1.8	14.53 ± 1.7	0.48
QRS (ms)	120.22 ± 32.75	123.73 ± 93.55	0.52
QTc (ms)	436.18 ± 50.77	438.91 ± 41.77	0.61
Intermittent arrhythmias (n/%)	15/13.76	64/14.22	1
Palpitations (n/%)	15/13.76	35/77.78	0.061
ICD (n/%) ^j	4/3.67	16/3.56	1
Pacemaker (n/%)	12/11.01	37/8.22	0.35
AUDIT ^k	2.39 ± 2.27	3.04 ± 3.19	0.47
Smoker (n/%)	16/14.68	49/10.89	0.32
ISS 10 ^l	15.07 ± 4.21	14.34 ± 4.22	0.11
Adherence (A-14) ^m	48.46 ± 7.53	49.84 ± 7.20	0.12
Physical activity (n/%)	54/49.54	294/65.33	0.001
HADS-A ⁿ	6.92 ± 3.94	5.58 ± 3.61	0.001
HADS-D ^o	4.41 ± 3.47	3.62 ± 3.18	0.026

^aClassification of heart defect severity, ^bNYHA: Severity of chronic heart failure according to New York Heart Association, ^chigh sensitivity C-reactive protein, ^dGamma-Glutamyltransferase, ^eGlutamat-Pyruvat-Transaminase, ^fGlutamat-Oxalacetat-Transaminase, ^gGrowth-Differentiation Factor, ^hN-terminal prohormone of brain natriuretic peptide, ⁱHemoglobin A_{1c}, ^jImplantable Cardioverter-Defibrillator, ^kalcohol use disorder identification test, ^linternet addiction scale, ^mquestionnaire for assessment of adherence and individual barriers, ⁿHospital anxiety scale, ^oHospital depression scale. Bold numbers represent significant values.

TABLE 3 | Clinical characteristics, demographic, psychiatric, lifestyle and laboratory data of patients' cohort, either keeping or postponing at least one medical appointment.

Parameter	Missed medical appointments (n = 91)	No missed medical appointments (n = 468)	p-value
Age (years)	39.71 ± 11.80	36.85 ± 11.98	0.036
Male sex (n/%)	29/31.87	266/56.96	<0.0001
Body Mass Index (kg/m ²)	25.54 ± 4.47	25.85 ± 5.17	0.59
Bethesda-classification (I/II/III) ^a	10/28/53	49/173/245	0.4
NYHA-Class I/II/ (II/IV) (%) ^b	52/32/6/1	343/95/28/1	0.003
Diabetes (n)	88/3	452/15	1.0
Hypertension (n)	73/8	367/101	0.78
Pulmonary arterial hypertension (n)	85/6	452/15	0.13
Obstructive lung disease (n)	83/8	437/30	0.37
Oxygen-saturation (%)	97.73 ± 2.94	97.83 ± 2.41	0.79
Hs-CRP (mg/l) ^c	1.88 ± 2.58	1.96 ± 2.94	0.79
Creatinine (μmol/l)	75.72 ± 14.29	82.92 ± 30.64	0.03
GGT (U/l) ^d	39.63 ± 43.13	36.17 ± 36.78	0.43
GPT (U/l) ^e	26.08 ± 14.17	27.94 ± 16.92	0.33
GOT (U/l) ^f	24.55 ± 6.37	26.59 ± 16.95	0.26
GDF15 (U/l) ^g	565.87 ± 491.8	537.16 ± 898.33	0.77
NT-proBNP (ng/l) ^h	257.04 ± 452.17	190.87 ± 322.83	0.1
HBA1c (%) ^j	5.44 ± 0.55	5.38 ± 1.40	0.44
Hemoglobin	14.46 ± 1.75	14.51 ± 1.71	0.84
QRS (ms)	116.22 ± 30.40	124.44 ± 92.14	0.4
QTc (ms)	445.22 ± 47.85	437.08 ± 42.74	0.13
Intermittent arrhythmias (n/%)	22/24.18	57/12.23	0.005
Palpitations (n/%)	14/15.38	36/7.71	0.026
ICD (n/%) ^j	6/6.59	14/3	0.12
Pacemaker (n/%)	7/7.69	41/8.78	0.84
AUDIT ^k	2.27 ± 2.55	3.04 ± 3.12	0.01
Smoker (n/%)	15/16.48	50/20.73	0.15
ISS 10 ^l	14.84 ± 4.43	14.4 ± 4.18	0.36
Adherence (A-14) ^m	47.83 ± 7.54	49.94 ± 7.18	0.021
Physical activity (n/%)	46/51.69	301/67.79	0.005
HADS-A ⁿ	6.73 ± 3.66	5.65 ± 3.69	0.01
HADS-D ^o	4.47 ± 3.6	3.61 ± 3.15	0.02

^aClassification of heart defect severity, ^bNYHA: Severity of chronic heart failure according to New York Heart Association, ^chigh sensitivity C-reactive protein, ^dGamma-Glutamyltransferase, ^eGlutamat-Pyruvat-Transaminase, ^fGlutamat-Oxalacetat-Transaminase, ^gGrowth-Differentiation Factor, ^hN-terminal prohormone of brain natriuretic peptide, ⁱHemoglobin A_{1c}, ^jImplantable Cardioverter-Defibrillator, ^kalcohol use disorder identification test, ^linternet addiction scale, ^mquestionnaire for assessment of adherence and individual barriers, ⁿHospital anxiety scale, ^oHospital depression scale. Bold numbers represent significant values.

hs-CRP levels ($p = 0.03\text{--}0.05$) remained in the analysis. Physical activity once again came up as a protective factor ($p = 0.019\text{--}0.02$). In contrast, adjustment for age and sex estimated HADS-D ($p = 0.028$), HADS-A ($p = 0.014$) and physical activity ($p = 0.012$) as independent predictors. Alcohol consumption remained as an independent predictor in the sex-adjusted model including HADS-D. Adjustment for BMI led to the exclusion of hs-CRP as a significant variable.

Importantly, adherence to treatment was only slightly different between the groups and did not emerge as a predictive factor in uni- or multivariate analysis (Table 4).

Sex Differences

There were no sex differences in terms of age, HADS-D, heart disease severity and the two interrelated parameters BMI and hs-CRP ($r = 0.305$). Male sex presented significantly higher creatinine levels (89.3 ± 31.6 vs. 73.4 ± 22.5 $\mu\text{mol/l}$; $p < 0.001$) and AUDIT scores (3.54 ± 3.3 vs. 2.2 ± 2.5 ; $p < 0.001$). Also, physical activity showed male preponderance ($p = 0.023$). In comparison women had significantly higher anxiety scores (6.3 ± 3.7 vs. 5.4 ± 3.7 ; $p = 0.006$) and worse functional capacity, regarding NYHA-class ($p = 0.045$). They postponed more medical appointments ($p < 0.0001$), whereas limited access to medical care did not show significant gender differences. Reported palpitations and documented arrhythmias did not show any sex differences.

DISCUSSION

Main Findings

In addition to their physical limitations that afford a consequent and specialized treatment (19), ACHD patients are burdened by a huge variety of mental diseases including depression and anxiety disorders as the most common mental illnesses (13–15). Although presumed that in ACHD depression and anxiety symptoms have an impact on attendance, the data from the present study are the first to confirm this assumption.

In general, women presented with significantly higher anxiety symptoms than men. They postponed more medical appointments, pointing to a higher vulnerability of women during the pandemic. It is worrying that patients with documented arrhythmias, which represents a frequent complication being associated with a higher morbidity and mortality risk, were more likely to postpone their medical appointments (20–22).

Depression and Anxiety as Comorbidity

In the present study in univariate analysis, patients with postponed medical appointments and those with limited access to medical treatment/delivery of pharmaceuticals showed significantly higher depression and anxiety levels. In line with previously published data, we found a close interrelationship between anxiety disorders and depression, attributable to shared common biological pathways and behavioral risk factors (23). Nevertheless, in unadjusted analysis we found a preponderance of anxiety symptoms in participants with reported limited access to medical supply, whereas postponed appointments were

particularly associated with depression. One might argue, that the described levels of HADS-D and HADS-A are pretty low. However, evaluation of the HADS-D score in ACHD established a cut-off point >5 as the optimum of detecting major depressive disorder (24). In the ACHD population a similar evaluation of the HADS-A score is still missing. Nevertheless, our data indicate that already low levels of anxiety and depressive symptoms are associated with a health behavior potentially linked to adverse cardiac outcome (25).

Risk Factors of Postponed Medical Appointments

In univariate analysis, postponed medical appointments were associated with more symptomatic heart disease, such as more severe symptoms of heart failure, palpitations and more documented arrhythmias. Irrespective of all adjusting factors, only documented arrhythmias remained as an independent predictor. Additional drivers were higher symptoms of anxiety and depression and female sex.

The postponement of medical appointments in patients with documented arrhythmias represents a finding of particular concern. Arrhythmias in ACHD reflect a major source of morbidity and mortality (20, 21, 26). There is a body of literature pointing to an unfavorable alliance of heart disease and depression/anxiety disorders. The underlying pathophysiology consists of a common biological pathway constituted via the hypothalamic-pituitary-adrenal axis providing bidirectional heart-brain interaction, which modulates cardiopulmonary reflexes and neuroendocrine signaling (23, 27–29). Stress response in anxiety and depression disorders provoke catecholamine related dysregulation of the autonomic nervous resulting in blunted heart rate response, higher heart rate at rest and increased QT-c variability (23). We recently published that ACHD patients with reduced heart rate variability comorbid with depression have a particularly high risk to develop heart failure/all-cause mortality, arrhythmias and unexpected hospitalization due to cardiac causes (30). In non-congenital heart disease, anxiety disorders have been linked to the onset of arrhythmias (31–33). Although the exact mechanism still needs to be determined, cardiac diseases comorbid with depression or anxiety disorders appear to have a higher risk of adverse outcome. Considering that our observations are derived from patients followed by a specialized congenital heart disease center, it is quite likely that outcome is even worse in patients already lost during follow-up (25, 34).

In our study, postponed medical appointments were independently predicted by female sex. During the COVID-19 pandemic observed sex disparities derived from the general population point to a higher vulnerability of women to develop depressive and anxiety symptoms (35).

Risk Factors of Limited Access to Medical Care

In contrast to patients with postponed medical appointments, those with limited access to medical supply did not suffer from more serious heart defects or symptomatic heart disease.

TABLE 4 | Factors that impact access to medical supply and adherence to medical appointments during the COVID-19 pandemic.

Binary logistic regression analysis	Limited access to medical supply (<i>n</i> = 109)		Postponed medical appointments (<i>n</i> = 91)	
	HR ^f (95%CI ^g)	<i>p</i> -value	HR ^f (95%CI ^g)	<i>p</i> -value
Univariate Analysis				
HADS-D ^a	1.073 (1.008–1.142)	0.027	1.078 (1.0101–1.151)	0.023
HADS-A ^b	1.096 (1.037–1.159)	0.001	1.077 (1.015–1.143)	0.014
Physical activity	0.486 (0.315–0.750)	0.001	0.508 (0.321–0.806)	0.004
Hs-CRP ^c	1.069 (1.002–1.139)	0.042	0.989 (0.911–1.073)	0.768
Creatinine	0.994 (0.982–1.005)	0.287	0.976 (0.961–0.992)	0.003
AUDIT Score ^d	0.917 (0.842–0.999)	0.048	0.896 (0.812–0.988)	0.028
Sex	0.703 (0.462–1.070)	0.100	2.829 (1.755–4.561)	<0.0001
NYHA-Class ^e	0.850 (0.854–1.643)	0.311	1.555 (1.119–2.163)	0.009
Documented intermittent arrhythmias	1.042 (0.568–1.909)	0.895	2.288 (1.315–3.982)	0.003
Reported palpitations	0.529 (0.277–1.007)	0.053	2.177 (1.1221–4.225)	0.022
Multivariate Analysis: HADS-D^a				
HADS-D ^a	1.061 (0.994–1.133)	0.074	1.094 (1.019–1.175)	0.013
Physical Activity	0.581 (0.367–0.919)	0.020	0.598 (0.361–0.990)	0.046
AUDIT Score ^d	0.910 (0.830–0.997)	0.043		
Hs-CRP ^c	1.070 (1.000–1.144)	0.050		
Documented arrhythmias			2.237 (1.217–4.605)	0.010
Sex			2.761 (1.656–4.605)	<0.0001
Multivariate Analysis: HADS-A^b				
HADS-A ^b	1.089 (1.028–1.154)	0.004	1.068 (1.000–1.140)	0.050
Physical Activity	0.580 (0.367–0.916)	0.019	0.548 (0.330–0.911)	0.020
CRP ^c	1.078 (1.007–1.153)	0.030		
Documented arrhythmias			2.375 (1.273–4.433)	0.007
Sex			2.444 (1.448–4.125)	0.001

^aHADS-D: Depression score of HADS, ^bHADS-A: anxiety score of HADS, ^chigh sensitivity C-reactive protein, ^dalcohol use disorder identification test, ^eNew York Heart association, ^fHazard ratio, ^gConfidence interval. Bold numbers represent significant values.

In unadjusted analysis these patients were characterized by significantly higher anxiety symptoms, physical activity, alcohol consumption and the elevated inflammatory marker hs-CRP. However, after adjustment for sex, age and BMI only HADS-D, HADS-A and physical activity remained as independent predictors, whereas higher alcohol consumption and an increase in hs-CRP were no longer significant. Increased hs-CRP levels have been linked to both, depression and anxiety disorders. However, in line with previous reports, our data support the assumption that BMI itself represents the major factor determining hs-CRP elevation. After adjustment with BMI, significant differences were eliminated (36–40).

Raw data analysis also identified higher alcohol consumption as an independent predictor of good medical supply. Male consumed larger amounts of alcohol. However, the overall reported number of drinks (1.8 ± 3.1 drinks/week; 1 drink=10 g alcohol) was low. In disease entities such as heart failure, frequent consumption of small amounts of alcohol is associated with better outcome, potentially suggesting better social relationships and physical wellbeing (41).

Protective Effect of Frequent Physical Activity

Our data confirm the assumption that physical activity acts as a protective factor, preventing chronically ill patients from

developing threatening fears, such as limited medical care during COVID-19 pandemic or from postponing medical appointments. Previous studies showed a correlation between higher anxiety and depression levels and a lack of physical activity (35), suggesting that increased physical activity might lower the psychological burden in ACHD patients, resulting in less canceled appointments and a higher satisfaction with the level of medical treatment. Moreover, it was described that doing sports according to patients individual physical capacity has a direct positive effect on their health by reducing inflammatory markers and BMI (42). Therefore, it would be desirable to extend sports interventions for ACHD patients (43). However, this inevitably requires an individual assessment of physical capacity as derived from cardiorespiratory exercise testing, which with respect to the underlying cardiac defect determines the extent of exercise training.

Adherence

As a common feature, adherence to treatment was only slightly different in the evaluated groups, suggesting a general good adherence in ACHD. However, German health insurance-based data approve that at present only half of all German ACHD patients have regular cardiac care (34). Considering that all participants were recruited from a specialized adult congenital heart disease center, our results seem to reflect a selection bias

toward better adherence. Previous reports outline that non-attendant patients appear to be linked to non-adherence to medication, which increases the risk of an unfavorable cardiac outcome (25, 44).

In particular, ACHD patients with their congenital heart disease associated long-term sequela and their great burden of mental illness, require essential medical care (15, 19).

It is remarkable, that even in this positive selection of attendant patients during the COVID-19 pandemic depressive and anxiety symptoms led to the postponement of medical appointments and a feeling of insufficient medical care with respect to limited access to medical treatment/delivery of pharmaceuticals. As outlined, ACHD patients with insufficient medical routine examinations and postponed medical appointments tend to have a higher morbidity and mortality (25). Therefore, as proposed in other chronic diseases, identification and treatment of mental health comorbidities, recommendation of remote healthcare support and the encouragement to keep the follow-ups on a regular basis may help to avoid adverse health consequences (45).

Influence of COVID-19 Pandemic on Lifestyle and Mental Health

The COVID-19 pandemic has put severe stress on particularly vulnerable individuals, such as patients with mental or with physical diseases such as ACHD. Sanctions such as lockdown, no-contact provision, and quarantine may have further increased stress burden in these populations (46). Acute and chronic stress can affect the cardiovascular system and mental well-being of individuals, thereby enhancing the risk for the development or further progression of CVD. This may particularly apply to patients comorbid with physical and mental illness (47). Further, social isolation has dramatically affected lifestyles such as reduced physical activity, sedentary lifestyle, altered dietary habits, and decreased engagement in meaningful activities. Recently, the negative effects of the pandemic and the associated quarantine were reviewed, pointing out that distress caused by social isolation not only worsens mental health, but also negatively affects lifestyle factors (48).

CONCLUSION

This is the first study approving that in ACHD anxiety and depressive symptoms directly impact medical care. ACHD patients are burdened by their inborn congenital heart defect related long-term sequela and a high prevalence of mood disorders (15). Depressive and anxiety symptoms are associated with limited access to medical care and the postponement of medical appointments. Female sex and the worrying finding that patients with documented arrhythmias, indicating a higher morbidity and mortality risk, were particularly prone to cancel medical appointments.

It appears, that advanced symptomatic heart disease comorbid with depression characterizes a particular subgroup of patients at high risk to get lost during follow-up which is potentially associated with adverse outcome. Considering the observed

inadequate care of mood disorders in ACHD, regular screening for depressive and anxiety symptoms appears to be advisable (15). In contrast, frequent physical activity emerged as a protective factor.

Our data confirm the need to screen for mental disorders to facilitate psychological treatment (potentially in form of telehealth or digital health advises) to limit anxiety and depression levels, probably leading to less canceled medical appointments and an improved medical treatment (45).

Moreover, we recommend to encourage patients to increase their physical activity, which generates a direct positive effect on their health and additionally works as a protective factor by minimizing anxiety and depressive symptoms (43).

We hypothesize that these interventions might have the potential to improve medical treatment and reduce the number of canceled medical appointments not just during pandemics but also in everyday clinical practice.

STRENGTHS AND LIMITATIONS

Although the COVID-19 pandemic offers the chance to exhibit problems in the medical care of ACHD patients, the lockdowns and restrictions caused a selection bias toward the exclusion of patients, who missed their scheduled appointment either suffering from anxiety disorders and depression or other limitations, hindering them from coming to the outpatient department. A further selection bias is given by the monocentric study design.

Moreover, the question regarding limited access to medical treatment and/or delivery of pharmaceuticals comprehends subjective feelings reflecting different perceptions.

As an advantage, the overall drop-off rate was low. Due to the large number of participants, application of standardized questionnaires and inclusion of a cross-sectional population, typically found in ACHD studies, the data appear to be representative for patients followed in a specialized adult congenital heart disease center.

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 Ethics Committee Hannover Medical School Carl-Neuberg-Straße 1, D-30625 Hannover. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

KK and MW-B are leading investigators in the PsyConHeart study and have been involved in all aspects of this study. In particular, they were involved in (i) experiment design, (ii) experiment realization, (iv) data collection, (v) data analysis, (vi) data interpretation and (vii) manuscript writing. TH

and TK were involved in experiment design, data collection, data analysis, and data interpretation and manuscript writing. SA was involved in experiment design, data collection, data analysis, and data interpretation and manuscript writing. FL was involved in data collection and data interpretation and revising the manuscript. TK, AS-P, and JB were involved in data interpretation and revising the manuscript. All authors have

materially participated in the research and/or article preparation and have approved the final article.

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Unraveling the Complexity of Cardiac Distress: A Study of Prevalence and Severity

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Introduction: While much research attention has been paid to anxiety and depression in people who have had a recent cardiac event, relatively little has focused on the broader concept of cardiac distress. Cardiac distress is a multidimensional construct that incorporates but extends beyond common mood disorders such as anxiety and depression. In the present study we assessed the prevalence, severity and predictors of a broad range of physical, affective, cognitive, behavioral and social symptoms of cardiac distress. This is the first study to investigate cardiac distress in this comprehensive way.

Method: A sample of 194 patients was recruited from two hospitals in Australia. Eligible participants were those who had recently been hospitalized for an acute cardiac event. Data were collected at patients' outpatient clinic appointment ~8 weeks after their hospital discharge. Using a questionnaire developed through a protocol-driven 3-step process, participants reported on whether they had experienced each of 74 issues and concerns in the past 4 weeks, and the associated level of distress. They also provided sociodemographic and medical information. Regression analyses were used to identify risk factors for elevated distress.

Results: Across the 74 issues and concerns, prevalence ratings ranged from a high of 66% to a low of 6%. The most commonly endorsed items were within the domains of dealing with symptoms, fear of the future, negative affect, and social isolation. Common experiences were "being physically restricted" (66%), "lacking energy" (60%), "being short of breath" (60%), "thinking I will never be the same again" (57%), and "not sleeping well" (51%). While less prevalent, "not having access to the health care I need," "being

concerned about my capacity for sexual activity,” and “being unsupported by family and friends” were reported as highly distressing (74, 64, and 62%) for those experiencing these issues. Having a mental health history and current financial strain were key risk factors for elevated distress.

Conclusion and Implications: Specific experiences of distress appear to be highly prevalent in people who have had a recent cardiac event. Understanding these specific fears, worries and stressors has important implications for the identification and management of post-event mental health and, in turn, for supporting patients in their post-event cardiac recovery.

Keywords: psychocardiology, cardiac distress, anxiety, stress, depression, fear of progression, secondary prevention

INTRODUCTION

The psychosocial impacts of an acute cardiac event have gained increasing recognition in the past two decades. It is now well-accepted that both anxiety and depression are common after heart attack and heart surgery (1–3). In a recent Australian study involving over 900 patients admitted to hospital after acute myocardial infarction (AMI) or to undergo coronary artery bypass graft surgery (CABGS), over 40% had elevated anxiety and over 20% had symptoms of depression in the period shortly after hospital discharge, while 31% had anxiety or depression at 6–12 months post-event (3). These rates are up to four times higher than in the general population.

There is also growing evidence that acute cardiac events are often experienced as traumatic, thereby predisposing survivors to experiencing post-traumatic stress symptoms (PTSS) or disorder (PTSD). The traumatic components of a cardiac event include its abruptness, the risk of death, and a sense of helplessness and loss of control during and after the event (4). It has been suggested that around 12% of patients experience acute coronary syndrome (ACS)-induced PTSD (5).

But is there more to a cardiac event than just anxiety, depression and PTSD? Qualitative studies involving cardiac event survivors and clinicians who support them provide greater insight into the breadth of experiences, concerns and worries expressed during convalescence after an acute cardiac event and therefore provide a nuanced understanding of cardiac distress. One qualitative study of survivors concluded that they experience “being forced into a demanding life-shaking journey” (6), while another study of clinicians described it as “a lonely journey, an existential crisis” (7). It appears that the acute cardiac event can trigger the beginning of a completely new life chapter, involving new and difficult emotions, changes in self-concept and identity, and other unexpected challenges, fears and concerns.

Reported experiences gleaned from qualitative studies include a range of emotions, such as feelings of uncertainty (8–10), vulnerability (6), loneliness and fear of being alone (7), hopelessness and helplessness (6, 7), anger and resentment (7), sadness, grief and loss (7, 8). Specific losses include loss of independence (7, 11), loss of health and physical strength (8, 11), and loss of control (7). Similarly, various changes in self-identify

and self-concept have been reported (12), as have worries about getting back to one’s previous sense of self (13). These are often tied to changes in roles and role function (8, 12), including loss of the ability to provide (11) or be the “breadwinner” or “homemaker” (7). Impacts on intimate relationships are also a concern for some survivors (13), including concerns about resuming sexual activity due to fear of causing another heart attack (7, 14). Challenges navigating the health system are also evident, including difficulties in obtaining information and advice (13), and concerns about having to rely on help from health professionals (9).

The cardiac event also triggers difficulties in coping with change (9), including difficulties adjusting to limitations in everyday life (6) and living with pain (7), resistance to being on medications (9), hypervigilance regarding bodily sensations (7), concerns about making lifestyle changes (7, 15), and difficulties associated with resuming work or being unable to work (7). Some survivors express difficulty in accepting the diagnosis and the disease itself (6). For some, the trauma associated with the cardiac event can trigger the resurfacing of past traumas or unresolved grief, with concomitant intrusive thoughts and nightmares (7). Fear about the future (8, 11, 13) and concerns about having to reprioritise goals and life plans in a foreshortened future (8, 11) have also been reported. Concerns about having another heart attack and fear of dying can also emerge (7, 10), as survivors are forced to confront their mortality, possibly for the first time in their life (7, 8).

These challenging emotions, changes and experiences that follow an acute cardiac event can all be conceptualized as “cardiac distress.” We have defined this multi-dimensional construct in previous publications:

Cardiac distress is a persistent negative emotional state rather than a transient state; involving multiple psychosocial domains; that challenges a patient’s capacity to cope with living with their heart condition, the treatment of the condition, and the resultant changes to daily living; and challenges the person’s sense of self and future orientation (16, 17).

Importantly cardiac distress spans multiple psychosocial domains, thereby incorporating patients’ responses to physical, affective, cognitive, behavioral and social symptoms and experiences related to their cardiac event and their recovery (16).

The definition also highlights both present and future concerns, thereby taking into account impacts on current self-perception as well as fears about the future (16).

Current understanding of the prevalence and correlates of cardiac distress has been limited by a lack of quantitative studies on this topic. While several qualitative studies have been undertaken to explore survivors' post-event experiences, as outlined earlier, no quantitative studies have investigated the broad range of cardiac distress experiences across multiple psychosocial domains, and incorporating both current and future-orientations.

Aims of the Study

In the present study we assessed the prevalence and severity of a broad range of physical, affective, cognitive, behavioral and social symptoms of cardiac distress. We also investigated the correlates of distress by identifying the patient characteristics that predict these distressing experiences. This is the first study to assess the prevalence, severity and predictors of cardiac distress in this comprehensive way.

METHODS

Item Generation and Distress Questionnaire Preparation

A broad pool of items was generated following a strict protocol which has been described in full elsewhere (17). In brief, the process involved three key steps. First, items included in instruments to measure cardiac anxiety, depression, quality of life and other cardiac-related constructs were reviewed, as were measures of distress used in the oncology and diabetes settings, with a view to creating a pool of cardiac distress-related items. Second, qualitative studies from the cardiac literature were reviewed to identify relevant constructs and generate further items. Third, the item pool was reviewed by an expert multidisciplinary committee of cardiac researchers and clinicians to identify missing constructs and fine-tune item wording. Following these steps, a set of 74 items addressing various issues and concerns was generated. These assessed issues and concerns across seven key conceptual domains, determined *a priori* by the project team, namely symptoms, self-perception, concerns about the future, negative affect, self-management, social functioning and role functioning. Participants reported on whether or not they had experienced each of 74 issues or concerns in the past 4 weeks by responding Yes or No for each item. For endorsed items, participants then reported on the level of distress associated with the issue, using a response scale where 0 = "no distress at all," 1 = "slight distress," 2 = "moderate distress," and 3 = "severe distress."

Demographic, Medical, and Psychosocial Questions

Questions regarding demographic, medical and psychosocial characteristics were also included. Demographic information included age, sex, country of birth, education, and employment status. Medical information included event type, cardiac rehabilitation (CR) attendance (Y/N), cardiovascular risk

factors (high blood pressure, high cholesterol, obesity, and positive family history), and significant comorbidity (diabetes, musculoskeletal conditions, chronic obstructive pulmonary disorder, cancer, stroke, and dementia). Psychosocial data included living alone (Y/N), partner status (partnered/unpartnered), presence of a close confidante (Y/N), loss of a close relative or friend in the past 12 months (Y/N; defined as "recent bereavement"), having been diagnosed with a mental health disorder prior to the cardiac event (Y/N, defined as "mental health history"), and financial strain reported on a 5-point Likert scale from 0 "no financial strain" to 4 "extreme financial strain." The questionnaire was prepared in both hardcopy form for mailout and return, and *via* the REDCap (Research Electronic Data Capture) system for online completion.

Inclusion and Exclusion Criteria

Eligible participants were those who have had an acute coronary event, namely acute myocardial infarction (AMI), percutaneous coronary intervention (PCI), coronary artery bypass graft surgery (CABGS), valve issues, heart rhythm disturbance, spontaneous coronary artery dissection (SCAD), or cardiac arrest in the previous 12 months and who attended an outpatient clinic at participating hospitals. Patients who did not have adequate English language proficiency to read and understand the PDCF and questionnaire were excluded.

Participant Recruitment

A sample of 194 patients was recruited from two hospitals in Australia, one in metropolitan Melbourne (Monash Health) and one in regional Victoria (Barwon Health, Geelong). The procedure at each of the two hospitals differed slightly.

At Barwon Health, the majority of participants were recruited while they were inpatients at the University Hospital Geelong following their hospital admission for either AMI, CABGS or PCI. At this contact, the Research Nurse provided eligible patients with a brief explanation of the study and asked if they would be willing to participate. Interested patients were then provided with the consent form. Consent was obtained to re-contact participants *via* telephone ~6–8 weeks later to complete the questionnaire. A smaller number of participants were recruited during their attendance at cardiac rehabilitation (CR).

At Monash Health, participants were recruited at the time of their appointment at the Cardiothoracic Preadmission Clinic, prior to their hospital admission for CABGS, or in the Cardiac Care Unit (CCU) for those with AMI, PCI, and other cardiac conditions. At this contact, the Research Nurse provided eligible patients with a brief explanation of the study and asked if they would be willing to participate. Interested patients were then provided with the consent form. Consent was obtained to re-contact participants at their routine 6–8-week follow-up appointment.

Questionnaire Completion

Due to the COVID-19 pandemic and imposed lockdowns, participant recruitment varied between face-to-face and *via* telehealth. Questionnaires were either completed in hard copy

TABLE 1 | Characteristics of participants.

		N	n	%
Sociodemographic characteristics				
Sex	Male	194	140	72.2
	Female		53	27.3
	Prefer not to say		1	0.5
Country of birth	Australia	194	138	71.1
	Outside Australia		56	28.9
Marital status	Married/living with partner	194	137	70.6
	Divorced/separated		26	13.4
	Widowed		15	7.7
	Never married		16	8.2
Education	Primary	193	3	1.6
	Secondary		83	43.0
	Trade or certificate		55	28.5
	University degree/post-graduate		52	26.9
Employment status	In workforce	194	98	50.5
	Not in workforce		96	49.5
Psychosocial characteristics				
Lives alone		189	43	22.8
Recent bereavement		179	43	24.0
Financial strain		179	73	40.8
Mental health history		194	64	33.0
Medical characteristics				
Event type	Acute myocardial infarction	194	102	52.6
	Coronary artery bypass graft surgery		74	38.1
	Percutaneous coronary intervention		57	29.4
	Other		41	21.1
Attended cardiac rehabilitation		180	80	44.4
Significant co-morbidity		194	113	58.2

N = 179–194 with variations due to incompleteness of some questionnaires. Recent bereavement = having lost of relative or friend in the past 12 months. Financial strain = reports of moderate, considerable, or extreme financial strain. “Other” event type includes valve issues (*n* = 21), heart rhythm disturbance (*n* = 15), SCAD (*n* = 6), and cardiac arrest (*n* = 6).

or online. Thus, instead of completing the questionnaire while waiting for their clinic appointments as originally intended, participants were either directed to the website of the Australian Center for Heart Health (ACHH) to use an online link to the REDCap questionnaire or were mailed a hard copy of the questionnaire for completion at home and return in a reply-paid envelope to the ACHH. The questionnaire took ~25 min to complete. No identifying information was collected as no participant follow-up was involved.

Ethics Approval

This study had ethics approval from the Monash Health Human Research Ethics Committee (approval number: RES-19-0000631A – 55979, which covered data collection at both the Monash Health and the Barwon University Hospital sites.

Data Analysis

Frequencies were calculated for the prevalence and the distress severity ratings of each of the 74 issues and concerns. Items were clustered into the seven pre-determined domains of Symptoms (15 items), Self-perception (nine items), Concerns about the future (eight items), Negative Affect (eight items),

Social functioning (16 items), Role functioning (five items), and Self-management (13 items). For prevalence, positively endorsed items within each domain were added together to provide domain prevalence scores. Within the “Symptoms” domain, two sub-domains of “physical symptoms” (seven items) and “cognitive symptoms” (five items) were also created. Higher domain and sub-domain prevalence scores indicated endorsement of more items (issues and concerns) within that domain. For distress severity ratings, a distress severity score for each domain was calculated by taking the mean severity ratings of endorsed items within that domain. For each domain and sub-domain, for both prevalence scores and distress severity scores, bivariate analyses (*t*-tests) were undertaken to identify variations in terms of demographic (age, sex, and employment status), medical (event type, CVD risk factors, comorbidities, and CR attendance), and psychosocial (mental health history, social isolation, and financial strain) characteristics. These particular psychosocial characteristics were selected for examination as they have been previously demonstrated to be strongly predictive of persistent or worsening post-event anxiety and depression (18). Using significant variables from the bivariate analyses, a series of multivariable linear regression analyses were then

TABLE 2 | Prevalence of issues and concerns in rank order.

Issue/item	<i>n</i>	%
Being physically restricted	126	65.6
Lacking energy	115	60.3
Being short of breath	115	59.6
Thinking I will never be the same again	110	57.0
Not sleeping well	98	50.5
Thinking about having another heart event	93	48.4
Being irritated by little things	93	48.4
Thinking my condition might get worse	91	46.9
Having chest discomfort	87	45.1
Avoiding situations and activities	86	45.0
Being unable to do things that I know will improve my health	87	44.8
Having difficulty concentrating	86	44.6
Being overly aware of my heart in my chest	85	44.0
Thinking that I am not the person that I used to be	84	43.8
Not knowing how my family will cope if something should happen to me	82	42.9
Having difficulty remembering things	78	40.4
Not knowing what the future holds for me	77	40.3
Avoiding activities that make my heart beat faster	76	39.4
Being unsure about how much exercise or physical activity I should be doing	75	39.3
Having changes in my usual roles	72	37.9
Being tearful more easily than before	72	37.1
Forgetting things more than before	70	36.6
Not knowing what will happen to other people if I die	68	35.4
Having to make difficult lifestyle changes because of my heart condition	65	33.9
Being emotionally exhausted	63	33.3
Being afraid of dying	64	33.0

N = 189–194 with variations due to incompleteness in some questionnaires.
Only items endorsed by >33% of participants shown.

undertaken to identify the key predictors of prevalence and severity for each domain and sub-domain. For each model the variables entered included: age (years), sex, event type (CABGS vs. non-CABGS), living alone status, financial stress, history of mental illness, bereavement, and employment status. For the financial strain variable, responses of 3 “moderate,” 4 “considerable,” and 5 “extreme financial strain” were combined to indicate presence of financial strain. CVD risk factors (high blood pressure, high cholesterol, obesity, positive family history), various event types (AMI, PCI, and “other”), CR attendance, and comorbidities (Diabetes Mellitus, musculoskeletal, and “other” comorbid conditions) were not significant at the bivariate level and were therefore not entered into the multivariate analyses.

RESULTS

Participants

Participants ranged in age from 22 to 90 years, with a mean (SD) age of 63.7 (11.2) years. Participant sociodemographic, psychosocial and medical characteristics are shown in **Table 1**.

As shown in **Table 1**, participants were mostly male (72%) and married or partnered (71%). Most (71%) were born in Australia and for those who were not (*n* = 56), the majority were born in the United Kingdom (*n* = 18), and New Zealand (*n* = 7). Nearly half of the participants were no longer in the paid workforce, and 40% were experiencing financial strain. Approximately one quarter lived alone and for those who lived with others (*n* = 146), the majority lived with their partner (*n* = 83), or their partner and children (*n* = 40).

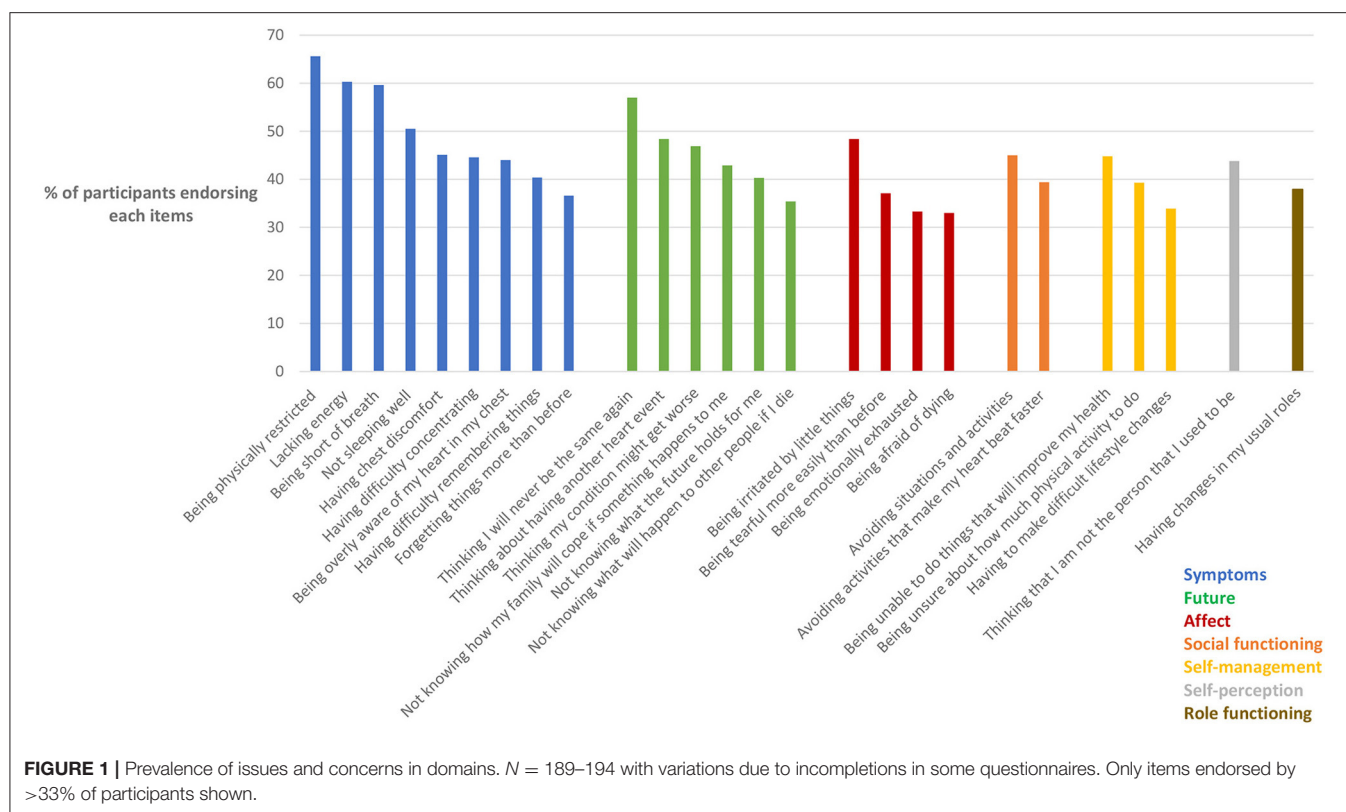
All participants had experienced their event in the previous 12 months, with the majority (94%) occurring within the past 3 months (mean = 2.2, SD = 1.9 months). Most participants had an AMI, CABGS, or PCI, while a smaller number (21%) reported having experienced other heart issues (valve issues, *n* = 21; heart rhythm disturbance, *n* = 15; SCAD, *n* = 6; cardiac arrest, *n* = 6). More than half (*n* = 100, 56%) of the participants did not attend CR, with the most common reasons being people waiting for CR (42%), declining attendance (21%), and concerns associated with COVID-19 (14%), including barriers associated with using telehealth. Just over half the participants (58%) had at least one significant co-morbidity, most often diabetes (*n* = 58, 30%) or musculoskeletal conditions (*n* = 40, 32%). In addition, cardiovascular risk factors such as hypertension (37%), high cholesterol (31%), obesity (13%), and obstructive sleep apnoea (12%) were present. One third of participants had a history of mental health problems (depression or anxiety), with one in four having experienced depression and one in five having experienced anxiety.

Most Common Issues and Concerns

The most commonly endorsed issues and concerns are shown in **Table 2** and **Figure 1**, with those items endorsed by over a third of participants depicted. The data indicate the proportion of participants who had experienced each of these in the previous 4 weeks. **Table 2** shows the items in rank order from highest to lowest, while **Figure 1** shows the same items grouped according to the seven pre-determined domains.

As shown in **Table 2**, the most commonly endorsed items were being physically restricted, lacking energy, being short of breath, thinking I will never be the same again, and not sleeping well. Each of these five items was endorsed by ≥50% of participants. A further 10 items were endorsed by between 40 and 50% of participants, including thinking about having another heart event, being irritated by little things, thinking my condition might get worse, having chest discomfort, avoiding situations and activities, being unable to do things that I know will improve my health, having difficulty concentrating, being overly aware of my heart in my chest, thinking that I’m not the person I used to be, and not knowing how my family will cope if something should happen to me. A further 11 items were endorsed by between 33 and 40% of participants. The remaining 48 items (from the full pool of 74 items) were each endorsed by fewer than 33% of participants (not shown in table).

As shown in **Figure 1**, four of the five most commonly endorsed items belonged to the “Symptoms” domain and more specifically, the “physical symptoms” sub-domain. Indeed, endorsement of items within the Symptoms domain was



common, with nine of the symptom-related items each being endorsed by over a third of participants. Items within the “Future” domain were the next most commonly endorsed, with three items from this domain being in the top 10, and six being endorsed by over a third of participants. Items in the “Affect” domain were the next most prevalent, with four being endorsed by over a third of participants. In contrast, items within the domains of “Social functioning,” “Self-management,” “Self-perception,” and “Role functioning” were the least commonly endorsed.

Most Distressing Issues and Concerns

While some items were highly prevalent, others were highly distressing. The items which elicited the highest ratings in terms of the severity of distress they caused are shown in **Table 3**. Not having access to needed health care was identified as the most distressing issue, being rated as either moderately or severely distressing by 74% of those who experienced this issue. Notably though, only 14% of participants actually reported experiencing this issue. Being concerned about capacity for sexual activity was the next most distressing issue, being rated as moderately or severely distressing by 64% of those who experienced it. However, only around one in five participants reported experiencing this issue. Being unsupported by family and friends, being isolated from family and friends, and being unavailable to family and friends were each reported as highly distressing albeit not commonly experienced issues. Notably, “not knowing how my family will cope if something happens

to me” and “not sleeping well” were rated as both distressing and common.

In terms of the experience of “severe distress,” having bad dreams and nightmares was identified as the most severely distressing for those who experienced it; 28% of those who experienced bad dreams and nightmares reported that this was “severely distressing.” Being unsupported by family and friends and being unable to work were also commonly identified as causing severe distress amongst those who experienced these issues.

As shown in **Figure 2**, the two most distressing issues belonged to the “Self-management” and “Self-perception” domains, although other items within these two domains were rated as less distressing. Three of the four next most distressing items belonged to the “Social” domain. For both the “Social” and “Symptoms” domains, three items were rated as moderately or severely distressing by over 50% of those who experienced these issues, whereas this was the case for only one item within each of the “Future,” “Affect,” and “Role functioning” domains. Overall though, the pattern evidenced in **Figure 2** shows that a range of items across all six domains were identified as highly distressing.

Predictors of Prevalence and Severity Ratings

Results of the multivariate regression analyses are shown in **Table 4**.

In terms of prevalence ratings, financial strain was a significant predictor for all domains, and history of mental illness was a significant predictor for all but two domains. Living alone was

TABLE 3 | Most distressing issues and concerns in rank order.

	Prevalence	Level of distress caused		
		Moderate	Severe	Moderate or severe
Not having access to the health care I need	14.0	66.7	7.4	74.1
Being concerned about my capacity for sexual activity	22.0	47.6	16.7	64.3
Being unsupported by my friends or family	6.8	38.5	23.1	61.6
Being isolated from family and friends	15.3	44.8	13.8	58.6
Not knowing how my family will cope if something happens to me	42.9	39.0	18.3	57.3
Being unavailable to my family and friends	17.3	45.5	9.1	54.6
Not sleeping well	50.5	43.3	10.3	53.6
Having more pain than I expected to have	22.8	36.4	15.9	52.3
Having bad dreams and nightmares	24.0	23.9	28.3	52.2
Not being able to cope effectively with my heart condition	27.1	40.4	11.5	51.9
Lacking energy	60.3	36.0	15.8	51.8
Becoming a burden to my family	31.4	38.3	13.3	51.6
Not knowing what the future holds for me	40.3	42.9	7.8	50.7
Being unsure about how much exercise I should be doing	39.3	45.3	5.3	50.6
Being emotionally exhausted	33.3	42.9	6.3	49.2
Being unable to deal with stress	32.8	38.7	9.7	48.4
Being unable to do things that will improve my health	44.8	41.4	6.9	48.3
Being unable to plan for the future	24.9	39.6	8.3	47.9
Not being able to return to work or continue working	23.7	25.6	22.2	47.8
Thinking that I'm not the person I used to be	43.8	40.5	7.1	47.6
Not having anyone to talk to who understands my difficulties	17.9	35.3	11.8	47.1
Being afraid of dying	33.0	35.9	10.9	46.8
Feeling lonely	24.5	38.3	8.5	46.8
Lacking purpose and meaning in life	27.1	28.8	17.3	46.1
Having difficulty making decisions	25.0	4.2	4.2	45.9

N = 189–194 with variations due to incompletions in some questionnaires. Only 25 most distressing items shown.

predictive of prevalence ratings for the “Cognitive symptoms” sub-domain and the “Social” domain. Females had significantly higher prevalence for the “Symptoms,” “Future,” “Affect,” and “Social” domains, and the “Physical symptoms” sub-domain, while those who had undergone CABGS had higher prevalence for the “Symptoms” domain and the “Physical symptoms” sub-domain. Bereavement was associated with higher prevalence for the Symptoms domain [aOR = 3.82 (95% CI 1.19–12.33), p = 0.025], while employment status was not significantly associated with prevalence ratings for any of the domains (not shown in table).

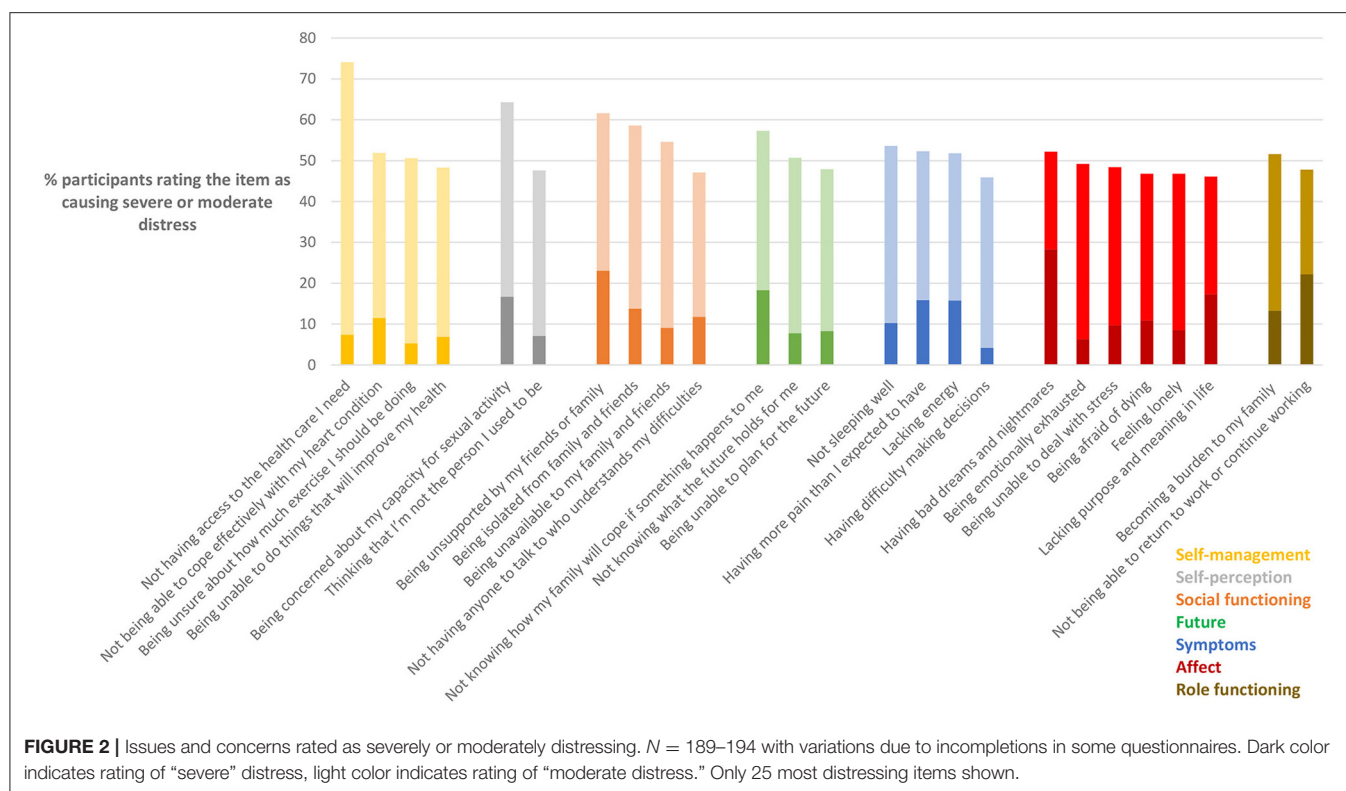
In terms of severity ratings, history of mental illness was a significant predictor across all but one domain, while financial strain was a significant predictor for the “Affect” and “Self-management” domains. Younger age was associated with higher severity ratings for the “Social” domain [aOR = 0.99 (95% CI 0.97–1.00), p = 0.016; not shown in table]. Female sex, event type, living alone, and employment status were not significantly associated with severity ratings for any of the domains.

DISCUSSION

The findings of the present study document the prevalence and severity of cardiac distress across 74 items within seven domains

relating to cardiac symptoms, self-perception, concerns about the future, negative affect, social functioning, role functioning, and self-management. The most commonly endorsed items were within the domains of dealing with symptoms, fear of the future, negative affect, and social functioning, and included “being physically restricted,” “lacking energy,” “being short of breath,” “thinking I will never be the same again,” and “not sleeping well.” While less prevalent, “not having access to the health care I need,” “being concerned about my capacity for sexual activity,” and “being unsupported by family and friends” were reported as highly distressing for those experiencing these issues. The study has also identified key demographic and psychosocial predictors of distress. In doing so, the study has expanded our understanding of the multi-faceted nature of distress caused by a cardiac event.

Many of the highly prevalent issues and concerns identified by these cardiac event survivors related to physical symptoms and the fear that they would not ever be the same again. Concerns about loss of health have been identified previously in qualitative studies (6, 8, 11), as have concerns about loss of one’s previous sense of self (13). Many of these concerns about symptoms and physical adjustment are addressed and normalized in CR, thereby reinforcing the need to increase the rate of referral to and attendance at CR as a crucial step in recovery.



Concerns about the future were also highly prevalent. These included fears about worsening symptoms, having a recurrent event and, ultimately, fears about death. Again, these issues have been identified in previous qualitative studies (7, 8, 10, 11, 13). Additionally, future-related items were also identified as highly distressing, particularly those centering on the issue of an uncertain future. Previous qualitative studies have similarly highlighted the distress caused by uncertainty and the inherent inability to plan for the future post-cardiac event (8–11).

While recognizing the highly prevalent nature of physical symptoms in particular, this study highlights the importance of assessing not just what people experience, but how distressing these issues are perceived to be. Not having access to needed health care was identified as the most distressing issue, extending previous qualitative findings regarding worries about obtaining professional help and advice (9, 13). Given that the present study was conducted during the COVID-19 pandemic, with concomitant restrictions in face-to-face healthcare delivery and pivoting to telehealth support options, it is perhaps not surprising that this issue was identified as highly distressing. Also extending previous qualitative studies (7, 14), ours is the first to highlight concerns about sexual capacity as amongst the most distressing of all issues faced by cardiac event survivors. Concern about future sexual capacity reflects not only a person's concern with physical functioning but represents an important dimension of personal identity that is under threat, and a concern with acceptance of potential limitations, whether psychological or physical in origin.

The present findings highlight a number of issues that can be addressed in cardiac rehabilitation. Difficulties due to sleep

disturbance, including poor sleep quality and nightmares, and concerns about how patients' families will cope, were both highly endorsed and very distressing. These issues are very important to address, to enhance patients' physical and emotional recovery. We have argued elsewhere for the need for screening for sleep disorders in the recovery phase during CR (19) so that survivors are given relevant and timely assistance with this issue. Similarly, health professionals engaging with cardiac patients in recovery need to be alert to survivors' concerns about family and, indeed, to the importance of knowing about the degree of connectedness survivors have with their family or within their community. Those experiencing difficulties in this area should be considered for referral to a family-oriented service.

It is notable that women experienced more of the issues and concerns listed than did men, with female sex a significant predictor of high prevalence across several domains. This is consistent with women's previously reported higher levels of anxiety and depression (20) and may also be due to women being more expressive than men and highly attuned to identifying and acknowledging their psychosocial concerns. Although female sex was not predictive of distress severity ratings, this may be due to the fact that these analyses were undertaken by domain rather than for individual items. Consistently, it was somewhat surprising that few age differences were identified and, again, this may be due to a lack of fine-tuned comparisons, which was outside the scope of the present study.

As may be expected, people with a mental health history experienced more of the issues and concerns, and also rated them as more distressing. Those with a mental health history tend to

TABLE 4 | Significant predictors of distress prevalence and severity ratings.

	Predictor variables									
	Female sex		CABGS		Live alone		Financial Strain		History of mental illness	
	aOR (95%CI)	p	aOR (95%CI)	p	aOR (95%CI)	p	aOR (95%CI)	p	aOR (95%CI)	p
Prevalence ratings										
Symptoms	4.29 (1.33–13.87)	0.015	2.97 (1.33–13.87)	0.042			6.95 (2.46–19.67)	<0.001	5.81 (1.95–17.33)	0.002
Sympt-Phys	1.89 (1.02–3.49)	0.042	1.98 (1.14–3.43)	0.015			2.27 (1.31–3.93)	0.004	2.15 (1.21–3.81)	0.009
Sympt-Cog					1.92 (1.08–3.44)	0.027	1.90 (1.17–3.07)	0.009	2.01 (1.21–3.34)	0.007
Future	2.45 (1.01–5.97)	0.049					3.73 (1.69–8.22)	0.001		
Affect	2.17 (1.06–4.47)	0.035					3.64 (1.91–6.90)	<0.001	5.12 (2.60–10.08)	<0.001
Social	3.82 (1.21–12.07)	0.023			6.29 (1.86–21.29)	0.003	6.66 (2.42–18.30)	<0.001	5.58 (1.92–16.12)	0.002
Self-perception							3.84 (1.92–7.71)	<0.001	2.47 (1.17–5.22)	0.018
Role function							2.44 (1.57–3.80)	<0.001		
Self-manage							8.38 (3.33–21.10)	<0.001	3.11 (1.17–8.30)	0.024
Severity ratings										
Symptoms									1.42 (1.18–1.72)	<0.001
Sympt-Phys									1.42 (1.15–1.76)	0.002
Sympt-Cog									1.45 (1.11–1.89)	0.007
Future									1.35 (1.08–1.69)	0.009
Affect							1.25 (1.02–1.54)	0.032	1.40 (1.13–1.74)	0.002
Social									1.53 (1.25–1.96)	<0.001
Self-perception									1.45 (1.12–1.87)	<0.001
Role function									1.59 (1.15–2.19)	0.005
Self-manage							1.29 (1.06–1.57)	0.012		

Full multivariable linear regression models for each rating included: age (years), sex, CABGS status, live alone status, financial stress, history of mental illness, and bereavement in past 12 months. aOR, adjusted odds ratio; CABGS, coronary artery bypass graft surgery; Symptoms, symptoms domain; Sympt-Phys, Physical symptoms subdomain; Sympt-Cog, Cognitive symptoms subdomain; Future, Concerns about the future domain; Affect, Negative Affect domain; Social, Social functioning domain; Self-Perception, Self-perception domain; Role Function, Role functioning domain; Self-Manage, Self-management domain.

have a lower base of resilience and coping and therefore will experience more cardiac-related issues and find them inherently more distressing. Previous anxiety/depression is a known risk factor for poor post-cardiac event mental health outcomes (3, 18), underscoring the importance of identifying these patients early on and targeting them for mental health support.

The present study also identified other known correlates of persistent anxiety and depression such as financial strain (3, 18), and social isolation (3, 18). Indeed, financial strain was a consistent predictor of prevalence ratings across all domains and sub-domains, highlighting this patient characteristic as an important and easily assessed “red flag” for poor post-event mental health recovery, as we have noted previously (3, 18). Feelings of isolation have been exacerbated by the COVID-related mandatory lockdowns and restrictions, and have brought this issue into sharp focus internationally (21). Poignantly, of those who reporting feeling unsupported by family and friends, over 60% found this severely or moderately distressing, with this distress likely heightened by the COVID-19 lockdowns (21). Social isolation as a barrier to good recovery has been identified as a contributor to persistent or worsening mental health post cardiac event (3, 22) as well as conferring a higher risk of premature death (23). Those who had experienced a recent bereavement endorsed more items related to cognitive

symptoms, raising concerns for this group in terms of their cardiac recovery. Consistently, a recent study found that death of a spouse or partner during the year prior to a first AMI is associated with an increased risk of recurrent AMI and cardiac-related death (24), highlighting bereavement as a red flag for compromised cardiac recovery.

Limitations

Some study limitations should be acknowledged. First, while the present results confirm our definition of cardiac distress as multifactorial and non-transient, a stronger case for the latter point may have been made if the questionnaire had been administered further into convalescence. The 8-week assessment point was chosen to coincide with routine follow-up clinic appointments, in order to optimize participation. However, at this relatively early point of recovery it is possible that symptoms of the cardiac blues, typical during the early post-event adjustment period (25), may not yet have resolved. Future longitudinal studies to investigate the trajectories of the components of distress are needed. Second, due to the large number of distress items assessed, we identified predictors for domains only, rather than for individual items. More fine-tuned analysis to investigate item correlates would provide a more nuanced understanding of sex and age-related differences

in particular, but was outside the scope of the present study. Again, this could be the focus of more targeted hypothesis testing within specific distress domains and/or for specific patient groups. Third, being undertaken during the COVID-19 pandemic, the study findings may have been impacted by transient and extraneous stressors that were not measured. Despite these limitations, the study was strengthened by the inclusion of consecutive series of cardiac patients from two large hospitals, representing both metropolitan and regional areas of Australia.

CONCLUSION AND CLINICAL IMPLICATIONS

The present study extends the findings of earlier qualitative studies by quantifying common issues and concerns experienced by cardiac event survivors and providing assessment of the level of distress caused by these issues and concerns. It is the first study to explore cardiac distress in this way. The findings highlight the importance of investigating both endorsement of these issues as well as ratings of distress severity in our attempts to understand cardiac distress. The fact that issues such as not being able to access suitable health care and concern about sexual functioning were highly distressing although not highly endorsed, shows the necessity for measuring both, and not simply assuming that high prevalence of an issue correlates with a high level of distress and vice versa. In terms of clinical implications, the findings underscore the importance of providing the opportunity for patients to express the specific nature of their worries and concerns, and to reveal the impacts of these on their psychological wellbeing. Patients expressing high levels of distress should be given the opportunity for psychocardiology-informed counseling to support them in their recovery. Indeed, the findings point to the need for implementing

routine screening for cardiac distress in primary care and cardiac rehabilitation settings. The present findings further our understanding of the relative importance of various post-event issues and concerns, thereby providing useful clinical guidance for health professionals working in cardiac rehabilitation and psychocardiology settings.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

This study had ethics approval from the Monash Health Human Research Ethics Committee (approval number: RES-19-0000631A – 55979). Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

BM, MR, ML, and AJ undertook data analysis and data interpretation. AJ, MR, and BM drafted the manuscript. JA, JS, VH, MA, RH, CS, and DT contributed to and approved the manuscript. All authors contributed to study design, questionnaire development, and data collection. All authors contributed to the article and approved the submitted version.

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Metacognitive Short-Term Intervention in Patients With Mental Disorders Following Cardiovascular Events

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Background: Mental disorders are common among patients with severe cardiovascular diseases (CVD). Yet, there is a lack of easily accessible evidence-based treatments. Recent research indicates elevated prevalence of dysfunctional metacognitions in patients with mental disorders following cardiovascular events. As metacognitive therapy (MCT) is an established treatment to modify metacognitions, we tested if a brief metacognitive intervention *via* videotelephony is effective in this patient group.

Methods: A brief MCT treatment was tailored to CVD patients and designed as a face-to-face internet-based intervention. Five patients with CVDs and comorbid mental disorders underwent a psychocardiological examination and diagnostic approach. Each patient participated in eight 50 min sessions *via* encrypted video messenger service. Metacognitions, depression and anxiety symptoms and quality of life were assessed by self-report measures pre- and post-treatment. Patients rated dysfunctional thought processes, current psychological impairment, and treatment satisfaction after each session. Intended follow-up measures were not reported due to missing data.

Results: For most patients, the brief metacognitive intervention was associated with a decrease in dysfunctional metacognitions and a reduction of symptoms of anxiety and depression post-treatment. Psychological and physiological quality of life improved. Patients reported high satisfaction with the tailored treatment.

Conclusion: Our results suggest that a brief internet-based metacognitive treatment may be a promising tool for patients with CVDs and comorbid mental disorders. Feasibility and acceptance of the intervention was rated high by the patients. Further research is necessary to support the preliminary findings and to adapt and evaluate the intervention in a controlled clinical trial setting.

Keywords: cardiovascular disease, mental disorder, metacognitive therapy, psychotherapy, psychocardiology

INTRODUCTION

The interaction of psychological and cardiovascular health is a subject of interest in many different fields of research. Studies regarding the comorbidity of cardiovascular and psychiatric diseases have shown that the prevalence of mental illnesses is increased across patients with different cardiovascular diseases (CVDs) (1–3). The most common disorders among CVD patients are pathological stress reactions after a cardiovascular event, depressive and anxiety disorders (3–6). Psychiatric symptoms and illnesses are in turn associated with several worse outcomes regarding the CVD: poorer prognosis of the course of the CVD, lower quality of life (QoL), increased risk of mortality, and interference with the CVD treatment, for example, due to worse adherence (3, 7–11). Many current guidelines for the different CVDs therefore include recommendations that vary from psychosocial support to psychotherapy, depending on the severity of the psychological distress (12–14). Offered psychological treatments, for example, for the most common CVD coronary heart disease (CHD), include a variation of components (e.g., relaxation techniques, cognitive strategies, psychological support) (15). Systematic reviews and meta-analyses report small to moderate effects of these psychological treatments on depressive and anxiety symptoms, but the quality of evidence was low to very low (15). Overall mortality and the risk of cardiovascular events were not affected by the treatments investigated (15). Richards et al. (16) also found no evidence that the currently used interventions of cognitive behavioral therapy in CHD patients, which is the gold standard in the treatment of anxiety and depression in general, were more effective than the other ones investigated. In clinical practice, only a fraction of CVD patients with a comorbid mental illness actually receives an adequate psychological treatment (5, 17, 18). Reasons for mental disorder treatment gaps in general include long waiting times and limited regional access (19, 20) which can plausibly be applied to mental disorders in the context of CVDs. Thus, there is the need for evidence-based, effective, and accessible treatments for CVD patients with mental disorders.

The metacognitive approach (21) provides a framework for mental disorders in CVD patients. Metacognitive theory (21, 22) posits that the cognitive processes that are involved in interpreting, monitoring, and controlling cognition (the so-called metacognitions) are transdiagnostically associated with mental disorders (23). A key role in the pathogenesis and maintenance of mental disorders is attributed to the Cognitive Attentional Syndrome (CAS): The CAS describes a dysfunctional cognitive pattern, characterized by inflexible attention, perseverative thinking like worry and rumination, threat monitoring and dysfunctional self-regulatory behaviors, e.g., avoidance (21). It is postulated to lead to the inability to process normal emotional distress and to result in its maintenance. One's positive and negative metacognitive beliefs, which state the assumed usefulness and uncontrollability as well as danger of thoughts and processes involved in the CAS, respectively, lead to its progression (21, 23). Recent research exploring metacognitions in CVD patients suggests that the application of a metacognitive framework onto the psychological processes

following a CVD poses a good fit, with repetitive negative thinking and metacognitive beliefs being found amongst patients with resulting mental disorders (24)¹. In metacognitive therapy (MCT) (23), these maladaptive metacognitive processes and beliefs are modified to establish more flexible thinking and therefore reduce psychological distress. MCT is an effective treatment, especially for anxiety and depression (25). Recently, the effectiveness of MCT for mental disorders among somatically ill patients has been explored. Findings show that MCT is a feasible treatment with promising effects in that patient group as well (26, 27). There is first evidence from a single case study that a brief MCT in an individual setting is a beneficial treatment for a mental disorder in a patient with a CVD (28): The treatment consisted of several MCT techniques with a focus on attention training (29) and detached mindfulness (23). After four sessions, the patient with an adjustment disorder showed a full remission from it and improvements in MCT specific scores.

The aim of this study was to further explore the effects of an individual metacognitive therapy in patients with the most common mental disorders following different CVDs. Next to the advantages of the metacognitive approach, which allows for a transdiagnostic treatment in a short period of time, the treatment was internet-based as it was conducted *via* videotelephony. During the last years, a wider use of internet-based treatments has been established. They have several advantages: Studies have shown internet-based CBT-treatments to be effective for several mental disorders, amongst them anxiety and depressive disorders (30). They ease the problem of regional restrictions of availability of psychological interventions and might be a promising way of alleviating the accessibility problem. Furthermore, they are feasible and gained in importance during the SARS-CoV-2 pandemic (31, 32). Thus, the delivery of MCT *via* internet should be investigated as well to take advantage of the benefits (33). Taken together, this study aims to explore the effectiveness of a short-term metacognitive intervention *via* videotelephony in a sample of CVD patients.

METHODS

Participants

Patients were referred by the Department of Cardiology and Angiology, the Department of Respiratory Medicine and the Department of Psychiatry, Social Psychiatry and Psychotherapy of Hannover Medical School. Patients were included if they met the following criteria: (1) confirmed diagnosis of a CVD, (2) minimum age of 18 years, (3) free of psychiatric medication or stable on medication for at least 3 months, (4) diagnosis of adjustment disorder, major depressive disorder and/or anxiety disorder according to DSM-V criteria, and (5) no acute suicidal tendency. All patients reported to fulfill the given criteria and provided written consent to be part of the study. For an overview of the somatic and psychiatric diagnoses of each patient, see **Supplementary Table 1**.

¹Caldarone F, Gebhardt P, Hoepfer MM, Olsson KM, Fuge J, Park D-H, et al. Metacognitions in patients with frequent mental disorders after diagnosis of pulmonary arterial hypertension. *Front Psychiatry*. (under review).

Initially, six patients were included. One patient received the treatment but was removed from the case series due to concurrent outpatient psychotherapy.

Patient 1

Patient 1 was a 40-year-old female who had been diagnosed with idiopathic pulmonary arterial hypertension (IPAH) three years prior. Additionally, she suffered from obesity, obstructive sleeping disorder, and endometriosis. She was diagnosed with major depressive disorder and a binge eating disorder in 2002. She received an 8-week cognitive behavioral therapy (CBT) at a day-clinic in 2004. Yet, since the IPAH diagnosis, depressive symptoms reoccurred. During inclusion, she met the diagnostic criteria for a depressive episode and persistent symptoms of the binge eating disorder. Patient 1 took anti-depressant medication (Venlafaxine) and did an outpatient CBT one year prior to the study. She had been unemployed for three years.

Patient 2

Patient 2 was a 38-year-old male who developed a two-vessel disease and suffered a myocardial infarction three and a half years prior to inclusion in this study. He received a stent for one vessel plus an implantable cardioverter-defibrillator as a treatment. The patient received a 7-week inpatient psychotherapy followed by two and a half years of outpatient psychotherapy after the cardiac event due to depression (still present during this study), panic disorder and reactivation of traumatic events from his youth. During inclusion, he was employed. He was free of medication and received no psychotherapy.

Patient 3

Patient 3 was a 54-year-old female who was diagnosed with IPAH in 2019. In addition, she suffered from fibromyalgia, diabetes mellitus type 2, rheumatic arthritis, polyneuropathy, gout, migraines, and obesity. The patient received a 3-month inpatient treatment due to depression followed by two years of outpatient psychotherapy before the IPAH diagnosis. She received a disability pension due to her somatic illnesses since 2019. During inclusion, she suffered from a depressive episode and was free of psychopharmacological medication.

Patient 4

Patient 4 was a 42-year-old male who developed ventricular extrasystoles half a year prior to inclusion during a foreign assignment. He met the diagnostic criteria for an adjustment disorder and reported symptoms of anxiety and low mood. Patient 4 was not on psychiatric medication and has not received any kind of psychotherapy. He was still employed but was currently unable to continue his work abroad due to the psychological impairment. He had been on sick leave for one month during inclusion.

Patient 5

Patient 5 was a 65-year-old female with a 14-year history of chronic thromboembolic pulmonary hypertension. Since the diagnosis, she reported to suffer from severe health-related restrictions, e.g., limitations of movement and a low activity rate. During inclusion, she met the diagnostic criteria for a major depressive disorder and a generalized anxiety disorder. She was

free of psychiatric medication; however, she previously received a 4-week inpatient CBT three years ago. Patient 5 was retired.

Measures

Hospital Anxiety and Depression Scale

The Hospital Anxiety and Depression Scale (HADS) (34) is a self-report measure assessing anxiety and depressive symptoms over the last week. It consists of 14 items, which are rated on a 4-point Likert scale from 0 to 3. The questionnaire includes two subscales with seven items each, resulting in subscale-scores ranging from 0 to 21. Higher scores indicate higher levels of anxiety and depressive symptoms (34). The HADS has good psychometric properties and is commonly used, especially in patients with somatic illnesses (35, 36). For the study, the German version was used (37).

Metacognitions Questionnaire-30

The Metacognitions Questionnaire-30 (MCQ-30) (38) is a self-report scale that measures beliefs about worry, monitoring tendencies and thinking itself. It consists of five subscales: positive beliefs about worry, negative beliefs about uncontrollability of thoughts and danger, beliefs about cognitive competence, beliefs about need to control thoughts, and cognitive self-consciousness. 30 items are answered on a 4-point Likert scale from 1 ("do not agree") to 4 ("agree very much"), giving a range from 30 to 120. Higher scores indicate a greater level of dysfunctional metacognitions. The instrument has good internal consistency, convergent, and construct validity and acceptable to good test-retest reliability (38). For the study, the German version of the MCQ-30 was used (39).

World Health Organization Quality of Life Assessment

The World Health Organization Quality of Life Assessment (WHOQOL-BREF) (40) is a short version of the WHOQOL-100 (41), and is a cross-cultural measurement of wellbeing and QoL. The assessment comprises four domains of QoL: physical health, psychological, social, and environment (40). In addition, one facet covering overall QoL and general health is assessed. The 26 items were self-rated referring to the last 2 weeks on a 5-point Likert scale. The sum scores of the domains are transformed on a scale from 0 to 100 with higher scores indicating a better QoL. The WHOQOL-BREF domain scores have demonstrated good discriminant validity, content validity, internal consistency, and test-retest reliability (40). For the study, the German version was used (42).

Visual Analog Scales

Visual analog scales (VAS) were used to evaluate the course of symptoms (e.g., self-focused attention, worry and rumination and perceived uncontrollability of thoughts) and treatment satisfaction. Patients rated nine items on a scale from 1 to 10. The VAS items are included in **Supplementary Table 2**.

Procedure

Patients were contacted by one of three therapists to confirm inclusion and exclusion criteria. The initial session was used for a psychocardiological examination. Trained psychologists conducted diagnostic interviews to assess mental disorders

according to DSM-V criteria. Subsequently, participants received seven sessions of 50 min duration twice a week. This was followed by two 25 min follow-up booster sessions after 6 and 12 weeks. All sessions were conducted online using an encrypted medical video messenger service. HADS, MCQ-30, and WHOQOL-BREF were completed at baseline, post-treatment and at 6 and 12-week follow-up. Additionally, the VAS were filled out at each treatment session.

Treatment

The treatment protocol was based on the MCT manual by Wells (23). The treatment plan was tailored to the specific needs of a person suffering from the co-occurrence of somatic and mental illness. To that end, statements of cardiologists, the patients with CVDs and their relatives were collected and analyzed. Accordingly, a modular treatment plan was developed. The treatments were provided by three of the authors (FC, PG, IH) after receiving training and under continuous supervision for FC and PG. The treatment was planned as a short-term intervention which aimed to be economic but efficient. Therefore, we decided to heighten the frequency to twice weekly sessions as there is evidence for improved treatment outcomes (43). A frequent examination of the correct execution and adherence to the treatment exercises (e.g., ATT) was an additional reason for the twice weekly sessions.

The treatment plan included the following modules:

- (1) Case formulation and Socialization
- (2) Attention Training Technique (ATT)
- (3) Detached Mindfulness (DM) strategies
- (4) Challenging positive and negative metacognitive beliefs
- (5) Modifying dysfunctional coping mechanisms
- (6) Relapse prevention

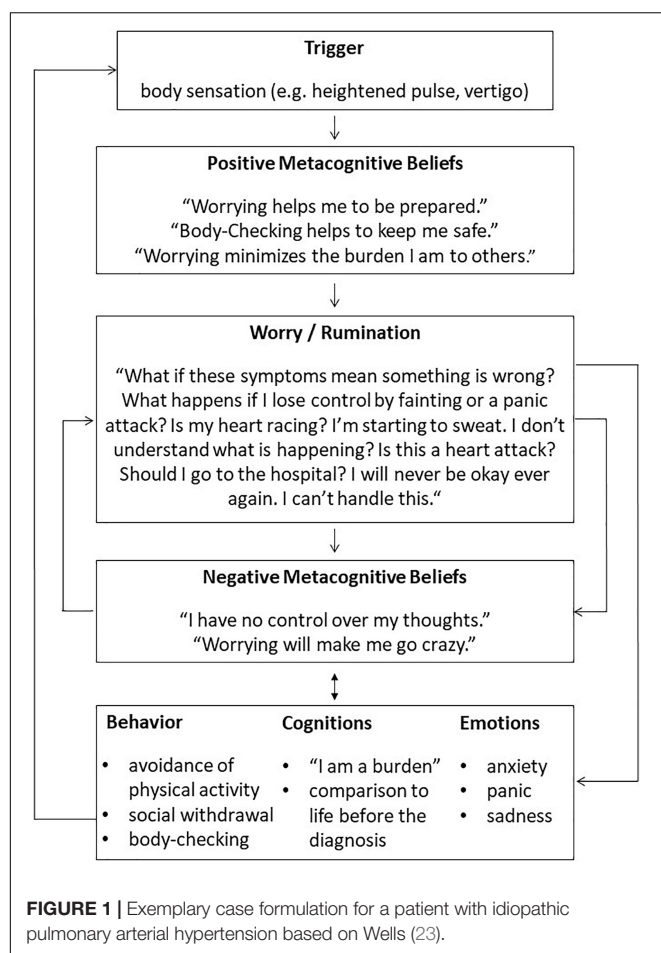
First, a personalized case conceptualization was drawn up using a transdiagnostic model adapted to the cardiovascular patients. Cardiovascular symptoms were incorporated with consequent thinking processes of the Cognitive Attentional Syndrome (CAS), such as worrying and an ongoing shift of attention to body sensations. Underlying positive and negative metacognitive beliefs were identified and linked to the reported thinking patterns. Consequences on an emotional, behavioral and cognitive level were discussed. For an exemplary case formulation, see **Figure 1**. The socialization to the model was supported by questions demonstrating the role of the different model elements and their circularity. The next step was the introduction of the ATT (29). Goal of the ATT is to strengthen attentional control, flexibility, and resources (23, 29). It has been shown to have the above mentioned attentional effects in anxiety, depression (44) as well as adjustment disorder in a CVD patient (28). Thus, the German Version of ATT was included in the treatment plan (23). Participants were asked to practice the ATT twice a day during the treatment. Next, DM was introduced using metaphors from the MCT manual (e.g., cloud or train metaphor) (23). DM focuses on the reactions to one's own thinking processes (21). It aims to raise metacognitive awareness and a detached perspective to dysfunctional thoughts by not reacting to them on purpose (23). DM was applied using

exercises (e.g., tiger task, prescriptive mind-wandering) during the sessions which were practiced independently throughout the intervention. Worry postponement was introduced and practiced by the participants in between the sessions. Further, positive and negative metacognitive beliefs were challenged: beliefs about the uncontrollability of thoughts were discussed in the context of the patients' experiences with worry postponement. Given the severe cardiovascular illnesses of the patients, the distinction between unhelpful attentional responses to body sensations and necessary reactions in case of aggravating symptoms was discussed. Metacognitive socratic dialog was used to challenge beliefs about strategies like constant threat monitoring, e.g., checking for signs of vertigo and irregular heartbeats. Behavioral experiments were used to test their helpfulness as well as the short and long term consequences. The usefulness of remaining maladaptive coping mechanisms such as avoidance of physical activity like stair climbing and withdrawal were discussed. The "old plan-new plan" protocol (23) was used to build and strengthen new strategies. A list of potential triggers of the CAS was composed. Lastly, relapse prevention was provided by summarizing the main strategies of the treatment. The use of the new strategies in potentially challenging situations was discussed. During the treatment, the adherence to work between sessions (e.g., ATT, DM exercises) was verbally queried in the following session. In the follow-up sessions, the implementation of the learned strategies was discussed. Patients reported examples of the "new plan" protocol and occurring difficulties and questions were examined. The objective of the follow-up sessions was to consolidate the knowledge and strategies patients acquired during the treatment. Due to the short intervention, the follow-ups were planned as short booster sessions shortly after the completion of the eight treatment sessions.

Data Analysis

To investigate whether the intervention affected metacognitions and psychological symptoms, visual analyses were used. Graphical representation is a common way to present data in case-series-research. Parsonson and Baer (45) argue that using visual analysis of graphs, only clear and distinguishable effects will be noted. Therefore, bar graphs are used to present the scores of the questionnaires (HADS, MCQ-30, WHOQOL-BREF) pre- and post-treatment for each patient. Additionally, the percentage of improvement was calculated for each patient. As the WHOQOL-BREF score is transformed into percentages, the change of that score is presented. Patient 2 did not attend the follow-up sessions, patients 1, 2, and 3 did not fully complete the follow-up questionnaires. Due to the amount of missing data and potential selection effects, the follow-up data is not reported. The courses over each session assessed by VAS are illustrated as line graphs for each patient. For patient 2, VAS values are missing at session 3.

To determine whether the change that occurred during the treatment was clinically significant, we used a two-step criterion proposed by Jacobson and Truax (46): First, it is evaluated if the patients are part of the functional or dysfunctional group after the treatment, based on their provided questionnaires scores. Hermann-Lingen, Buss, and Snaith (37) reported standard cut-off scores of <8 for both HADS-subscales, which were shown



to have good sensitivity and specificity for identifying possible anxiety or depressive disorders (37). In the second step, the reliable change index (RCI) is used to determine whether the amount of change that occurred was reliable. When the calculated RC score is >1.96 , it is unlikely that the change that occurred during the treatment does not reflect real change (46). The data needed for its calculation was drawn from the German HADS manual as well (37). Based on the two-step criterion, patients' changes are then classified as recovered, if they pass both the cut-off and the RC criterion, as improved, if they only pass the RC criterion, as unchanged, if they pass neither, or as deteriorated, if their scores worsened and passed the RC criterion (46).

RESULTS

For the sum score of the MCQ-30, all patients except patient 3 showed a reduction from pre- to post-treatment. The percentage change ranged from +14 to -41%. The subscales of the MCQ-30 show a heterogeneous pattern for the individual patients. For details, see Figure 2.

For the HADS-D, all patients showed a reduction from pre- to post-treatment (see Figure 3). The percentage change ranged from -8 to -72%. For HADS-A, there was a reduction

from pre- to post-treatment for four patients. One patient reported increasing scores. The percentage change ranged from +50 to -47%.

Regarding the clinical significance of the changes, only patient 4 can be classified as recovered for the HADS-D. All other patients did not meet the RC criterion and can therefore be classified as unchanged. However, HADS-D scores of patient 1 and 5 were in the functional group pre- and post-treatment. In contrast, patient 5 can be classified as recovered and patient 2 and 4 can be classified as improved concerning the anxiety scores. Patient 1 and 3 were classified as unchanged; however, their HADS-A post-treatment scores were below the given cut-off.

For the WHOQOL-BREF (see Figure 3), the scores of the subscale psychological QoL increased from pre- to post-treatment for all patients. The improvement in the psychological QoL ranged from +21 to +33. The scores of the subscale physiological QoL increased for all patients. The improvement in the physiological QoL ranged from +10 to +22. For the overall QoL, the pre- to post-treatment scores remained stable for two patients and increased for the other three patients. The improvement in the overall QoL from ranged from ± 0 to +37.

The courses of the VAS during the sessions for each patient are shown in Figure 4. Patients reported to be highly affected by worry and rumination at the beginning of the treatment. Over the course of the intervention, patient 3 reported fluctuating levels of worry and rumination. The scores of patient 1, 2, 4, and 5 showed a tendency toward reduction. At the beginning of the treatment the perceived uncontrollability of thoughts varied widely. Patient 1 and 3 who reported a comparatively low level of perceived uncontrollability showed a fluctuating course on a consistent level. Patient 1, 2, and 4 reported a higher level of uncontrollability at first and showed a continuous reduction over the course of the intervention. The course of the reported self-focused attention is heterogeneous with continuously high values for patient 1 and 2, decreasing scores for patient 4 and an increasing course for patients 3 and 5. The reported treatment satisfaction was overall high for patients 1 and 3, the three other patients reported an increasing satisfaction over the course of the treatment.

DISCUSSION

We developed a brief metacognitive treatment adapted to the needs of CVD patients with consecutive mental disorders. Further, we investigated the effects of the treatment delivered face-to-face *via* videotelephony.

After the treatment, most patients reported a reduction of dysfunctional metacognitions, improved psychological QoL and a reduction of anxiety and depressive symptoms. According to the criteria regarding clinical significance of change, particularly anxiety symptoms were improved after the psychotherapeutic intervention, with three out of five patients displaying recovery or improvement. Our data suggests that a tailored metacognitive approach could be suitable for CVD patients, as it seemed to target the intended mechanisms. This is consistent with studies showing the effectiveness of MCT for patients with

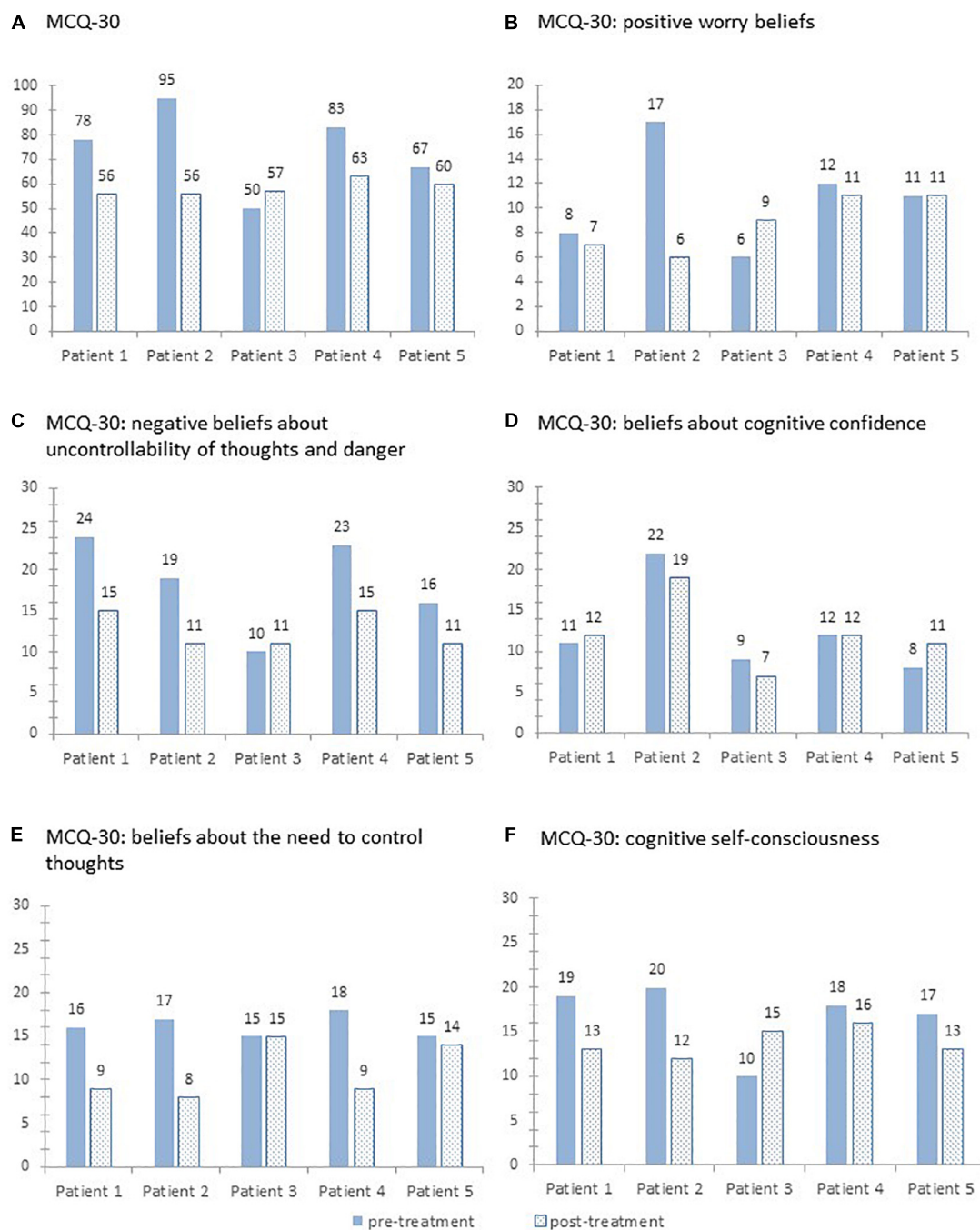


FIGURE 2 | Sum scores on the Metacognitions Questionnaire-30 (A) and its five subscales (B–F) pre- and post-treatment for each patient.

somatic diseases that caused or worsened psychiatric disorders (26–28). As this case series only included five patients, the tailored treatment should be further investigated in a randomized controlled setting to probe the preliminary effects. Despite the promising tendency, there is room for improvement regarding the amount of reduced psychological symptoms and dysfunctional metacognitions. A possible reason for the effects observed in our patient sample may be the

standardized procedure in a clinically heterogeneous group of patients. A treatment adaptation to the specific psychiatric symptoms consecutive to the underlying CVD could be used in further research.

The findings indicate that there might be some characteristic dysfunctional metacognitions that are associated with the specific somatic symptoms of CVDs. For example, as shown in the model (see **Figure 1**), for anxiety and depressive symptoms developed

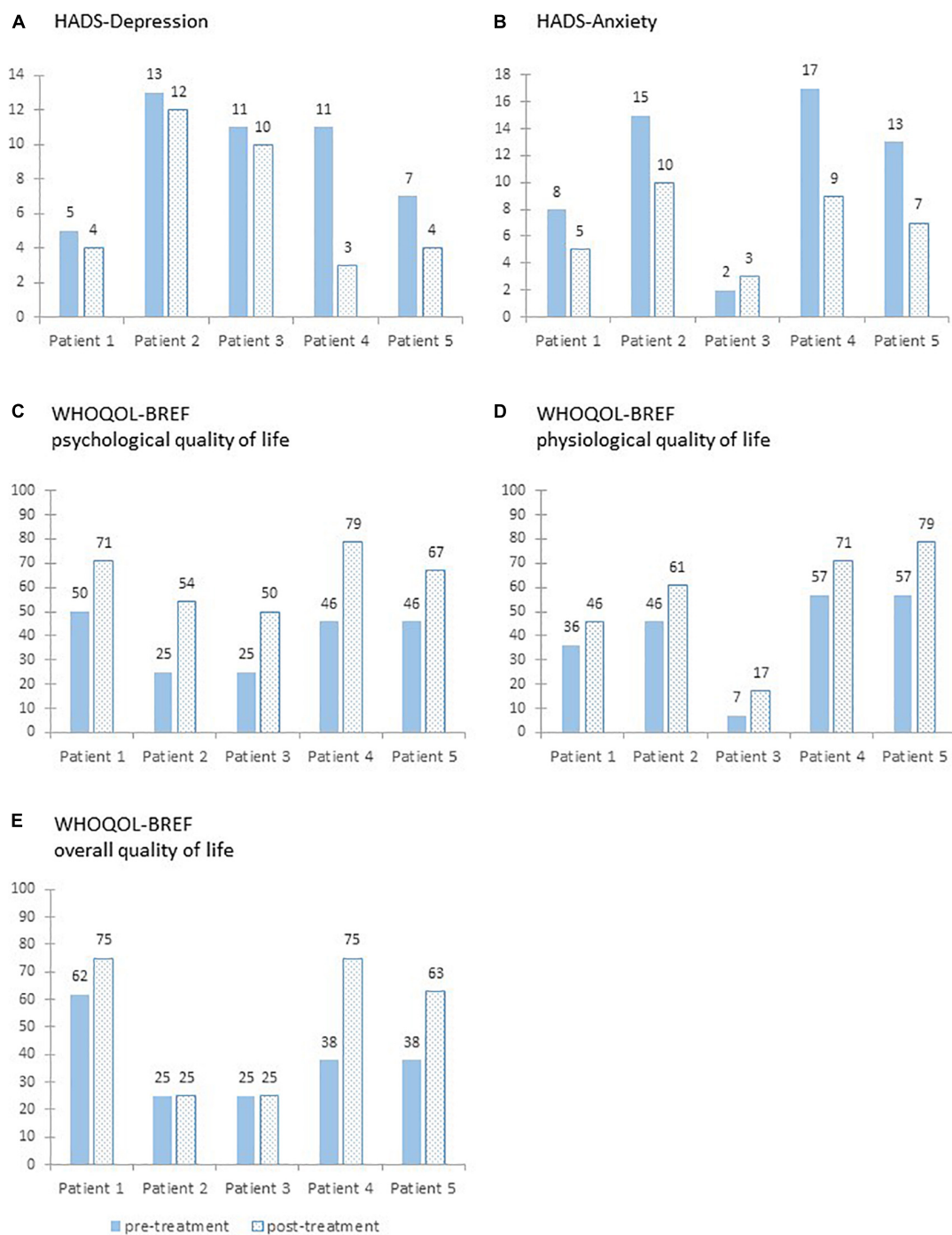
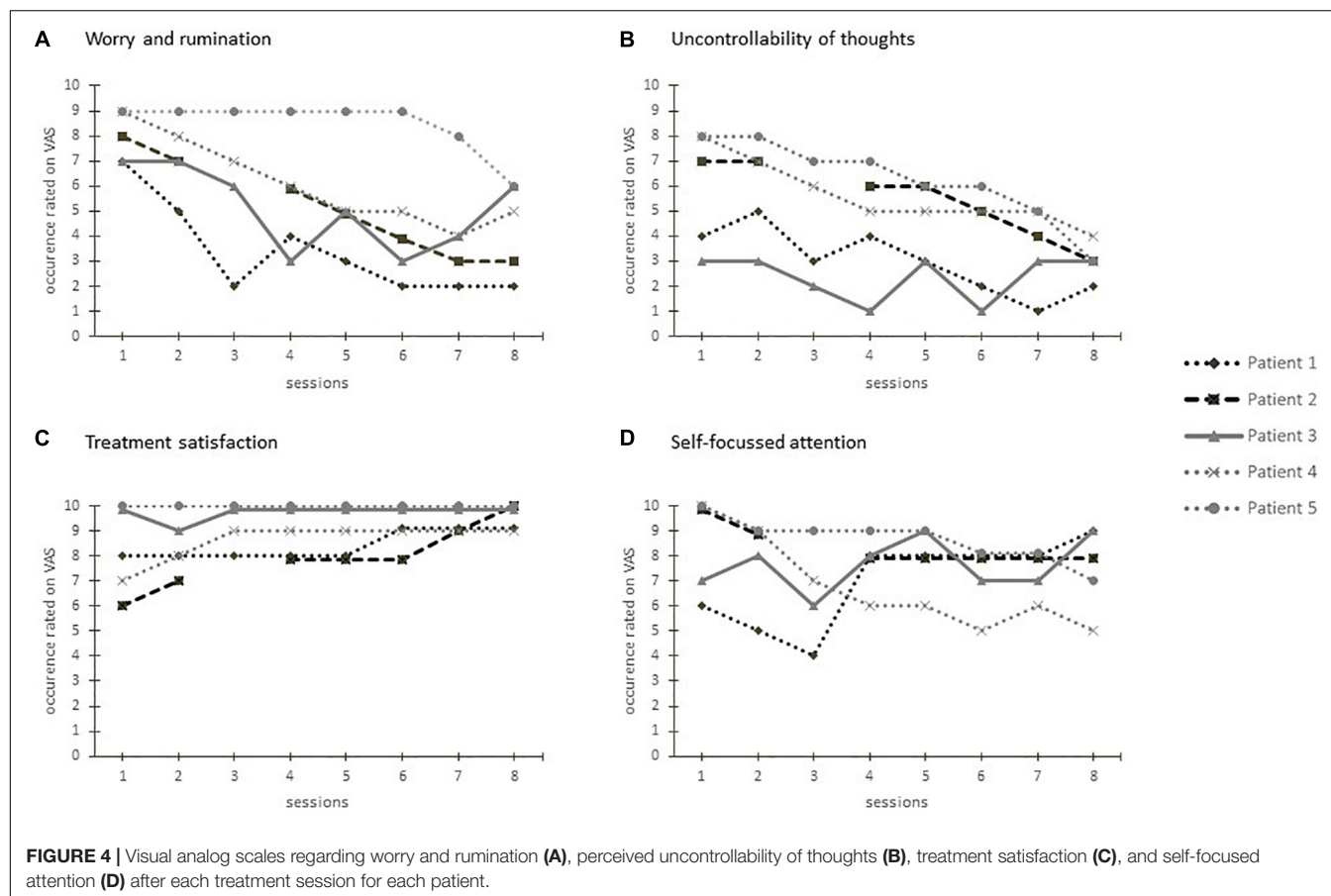


FIGURE 3 | Sum scores on the two subscales of the Hospital Anxiety and Depression Scale (A,B) and transformed sum scores on the World Health Organization Quality of Life Assessment (C–E) pre- and post-treatment for each patient.

after an IPAH diagnosis, there are triggers induced or related to the CVD. An exemplary trigger is an increased pulse rate. The association of metacognitions and the underlying somatic illnesses supports the findings of prominent health worry among certain CVD patients (see text footnote 1). During the individual case conceptualizations, different foci became apparent: For

some patients, self-focused attention and body-checking were most present, others reported to suffer most from rumination. This was also reflected in the heterogeneous courses of the MCQ-30 subscales. Therefore, the modular structure of the treatment plan could be used to prioritize the most prominent dysfunctional metacognitions and maladaptive coping behaviors.



This is in agreement with Wells (23), who suggests using adapted versions of the generic MCT model and treatment, depending on the diagnoses.

The treatment was based on eight twice-weekly sessions. The given reductions of psychological symptoms and improvement of QoL in the short amount of time indicate the usefulness of brief treatments presented in a high frequency. This opens up potential for short interventions to efficiently improve psychological health, for example, shortly after a diagnosis of a CVD.

We tested the brief CVD-tailored metacognitive treatment *via* videotelephony. Treatment satisfaction was overall high and no apparent problems were reported or occurred. Thus, an internet-based approach seems to be a feasible way to apply MCT. Especially considering the physical constraint accompanying CVDs and the additional restrictions during the SARS-CoV-2 pandemic, internet-based treatments like the present one are a necessary mean to enhance traditional face-to-face psychotherapy.

Our study has limitations: The small sample size and absence of a control group limits the generalizability of the findings. The concurrent pharmacological treatments may distort the results. The lack of a no-treatment baseline limits the interpretability of the treatment effects. Due to the missing data for the follow-up period, the long-term stability of the effects is unclear. The treatment was based on the manual by Wells (23) and the

execution was supervised, but there was no rating of therapist adherence. Patients verbally reported a high adherence to the treatment exercises but there was no standardized measurement to control the proper execution.

In conclusion, the outcomes provide preliminary evidence that an internet-based metacognitive approach might be promising for treating psychological distress following CVDs. The treatment plan, including the duration and adaptation to psychiatric as well as cardiovascular diagnoses, should be further investigated by using randomized and controlled studies.

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 Hannover Medical School Ethics Committee. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

FC and PG were responsible for study design, implementation of the study, data collection, statistical analysis, data interpretation, and drafted the manuscript. MW-B, D-HP, KO, and MH were responsible for implementation of the study and data collection. IH was responsible for study design, implementation of the study, data collection, statistical analysis, data interpretation, and revised the manuscript. KK was responsible for study design, implementation of

the study, data interpretation, and revised the manuscript. All authors contributed to the article and approved the submitted version.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: <https://www.frontiersin.org/articles/10.3389/fpsy.2022.812807/full#supplementary-material>

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Adipose Tissue Compartments, Inflammation, and Cardiovascular Risk in the Context of Depression

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The neurobiological and behavioral underpinnings linking mental disorders, in particular, major depressive disorder (MDD), with cardiovascular disorders are a matter of debate. Recent research focuses on visceral (intra-abdominal and epicardial) adipose tissue and inflammation and their impact on the development of cardiometabolic disorders. Intra-abdominal adipose tissue is defined as an endocrine active fat compartment surrounding inner organs and is associated with type 2 diabetes mellitus, a risk factor for the later development of cardiovascular disorders. Epicardial (pericardial) adipose tissue is a fat compartment surrounding the heart with close proximity to the arteries supporting the heart. Visceral adipose tissue (VAT) is an important source of inflammatory mediators that, in concert with other risk factors, plays a leading role in cardiovascular diseases. In conjunction with the behavioral (physical inactivity, sedentary lifestyle), psychological (adherence problems), and hormonal (dysfunction of the hypothalamus–pituitary–adrenal axis with subsequent hypercortisolism) alterations frequently accompanying MDD, an enhanced risk for cardiovascular disorders results.

Keywords: adipose tissue, inflammation, major depressive disorder, cardiovascular disease, HPA axis, body composition

DEPRESSION AND CARDIOMETABOLIC DISORDERS

Major depressive disorder (MDD) is associated with excess mortality (1, 2). This appears to be in part mediated by an increased lifetime risk for obesity-related comorbidities, including cardiovascular disease (CVD), stroke, and type 2 diabetes mellitus (2–4). Overall, the association of cardiometabolic disorders and depression appears bidirectional as has been shown for obesity (5), metabolic syndrome (MetS) (6), type 2 diabetes (7), and CVD (8).

Abbreviations: ACHD, Adult congenital heart disease, AGV, Adrenal gland volume, BMI, Body mass index, BPD, Borderline personality disorder, CBT, Congenital behavioral therapy, CES-D, Center for Epidemiologic Studies Depression, CRP, C-reactive protein, CT, Computed tomography, CVD, Cardiovascular disease, EAT, Epicardial adipose tissue, ECM, Extracellular matrix, GDS, Geriatric Depression Scale, HPA, Hypothalamus–pituitary–adrenal, ICAM, Intercellular adhesion molecule, IL, Interleukin, MCP, Chemoattractant protein, MDD, Major depressive disorder, MetS, Metabolic syndrome, MRI, Magnetic resonance imaging, PAT, Paracardial adipose tissue, PET, Pericardial adipose tissue, ROS, Reactive oxygen species, SASP, Senescence-associated secretory phenotype, SAT, Subcutaneous adipose tissue, SDS, Zung's Self-Rating Depression Scale, SHBG, Sex hormone binding globulin, SMD, Severe mental disease, TNFR, Tumor necrosis factor receptor, VAT, Visceral adipose tissue.

Several contributing factors are proposed to underlie the high prevalence of comorbid severe mental disease (SMD) and CVD, ranging from shared pathological dysregulations of biological systems to adverse health behaviors (9, 10) and limited social and economic support (11–13). Biological pathways that are associated with SMD include pathological alteration in stress response systems (14) as well as systemic chronic inflammation (15), which, in turn, is shown to profoundly impact metabolic pathways that contribute to the observed increase in metabolic conditions that often precede CVD, including obesity, dyslipidemia, insulin resistance, type 2 diabetes mellitus (16, 17). Additionally, adverse health behaviors, including increased tobacco and alcohol consumption, sedentary behavior, and poor diet, are common in people with SMD and contribute to the onset and progression of cardiometabolic disorders (9, 10). Furthermore, people with SMD are less likely to adhere to treatment regimens for conditions associated with increased CVD risk (18, 19), and especially, patients with schizophrenia were reported to be subjected to insufficient physical health care (20). Finally, iatrogenic effects of medications for SMD are described (21, 22).

BODY FAT DISTRIBUTION AND CARDIOVASCULAR DISEASE

Obesity in general is associated with a significant prevalence of cardiovascular risk factors and heightened risk of cardiovascular events (23). However, distinct body fat distributions have previously been shown to profoundly impact cardiometabolic parameters, and accordingly, numerous studies find that alterations in body fat distribution rather than the amount of total body fat increase the risk for CVD (24). In this regard, abdominal obesity, indicated by high waist circumference, is associated with cardiometabolic disease and CVD and constitutes a predictor for mortality even in individuals within the normal weight range (25–29). As increasing evidence indicates abdominal obesity as a cardiovascular risk marker, in addition to BMI (30–32), assessment of waist circumference is frequently recommended in clinical evaluations (33–36).

Of note, the detrimental impact of abdominal obesity on physical health is not limited to cardiometabolic diseases. Albeit less studied compared with its impact on cardiometabolic diseases, abdominal obesity is associated with numerous physical diseases, including an increased risk for several cancer types (37–39), chronic kidney disease (40), dementia, and Alzheimer's disease (41, 42), and worsened asthma symptomology (43). As these diseases also appear more prevalent in patients suffering from depression, it appears reasonable that pathological increases in abdominal adipose tissue might contribute to this overall elevated risk of various physical disorders in this patient population (44–48).

Imaging techniques, such as magnetic resonance imaging (MRI) and computed tomography (CT), allow for a more detailed assessment of body composition and a broadened understanding of its role in regard to CVD risk (49, 50). Adipose tissue accumulates predominantly as subcutaneous adipose tissue

(SAT) and as ectopic fat deposits that include visceral adipose tissue (VAT) surrounding the inner organs of the abdominal cavity and intrathoracic fat surrounding the heart (51, 52). Based on its location and developmental origin, intrathoracic adipose tissue is classified as epicardial adipose tissue (EAT), located directly on the surface of the heart in close proximity to the coronary vessels; as paracardial adipose tissue (PAT), situated on the surface of the pericardium; or as pericardial adipose tissue (PET) that is quantified as the sum of EAT and PAT (53). Exemplary MR images of SAT, VAT, EAT, and PAT are depicted in **Figure 1**, and for comparison of MR and CT images regarding the measurements of VAT and SAT, the reader is referred to a dedicated study by Klopfenstein et al. (54). Whereas cohort imaging studies indicate that all fat and ectopic adipose tissue deposits are correlated with each other (55), significant interindividual differences regarding the ratio of SAT to VAT are reported independent of BMI or total adiposity level (56–58). Augmented VAT volumes are shown to exhibit prognostic value in the context of MetS (59–61), and additionally, individuals with excess VAT are found to display high CVD risk independent of BMI (56, 58, 62). With regard to cardiac ectopic fat content, associations of PET with increased BMI, with common risk factors of CVD, and with elevations in lipoprotein particles (63) as well as with a heightened risk of all-cause CVD, atherosclerotic CVD, and heart failure were observed (64). Additionally, correlations of PET with CVD were found after adjustment for age, sex, BMI, and waist circumference, but not when cardiovascular risk factors were included as confounders (65). Similarly, EAT that derives from brown adipose tissue and is demonstrated to secrete cytokines and chemokines (66) is shown to be negatively associated with cardiovascular health scores and to positively correlate with arterial stiffness in patients with type 2 diabetes and CVD (67, 68). Finally, it is demonstrated that EAT thickness is associated with waist circumference, blood pressure, dyslipidemia, and insulin resistance (67, 69), thereby implicating EAT as an early indicator of cardiovascular risk.

METHODS

Based on the recommendations by Bramer et al. (70), we developed the following search algorithm based on the Medical Subject Headings (MeSH) thesaurus by the National Library of Medicine. The search algorithm automatically explores the MeSH terms, that is, searches not only for the terms themselves, but also for all subordinate terms. The following search terms were entered: ((Major depressive disorder [MeSH Terms]) OR (Depression [Title/Abstract]) OR (Depressive disorder [Title/Abstract]) OR (mood disorder [Title/Abstract])) AND ((adipose tissue [MeSH Terms]) OR (body composition [MeSH Terms]) OR (Adipose tissue [Title/Abstract]) OR (Tissue, Adipose [Title/Abstract]) OR (Body Fat [Title/Abstract]) OR (Body Composition* [Title/Abstract]) OR (Composition*, Body [Title/Abstract]) OR (Fat Distribution [Title/Abstract]) OR (Fat Patterning [Title/Abstract]) OR (Abdominal Fat [Title/Abstract]) OR (Abdominal obesity [Title/Abstract])

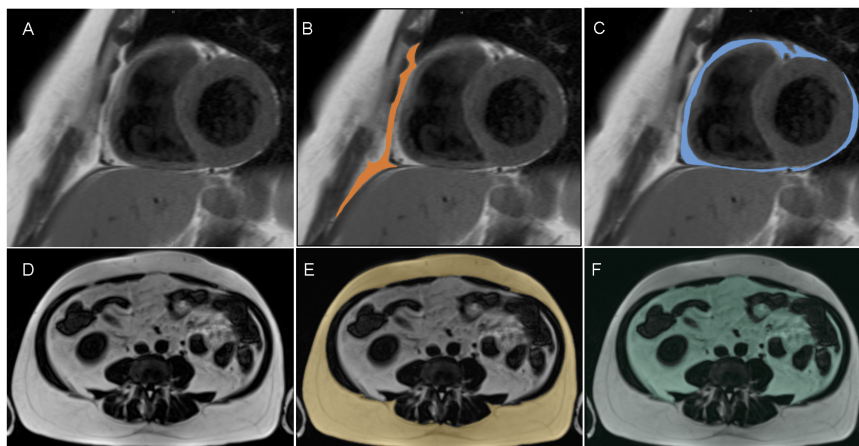


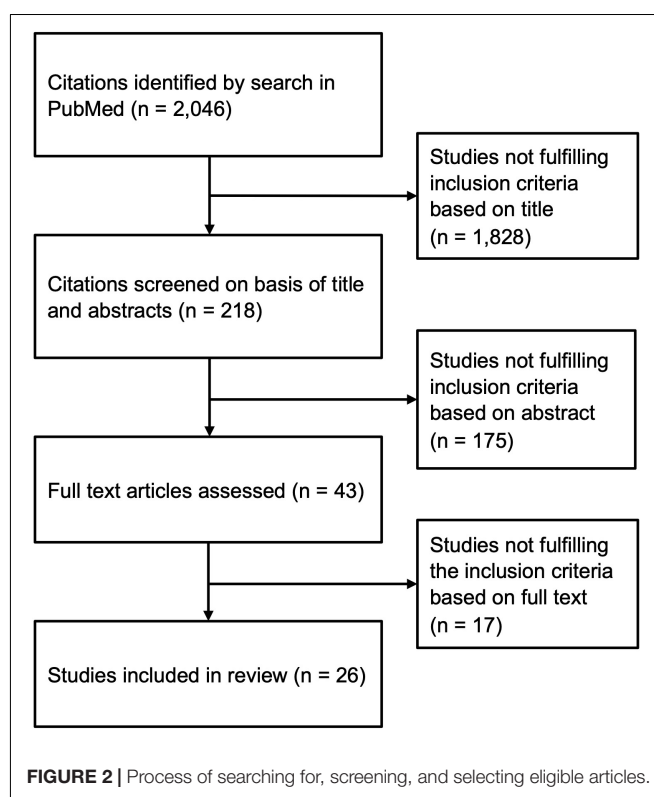
FIGURE 1 | Segmentation of paracardial adipose tissue (PAT; **B**, colored) and epicardial adipose tissue (EAT; **C**, colored) from short axis dark blood t1-weighted turbo spin echo MR images (**A**; representative slice) and segmentation of subcutaneous adipose tissue (SAT; **E**, colored) and visceral adipose tissue (VAT; **F**, colored) from t1-weighted 3-D Volume Interpolated Breathhold Examination (VIBE) Dixon MR images (**D**, representative slice).

OR (intra-abdominal fat [Title/Abstract]) OR (intra-abdominal adipose tissue [Title/Abstract]) OR (Epicardial Fat [Title/Abstract]) OR (Epicardial Adipose Tissue [Title/Abstract]) OR (Paracardial Fat [Title/Abstract]) OR (Paracardial Adipose Tissue [Title/Abstract]) OR (Pericardial Fat [Title/Abstract]) OR (Pericardial Adipose Tissue [Title/Abstract])).

We reviewed articles listed in PubMed/Medline up to December 2021. These included original, review, and systematic review articles and meta-analysis. We additionally scanned the reference lists of identified review articles and meta-analyses for studies fulfilling the inclusion criteria. We identified 25 studies that investigated VAT and/or intrathoracic adipose tissue using CT or MRI measurement in the context of depression. We included one additional study that used echocardiography to detect intrathoracic adipose tissue compartments (94) (**Figure 2**). All studies included in this narrative review are listed in **Table 1**.

VISCERAL ADIPOSE TISSUE AND DEPRESSION

A considerable number of studies assessed VAT content using MRI or CT in women with MDD or with regard to depressive symptoms. In this regard, most studies report increased VAT values and a positive association of VAT and depressive symptoms in both pre- as well as post-menopausal subjects. The first study that investigated the association of abdominal fat compartments in the context of depression was conducted by Thakore and colleagues, who found approximately twofold higher VAT content measured by CT in seven normal weight, female MDD patients compared with seven normal weight healthy women (71). Similarly, an MRI study including 10 women with MDD and 12 healthy controls found significantly increased VAT content in the upper abdomen, defined as “a 10 cm slab on the niveau of the upper part the liver” of the MDD group (72). Additionally, partial correlation analysis showed a



significant association of VAT in the upper abdomen but not of total VAT or SAT and depressive symptoms assessed by BDI after adjustment for BMI and age (72). A second study by the same group identified increased total body fat, VAT, and SAT levels in 11 female MDD patients compared to 45 healthy women that were matched regarding BMI and waist-to-hip ratio (73). Lee and colleagues recruited 101 overweight, premenopausal women and assessed VAT and SAT by CT. After adjustment

TABLE 1 | Summary of MRI and CT studies regarding the association of depression and depressive symptoms with alterations in abdominal tissue distribution.

Study	Sample	Adipose tissue compartment and method of measurement	Finding
Thakore et al. (71)	7 female, NW MDD patients vs. 7 female, NW CTRLs	VAT by CT	Twofold increase in VAT in MDD
Ludescher et al. (72)	10 female MDD patients vs. 12 female CTRLs	VAT by MRI	Significant increase in VAT in MDD; partial correlation of upper abdomen VAT but not of SAT with BDI
Ludescher et al. (73)	11 female MDD patients vs. 45 female CTRLs	VAT and SAT by MRI	Significant increase in SAT and VAT in MDD
Lee et al. (74)	101 premenopausal, OW women	VAT and SAT by CT	Positive association of VAT with Zung's SDS
Kahl et al. (75)	48 female BPD and/or MDD patients vs. 20 female CTRLs	VAT by MRI	Significant increase in VAT in MDD and BPD/MDD patients
Greggersen et al. (76)	78 premenopausal, female BPD and/or MDD patients vs. 34 CTRLs	VAT by MRI	Significant increase in VAT in BPD/MDD patients
Everson-Rose et al. (77)	409 women (mean age 50.4 years)	VAT and SAT by CT	Significant increase in VAT in presence of a CES-D ≥ 16 ; positive association of VAT but not SAT with CES-D
Kahl et al. (78)	67 middle-aged MDD patients vs. 26 healthy CTRLs	VAT by MRI	Increase in VAT in male and female MDD patients by trend
Scharnholtz et al. (96)	20 MDD patients and 34 CTRLs without HPA axis activation determined by dexamethasone response	VAT by MRI	No significant group differences in VAT
Murabito et al. (95)	1,581 middle-aged women and 1,718 middle-aged men (community-based study)	VAT and SAT by CT	Positive association of VAT but not SAT with CES-D in women only
Alsheri et al. (79)	6,459 middle-aged individuals (mean age 55.4 years) of whom 24.3% had EDS, and 2,745 underwent MRI measurements (community-based study)	VAT by MRI	Graded, positive association of VAT and ESD was substantially diminished following adjustment for total body fat
Cho et al. (80)	4,945 men and 2,293 women, including 333 clinically depressed participants (community-based study)	VAT by CT	Positive association of VAT with BDI in women but not in men
Remigio-Baker et al. (81)	1,017 multiethnic men and women (age 45–87 years), of whom 18.8% had EDS (community-based study)	VAT by CT	Positive association of VAT with EDS in men but not in women, no significant effect of race
Yamamoto et al. (82)	4,333 male employees (community-based study)	VAT and SAT by CT	Positive association of VAT but not SAT with elevated depressive symptoms
Ferrari et al. (83)	101 women with gestational diabetes mellitus	VAT by MRI	Positive association of VAT and BDI-I/II
Xiong et al. (84)	117 postmenopausal, NG, women with depressive symptoms vs. 320 CTRLs	VAT and SAT by MRI	Significant increased VAT and SAT in depressed women; positive association of VAT with SDS
Weber-Hamann et al. (85)	22 postmenopausal MDD patients vs. 23 age-matched female CTRLs	VAT by CT	No significant group differences in VAT
Portugal-Nunes et al. (86)	96 participants (age > 50 years)	VAT and SAT by MRI	Positive association of VAT but not SAT and GDS.
Vogelzangs et al. (87)	2,540 elderly (mean age 73.6 years) non-depressed individuals; baseline and annual follow-up over 5 years	VAT by CT	Positive association of VAT and new onset depressive symptoms in men (GES-D ≥ 10 or AD prescription)
Weber-Hamann et al. (88)	29 elderly MDD patients (mean age 61.5 years) and 14 CTRLs (mean age 61.8 years); baseline and 14-month follow-up	VAT by CT	No significant group differences in VAT at baseline or follow up; significant increase in VAT in MDD but not CTRL over follow-up period
Vogelzangs et al. (89)	2,088 participants (age > 70 years); baseline and 5-year follow-up	VAT by CT	Association of CES-D ≥ 16 at baseline and increased VAT at follow-up
Kahl et al. (90)	27 MDD patients vs. 19 CTRLs	PAT, VAT, and SAT measured by MRI	Significant increase in PAT, increase in VAT by trend in MDD, no group differences in SAT
Kahl et al. (91)	50 MDD patients vs. 25 CTRLs	EAT, PAT, PET, IAT, and SAT by MRI	Significant increase in PAT and PET in males and females with MDD; no group differences in EAT, VAT, and SAT
Kahl et al. (92)	16 chronic and 34 acute MDD patients vs. 25 CTRLs	PAT by MRI	Significant increase in PAT in chronic vs. acute MDD and in acute MDD vs. CTRL; positive association of PAT with BDI and MADRS
Richter et al. (93)	28 female patients with BPD/MDD, 22 with MDD and 26 CTRLs (mean age < 35 years)	EAT by MRI	Significant increase in EAT in BPD/MDD vs. MDD and CTRL. No significant difference in MDD vs. CTRL; no significant association between EAT and MADRS in the combined MDD sample
Kahl et al. (94)	210 young adults (mean age 35.5 years) with ACHD, of which 53 were diagnosed with MDD	EAT by echocardiography	Significant increase in EAT in MDD; positive association of EAT with MADRS

ACHD, adult congenital heart disease; AD, antidepressant; BDI, Beck's Depression Inventory; BPD, borderline personality disorder; CES-D, Centre for Epidemiologic Studies Depression; CT, computed tomography; CTRL, control; EDS, elevated depressive symptoms; MADRS, Montgomery-Åsberg Depression Rating Scale; MDD, major depressive disorder; EAT, epicardial adipose tissue; GDS, geriatric depression scale; MRI, magnetic resonance imaging; NG, normoglycemic; PAT, paracardial adipose tissue; PET, pericardial adipose tissue; SAT, subcutaneous adipose tissue; SDS, Self-rating Depression Scale; VAT, visceral adipose tissue.

for potential confounders, VAT was positively associated with depression scores determined by Zung's Self-Rating Depression Scale (SDS), whereas no association between SAT and depressive symptoms was found (74). Kahl and colleagues investigated VAT measured by MRI in 48 women diagnosed with MDD and/or borderline personality disorder (BPD) (75). Compared with 20 healthy women, area of VAT was significantly higher in patients comorbid with MDD and BPD and in MDD patients after adjustment for BMI, whereas VAT accumulation was less pronounced in BPD patients without comorbid MDD (75). Similarly, an MRI-based study by Greggersen and colleagues confirms increased VAT content in a sample of 78 premenopausal women with MDD and/or BPD compared with 34 healthy female controls with similar BMI values (76). In a cross-sectional CT study that included 409 middle-aged women, individuals who presented with clinically relevant depressive symptomatology [Center for Epidemiologic Studies Depression (CES-D) score ≥ 16] displayed significantly increased VAT after adjustment for age, race, total percentage of fat, and sex hormone binding globulin (SHBG). Additionally, VAT but not SAT was significantly associated with depressive symptoms after correction for the aforementioned parameters as well as for physical activity and Framingham risk score (77). In a cross-sectional study, Kahl and colleagues assessed muscle mass, adrenal gland volume (AGV), and intra-abdominal adipose tissue in 67 middle-aged, depressed patients and 26 healthy control subjects using MRI. Whereas only male patients, particularly those with chronic depression, displayed reduced muscle mass, both male and female patients showed a trend toward increased VAT content in this study that, however, was not statistically significant (78).

In line with these results, a community-based study that included 1,581 middle-aged women and 1,718 middle-aged men drawn from the Framingham Heart Study (49) found an association between VAT measured by CT and depressive symptoms assessed by CES-D scale in women but not in men after adjustment. Contrarily, no association between SAT and depressive symptoms was observed in either sex (95).

Another community-based study included 6,459 middle-aged individuals of whom 2,475 underwent MRI for assessment of VAT. Using the IDS-SR30 questionnaire, 24.3% of participants with significant depressive symptoms were identified (IDS-SR30 ≥ 14). The study reports a graded, positive association of all measures of abdominal adipose tissue with depressive symptom severity. However, total fat showed a stronger association with depressed mood than other parameters, including waist circumference and VAT, and adjustment for total body fat reduced the magnitude of the association between VAT and depressive symptoms substantially. No significant sex differences were observed in this study (79).

A large community-based study by Cho and colleagues investigated the relationship between VAT assessed by abdominal CT and depressive mood in 4,945 men and 2,293 women. Overall, 333 participants were clinically depressed based on BDI scores. After adjustment for factors of hypertension, diabetes, and BMI, VAT showed a positive association with depressive symptom severity in women but not in men (80).

A study that utilized data from the Multi-Ethnic Study of Atherosclerosis and included 1,017 men and women between the ages of 45 and 87 years analyzed the relation of VAT measured by CT and elevated depressive symptoms defined as a CES-D score ≥ 16 and/or use of an antidepressant. After adjustment for age and BMI, among others, significantly higher VAT values were detected in men but not in women with elevated depressive symptoms compared with individuals of the same sex and with a CES-D score below 16. Contrarily to sex, no significant effect of race was found (81).

In a study that included 4,333 male employees, VAT and SAT were measured by abdominal CT. Whereas no standard tool was employed to assess depressive symptoms, the utilized questionnaire included items similar to those of Zung's SDS and the CES-D. After multivariable adjustment, including lifestyle factors, physical activity, and BMI, VAT but not SAT was found to be significantly associated with elevated depressive symptoms (82).

In the context of pregnancy, Ferrari and colleagues assessed VAT by MRI in 101 women with gestational diabetes mellitus and report increased VAT to be associated with an elevated risk for greater depressive symptoms assessed by BDI-I or BDI-II after adjustment for BMI (83).

Regarding the effect of abdominal fat content on depressive symptoms in older adults, an MRI study compared normoglycemic, postmenopausal women with depressive symptoms ($N = 117$) to those without current depressive symptoms ($N = 320$) assessed using SDS. Whereas mean age was comparable in both groups, BMI was higher in the group that was characterized by the elevated depression scores, and similarly significantly higher SAT and VAT values were found (84). Furthermore, logistic regression analysis showed a positive association between depressive symptoms and VAT after correcting for age and life conditions. However, no adjustment for BMI was included (84). Contrarily, in a cross-sectional study that compared 22 postmenopausal women with MDD to 23 age-matched healthy women, no significant group differences regarding VAT measured by CT were found (85). However, effects on VAT content dependent on cortisol status were observed as outlined in the respective paragraph below (85).

A study by Portugal-Nunes et al. included 120 individuals above the age of 50 residing in community dwelling of which 96 underwent MRI measurements for VAT and SAT. After adjustment for main confounders, VAT was found to be a significant predictor of depressive mood determined by the Geriatric Depression Scale (GDS), independent of age. Contrarily, SAT showed no significant association with depression scores. However, age was found to significantly moderate the association of SAT with depressive mood, i.e., higher overall adiposity was positively associated with GDS scores in younger individuals, whereas in older participants, a null or negative association was detected. This was interpreted as a potential protective role of SAT in the geriatric population (86). Similarly, in a sample of 2,540 non-depressed older individuals, Vogelzangs and colleagues found that higher VAT volumes assessed by CT were predictive for new onset of persistent depressive symptoms in men after adjustment

for sociodemographic parameters and BMI. Contrarily, the association was not significant in women over a follow-up period of 5 years (87). In a longitudinal CT study, Weber-Hamann et al. assessed VAT content in a sample of 29 elderly patients initially diagnosed with a major depressive episode at baseline and after a 14-month follow-up. VAT content was comparable to that of a respective control sample ($N = 17$) at baseline, and similarly, no significant differences between MDD and the control group were observed at the follow-up time point. Depressive symptoms significantly decreased in the MDD group over the follow-up period, whereas weight gain was comparable in both groups. However, a significant increase in VAT content was only detected in the patient group (88). Finally, a prospective cohort study with a 5-year follow up included 2,088 individuals above the age of 70 years living in a community dwelling. Vogelzangs and colleagues found that depression at baseline, defined as a CES-D score ≥ 16 , was associated with a significant increase in VAT at follow-up after adjustment for sociodemographics, lifestyle, diseases, and overall obesity (89).

INTRATHORACIC CARDIAC ADIPOSE TISSUE AND DEPRESSION

When compared with studies assessing total VAT content in the context of depression, studies investigating intrathoracic adipose tissue compartments are limited. In this regard, a study by Kahl et al. measured intrathoracic PAT volume in addition to VAT content in 27 MDD patients compared with 19 healthy controls (90). After controlling for age, weight, and height, significantly increased PAT values were detected in the MDD group, whereas a trend of VAT volume increase in the MDD group and no effect on SAT was observed (90). A case-controlled study by the same group assessed intrathoracic fat content in 50 male and female inpatients with MDD and 25 healthy controls (91). After adjustment for age, height, weight, and physical activity, increased values for PAT and PET were found in depressed men and women, whereas contrarily, no significant effect of depression was observed with regard to EAT, VAT, or SAT (91). In a further study, Kahl and colleagues assessed PAT volume in a cross-sectional study that included 16 patients with chronic and 34 patients with acute depression compared with 25 healthy controls (92). Male and female patients were included in the study, and PAT volume was assessed by MRI. Overall, PAT volume was increased in patients with chronic MDD compared with patients with acute depression and controls after adjustment for age, height, and weight as potential confounding factors. Additionally, PAT volumes were significantly increased in patients with acute MDD compared with the control group, and similar results regarding PAT content were obtained when results were stratified according to sex. Furthermore, a positive association of PAT with self-reported and clinician-rated depressive scores was observed after adjustment for confounders (92). In a recent study, Richter et al. compared EAT volumes measured by MRI in younger (mean age < 35 years) female patients with MDD and with MDD comorbid with BPD to a healthy control collective of comparable age (93).

Contrary to prior studies, EAT volumes were comparable in the MDD and control groups after adjustment for age, BMI, and physical activity. However, patients comorbid with MDD and BPD displayed significantly increased EAT volumes compared with the MDD and control groups. In this study, no significant association between EAT volumes and clinician-rated depression scores was observed in the combined MDD sample (93). Finally, Kahl and colleagues determined ectopic cardiac tissue using echocardiography as well as depressive symptoms in 210 young adults with adult congenital heart disease (ACHD) (94). In this sample, MDD was diagnosed in 53 individuals and was associated with increased EAT values. Additionally, a positive association of EAT and depression severity and BMI and a negative association with physical activity was found (94).

Overall, two recent meta-analyses concluded that MDD as well as self-reported depressive symptoms were associated with enlarged VAT compartments. This association appears independent of sex, age, and method of VAT content assessment (i.e., MRI or CT) as well as method of depression assessment (97, 98). Additionally, the association of VAT with depression remained significant when only studies controlling for BMI were taken into account (98).

ADIPOSE TISSUE COMPARTMENTS, HYPOTHALAMUS-PITUITARY-ADRENAL AXIS, AND DEPRESSION

Several mechanistic links between obesity and depression, including augmented secretion of cortisol secondary to hypothalamus-pituitary-adrenal (HPA) axis activation, dysregulation of the serotonergic system, alterations in adipokine secretion, and chronic inflammation are proposed (99). The HPA axis as a neuroendocrine system plays a central role in the body's response to stress. HPA axis hyperactivity in the context of MDD constitutes one of the most common findings in psychiatric research. Assessments of HPA axis activity in the context of depression mostly rely on measurements of cortisol, which constitutes the primary effector of the system and is released by the adrenal glands. A recent systematic review concluded that biologically active cortisol levels, indicated by elevated basal levels for the cortisol awakening response, increased salivary diurnal profiles, urinary and hair cortisol, were elevated in the context of depression, whereas measurement of non-protein-bound cortisol in blood serum resulted in overall inconclusive results (100). The critical impact of the HPA axis with regard to body weight control, obesity, and body fat distribution is highlighted by conditions associated with extreme cortisol levels, i.e., Addison's disease characterized by hypocortisolism and weight loss and Cushing's syndrome characterized by hypercortisolism and rapid weight gain (101). Additionally, an association of cortisol and obesity is consistently indicated in the literature. A recent meta-analysis that reviewed studies in humans regarding cortisol awakening response as a state measure for HPA axis activity and hair cortisol as a trait measure found that trait rather than state measures were associated with general and abdominal adiposity in humans (102). Therefore,

TABLE 2 | Summary of MRI and CT studies regarding the association of depression and depressive symptoms with alterations in abdominal tissue distribution and changes in parameters of HPA axis activity.

Study	Sample	Parameters of HPA axis activity	Finding
Weber-Hamann et al. (85)	22 postmenopausal MDD patients vs. 23 age-matched female CTRLs	Morning cortisol (saliva) over 7 days	Significant increase in VAT in HC MDD vs. NC MDD patients; no significant difference in VAT between HC MDD vs. NC CTRL
Weber-Hamann et al. (88)	29 elderly MDD patients (mean age 61.5 years) and 14 CTRLs (mean age 61.8 years); baseline and 14-month follow-up	Morning cortisol (saliva) over 7 days	Similar increase in VAT in NC and HC MDD patients over 14-month follow-up; no significant association of VAT and cortisol at baseline or follow-up
Thakore et al. (71)	7 female, NW MDD patients vs. 7 female, NW CTRLs	Morning cortisol	Increased cortisol in MDD vs. CTRL; positive association of VAT and cortisol
Ludescher et al. (72)	10 female MDD patients vs. 12 female CTRLs	AGV by MRI	No significant group differences in AGV; positive association of VAT and AGV in combined sample
Kahl et al. (92)	16 chronic and 34 acute MDD patients vs. 25 CTRLs	AGV by MRI, Morning cortisol (serum)	No significant group differences between chronic and acute MDD and CTRL in AGV; positive association of AGV with PAT and BDI in combined sample; significant increase in cortisol in MDD groups vs. CTRL; positive association of cortisol with BDI and MADRS; no significant association of cortisol with PAT or AGV
Kahl et al. (75)	48 female BPD and/or MDD patients vs. 20 female CTRLs	Morning cortisol (serum)	Significant increase in cortisol in MDD vs. CTRL; no significant association of VAT and cortisol in combined sample
Kahl et al. (91)	50 MDD patients vs. 25 CTRLs	Morning cortisol (serum)	Significant increase in cortisol in MDD vs. CTRL; no significant association of cortisol with VAT, SAT, or intrathoracic fat in combined sample
Kahl et al. (90)	27 MDD patients vs. 19 CTRLs	AGV by MRI, Morning cortisol (serum)	Significant increase in AGV and cortisol in MDD vs. CTRL; positive association of AGV with VAT and PAT; no association of AGV and SAT or cortisol and AGV, SAT, VAT, and PAT in combined sample
Greggersen et al. (76)	78 premenopausal, female BPD and/or MDD patients vs. 34 CTRLs	Morning cortisol (serum)	No significant group differences in cortisol; no significant association of cortisol and VAT
Richter et al. (93)	28 female patients with BPD/MDD, 22 with MDD and 26 CTRLs (mean age < 35 years)	AGV by MRI	Significant increase in AGV in BPD/MDD vs. MDD and CTRL; no group difference between MDD and CTRL in AGV; positive association of AGV with EAT and with MADRS in combined MDD sample
Scharnholtz et al. (96)	20 MDD patients and 34 CTRLs without HPA axis activation determined by dexamethasone response	Dexamethasone suppression test, Cortisol awakening response (saliva), 24 h cortisol (urine), AGV by MRI	No significant group differences in HPA axis measures or in VAT

AGV, adrenal gland volume; BDI, Beck's Depression Inventory; BPD, borderline personality disorder; CTRL, control; EAT, epicardial adipose tissue; MADRS, Montgomery-Åsberg Depression Rating Scale; MDD, major depressive disorder; MRI, magnetic resonance imaging; HC, hypercortisolemic; NC, normocortisolemic; PAT, paracardial adipose tissue; SAT, subcutaneous adipose tissue; VAT, visceral adipose tissue.

HPA axis dysfunction might constitute a critical factor that links obesity and depression. In this regard, 9 studies, summarized in **Table 2**, assessed measures of HPA axis activation in relation to visceral, intrathoracic, or SAT. In these studies, markers for HPA axis activity included (morning) cortisol levels assessed in saliva or blood serum as well as AGV that has been previously identified as a robust proxy marker for chronic cortisol burden in population-based studies (103).

Weber-Hamann and colleagues assessed cortisol status in 23 postmenopausal inpatients diagnosed with MDD by use of morning saliva cortisol measurements over 7 consecutive days. Patients who presented with hypercortisolism showed an increase in VAT content when compared with depressed patients characterized by cortisol levels within the normal range (85). However, in this study, no significant difference regarding VAT values was observed between hypercortisolemic patients and the normocortisolemic control sample (85). Contrarily, in a

longitudinal study by the same group, hypercortisolemic and normocortisolemic depressed patients showed a comparably larger accumulation of visceral fat mass over a time course of 14 months, and no significant association between cortisol measures and VAT was observed either at the baseline measurement or at follow-up (88). Thakore and colleagues found elevated baseline cortisol levels in a sample of 7 female patients with non-psychotic, unipolar major depression, melancholic subtype compared with 7 healthy control individuals. In this study, cortisol levels showed a positive association with VAT content (71).

In a study including 10 women with MDD and 12 controls, AGV was assessed in parallel to VAT content (72). Whereas no significant group difference regarding AGV was observed, VAT correlated significantly with AGV in the combined sample (72).

Similarly, Kahl et al. found no significant differences regarding AGV when comparing patients with chronic or acute depression to healthy controls (92). However, in the combined sample, AGV

displayed a positive association with PAT and with self-rated depression scores in a partial correlation analysis controlled for age, height, and weight. Contrarily, whereas morning cortisol levels, assessed in serum samples, were higher in the MDD groups and showed a positive association with self- as well as clinician-rated depressive scores, no association between cortisol levels and PAT or AGV was observed following adjustment for potential confounders (92). This is in line with further studies by Kahl and colleagues that report elevated morning cortisol levels in serum samples from MDD patients compared with the respective control groups (75, 91) but fail to identify significant associations between cortisol levels and VAT content in the combined sample of women with depression and BPD and healthy women (75) and between cortisol levels and VAT, SAT, and intrathoracic cardiac fat content in the context of MDD (91). Contrarily, Kahl et al., report increased AGV in a sample of 27 MDD patients when compared with 19 healthy control subjects after controlling for age, height, and weight (90). In line with the aforementioned studies, a significant positive association of AGV with VAT as well as with PAT was reported for the combined sample with age, weight, and height as covariates, whereas no association between AGV as SAT was observed (90). Additionally, whereas the MDD group displayed increased cortisol levels compared with the control sample, no significant association was observed between cortisol values and parameters of body composition or AGV (90). Contrarily, a study that included female MDD patients with and without comorbid BPD failed to detect significant differences regarding morning cortisol levels in either of the MDD groups when compared with the control sample (76). Additionally, in line with other studies, no significant relation between cortisol levels and VAT was observed in a simple regression analysis (76). Finally, in a recent study, increased AGV was detected in a sample of female patients comorbid with MDD and BPD compared with patients with MDD and an age-matched control group (93). Adrenal gland volume showed a significant association with EAT in the combined MDD sample following adjustment for age, BMI, and physical activity, and additionally, AGV was positively correlated with clinician-rated depression scores (93).

In a dedicated study, Scharnholtz and colleagues compared VAT content assessed by MRI in 20 depressed patients who did not display alterations in HPA axis parameters to 34 non-depressed individuals (96). Measures of HPA axis function included dexamethasone suppression test, cortisol awakening response, cortisol excretion, and AGV. All parameters of HPA axis function did not significantly differ between groups following adjustment for age, sex, and BMI. Additionally, no significant effect was observed with regard to VAT volume (96).

Taken together, most studies that assessed parameters of HPA axis function in the context of visceral and intrathoracic adipose tissue measures report cortisol levels and/or AGV with distinct results regarding both measures. Eight studies that report cortisol levels mostly find increased values in the respective patients samples with depression compared with the corresponding control groups (71, 75, 85, 90–92) or included depressed patients characterized by hypercortisolism (88). However, only in one study did cortisol measurements show a significant association with VAT or intrathoracic adipose tissue compartments (71),

and one study associated hypercortisolism with increased VAT content (85). Additionally, two studies that assessed morning cortisol levels as well as AGV failed to find a significant association between both parameters (90, 92).

Contrarily, whereas group differences between depressed patients and respective control samples were less homogenous between studies, a positive association between AGV and VAT or intrathoracic fat compartments was reported in four studies (72, 90, 92, 93). The observed differences between the different measures of HPA axis function and their association with parameters of body composition might be in part attributable to the reported shortcomings of single time point measurements of cortisol measurements as a reliable marker of chronic cortisol burden (103). Overall, robust positive associations between VAT and AGV and between measures of intrathoracic adipose tissue and AGV were found in all applicable studies, highlighting the potential impact of chronic HPA axis dysfunction on adverse body composition and subsequent cardiometabolic consequences in the context of MDD.

ADIPOSE TISSUE, INFLAMMATION, AND CARDIOVASCULAR RISK

Adipose tissue plays an important role in immune regulation. It is well-recognized that adipose tissue is a reservoir for innate and adaptive immune cells (104). In obesity, adipose tissue becomes dysfunctional, promoting inflammation, hyperlipidemia, and insulin resistance, which contributes to the development of type 2 diabetes and CVD (105). A major driver for adipose tissue dysfunction is adipose tissue expansion, a hallmark of obesity (106, 107). In obesity, excess adipose tissue expansion promotes inflammation via a range of mechanisms (i.e., hypoxia, lipolysis, immune cell recruitment, adipokine dysregulation, mechanical stress/pressure, senescence, and adipocyte death) (108, 109). Under conditions of excessive energy intake, adipose tissue expands by both proliferation (hyperplasia) and increased adipocyte size (hypertrophy) (105). In the case of adipocyte hypertrophy, adipose capillary density is reduced. Moreover, hypertrophic adipocytes have a reduced surface area-to-volume ratio, and ultimately, tissue oxygen consumption is diminished, which, in turn, creates a local hypoxic state to propagate ROS production (110). The local hypoxia and subsequent adipocyte death and damage attract macrophages, which initiates a sterile inflammatory response (i.e., inflammation in the absence of infection) (111).

Sterile inflammation is a key contributor to the pathogenesis of CVD, particularly in settings with increased adiposity, such as obesity and type 2 diabetes (112). Sterile inflammation begins when endogenous “danger signals” released from damaged, dead, or dying cells or degrading extracellular matrix (ECM) stimulate pattern recognition receptors on innate immune cells (such as macrophages and dendritic cells) (113). This activates multiprotein oligomers termed inflammasomes, which initiate inflammatory cascades by stimulating the release of cytokines, such as interleukin (IL)-1 β and other proinflammatory mediators, including chemokines,

predominantly monocyte chemoattractant protein (MCP)-1 in adipose tissue, to recruit additional leukocytes to the site (111, 114). These leukocytes produce more pro-inflammatory mediators, ultimately driving tissue dysfunction and damage. Sterile inflammation is recognized as a key contributor to the pathogenesis of end-organ damage in CVD (115).

Adipose tissue mass and volume can be a powerful tool to predict/measure inflammation. Findings from the Framingham Heart Study indicate that SAT and VAT volumes positively correlate with a number of inflammatory markers (i.e., C-reactive protein (CRP), fibrinogen, IL-6, P-selectin, and tumor necrosis factor receptor (TNFR)-2) (116). In a separate study, VAT but not SAT volume was associated with inflammatory markers [i.e., CRP, MCP-1, and intercellular adhesion molecule (ICAM)-1] in type 2 diabetics (117), and similarly, a correlation of white blood cell count and CRP with VAT but not SAT was found in a cohort of overweight individuals without diabetes, hypertension, or dyslipidemia (118). Indeed, systemic inflammation with increased levels of cytokines appears to be a central feature of metabolically unhealthy obesity, which, in turn, is characterized by an increase in VAT and SAT. Contrarily, metabolically healthy obesity that is characterized by an increase in SAT only does not appear to be associated with an increase in pro-inflammatory markers (105). More recently, Antoniadou and colleagues described a CT imaging metric, “the fat attenuation index,” which uses perivascular adipocyte lipid content and size to detect coronary artery inflammation and accurately identify early subclinical coronary artery disease (119).

ADIPOSE TISSUE COMPARTMENTS, INFLAMMATION, AND DEPRESSION

Low-grade chronic inflammation is proposed as one of the shared underlying condition in the pathoetiology of depression and CVD (15). Additionally, accumulation of visceral fat constitutes one of the most studied potential mechanisms that links chronic activation of stress systems to inflammatory biomarkers. Several

dedicated meta-analyses most commonly identify tumor necrosis factor (TNF)- α and IL-6 as the two cytokines that are significantly upregulated in depressed patients (120–123). Studies based on animal models find TNF- α to interfere with insulin receptor signaling as well as with glucose transport in glucose-sensitive tissues, thereby implicating this cytokine as a key component in obesity-associated insulin resistance (124).

Animal studies also support the link between adiposity (or obesity), inflammation, and depression. Anxiety- and depression-like behavior in obese high fat diet-fed rats is associated with increases in hippocampal proinflammatory cytokine (IL-1 β , IL-6, and TNF- α) levels (125). P2X7 receptor antagonist treatment in these obese rats, which blocks inflammasome activation and cytokine production, reverses obesity-induced behavioral abnormalities, indicating that sterile inflammation may be the common link between adiposity and anxiety and depression

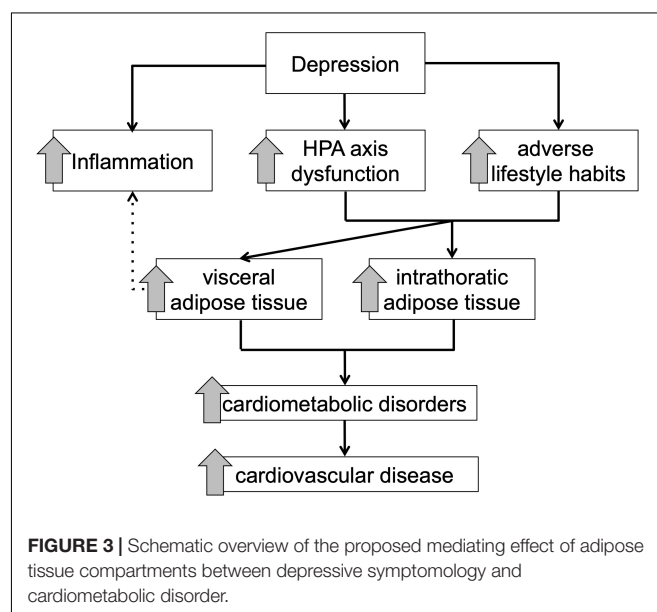


TABLE 3 | Summary of MRI and CT studies regarding the association of depression and depressive symptoms with alterations in abdominal tissue distribution and changes in parameters of inflammation.

Study	Sample	Parameters of inflammation	Finding
Kahl et al. (75)	48 female BPD and/or MDD patients vs. 20 female CTRLs	TNF- α and IL-6 serum levels	Significant increase in TNF- α and IL-6 in MDD groups vs. CTRL; positive association of IL-6 but not TNF- α with VAT in combined sample
Greggersen et al. (76)	78 premenopausal, female BPD and/or MDD patients vs. 34 CTRLs	TNF- α and IL-6 serum levels	Significant increase in TNF- α but not in IL-6 in MDD groups vs. CTRL; positive association of TNF- α but no IL-6 with VAT in combined sample
Kahl et al. (90)	27 MDD patients vs. 19 CTRLs	TNF- α and IL-6 serum levels	Significant increase in TNF- α but not in IL-6 in MDD vs. CTRL; no correlation analyses available
Kahl et al. (91)	50 MDD patients vs. 25 CTRLs	TNF- α and IL-6 serum levels	Significant increase in TNF- α in male but not in female MDD vs. CTRL; no group differences in IL-6 in either sex; no significant association of TNF- α or IL-6 with EAT, PAT, VAT, and SAT
Kahl et al. (92)	16 chronic and 34 acute MDD patients vs. 25 CTRLs	TNF- α and IL-6 serum levels	Significant group differences for TNF- α but not IL-6; no significant association between PAT and TNF- α or IL-6

BPD, borderline personality disorder; CTRL, control; MDD, major depressive disorder; EAT, epicardial adipose tissue; IL, interleukin; PAT, paracardial adipose tissue; SAT, subcutaneous adipose tissue; TNF, tumor necrosis factor; VAT, visceral adipose tissue.

(126). An additional mechanism that has recently been indicated in the pathoetiology of inflammation-associated depression as well as a potential link between depression and aging processes in the brain on the cellular level is senescence. Cellular senescence is characterized by stable cell cycle arrest and by a pro-inflammatory secretory phenotype (127). This senescence-associated secretory phenotype (SASP), while differing on the basis of cell type, usually is characterized by alterations in the levels of several cytokines and chemokines (127). By measuring this SASP index, Diniz and colleagues found that the interaction of depression and somatic health variables, in particular obesity, was associated with greater cellular senescence in young and middle-aged adults (128). Together with animal studies that link obesity to increased senescence and depression and anxiety-like phenotypes (108, 129), these data suggest senescence as a potential key contributor in the interaction of depression, obesity, and inflammation.

In the setting of human depression, correlations between adipose tissue mass and inflammation have been much less studied, assessment of inflammatory markers was limited to measures of IL-6 and TNF- α and findings to date are somewhat contradictory. We identified 6 studies, summarized in **Table 3**, that assessed inflammatory cytokines TNF- α and/or IL-6 together with visceral or intrathoracic fat compartments in the context of depression.

For instance, Kahl and colleagues assessed TNF- α and IL-6 levels in conjunction with VAT and/or intrathoracic tissue content in several samples of depressed patients compared with respective corresponding control samples. Increased levels of TNF- α and IL-6 were found in a study that included female patients with MDD with and without comorbid BPD in comparison to healthy controls (75). In this study, IL-6 but not TNF- α serum levels were significantly associated with measures of VAT in a partial correlation analysis corrected for age (75).

Contrarily, Gregersen et al., report increased TNF- α levels in a sample of female MDD patients with and without BPD, whereas IL-6 levels did not differ significantly between groups. Accordingly, a positive association between VAT and TNF- α but not between VAT and IL-6 was observed (76). Similarly, a study that included depressed patients of both sexes found increased serum concentrations of TNF- α in MDD patients, whereas IL-6 levels were comparable to control values. Whereas this study reports a trend toward increased VAT and significantly higher PAT and AGV in the depressed sample, no data regarding the potential association of parameters of body composition and inflammatory cytokines were provided (90).

In a study that assessed parameters of body composition and pro-inflammatory cytokines in depressed patients stratified by

sex, increased TNF- α levels were found in male but not in female patients, whereas IL-6 was found comparable to values of the respective control sample in both sexes. This study did not detect a significant association of cytokine levels and any parameter of body composition, including EAT, PAT, VAT, and SAT (91). Finally, Kahl and colleagues assessed PAT volume as well as IL-6 and TNF- α levels in a patient sample subdivided into acute and chronic depression. Group differences regarding TNF- α but not IL-6 were observed, and partial correlation analysis indicated an association between TNF- α and clinician-rated depression scores over the complete sample when controlling for age, weight, and height. However, and in line with most other studies, no significant association was detected between TNF- α and PAT volume (92).

In summary, whereas several studies report increased serum levels of pro-inflammatory cytokines, especially of TNF- α , in their respective MDD samples, only two studies, both including female patients with comorbid BPD, found significant associations of IL-6 and VAT (75) or of TNF- α and VAT (76). Overall, based on the limited number of studies that additionally vary with regard to patient characteristics, assessed adipose tissue compartment and statistical methods used to determine potential correlations, a potential link between increased VAT or intrathoracic adipose tissue and pro-inflammatory cytokines, i.e., TNF- α and IL-6, could not be confirmed.

CONCLUSION

MDD as well as self-reported depressive symptoms are associated with severe body composition changes starting in early adulthood, predisposing this group of patients for common physical disorders, such as diabetes mellitus type 2 and cardiovascular disorders. Several MDD-associated mechanisms, such as increased activity of the HPA axis, physical inactivity, poor nourishment, and poor adherence to treatment recommendations, and low-grade inflammation might directly or indirectly worsen this vicious circle, resulting in higher morbidity and mortality rates due to cardiometabolic disorders (**Figure 3**).

AUTHOR CONTRIBUTIONS

BS and MJ: investigation and writing—original draft. GD: writing—review and editing. KK: conceptualization and writing—review and editing. All authors contributed to the article and approved the submitted version.

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Transdiagnostic Cognitive-Behavioral Therapy for Depression and Anxiety Disorders in Cardiovascular Disease Patients: Results From the CHAMPS Pilot-Feasibility Trial

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Objective: The aim of the Cardiovascular Health in Anxiety and Mood Problems Study (CHAMPS) is to pilot the Unified Protocol (UP) for the transdiagnostic treatment of depression and anxiety disorders in patients recently hospitalized for cardiovascular diseases (CVDs) and evaluate the feasibility.

Methods: The present study is a controlled, block randomized pragmatic pilot-feasibility trial incorporating qualitative interview data, comparing UP ($n = 9$) with enhanced usual care (EUC, $n = 10$). Eligible trial participants had a recent CVD-cause admission and were above the severity threshold for depression or anxiety denoted by Patient Health Questionnaire (PHQ-9) total scores ≥ 10 and/or Generalized Anxiety Disorder (GAD-7) total scores ≥ 7 respectively on two occasions, and met criteria for one or more depression or anxiety disorders determined by structured clinical interview. Study outcomes were analyzed as intention-to-treat using linear mixed models and qualitative interview data were analyzed with content analysis.

Results: Quantitative and qualitative measures indicated acceptability of the transdiagnostic CBT intervention for CVD patients with depression or anxiety disorders. Satisfaction with UP was comparable to antidepressant therapy and higher than general physician counseling. However, there were difficulties recruiting participants with current disorders and distress on two occasions. The UP was associated with a reduction in total number of disorders determined by blinded raters. Linear mixed models indicated that a significantly greater reduction in anxiety symptoms was evident in the UP group

by comparison to the EUC group (GAD-7, p between groups = 0.011; Overall Anxiety Severity and Impairment Scale, p between groups = 0.013). Results favored the UP group by comparison to EUC for change over 6 months on measures of physical quality of life and harmful alcohol use. There was no difference between the two groups on changes in depression symptoms (PHQ-9), stress, metacognitive worry beliefs, physical activity, or adherence.

Discussion: In conclusion, this feasibility trial indicates acceptability of transdiagnostic CBT intervention for CVD patients with depression or anxiety disorders that is tempered by difficulties with recruitment. Larger trials are required to clarify the efficacy of transdiagnostic depression and anxiety disorder CBT in populations with CVDs and depressive or anxiety disorders.

Clinical Trial Registration: <https://www.australianclinicaltrials.gov.au/anzctr/trial/ACTRN12615000555550>, identifier: ACTRN12615000555550.

Keywords: depression, major depression (MDD), anxiety, anxiety disorders, cardiovascular disease, coronary heart disease, randomized controlled trial, cognitive-behavioral therapy (CBT)

BACKGROUND

Depressive disorders are prevalent in 10–15% of the population with cardiovascular diseases (CVD) such as coronary heart disease and heart failure (1, 2). Comorbid depression in patients with CVD portends an increased risk for morbidity and mortality (3, 4) and higher healthcare costs (5). To date, antidepressant and cognitive-behavioral therapy (CBT) interventions have resulted in significant reductions in depression symptoms, albeit inconsistent reductions on major adverse cardiac outcomes (MACE) (6, 7). One limitation of past interventions is the predominant focus on depression in isolation of other psychosocial risk factors. Psychosocial risk factors for CVD tend to cluster together within individuals or groups (8–10). These interrelated psychosocial factors include anxiety disorders, hostility, anger, stress, worry, rumination, anxiety sensitivity, phobic anxiety, distress tolerance, and the specific combination of negative affect and social inhibition (11–17). Anxiety disorders in particular are associated with onset of CVD and adverse cardiovascular prognosis (18–22). Moreover, anxiety disorders have high concurrent and lifetime comorbidity rates with depression disorders in the general population (23) and those with CVD (15, 24). Collectively, these findings point to the likelihood that common processes underlying negative emotions generally elevate CVD risk and *vice versa* (12). This raises the possibility that an intervention transcending diagnostic boundaries, targeting core emotional processes, would be a step toward improving mental health interventions amongst CVD populations.

Indeed, parallel trends in clinical psychology are exploring the tenet that CBT interventions transcending diagnostic boundaries may offer advantages over disorder-specific treatments (25, 26). For example, transdiagnostic interventions may be more appropriate in the common clinical situation of comorbid disorders, without the need to prioritize one

disorder over another (i.e., selecting one single-disorder protocol over another) (27). To date, few studies have examined transdiagnostic CBT interventions for depression and anxiety disorders in CVD populations. A RCT of meta-cognitive therapy in cardiac rehabilitation patients showed that results favored the meta-cognitive therapy arm for reduction in Hospital Anxiety and Depression Scale total score at 4 and 12 months post-intervention compared to usual care (standardized effect size 0.52 and 0.33 respectively) (28). Moreover, transdiagnostic approaches have been successfully applied to other health conditions including functional gastrointestinal diseases (29, 30), cancer (31), HIV (32), headache (33).

The aim of the Cardiovascular Health in Anxiety and Mood Problems Study (CHAMPS) is to prospectively study the feasibility and acceptability of the Unified Protocol (UP) for the Transdiagnostic Treatment of Emotional Disorders (34) in patients with a recent CVD hospitalization and comorbid depression or anxiety disorder. A feasibility study is considered preliminary work undertaken to estimate important parameters necessary for the design of a larger clinical trial.

METHODS

Study Design

This prospective study is a feasibility randomized controlled trial, of parallel design, comparing the UP for emotional disorders vs. enhanced usual care (EUC). A trial protocol was registered (ACTRN12615000555550) and summarized elsewhere (35). This study was approved by Human Research Ethics Committee of the Queen Elizabeth Hospital (Approval #HREC/15/TQEH47). A power calculation was not performed for this feasibility trial with the self-rated outcome measures collected to provide the standard deviation of patient outcomes which is necessary to perform a power calculation in a larger and more definitive trial.

Study Population

Participant eligibility criteria were: (1) age ≥ 18 years; (2) a primary hospital admission for CVD (specified by relevant International Classification of Disease codes (36) for myocardial infarction, coronary revascularization, symptomatic coronary disease, heart failure, heart valve disease, atrial or ventricular arrhythmia); (3) above the threshold for depression and/or anxiety denoted by Patient Health Questionnaire (PHQ-9) total scores ≥ 10 (37) and/or Generalized Anxiety Disorder (GAD-7) total scores ≥ 7 (38) respectively on two occasions (index admission and 2 weeks later); and a MINI International Neuropsychiatric Interview (MINI) 5.0.0 diagnosis of any major depression $\pm$ melancholic features, dysthymia, panic disorder, agoraphobia, social anxiety disorder, generalized anxiety disorder (GAD) or post-traumatic stress disorder (PTSD); and (4) fluency in English. Participants who were no longer above the threshold for depression and anxiety symptoms on the PHQ-9 and GAD-7 at the second assessment were invited to continue their involvement in an observational sub-study as a non-distressed control group.

Participant exclusion criteria were: (1) psychosis or bipolar disorder determined by medical history or randomization naïve assessors; (2) high suicide risk; (3) cognitive impairment or dementia impeding delivery of psychotherapy or provision of informed consent; (4) neurodegenerative condition such as Parkinson's Disease; (5) receiving psychologist or psychiatrist counseling elsewhere or psychotropic treatment at enrollment; (6) a diagnosis of drug and alcohol dependence or abuse determined by randomization naïve assessors; (7) a medical condition likely to be fatal within 1 year.

Participants were recruited from the Queen Elizabeth Hospital, a public hospital in the Western urban area of Adelaide, South Australia. Parallel to the main trial, a non-distressed control group was recruited, comprised of patients below the severity threshold for depression or anxiety denoted by PHQ-9 and GAD-7 2 weeks post-admission, or not meeting criteria for a depression or anxiety disorder specified by inclusion criterion #3 (Figure 1). The non-distressed control group were recruited to evaluate screening procedures (39) and determine longer-term symptom trajectories similar to previous trials (40), and are not described further here.

Protocol Deviations

In contrast to the published protocol (35), participants were only included if they met criteria for a current depression and/or anxiety disorder and had elevated symptoms on two occasions, as opposed to the original criteria of elevated symptoms $\pm$ a depression or anxiety disorder. Consequently, randomization was not stratified by primary CVD-cause admission and the target recruitment of 50 patients was revised to 20 participants due to recruitment difficulties of severe mental disorders among the CVD population as other trials have noted (41). Also, during the roll-out phase, an amendment was made to include a questionnaire measuring meta-worry, along with a qualitative sub-study. During the ethics amendment process, trial recruitment was suspended as the ethics committee mandated,

for all patients with a severe depressive symptoms in the control group (i.e., PHQ-9 scores ≥ 20) at any stage of the study, that a community based acute crisis mental health triage service was contacted as part of duty of care. Similarly, for any control patients with moderate to moderately severe depressive symptoms (i.e. PHQ scores ≥ 10 and ≤ 19) at any stage of the study, that the patient and their general physician be notified.

Randomization and Masking

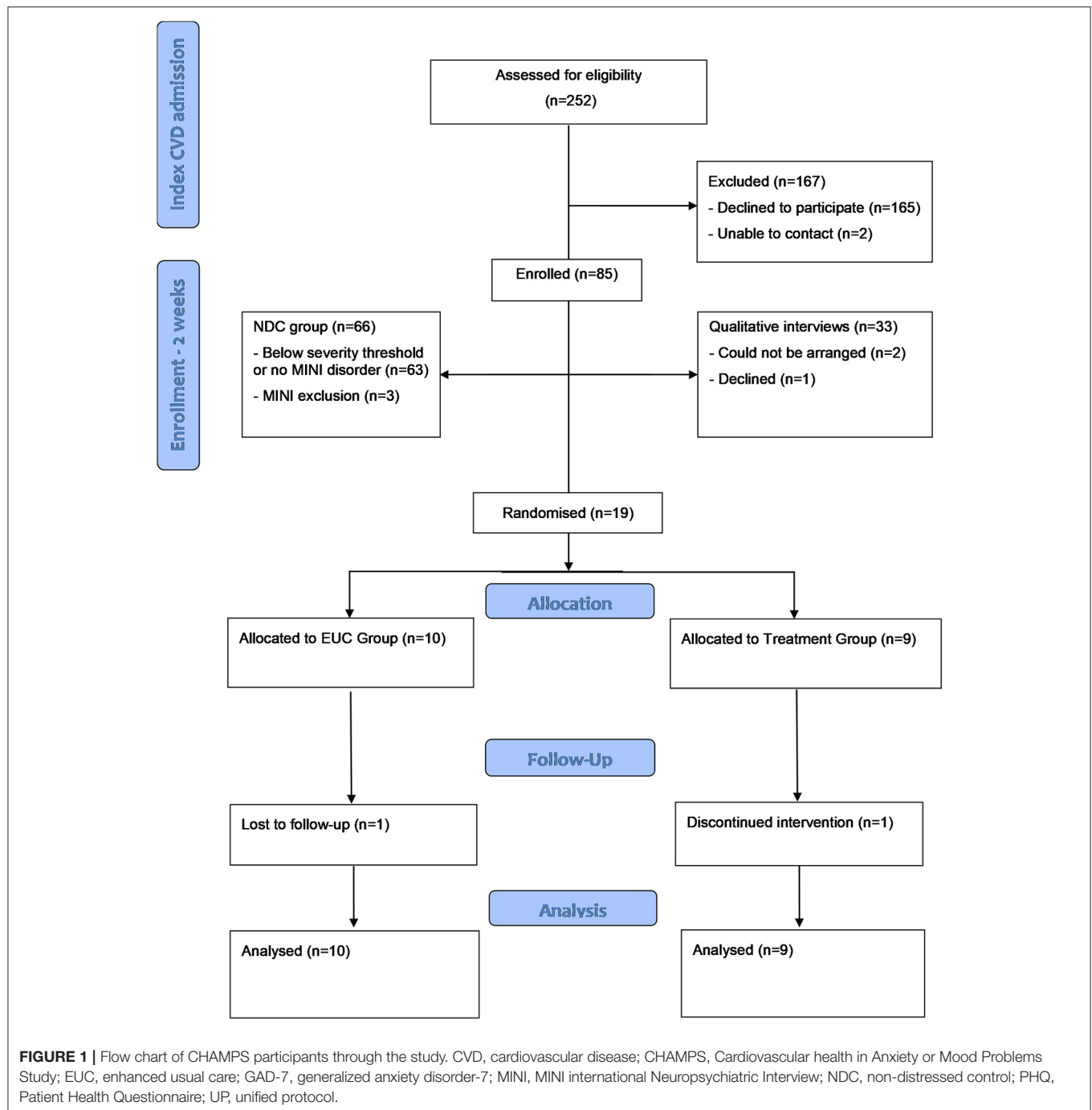
An independent statistician generated the randomization codes. Patients were block randomized according to a random number generator in alternating block sizes of four and six. After baseline measures were completed, an electronic and automated email was sent to the clinical trial manager containing a code for randomization to either the UP or EUC. In psychotherapy trials, the patients, therapist, and clinical trial manager are aware of treatment allocation. The research assistants who performed the assessments, data extraction and entry remained blind to treatment allocation through all stages of the study and follow-up.

Transdiagnostic Unified Protocol Intervention

The UP is a type of CBT explicitly designed to address the full range of emotional disorders (anxiety, depressive, and related disorders) by targeting core and underlying emotional processes that lead to the development and maintenance of symptoms across disorders. The UP was designed by Barlow et al. for weekly and face-to-face delivery up to a maximum of 18 weeks (42). The UP comprises eight modules: (1) enhancing motivation for change and treatment engagement, (2) facilitating better understanding of patients' emotional experiences, (3) increasing present focused emotion awareness, (4) increasing cognitive flexibility, (5) identifying and preventing patterns of emotion avoidance and maladaptive emotion driven behaviors, (6) increasing awareness and tolerance of emotion-related physical sensations, (7) interoceptive and situation-based emotion focused exposure, and (8) the final module was devoted to summarizing the relevant techniques attained and developing relapse prevention strategies. Owing to the highly medicalized nature of treating anxiety and depression in CVD populations and patient preference for shorter therapies (43), during piloting we refined the UP from 18 sessions, covering 8 modules (and the preliminary module), down to 12 sessions, opting for 50 to 90 min weekly sessions (see eSupplement1 in Supplementary Material). An experienced psychologist (CGB), who was trained in both the manualized UP (42) and on common CVDs, delivered the intervention. Intervention fidelity was maintained by weekly supervision with a senior psychologist and discussion of cases.

Enhanced Usual Care

Patients randomized to the EUC group received an education package which was delivered by the clinical trial manager, consisting of the beyondblue[®] fact sheet regarding anxiety, depression and coronary heart disease (44), conforming with



the National Heart Foundation of Australia's[®] guidelines (37). Participants and their general physician were informed of the baseline depression severity results and directed to available clinical services (psychologist, psychiatrist, telephone counseling), advising participants to seek assistance for achieving mental wellbeing. As abovementioned, additional duty of care practices and general physician notification was implemented for patients with depressive symptoms at the request of the ethics committee. There were no other restrictions placed on usual care.

Procedure

Potentially eligible patients were identified 1–4 days after the index CVD admission by the clinical trial manager in the cardiology department. Eligible and consenting participants underwent a basic screening procedure consisting of the PHQ-9 and GAD-7. Participants were re-assessed at 2 weeks post-index CVD admission to complete the PHQ-9, GAD-7, and a structured clinical interview to confirm symptom severity and study eligibility, as well as complete the baseline patient rated

measures (see eSupplement 2 in **Supplementary Material**). After confirmation of study eligibility and completion of baseline study measures, the allocation was revealed to the clinical trial manager, and arrangements made for either the UP or EUC arm. Patients ineligible for the trial at 2 weeks due to low symptom severity on the PHQ-9 or GAD-7 were invited to participate in the non-distressed control group. The qualitative sub-study sampled equally from the UP, EUC, and non-distressed control group.

Patient Rated Measures

The complete battery of measures and their timing of assessment is described in eSupplement 2 in **Supplementary Material**.

Generalized Anxiety Symptoms

The GAD-7 approximates Diagnostic and Statistical Manual 5 (DSM-5) criteria for GAD (45). The GAD-7 is scored on a scale of 0–3 (not at all, several days, more days than half the days, and nearly every day). The GAD-7 is considered valuable for use the detection of anxiety disorders in medical and primary care populations because the measure does not contain any somatic items (45). The GAD-7 severity threshold for clinically relevant symptoms are total GAD scores ≥ 7 (38) which has favorable validity to identify depression and anxiety disorders in medical patients (38).

Anxiety Severity

The Overall Anxiety Severity and Impairment Scale (OASIS) was developed as a self-report measure that assesses clinical severity and functional impairment of anxiety disorders (46, 47). Participants respond to 5 items that best describe their experience on a five-point scale (0, little or none; 1, mild; 2, moderate; 3, severe; 4, extreme). Scores >8 are indicative of severe anxiety in primary care and psychiatric samples (47).

Depression Symptoms

The PHQ-9 is a standardized instrument that incorporates DSM-5 major depression disorder criteria (48). Each item of the PHQ-9 is scored from 0 to 3, with scores ranging from 0 to 27. Scores of 10, 15, and 20 represent the thresholds for moderate-, moderately severe-, and severe-depression respectively (48). The PHQ-9 is recommended for depression screening in CVD populations because of its specificity to detect depression and sensitivity to clinical change (14, 37, 49).

Stress

The Depression, Anxiety and Stress Scales (DASS-21) is a 21 item measure validated in adults to age 90 years (50, 51). Scores range from 0 to 21 for the stress subscale with higher scores denoting higher stress symptoms. The DASS-21 factor structure approximates a tripartite structure, with stress broadly indicative of negative affectivity shared between depression and anxiety disorders (52).

Meta-Cognitions

The Metacognitions about Symptoms Control Scale (MaSCS) assesses metacognitive beliefs pertaining to symptoms in chronic health conditions (53). The MaSCS is a 17-item questionnaire, asking participants to rate on a 4-point Likert scale (1 = *Do*

not agree, 4 = *Agree strongly*) how much a statement applies to them (e.g., “If I focus on the symptom, I can take the appropriate action to get better”). In line with conceptualizations of meta-worry, the MaSCS has two subscales, one each tapping into positive metacognitive worry beliefs and negative metacognitive worry beliefs. The MaSCS was developed for a variety of chronic conditions. The MaSCS instructions were adapted to state “*This scale is concerned with how people with cardiovascular disease experience and cope with their symptoms.*”

Quality of Life and Health Behaviors

Quality of life (QOL) was assessed with the 12-item short-form health survey (SF-12) (54). The SF-12 is one of the most commonly utilized and generalizable measures of QOL in general populations as well as CVD populations (55). The SF-12 sub-scale scores were arranged into the Physical Components Scale (PCS) and Mental Components Scale (MCS) in accordance with the manual. The PCS and MCS are weighted summary scales (range width 0–100) with higher scores representing higher QOL.

Behavioral factors such as alcohol use and smoking are pertinent to cardiovascular functioning, and are potential emotion-driven behaviors under the UP conceptualization of responses to anxiety and depression. Harmful alcohol use was measured by the Alcohol Use Disorders Identification Test Shortened Clinical (AUDIT-C) version which provides favorable sensitivity and specificity for the detection of problematic drinking (56). The physical activity questions from the Australian National Health Surveys was used to classify participants level of physical activity (57). Due to inconsistent reporting and missing data, it was not possible to calculate metabolic equivalents and thus only total activity (in minutes) is reported. Lifetime and current tobacco use was measured by items from the Global Adult Tobacco Survey (GATS) (58).

Adherence

Adherence was measured by 5 items from the Medical Outcomes Study Specific Adherence Scale (MOS SAS) (59). The items used in CHAMPS covered adherence to diet, exercise, stress management, cardiac rehabilitation and medication.

Mental Disorders

The MINI version 5.0.0 is a brief structured interview to diagnose common depression and anxiety disorders as well as alcohol and substance abuse and psychosis as outlined in the inclusion and exclusion criteria (60, 61). The MINI modules utilized in this study covered; major depressive disorder, major depressive disorder with melancholic features, dysthymia, hypomanic and manic episode (bi-polar I and II), panic disorder, agoraphobia, social anxiety disorder, obsessive-compulsive disorder (OCD), PTSD, alcohol dependence/abuse, substance dependence/abuse (non-alcohol), psychotic disorders, mood disorders with psychotic features, GAD, and antisocial personality disorder. Specific phobias are not assessed by the MINI 5.0.0 and the modules relating to anorexia and bulimia nervosa were omitted. Assessments were performed to determine the mental health diagnosis at baseline and remission at the end of the study by qualified junior psychologist assessors who were

blinded to treatment allocation and the timing of the assessment (e.g. pre-, post).

Medical Outcomes, Intervention Acceptability and Feasibility, Qualitative Analyses

These methods are described in the eSupplement 3 in **Supplementary Material**.

Statistical Analysis

For participants missing any self-reported data at 18 weeks or 6 months, data were imputed to increase statistical power using multiple imputation procedures based on demographic and medical comorbidities. All analyses were performed based on intention-to-treat. Comparisons between UP and EUC were made at baseline on demographics and clinical risk factors using independent samples *t*-tests, Kruskal–Wallis test, and the chi-square statistic with Fisher's exact test where appropriate. Continuous data were analyzed with linear mixed models to assess between UP and EUC group differences in the change of a given variable from baseline to 6 months follow-up (62). Mixed model data assumptions were met and each mixed model specified correlated residuals within subjects, random effects with restricted maximum likelihood function, and robust covariance estimation, utilizing a random slope and random intercept. Mixed model data are reported with $M \pm SD$ at each observation point to assist with effect size estimates in future studies or meta-analyses. For depression and anxiety disorder diagnoses at 6-month follow-up, the total number of disorders were tallied to calculate the change in number of baseline and follow-up disorders. For hospital readmissions, MACE and psychiatric admissions were analyzed with the chi-square statistic with Fisher's exact test. For satisfaction with care, only descriptive statistics are reported. As a feasibility trial and largely exploratory study to help inform the power calculations of a larger trial, no adjustment was made for multiple comparisons.

RESULTS

A total of 19 participants were randomized to either UP ($n = 9$) or EUC ($n = 10$). Two participants dropped out (1 from each arm) by 6 months. There were no differences between UP and EUC patients in any baseline demographic, cardiovascular or mental health variables (**Tables 1, 2**). The most common mental disorders at baseline were major depressive disorder, agoraphobia, and GAD. At baseline, 5 patients met criteria for 1 disorder (26.3%), 4 met criteria for 2 disorders (21.1%), 8 met criteria for 3 disorders (42.1%), and 2 met criteria for 4 disorders (10.5%).

Psychological and QOL Outcomes

The number of disorders determined by blinded MINI raters was significantly lower in the UP group by comparison to the EUC (**Table 3**). Linear mixed models indicated that a significantly greater reduction in anxiety symptoms was evident in the UP group by comparison to the EUC group on the GAD-7 (p between groups = 0.011) and also the Overall Anxiety

TABLE 1 | Baseline demographic and cardiovascular characteristics of the sample N (%).

	Enhanced usual care ($N = 10$)	CBT-Unified Protocol ($N = 9$)	P
Median age, years (IQR) ^a	62 (55–72)	62 (41–72)	0.39
Male sex	5 (50.0)	4 (44.4)	0.99
Employment status			0.87
Currently employed	5 (50.0)	4 (44.4)	
Retired	4 (40.0)	5 (55.6)	
Unemployed	1 (10.0)	–	
Current tobacco smoking	1 (10.0)	1 (11.1)	0.99
Index-CVD admission			
Acute myocardial infarction	1 (10.0)	2 (22.2)	
Heart failure	2 (20.0)	3 (33.3)	
Arrhythmia	3 (30.0)	3 (33.3)	
Angina pectoris	4 (40.0)	1 (22.2)	
CVD comorbidities			
Previous revascularization	2 (20.0)	–	0.47
Previous myocardial infarction	2 (20.0)	1 (11.1)	0.99
Valvular disease	1 (10.0)	1 (11.1)	0.99
Biventricular pacemaker	1 (10.0)	1 (11.1)	0.99
Implanted cardiac defibrillator	1 (10.0)	1 (11.1)	0.99
Prior stroke or TIA	2 (20.0)	–	0.47
Hypertension	8 (80.0)	5 (55.6)	0.35
Dyslipidemia	5 (50.0)	5 (56.6)	0.99
Other pertinent comorbidities			
Lung disease	2 (20.0)	1 (11.1)	0.99
Renal disease	2 (20.0)	–	0.47
Diabetes	2 (20.0)	1 (11.1)	0.99
BMI, $\text{kg}/\text{m}^2 \geq 30$	5 (50.0)	5 (55.6)	0.99
Sleep apnea	1 (10.0)	2 (22.2)	0.58
Chronic pain	4 (40.0)	1 (11.1)	0.30

^aAll data presented as $N(\%)$ unless otherwise indicated.

BMI, body mass index; CBT, cognitive-behavioral therapy; CVD, cardiovascular disease; IQR, interquartile range; TIA, transient ischemic attack.

Severity and Impairment Scale (p between groups = 0.013). There was no difference between the UP and EUC groups on change in depression symptoms (PHQ-9), stress (DASS-21) or metacognitive worry beliefs. There was evidence favoring the UP group for greater improvement over 6 months in physical QOL, but not mental QOL.

CVD Health Behaviors and Adherence

The CVD health behavior and adherence data are reported in **Table 4**. Linear mixed models indicated that a significantly greater reduction in harmful alcohol was evident in the UP group by comparison to the EUC group on the AUDIT-C. There were no differences between the UP group by comparison to the EUC group in physical activity or adherence. There were only two current smokers in the study and therefore GATS data was not analyzed.

TABLE 2 | Baseline mental health characteristics of the sample.

	Enhanced usual care (<i>N</i> = 10)	CBT-unified protocol (<i>N</i> = 9)	<i>P</i>
MINI diagnoses			
Major depressive disorder	7 (70.0)	9 (100.0)	0.21
Depressive disorder with melancholic features ^a	5 (50.0)	4 (44.4)	0.99
Panic disorder	4 (40.0)	1 (11.1)	0.30
Agoraphobia	4 (40.0)	2 (22.2)	0.63
Social Anxiety Disorder	1 (10.0)	-	0.99
Generalized anxiety disorder	2 (20.0)	4 (44.4)	0.35
Obsessive compulsive disorder	-	1 (11.1)	0.47
Post-traumatic stress disorder	-	1 (11.1)	0.47
Number of disorders on MINI^b			0.76
1	3 (30.0)	2 (22.2)	
2	2 (20.0)	2 (22.2)	
3	4 (40.0)	4 (44.4)	
4	1 (10.0)	1 (11.1)	
Psychological symptoms at index admission			
PHQ-9 score	12.6 ± 6.2	13.4 ± 4.6	0.74
GAD-7 score	9.5 ± 3.3	10.7 ± 5.6	0.59

^aPatients must also meet criteria for major depressive disorder.

^bInclusive of obsessive compulsive disorder which was not an eligibility disorder.
CBT, cognitive-behavioral therapy; GAD-7, Generalized Anxiety Disorder 7-item scale;
MINI, Mini International Neuropsychiatric Interview; PHQ-9, Patient Health Questionnaire
9-item scale.

Hospital Admissions

Hospital admissions for CVD causes at 6 months follow-up were comparable (UP 20.0% vs. EUC 22.2%, $p = 0.99$). One psychiatric admission occurred in the study (UP group 11.1% vs. EUC 0%, $p = 0.47$). This admission occurred in the context of concerns over cognitive function and personality change that was subsequently identified as a transient ischemic attack.

Satisfaction With Care

Participants randomized to UP reported high satisfaction with the psychologist delivered UP intervention, median satisfaction = 4 “quite a bit satisfied,” and low satisfaction with psychological care provided by their GP, median = 1 “not at all satisfied.” However, EUC participants reported equally high satisfaction with antidepressants, median satisfaction = 4 “quite a bit satisfied” and equally low satisfaction with GP psychological care, median = 1 “not at all satisfied.”

Qualitative Analysis

The CVD participants discussed numerous factors that contributed to their satisfaction or dissatisfaction with care. These were categorized into two overarching themes: characteristics of the treatment and of health professionals. Pertaining to CVD treatment, themes included identifying the problem and fixing it. Hence, accurate diagnoses and a successful outcome led to improvements in CVD symptom severity.

By contrast, psychological treatment under the UP related to reducing severity, which impacted on overall satisfaction with medical care. With regard to medical professionals in general, including the psychologist, two main themes were developed. Firstly, the practitioner’s personal characteristics which included subthemes of competence, efficiency, and personality. Competence was discussed in association with knowledge and expertise. Finally, being caring, helpful, and kind were crucial elements of practitioners’ personal characteristics. The second theme pertaining to medical professionals was the practitioner-patient interaction. An important subtheme was quality of communication as perceived by patients, specifically—as mentioned by nearly all participants—receiving comprehensive information. Taken altogether, for patients to be satisfied, professionals must not only be competent (i.e., have knowledge and expertise), but also communicate effectively and explain information in a caring, helpful, and kind manner. Respect for the patient was identified as a subtheme that overlapped across practitioners’ personal characteristics and practitioner-patient interactions.

DISCUSSION

This feasibility RCT showed that the UP intervention for emotional disorders was associated with greater change, by comparison to the EUC, on the total number of psychiatric disorders, anxiety, harmful alcohol use, and improvement in physical QOL. The UP was not associated with reductions in depression, stress, or metacognitive worry about symptoms. Likewise, the UP was not associated with changes in pertinent health behaviors such as physical activity level, adherence, or major hospitalization rates. As a feasibility study, the trial was not powered to detect significant clinical effects, thus all results need to be interpreted as preliminary. Moreover, there were difficulties with recruiting CVD patients who met criteria for current disorders and were distressed after the index admission which points to low feasibility of an outpatient intervention for patients with severe mental health concerns.

This study is perhaps the first CBT intervention in CVD populations to target anxiety disorders as part of its inclusion criteria. The current study indicated that the UP was associated with reductions in GAD-7 and OASIS scores, as well as cumulative number of disorders as adjudicated by blinded raters. The findings are highly significant because less is known about the treatment of anxiety disorders in CVD populations. Given that access to community mental health services is often limited to persons with a verified mental disorder (e.g., better access initiatives in Australia and Improving Access to Psychological Therapies in UK) (63, 64), the study findings support the referral of these patients with comorbid CVDs to mental healthcare professionals for transdiagnostic CBT. Indeed, as little empirical data currently exists pertaining to anxiety disorder treatment in CVD populations, it remains largely unknown whether transdiagnostic approaches are equivalent to single-disorder protocols in general (65) and in chronic diseases specifically (66). Recently, the UP has been tested in diverse

TABLE 3 | Change in psychological outcomes for patients randomized to unified protocol vs. enhanced usual care.

		Control <i>N</i> = 10		UP <i>N</i> = 9		<i>P</i> between groups
		<i>M</i> (SD)	Δ (SD)	Pre <i>M</i> (SD)	Δ (SD)	
MINI disorders	Pre	2.30 (1.06)	–	2.44 (1.02)	–	0.009*
	Post	1.00 (1.10)	–1.30 (0.48)	0.5 (1.00)	–1.94 (0.45)	
	6 month	3.00 (2.16)	0.70 (1.46)	1.40 (1.14)	–1.04 (0.69)	
Anxiety (GAD-7)	Pre	9.50 (3.31)	–	10.67 (5.57)	–	0.011*
	Post	3.30 (5.16)	–6.20 (3.21)	1.67 (2.78)	–9.00 (3.74)	
	6 month	4.65 (6.61)	–4.85 (4.43)	4.51 (3.66)	–6.16 (3.43)	
Anxiety impairment and avoidance (OASIS)	Pre	4.32 (3.95)	–	4.11 (4.82)	–	0.013*
	Post	1.80 (3.91)	–2.52 (2.48)	0.22 (0.67)	–3.89 (4.30)	
	6 month	2.89 (3.52)	–1.43 (2.39)	1.30 (2.21)	–2.81 (3.32)	
Depressive symptoms (PHQ-9)	Pre	12.60 (6.22)	–	13.44 (4.59)	–	0.16
	Post	5.81 (7.99)	–6.79 (4.80)	4.03 (5.99)	–9.41 (3.60)	
	6 month	8.97 (10.16)	–3.63 (6.39)	7.67 (6.40)	–5.77 (3.88)	
Stress (DASS-stress)	Pre	4.76 (5.44)	–	6.11 (7.64)	–	0.59
	Post	2.60 (6.65)	–2.16 (3.99)	0.78 (1.39)	–5.33 (6.58)	
	6 month	2.60 (6.65)	–3.86 (4.08)	0.78 (1.39)	–2.44 (4.58)	
Positive metacognitive worry beliefs (MaSCS)	Pre	16.00 (14.68)	–	21.33 (8.76)	–	0.95
	Post	4.40 (10.01)	–11.60 (8.98)	8.56 (14.52)	–12.78 (9.17)	
	6 month	9.10 (14.88)	–6.90 (9.35)	15.44 (14.92)	–5.89 (9.50)	
Negative metacognitive worry beliefs (MaSCS)	Pre	13.60 (12.39)	–	19.00 (9.19)	–	0.17
	Post	3.00 (6.75)	–10.60 (8.08)	3.00 (4.58)	–16.00 (5.45)	
	6 month	5.70 (10.11)	–7.90 (7.44)	9.11 (9.87)	–9.89 (6.06)	
Quality of life—(SF-12 PCS)	Pre	40.00 (5.10)	–	38.99 (8.67)	–	0.023*
	Post	42.23 (5.88)	2.23 (2.57)	47.74 (8.48)	8.75 (3.84)	
	6 month	43.18 (10.97)	3.18 (7.54)	46.17 (11.83)	7.18 (7.14)	
Quality of life—(SF-12 MCS)	Pre	35.47 (7.06)	–	34.80 (8.34)	–	0.59
	Post	37.84 (11.13)	2.37 (5.68)	41.60 (6.70)	6.80 (3.72)	
	6 month	40.49 (8.17)	5.02 (4.93)	40.41 (9.84)	5.61 (5.92)	

CI, confidence interval; DASS, Depression Anxiety and Stress Scales; GAD-7, Generalized Anxiety Disorder 7-item scale; MaSCS, Metacognitions about Symptoms Control Scale; OASIS, Overall Anxiety Severity and Impairment Scale; PHQ-9, Patient Health Questionnaire 9-item scale; UP, Unified Protocol for the Transdiagnostic Treatment of Emotional Disorders. $p < 0.05$.

TABLE 4 | Change in health behaviors and adherence for patients randomized to UP.

		Control (<i>N</i> = 10)		UP (<i>N</i> = 9)		<i>P</i>
		<i>M</i> (SD)	Δ (SD)	Pre <i>M</i> (SD)	Δ (SD)	
Physical activity, minutes	Pre	16.00 (13.42)	–	15.71 (9.25)	–	0.15
	Post	35.00 (17.00)	19.00 (7.64)	43.33 (12.38)	27.62 (5.72)	
	6 month	43.00 (19.33)	27.00 (11.78)	53.00 (15.56)	37.29 (9.87)	
Alcohol use (AUDIT-C)	Pre	2.10 (3.25)	–	3.44 (3.58)	–	0.011*
	Post	3.10 (2.64)	1.00 (1.44)	2.11 (2.93)	–1.33 (1.58)	
	6 month	2.60 (1.65)	0.50 (2.17)	1.67 (2.29)	–1.77 (2.22)	
Adherence (MOS-SAS)	Pre	2.61 (1.67)	–	2.78 (1.44)	–	0.35
	Post	2.80 (1.13)	0.19 (0.82)	3.30 (1.21)	0.52 (0.63)	
	6 Month	3.67 (1.46)	1.06 (1.01)	3.44 (1.67)	0.66 (1.00)	

AUDIT-C, Alcohol Use Disorders Identification Test-Shortened Clinical version; MOS-SAS, Medical Outcomes Study Specific Adherence Scale. $p < 0.05$.

health conditions including functional gastrointestinal diseases (30), cancer (31), HIV (32), and headache (33). The UP was particularly effective for emotional disorder and disease-related symptoms across multiple measures in functional gastrointestinal

diseases (30), cancer (31), and HIV populations (32). Not all findings concerning the UP have been supportive, with this type of CBT found to be less effective across multiple outcomes among youth with anxiety disorders and headache (33). Similarly,

in the present study there was no evidence of significant difference by comparison to EUC on depression, adherence, stress, metacognitive worry, physical activity, or adherence. The findings may raise preliminary questions of the suitability of UP to certain health conditions, or alternatively point to the need for refinements in intervention delivery and the results of larger more definitive trials.

One clinical implication of these findings is that the treatment of depressive symptoms and mental QoL in CVD may require a treatment approach other than the UP or in combination with other interventions. A recent Cochrane review (10) showed that both psychotherapy and pharmacological interventions have moderate to large effects on end of treatment depression scores though RCT evidence on the impact upon QoL remains sparse. Emerging data suggests that the sequential delivery of pharmacotherapy in the acute phase of depression and a short-term course of cognitive-behavioral therapy in the residual phase may be a suitable approach (67). Furthermore, the combination of CBT with other therapies such as wellbeing therapy could be optimal to enhance psychological wellbeing and improve quality of life (68, 69).

There is limited use of transdiagnostic interventions in CVD populations however past interventions have utilized collaborative care to treat depression and anxiety symptoms simultaneously in CVDs. For example, the Management of Sadness and Anxiety in Cardiology (MOSAIC) RCT (70) screened patients with the PHQ-9, GAD-7, and a panic-attack questionnaire to enroll participants into a multicomponent collaborative care intervention. Contrasting to the current findings, the MOSAIC trial showed that participants exposed to the intervention displayed significant reductions in depressive but not anxiety symptoms (70). A possible explanation is that the EUC group here were provided with enhanced monitoring at the recommendation of the ethics committee, though large trials have called into question the effectiveness of depression screening in patients with CVD (71). An alternative explanation is that the UP intervention group consisted of patients with GAD, panic disorder, agoraphobia, social anxiety disorder, OCD and PTSD, whereas the MOSAIC trial did not report anxiety disorder prevalence other than for GAD-7 symptom severity and responses to the panic attack screening question.

CBT may lead to improvements in health behaviors and adherence pertinent to CVD. A past CBT intervention combined with motivational interviewing as part of cardiac rehabilitation led to improvements in physical activity, dietary fat intake, medication adherence, and smoking abstinence (72). Here there was only a reduction in harmful alcohol intake, thus paralleling a transdiagnostic CBT intervention for eating disorders that led to reductions in alcohol intake (73). Concomitant reductions in harmful alcohol intake are theorized to relate to the UP's modules covering emotion-driven behaviors, which may include alcohol and illicit drug intake, smoking, and binge-eating behaviors pertinent to cardiovascular health (27). However, we emphasize that there is insufficient data from our trial to support the UP as a means to target binge-eating and smoking.

Participants randomized to UP reported high satisfaction with the psychologist delivered CBT intervention though this

level of satisfaction was comparable to the EUC groups rating of satisfaction with antidepressants. In both cases, satisfaction with UP or antidepressants was higher than general physician counseling for mental health. The qualitative interviews suggested that medical and psychological care was viewed as related to the practitioner's personal characteristics, which included subthemes of competence, efficiency, and personality. Respect for the patient was identified as a subtheme that overlapped across practitioners' personal characteristics and practitioner-patient interactions. However, these themes likely parallel the therapeutic alliance, which is not specific to any particular psychotherapy, whether UP or otherwise.

This study is presented with several strengths including use of a manualized and transdiagnostic CBT intervention, blinded outcome ratings, and use of qualitative interviews to determine acceptability. There are several limitations of this feasibility trial including changes to the study protocol and difficulties recruiting similar to other recent trials in the CVD population (41), which points toward low feasibility for outpatient, face-to-face, and individual therapy. Consequently, a small sample size was obtained, thereby precluding definitive conclusions on UP treatment efficacy in CVD populations. Also, the small sample size precludes stratification of the findings by sex or age. The findings will require replication in adequately powered samples and potentially more homogenous samples such as post-acute coronary syndromes where depression treatment effect sizes are well characterized. The UP intervention is designed for multiple emotional disorders, likely resulting in heterogeneity in study participants' treatment needs that may be less related to the index CVD admission. For example, though depression and anxiety frequently occur in CVD populations, it is perhaps less likely that disorders such as social anxiety disorder would result from a CVD admission. A related limitation is that only 1 patient met criteria for PTSD thus it is unknown if the UP could be extended to PTSD in CVD populations. This is an important limitation to reconcile in future research as there are few RCT interventions for PTSD in CVD populations (74).

Another limitation of this study is that implementation of usual care was not possible, and the EUC design likely resulted in a level of monitoring and treatment greatly exceeding usual depression care (75). The increased intervention in EUC could potentially explain the lack of difference in PHQ-9 scores between UP and EUC groups. This somewhat parallels the findings of the 2 × 2 factorial CREATE trial where interpersonal therapy was not superior over clinical management in terms of depression outcomes (76). Other limitations concern the procedural challenges during the roll-out and intervention phase which included recruitment postponement, as well as staff unavailability and turnover which may have contributed to acceptability, attrition, and contaminate the feasibility of the intervention. Finally, the follow-up was limited to 6 months after the intervention period and longer-term follow-up would be required to examine durability of the intervention and the impact on CVD events and psychiatric readmissions.

In conclusion, our feasibility trial indicates acceptability of transdiagnostic CBT intervention for CVD patients with depression or anxiety disorders. The feasibility trial of UP

intervention suggested superiority over enhanced usual care regarding the total number of disorders, anxiety symptoms, alcohol intake, and improvements in physical QOL. CVD patients with depression and anxiety disorders however may not benefit from UP with regards to depression, mental QOL, adherence, physical activity or hospitalization rates. Satisfaction with UP was comparable to antidepressant therapy and higher than general physician counseling. Future trials of the UP in CVD populations are warranted to confirm if treatment benefits are restricted to anxiety symptoms or might extend to depressive symptoms.

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 Human Research Ethics Committee of the Queen Elizabeth Hospital (Approval #HREC/15/TQEH47). The patients/participants provided their written informed consent to participate in this study.

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PT, DT, JH, JB, BB, SS-Z, HB, and GW: study design. CB and RP: data collection. PT and HB: drafting manuscript. PT, DT, JH, JB, BB, SS-Z, HB, CB, RP, SC, and GW: critical revision of manuscript. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: <https://www.frontiersin.org/articles/10.3389/fpsy.2022.741039/full#supplementary-material>

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Metacognitions in Patients With Frequent Mental Disorders After Diagnosis of Pulmonary Arterial Hypertension

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Background: The prevalence of mental disorders, particularly adjustment disorder (AD), major depressive disorder (MDD) and panic disorder (PD) is increased in patients with pulmonary arterial hypertension (PAH). However, it is unclear which pathogenic mechanisms determine their development and could therefore be targeted in prevention or therapeutic interventions. Here, we assessed metacognitions in a sample of PAH patients with and without MDD and PD. Moreover, we reconstructed the course of mental illnesses following the PAH diagnosis.

Methods: Two hundred seventeen PAH patients were included in this cross-sectional study. The prevalence of AD was assessed retrospectively using DSM-V criteria. Current mental disorders were assessed using the structured clinical interview for DSM-V. Additionally, metacognitive beliefs and processes were assessed using established questionnaires (MCQ-30, AnTI).

Results: Patients with an AD consecutive to the PAH diagnosis more frequently developed MDD (37.5 vs. 13.9%, $p < 0.001$) and PD (26.3 vs. 8.8%, $p = 0.001$) later on compared to PAH patients without a former AD. Moreover, patients with current MDD/PD displayed more dysfunctional metacognitions than those without current MDD/PD ($p < 0.001$). Patients with current MDD/PD in the context of former AD had more dysfunctional metacognitive worries and beliefs compared to patients with current MDD/PD without former AD ($p = 0.009$).

Conclusion: Our results suggest that in the context of PAH, dysfunctional metacognitions are associated with MDD and PD. Therefore, a metacognitive approach to treat and prevent those mental illnesses seems promising and should be investigated in future studies.

Keywords: pulmonary arterial hypertension (PAH), pulmonary hypertension, adjustment disorder, depressive disorder, panic disorder, metacognitions, psychocardiology

INTRODUCTION

Pulmonary arterial hypertension (PAH) is a rare cardiopulmonary disease characterized by increased pressure in the pulmonary arteries and increased pulmonary vascular resistance (1). Clinically, it often manifests as impaired physical capability due to dyspnea at exertion, fatigue, weakness as well as angina, syncope, and edema (1). Although there have been tremendous advances in therapy in the past years which have led to improved survival rates and disease control, PAH remains progressive, to date incurable and may lead to right heart failure and death (2, 3).

The impact of PAH extends beyond impaired physical capabilities. Research shows that PAH is associated with limitations regarding work and employment, finances, relationships, and emotional wellbeing (4). For many patients, the emotional distress caused by the disease and its associated limitations persists and mental illness arises. Previous studies showed that over one third of PAH patients develop symptoms of mental disorders (5–8). Olsson et al. (9) systematically investigated the prevalence of mental disorders in PAH patients with structured face-to-face interviews and found that current or past adjustment disorder (AD), current major depressive disorder (MDD) and panic disorder (PD) were the most prominent illnesses. Little research focused on the actual psychological mechanisms that lead to the increased risk of developing a mental disorders being a PAH patient. The current ESC/ERS guidelines for pulmonary hypertension take the psychological impact and prevalence of mental disorders into account and include a recommendation for psychosocial support (1). In daily clinical practice, however, only a small amount of patients receive adequate psychological treatment (5, 6). To gain an understanding of mental disorders in the context of PAH and to develop an evidence-based and tailored treatment, the underlying mechanisms of the development and maintenance of mental disorders have to be investigated.

One approach to transdiagnostically address mental illnesses, also in the context of severe physical illnesses, is the metacognitive theory by Wells (10), which is based on the Self-Regulatory Executive Function model (S-REF) (11). Metacognitive theory postulates that metacognitions, i.e., the cognitive processes that are involved in interpreting, monitoring and controlling ones' cognition, play a decisive role in the development and maintenance of mental disorders (12). The Cognitive Attentional Syndrome (CAS), which is characterized by inflexible attention, worry and rumination, threat monitoring and dysfunctional coping, leads to the inability to process normal emotional distress and results in its maintenance (10). So-called metacognitive beliefs, i.e., beliefs about cognitive processes, are assumed to have an important impact on the individual thinking styles (11). The beliefs can be separated into five different domains: 1) Positive beliefs about worry, 2) negative beliefs about worry, 3) beliefs about cognitive competence, 4) beliefs about the need to control thoughts, and 5) cognitive self-consciousness (13–15).

A number of studies examined the role of metacognitions in psychopathology: Metacognitions are associated with major

depressive disorder, generalized anxiety disorder, obsessive-compulsive disorder (16), shyness and social anxiety (17, 18), eating disorders (19), psychosis (20), PTSD (21), addictive behaviors (22), and also risk factors for psychopathology, for example adverse childhood experiences (23). Research indicates that the degree of metacognitions differs depending on the course of the mental disorder. For example, Halvorsen et al. (24) found that there are higher levels of metacognitions in currently depressed patients than in formerly or never depressed patients. Research regarding the temporal sequence also showed that metacognitions predict later psychiatric symptoms, for example of depression and anxiety (25–27). Regarding somatic illnesses, two recent systematic reviews have shown that dysfunctional metacognitions are associated with psychiatric symptoms and poor life quality in patients with chronic physical illnesses (27, 28). Most studies investigating metacognitions in physical illnesses appear to focus on cancer and neurological disorders. Winter et al. (29) performed a case study using a metacognitive approach for AD in a PAH patient, which supports the assumed role of metacognitions in PAH patients as well: After a short treatment targeting dysfunctional metacognitions the psychiatric disorder was in remission. To our knowledge, no study has systematically assessed metacognitions and their associations with mental illnesses in patients with cardiopulmonary disorders. Based on the research on metacognitions in mental disorders in general and specifically in chronic physical illnesses, it seems plausible that metacognitions play a role in psychiatric symptoms in patients with PAH as well.

The aim of this study is to explore the underlying mechanisms of mental disorders in patients with PAH in a theory-driven manner. We aim to assess metacognitions in PAH patients and investigate whether there is a difference in metacognitions in patients who do not develop one of the most common mental disorders after the PAH diagnosis and those who do. Additionally, we are interested in reconstructing the course of mental disorders after the diagnosis and in the metacognitions associated with it.

METHODS

Participants and Procedure

Patients were recruited from two German pulmonary hypertension referral centers (Hannover Medical School and University of Gießen and Marburg). The local institutional review boards of the participating universities approved all study procedures (Nr. 8540_BO_K_2019 for Hannover and Nr. 21119 for Gießen and Marburg). Inclusion criteria were: 1. confirmed diagnosis of PAH (1), 2. minimum age of 18 years and 3. ability to complete the questionnaires and the clinical interview in German. Patients meeting the inclusion criteria were either identified from a database and invited to participate via mail or recruited during their ambulatory visits. After providing informed written consent, patients completed a set of questionnaires and the structured clinical interview for DSM-V. We contacted 327 patients, 217 of them fulfilled the inclusion criteria and completed the questionnaires and the clinical interview. The final study

group consisted of 155 females (71%), with an average age of 55 ± 14.58 years.

Measures

Metacognitions Questionnaire-30

The MCQ-30 (13) is a self-report scale that measures beliefs about worry, monitoring tendencies and thinking itself. As the short-form of the MCQ (14), the five-factor structure of the original form was confirmed for the MCQ-30 as well. The resulting subscales are positive worry beliefs, beliefs about uncontrollability and danger of thoughts, beliefs about cognitive competence, beliefs about need to control thoughts, and cognitive self-consciousness. The 30 items are answered on a 4-point Likert scale from 1 (“do not agree”) to 4 (“agree very much”). The instrument has good internal consistency, convergent and construct validity and acceptable to good test-retest reliability (13).

Anxious Thoughts Inventory

The AnTI is a multidimensional self-report measure of worry (30). It consists of three subscales: social worry, health worry and meta-worry (worry about worry), which are factorially reliable. The 22 items are rated using a 4-point Likert scale from 1 (“almost never”) to 4 (“almost always”). The instrument has good psychometric properties (alpha coefficients of the subscales range between 0.75 and 0.84, 6-week test-retest reliability shows correlations between 0.76 and 0.84) (30).

Structured Clinical Interview for DSM-V

The SCID-V was used to examine currently present mental illnesses according to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) (31). Diagnoses during the last 4 weeks were evaluated. Additionally, patients were asked whether their current symptoms were independent from, worsened or caused by the PAH diagnosis. The SCID-V was also used for a retrospective appraisal to assess the prevalence of adjustment disorders within 3 months after the PAH diagnosis.

Statistical Analysis

IBM SPSS Statistics 26.0 (IBM Corp, Armonk, NY, USA) was used for data analysis. Prevalence of current mental disorders in patients with and without former AD following PAH diagnosis were compared using Chi²-tests. To examine the prevalence of dysfunctional metacognitions in individuals with or without MDD/PD diagnosis, multivariate analyses were performed with questionnaire scores as dependent variables and current psychiatric diagnosis (MDD and PD) as well as former AD as independent variables. To determine specific group differences, *post-hoc* tests with Bonferroni correction were used. Patients who reported that their current mental illness was not connected to the somatic diagnosis were excluded. *P*-values below 0.05 were considered statistically significant.

RESULTS

Descriptive Statistics

Subject characteristics are shown in Table 1.

TABLE 1 | Participant characteristics.

	Study sample (<i>n</i> = 217)
Age (years)	55 (± 14.58)
Female sex (%)	155 (71%)
Time since PAH diagnosis (years)	8.11 (± 7.08)
Current MDD	50 (23.0%)
MDD caused or worsened by PAH diagnosis ^a	49 (22.6%)
Current PD	33 (15.2%)
PD caused or worsened by PAH diagnosis ^a	33 (15.2%)
AD following PAH diagnosis	80 (36.9%)
Current psychotherapy	22 (10.1%)
Current psychopharmacological treatment	25 (11.5%)

Continuous variables are reported as mean and SD, categorical variables as *n* and percent.

^aReported by patients.

Prevalence of MDD and PD Considering Former AD

Patients who reported an AD following the diagnosis of PAH showed significantly higher rates of current MDD, compared to patients without AD after diagnosis of PAH [$\chi^2_{(1)} = 16.13$, $p < 0.001$, $\phi = 0.24$]. PD also was more prevalent in patients with former AD following PAH compared to those without former AD [$\chi^2_{(1)} = 11.93$, $p = 0.001$, $\phi = 0.27$]. See Table 2 for full data.

Metacognitions

To examine dysfunctional metacognitions, a MANOVA with AnTI and MCQ-30 scores as dependent variables and current MDD/PD and former AD as independent variables was performed.

There was a significant multivariate main effect of current MDD/PD on the combined dependent variables [Wilks's $\Lambda = 0.68$, $F_{(8,206)} = 11.88$, $p < 0.001$, partial $\eta^2 = 0.32$]. The multivariate main effect of former AD on the combined dependent variables was not significant [Wilks's $\Lambda = 0.94$, $F_{(8,206)} = 1.78$, $p = 0.079$, partial $\eta^2 = 0.07$]. The multivariate interaction effect remained significant [Wilks's $\Lambda = 0.91$, $F_{(8,206)} = 2.71$, $p = 0.07$, partial $\eta^2 = 0.10$].

Univariate analyses revealed a significant main effect showing that patients with current MDD/PD displayed more dysfunctional metacognitions than currently mentally healthy individuals for both sum scores of the questionnaires [AnTI: $F_{(1,213)} = 84.03$, $p < 0.001$, partial $\eta^2 = 0.28$; MCQ-30: $F_{(1,213)} = 44.71$, $p < 0.001$, partial $\eta^2 = 0.17$], see Figure 1. Following univariate analyses of the subscales of both questionnaires showed that patients with current MDD/PD reported higher levels of metacognitions than those without current MDD/PD regarding all subscales of the AnTI and the MCQ-30. Albeit, effect sizes of the respective subscales differed in magnitude. For Details, see Table 3.

For the AnTI, there was a significant main effect showing that patients with former AD displayed more dysfunctional metacognitions than those without former AD [$F_{(1,213)} = 9.66$, $p = 0.002$, partial $\eta^2 = 0.04$]. For the MCQ-30, this main effect was

TABLE 2 | Prevalence of MDD and PD in patients with and without former AD.

	AD after PAH diagnosis (n = 80)		no AD after PAH diagnosis (n = 137)		p-value	ϕ
	n	%	n	%		
Current MDD	30	37.5	19	13.9	<0.001	0.24
Current PD	21	26.3	12	8.8	0.001	0.27

AD, adjustment disorder; MDD, major depressive disorder; PD, panic disorder. The p-values and the effect size ϕ of the χ^2 -test are reported.

not significant [$F_{(1,213)} = 2.50$, $p = 0.115$, partial $\eta^2 = 0.01$]. For the AnTI, there was a significant effect regarding the interaction of current MDD/PD and former AD [$F_{(1,213)} = 6.99$, $p = 0.009$, partial $\eta^2 = 0.03$]. For the MCQ-30, this interaction effect was not significant [$F_{(1,213)} = 1.16$, $p = 0.282$, partial $\eta^2 = 0.01$]. A *post-hoc* t-test with Bonferroni correction was performed. The *post-hoc* test remained significant [$t_{(60)} = -3.25$, $p = 0.002$], showing that patients with current MDD/PD and former AD ($M = 49.78$, $SD = 9.85$) had more dysfunctional metacognitions than patients with current MDD/PD without former AD ($M = 42.12$, $SD = 7.88$).

DISCUSSION

The current study revealed an association between an AD after the diagnosis of PAH and consecutive mood and anxiety disorders. Elevated levels of dysfunctional metacognitions were shown amongst PAH patients with mental disorders, varying depending on the course of the mental disorder.

Patients who suffered from AD after the somatic diagnosis frequently developed MDD and PD. This finding is consistent with research regarding the long-term prognosis of AD, which considers AD as a gateway to a severe psychiatric illness (32). This provides further insights into the psychological process that may be induced by living with PAH. It also stresses the importance of early screening for possible psychological distress after the somatic diagnosis. A screening could be done via a short questionnaire issued by the attending physician, after an acute somatic event or the diagnosis itself. As a screening tool, the Hospital Anxiety and Depression Scale could be used, which's utility was shown for PAH patients (9). Olsson et al. (9) also suggested developing a specific questionnaire for the symptoms of AD. An affirmative screening would path the way to more in depth diagnostics and enable a timely multidisciplinary approach including psychological treatment.

Patients with current MDD/PD reported more dysfunctional metacognitions than those without current mental health issues. This result adds to the current state of knowledge regarding metacognitions in patients with somatic disorders (27, 28), demonstrating that they are also associated with mental disorders in the context of PAH. Findings show a heightened rate of dysfunctional metacognitions in general, however, some facets appear more salient. Especially all three facets of the AnTI (social, health and meta-worry) and beliefs about the uncontrollability and danger of thoughts are most prominent in PAH patients with current MDD/PD. Additionally, findings suggest that

metacognitions vary across the course of mental disorders. This is shown by the different amount of metacognitions in currently mentally ill patients depending on a former AD. Possibly, dysfunctional metacognitions are a pathogenic mechanism for the risk AD states for the development of a later MDD/PD: If a person develops an AD and the correlating metacognitions, these metacognitions might persist and even increase over time, leading to a higher chance of a MDD or PD with a high amount of dysfunctional metacognitions. A longitudinal study assessing metacognitions and their development over the course of these mental disorders is needed to investigate this assumption. Furthermore, the severity of the later on developed mental disorder should be assessed to see whether the former AD and more metacognitions lead to a higher symptom load. Contrary to our expectations, a higher level of metacognitions in MDD/PD patients with former AD compared to those without former AD only appeared in the AnTI, not in the MCQ-30. Both questionnaires are self-report measures assessing metacognitions. The MCQ-30 covers a broader spectrum of metacognitive processes and beliefs (13) while the AnTI focuses on different dimensions of worries (30). A possible reason for the discrepancy described above might be that the target group consisted of patients with a severe somatic illness with a bad prognosis. It seems plausible that in this specific group, especially in those who struggle with adjusting to the diagnosis, continuous health worries are most prominent. As the AnTI focuses more on worries about physical health than the MCQ-30, this stronger representation could be an explanation for the difference.

The findings have clinical implications: To prevent or treat the investigated mental disorders in the context of PAH, targeting dysfunctional metacognitive beliefs and processes seems promising. In metacognitive therapy (MCT) (12), techniques like attention training and detached mindfulness are used to modify metacognitions, establish a more flexible thinking style and thus reduce psychological distress. The effectiveness of MCT has been shown, especially for anxiety and depression (33). The current findings also contribute to the preliminary evidence that targeting dysfunctional metacognitions through MCT seems promising in this specific patient group in the context of PAH (29).

Our study has limitations: The cross-sectional design does not allow causal interpretation and limits conclusions about the course of the psychiatric illnesses and the underlying mechanisms. We decided to include the diagnosis of adjustment disorder in our study, however, there is an ongoing controversy regarding its validity. The retrograde assessment of AD bears

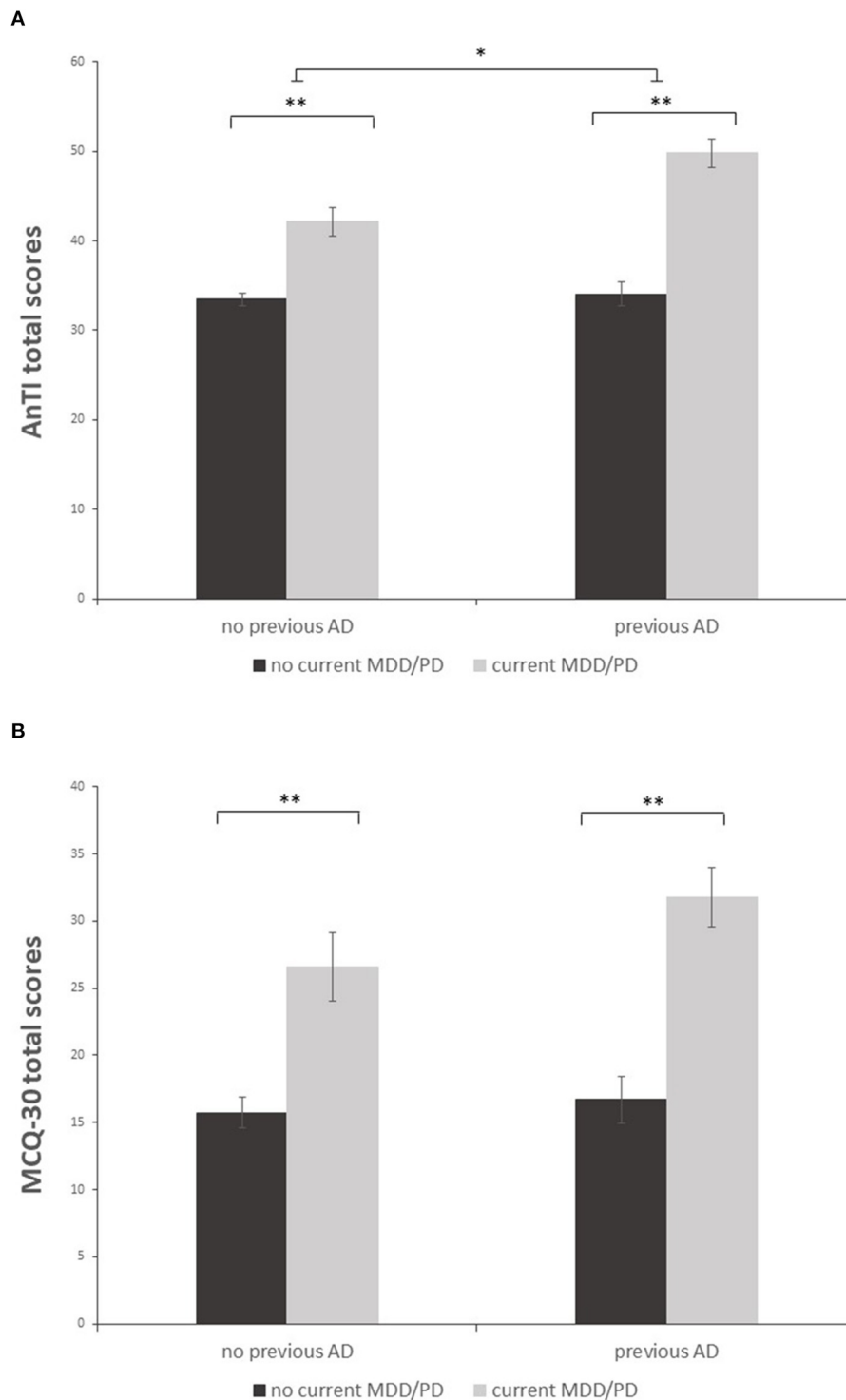


FIGURE 1 | Mean sum scores of the AnTI (A) and MCQ-30 (B) in patients with and without both previous AD and current MDD/PD. Depicted are two significant main effects for the factors current MDD/PD and previous AD (A) and one significant main effect for the factor current MDD/PD (B). Error bar indicate ± 1 standard error of the mean. ** $p < 0.001$; * $p < 0.01$.

a risk of recall bias. A longitudinal study should be conducted to examine the assumed positive correlation between severity of psychiatric symptoms and of metacognitions.

Future studies will have to continue to explore the proposed assumption that in the PAH patient group health worries might be more prominent than other

TABLE 3 | Mean scores of the AnTI and MCQ-30 and their subscales in patients with and without current MDD/PD.

	No current MDD/PD, M (SD)	Current MDD/PD, M (SD)	F(df 1, 213)	p	Partial η^2
AnTI sum score	33.60 (8.17)	46.69 (9.80)	84.03	<0.001	0.28
AnTI: social worry	13.16 (3.47)	18.50 (5.19)	62.27	<0.001	0.23
AnTI: health worry	10.28 (2.74)	13.53 (3.81)	41.00	<0.001	0.16
AnTI: meta-worry	10.16 (3.20)	14.66 (3.91)	62.81	<0.001	0.23
MCQ-30 sum score	15.99 (11.93)	29.68 (13.32)	44.71	<0.001	0.17
MCQ-30: positive worry beliefs	2.38 (2.73)	4.69 (3.40)	22.04	<0.001	0.09
MCQ-30: beliefs about uncontrollability and danger of thoughts	2.95 (3.20)	7.55 (3.84)	67.58	<0.001	0.24
MCQ-30: beliefs about cognitive competence	2.85 (3.01)	4.29 (3.94)	6.01	0.015	0.02
MCQ-30: beliefs about need to control thoughts	3.48 (3.16)	5.63 (3.50)	17.68	<0.001	0.08
MCQ-30: cognitive self-consciousness	4.34 (3.37)	7.52 (3.41)	32.80	<0.001	0.13

AnTI, Anxious Thoughts Inventory; MCQ-30, Metacognitions Questionnaire-30; MDD, major depressive disorder; PD, panic disorder. Mean and standard deviation of the questionnaire scores and subscores, F-statistics, degrees of freedom, p-values and effect size partial η^2 are reported.

metacognitions. Furthermore, it is necessary to address the role of metacognitions and their variation across the course of the mental disorders in more detail. The development of a tailored treatment based on the findings regarding metacognitions could be promising. That treatment could address the persevering health worry and other prominent metacognitions by using the MCT.

In conclusion, metacognitions are associated with MDD and PD in patients with PAH. That opens up potential for psychological support based on MCT: After a PAH diagnosis, a preventive metacognitive approach could be used to avoid the development of AD and later on MDD/PD and metacognitive therapeutic approaches could be used to treat AD, MDD and PD.

DATA AVAILABILITY STATEMENT

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

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ETHICS STATEMENT

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

AUTHOR CONTRIBUTIONS

FC and PG were responsible for statistical analysis, data interpretation, and drafting the manuscript. MH was responsible for study design and implementation of the study. KO and HG was responsible for study design, implementation of the study, and data collection. JF and HAG were responsible for implementation of the study and data collection. TM was responsible for study design, implementation of the study, data collection, and conducting the interviews. JK and MR were responsible for implementation of the study. IH was responsible for study design, statistical analysis, and data interpretation. KK was responsible for study design, implementation of the study, statistical analysis, and data interpretation. All authors contributed to the article, revised the manuscript and approved the submitted version.

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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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Measurement of Noradrenaline and Serotonin Metabolites With Internal Jugular Vein Sampling: An Indicator of Brain Monoamine Turnover in Depressive Illness and Panic Disorder

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In research spanning three decades we have estimated brain monoamine turnover (approximately equating with synthesis rate) with sampling from the internal jugular veins and measurement of trans-cerebral plasma monoamine metabolite concentration gradients. Here we report indices of brain noradrenaline and serotonin turnover in patients with major depressive illness (MDD) and panic disorder (PD). Brain noradrenaline turnover was assessed from the combined flux into the internal jugular veins of the metabolites dihydroxyphenylglycol (DHPG) and 3-hydroxy-4-methoxyphenylglycol (MHPG), and brain serotonin turnover from the overflow of the primary metabolite, 5-hydroxyindole acetic acid (5HIAA). Comparison was made with matched healthy research participants. In both MD and PD the estimate of brain noradrenaline turnover provided by metabolite overflow was unremarkable. In contrast, in both patient groups the estimate of brain serotonin turnover provided by 5HIAA overflow was increased 3–4-fold ($P < 0.01$). This neurotransmitter abnormality was normalized in MDD and PD in clinical remission, during selective serotonin reuptake blocker (SSRI) dosing. We cannot be sure if the brain serotonergic abnormality we find in MDD and PD is causal or a correlate. Measurements in PD were not made during a panic attack. The increased estimated serotonin turnover here may possibly be a substrate for panic attacks; serotonergic raphe nuclei participate in anxiety responses in experimental animals. It is puzzling that the findings were identical in MDD and PD, although it may be pertinent that these psychiatric diagnoses are commonly comorbid. It is unlikely that activation of brain serotonergic neurons is driving the sympathetic nervous activation present, which contributes to cardiovascular risk, persistent sympathetic activation in MDD and episodic activation in PD during panic attacks. We have previously demonstrated that the mechanism of activation of human central sympathetic outflow in other contexts (hypertension, heart failure) is activation of noradrenergic brainstem neurons projecting to the hypothalamus and amygdala.

Keywords: brain serotonin turnover, brain noradrenaline turnover, sympathetic nervous system, cerebral venous sinuses, panic disorder, depressive illness

INTRODUCTION

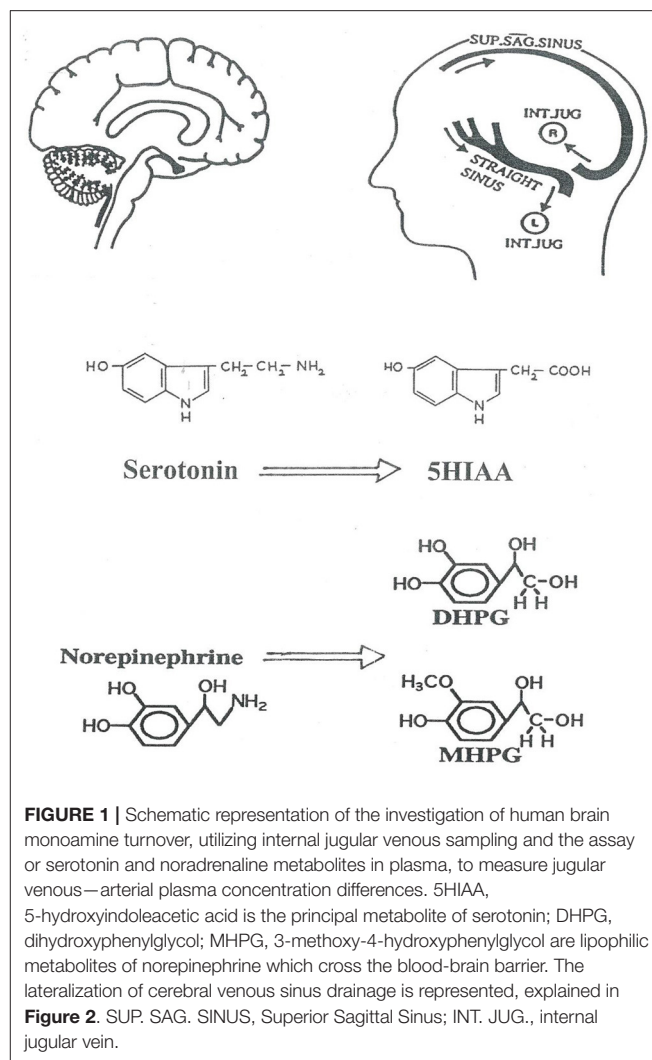
The brain neurotransmitter changes characterizing psychiatric disorders are uncertain. Reserpine, a now almost obsolete antihypertensive drug, which depletes the brain of noradrenaline, quite commonly caused depressive illness, observations which Schildkraut drew on in the formulation of his historic noradrenaline deficiency hypothesis of depression causation (1). More recently, it has been a common practice to infer brain neurochemical mechanisms of psychiatric illness from the known pharmacological actions of efficacious psychotropic drugs. Tricyclic antidepressant drugs are neuronal noradrenaline reuptake-blockers. The efficacy of this drug class has sometimes been taken to directly derive from augmentation of CNS noradrenaline neurotransmission, by transmitter uptake blockade correcting the deficiency hypothesized by Schildkraut (1). Analogous thinking saw the clinical benefit of selective serotonin reuptake blocking drugs in depressive illness and panic disorder attributed to a correction of an existing “serotonin neurotransmission deficiency” (2). This line of thinking although provocative is imprecise. There is a need to evaluate noradrenergic and serotonergic neuronal systems directly in the human brain in depressive illness and panic disorder. This, however, has proven difficult. More commonly, monoamine chemistry has been studied outside the brain, as a surrogate for CNS neurochemistry.

INVESTIGATION OF MONOAMINE CHEMISTRY OUTSIDE THE BRAIN AS A SURROGATE FOR CNS NORADRENALINE AND SEROTONIN NEUROCHEMISTRY

It turns out that this widely adopted approach is rather dubious. Peripheral monoamine chemistry casts a pale shadow of brain neurochemistry. The brain is the source of <10% of the major serotonin metabolite, 5-hydroxyindole acetic acid (5-HIAA) found in plasma and urine (3) rendering systemic plasma measurements and urine collections unsuitable for studying brain serotonin release. Further, serotonin sampled in plasma mainly originates from platelets activated in the blood sampling process. With lumbar CSF, the serotonin is derived more from the terminals of descending serotonergic neuronal projections to the spinal cord than from the brain (4). For a time, measurement of the deaminated methylated metabolite of noradrenaline, MHPG, in plasma and urine was proposed and widely used as an index of brain noradrenaline turnover. This was not valid. Our subsequent investigation of regional inputs of MHPG to the plasma pool demonstrated that no more than 10% was derived from the brain, the primary source being noradrenaline contained in and released from sympathetic nerves (5).

ASSESSING BRAIN MONOAMINE TURNOVER USING INTERNAL JUGULAR VEIN SAMPLING

The Human Neurotransmitters Research Laboratory of the Baker Institute in Melbourne, following the lead of James Maas



working with non-human primates (6) developed techniques for assessing brain monoamine turnover in human illness based on jugular venous sampling of monoamine metabolites (7–10). CNS monoamine turnover approximately equates with monoamine synthesis rates. This is certainly not a direct measure of neurotransmitter release (11). The predominant determinant of turnover is cytosolic metabolism of monoamines released from stored vesicles (11). Neurotransmitter release, however, does contribute to monoamine turnover. We use brain monoamine metabolite overflow as a semiquantitative index of neurotransmitter release. As applied here in the assessment of brain noradrenaline and serotonin turnover in MDD and PD (**Figure 1**), the technique involves measuring the overflow of metabolites of noradrenaline (MHPG, 3-methoxy-4-hydroxyphenylglycol; DHPG dihydroxyphenylglycol) and serotonin (5-hydroxyindoleacetic acid) into the internal jugular veins (3, 4, 8–10). Simultaneous arterial and jugular venous blood samples are obtained. Brain noradrenaline and serotonin turnover can be assessed, using the Fick principle, from venous-arterial plasma concentration differences and thermodilution measurements of internal jugular blood or plasma flows (8–10).

For applying the Fick principle the preferred flow measurement differs for individual metabolites (3, 4).

Existing asymmetry in human cerebral venous drainage (**Figure 2**) can be drawn on to study the regional CNS origins of monoamine metabolites (8, 12). The right internal jugular vein typically has the superior sagittal sinus as its major tributary, and accordingly drains the cerebral cortex (**Figure 2**). In contrast, the left internal jugular vein typically is a continuation of the straight sinus and drains suprabulbar, subcortical brain regions (8, 12). This lateralized pattern of flow is occasionally reversed. Performing a Technetium 99 single photon emission computed tomographic (SPECT) scan of the brain venous sinuses (8, 10) allows identification of the drainage pattern (**Figure 2**). Further, venous scanning demonstrates that typically, although not invariably the two drainage pathways are distinct, with little or no blood admixture at the confluence of the sinuses (**Figure 2**) (8, 10).

The hypothesis tested was that brain neuronal noradrenergic and serotonergic activity is low in untreated patients with MDD and PD. Here we report our findings in two clinical data sets, in untreated patients with major depressive disorder (MDD)

and panic disorder (PD). These patient groups were selected to minimize comorbidity, and described separately previously (10, 13). Because of the remarkable and unexpected similarities in the findings in both disorders they are analyzed together in this manuscript.

METHODS

Brain monoamine metabolite overflow in major depressive disorder, and in panic disorder was studied with arterial and internal jugular venous blood sampling as previously reported (3, 4, 8, 10, 13) and described above. High internal jugular venous sampling was used, with the catheter tip placed beyond the angle of the jaw to exclude sampling from the venous drainage of the face. The central venous catheter, a 7F coronary sinus thermodilution catheter (Webster laboratories, type CCS-7U-90B) introduced *via* an antecubital venous sheath, was percutaneously inserted under local anesthesia, and placed with fluoroscopic control high in one internal jugular vein, or both if this could be achieved without difficulty. Measurement of internal jugular blood flow by thermodilution using the Webster

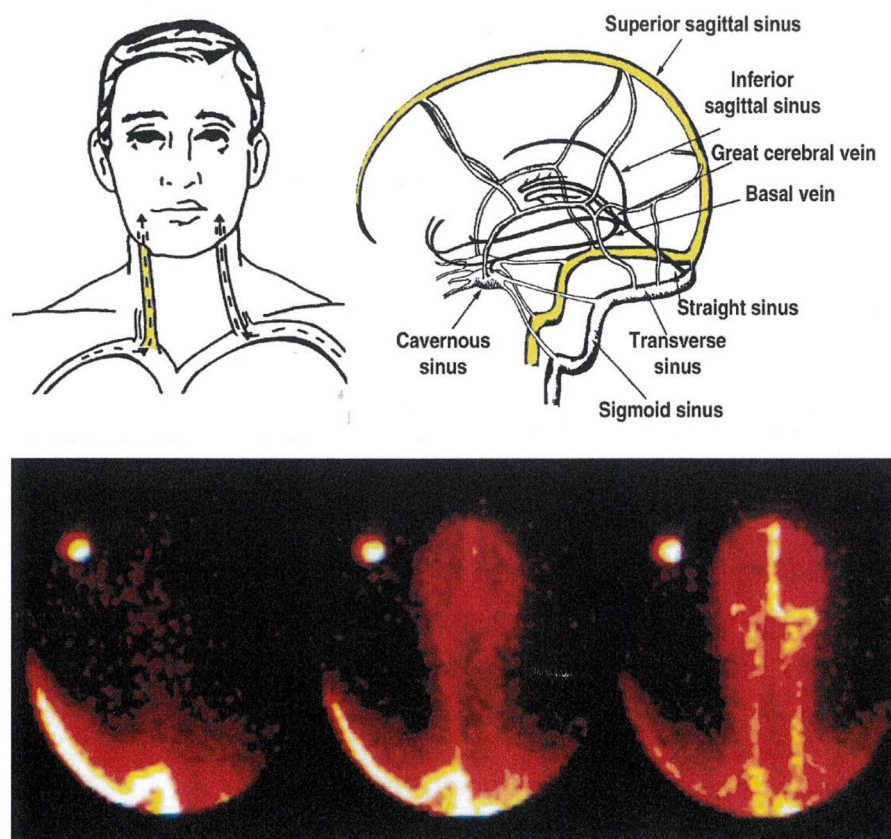


FIGURE 2 | The cerebral venous sinuses of the brain. The lower panel is of a Technetium-99 scan of the sinuses, recorded from behind. In this patient, the sagittal sinus drains to the right, into the transverse sinus and the right internal jugular vein. The straight sinus, with flow from the hypothalamus and amygdala in particular, drains into the left internal jugular vein. This is the commonest anatomical pattern, but is reversed in some people. Knowledge of the pattern of brain venous drainage in individual patients, with bilateral internal jugular vein sampling, allows selective quantification of monoamine turnover in cortical, and in suprabulbar subcortical brain regions. The brainstem drains into the spinal veins.

TABLE 1 | Brain 5HIAA overflow in panic disorder.

	Panic disorder	Healthy subjects
Age	43.2 (2)	44 (1)
BMI	23.7 (0.7)	23.4 (0.6)
Bright Sunlight (hours/day)	5.7 (0.8)	5.0 (0.9)
Jugular vein blood flow (bilateral - ml/min)	994 (70)	868 (64)
Arterial plasma 5-HIAA conc. (pmol/ml)	32.7 (1.3)	40.8 (4.2)
Jugular vein plasma 5-HIAA conc. (pmol/ml)	35.9 (1.4)	41.5 (4.2)
Brain 5-HIAA overflow (pmol/min)	1,815 (223)**	361 (73)

Listed jugular blood flow represents the sum of bilateral measurements, or doubled unilateral measurement when only this is available. Bright sunlight hours on the study day was provided by the Melbourne Bureau of Meteorology (15). ** $P < 0.01$ (Mann Whitney rank sum test).

Means and standard errors are listed.

BMI, body mass index; 5-HIAA, 5-hydroxyindoleacetic acid.

catheter (8, 10) was performed in the panic disorder patients. In MDD patients, jugular flow measurements could not be done, as just prior to the commencement of the study the Webster catheter became unavailable. Arteriovenous blood and plasma concentration differences of the metabolites across the brain, without flow measurements, were used.

Panic Disorder

Thirty-four patients meeting DSM IV (14) diagnostic criteria for panic disorder, who were either never treated or had received no medication in the preceding 3 months, and 24 healthy volunteers participated. The PD patients and healthy participants were of similar age (Table 1). Clinical evaluation was independently performed by a clinical psychologist and psychiatrist participating in the study. After initial screening, a structured clinical interview based on DSM-IV was used to make a clinical diagnosis of panic disorder (14). Patient selection attempted to minimize psychiatric comorbidity. Fourteen panic disorder patients had a secondary diagnosis of depression. Assessment of overall panic disorder severity was obtained using the patient self-rating Panic Disorder Severity Scale (PDSS) (16) and with a clinician-applied scale, ADIS-IV (17).

Major Depressive Disorder

Twenty-one patients fulfilling DSM IV diagnostic criteria for major depressive disorder and 40 healthy volunteers participated. Patients were either newly diagnosed or currently untreated after relapse and had not been receiving antidepressant medication for at least 4 weeks prior to the study. The MDD patients and healthy participants were of similar age (Table 2). After initial screening, patients were interviewed by a psychiatrist using a structured clinical interview, the Mini International Neuropsychiatric Interview (MINI) (18). The 17-item Hamilton Depression Scale (HAM-D) (19), Spielberger's State and Trait Anxiety Inventories (20, 21), and the Beck Depression Inventory

TABLE 2 | Estimated brain 5HIAA overflow in depressive illness.

	Depressive illness	Healthy subjects
Age	45 (1)	41 (1)
BMI	25 (1)	24 (1)
Bright Sunlight (hours/day)	6.6 (0.8)	6.0 (0.9)
Arterial plasma 5-HIAA conc. (pmol/ml)	46 (5)	42 (4)
Arterial - Jug. vein plasma 5-HIAA conc. difference (pmol/ml)	4.4 (0.9)**	1.6 (0.5)

Listed bright sunlight hours on the study day was provided by the Melbourne Bureau of Meteorology (15). ** $P < 0.01$ (Mann Whitney rank sum test).

Means and standard errors are listed.

BMI, body mass index; 5-HIAA, 5-hydroxyindoleacetic acid.

(BDI) (22) were used to assess severity. Patients had HAM-D and BDI scores of 18 or higher, and were assessed as having MDD as the primary illness at Psychiatric interview. Patient selection attempted to minimize recruitment of patients with psychiatric comorbidity. Those assessed to have high suicide risk were excluded. The initial research studies were performed within 10 days of confirmed diagnosis of MDD.

Avoidance of Potential Confounding by Season, Sunlight and Adiposity

Brain serotonin releasing neurons subserve diverse, although incompletely understood functions related to feeding and adiposity (23) and to light stimulation (24). We have previously demonstrated an influence of these on brain 5HIAA overflow in humans (15, 25). By appropriate selection and matching of healthy reference populations, with matching of healthy subjects and patients in terms of body mass index and sunlight hours on the study day, we were able to avoid a confounding effect of serotonergic neuronal systems activated by sunlight and in obesity. Mean body mass index was 24–26 kg/m² for the four study groups. With the assistance of the Melbourne Bureau of Meteorology (25) the two healthy volunteer groups were chosen from a large pool of subjects studied by the laboratory such as to achieve matching for sunlight hours on the day of the catheter sampling study, with mean sunlight hours being 5–6 h for the four participant groups (12, 13).

Selective Serotonin Reuptake Inhibitor Dosing

In both patient groups, after the initial investigational study, testing was performed for an influence of SSRI dosing on brain 5HIAA generation. This was done open-label in 11 patients with PD, using citalopram at a dose of 20–60 mg daily, given for a minimum of 3 months, followed by a repeat investigational study. Dosage was determined by clinical response. Similarly, 11 patients with MDD were treated with differing SSRIs, the choice of drug being made on clinical grounds, for ~12 weeks, followed by the second investigational study. The patients with MDD were followed weekly for the purposes of the study, or more frequently if required on clinical grounds.

Monoamine Plasma Assays, Brain Monoamine Turnover Estimation

Jugular-arterial venous-arterial plasma concentration differences of MHPG, DHPG and 5-HIAA were measured, with sampling from an internal jugular catheter and from an indwelling radial or brachial artery cannula. In patients with MDD and the matching reference population of healthy volunteers only the transcerebral metabolite plasma concentration differences were available. In patients with PD and matched healthy participants brain noradrenaline and serotonin turnover were assessed using the Fick principle, from the venous-arterial plasma concentration differences and from internal jugular flows, measured by thermodilution (3, 4, 10, 13). Because of differing equilibration of monoamine metabolites between blood and plasma (fast for MHPG and DHPG, slow for 5-HIAA), the turnover calculation used blood flow for MHPG and DHPG, and plasma flow for 5-HIAA (3, 5). Measurements were made at quiet rest, and in the absence of a panic attack in PD patients. Assay of DHPG, MHPG and 5-HIAA was by high performance liquid chromatography, using previously described methods (3, 4).

Statistics

All results, unless otherwise specified, are expressed as mean (standard error of mean). Tests of significance were carried out using ANOVA, paired *t*-tests or distribution-free non-parametric tests where appropriate. The possible relation between variables was evaluated using least squares linear regression analysis. All statistical tests were two-tailed and statistical significance was set at a probability level of 0.05.

Research Ethics

The research procedure was performed by cardiologists who are expert in the technique. The process of written consent, to which an honest, open and explicit participant information sheet was central, conformed to the standards expected to preserve the autonomy of the participants. The research was approved by the Alfred Hospital Medical Research Ethics Committee.

RESULTS

Brain 5HIAA overflow in humans is higher with overweight (15), and with longer periods of intense sunlight exposure (25). For both the PD and MDD patient cohorts, good matching for these variables was achieved with the two comparator groups of healthy participants, to avoid potential confounding (Tables 1, 2) (10, 13).

Panic Disorder

In panic disorder patients the brain noradrenaline turnover biomarker, internal jugular venous overflow of MHPG plus DHPG, was 1,454 pmol/min, SEM 142, similar to that in healthy participants, 1,336 pmol/min, SEM 77. These values were calculated with bilateral jugular venous sampling, or from doubling the combined unilateral jugular venous overflow of MHPG plus DHPG (findings in volunteers having bilateral sampling justified this adjustment). In contrast, the brain serotonin turnover biomarker (jugular venous overflow of

5HIAA), was increased more than 4-fold in panic disorder, 1,815 pmol/min, SEM 424 compared with 361 pmol/min, SEM 73 in healthy subjects ($P < 0.01$). The arterial plasma 5-HIAA concentrations was not elevated in panic disorder; the brain contributes only 8% to the central plasma pool of 5-HIAA (3). The venoarterial plasma concentration step-up across the brain, however, was higher (Table 1). Severity of panic disorder, scored with the patient self-rating Panic Disorder Severity Scale was strongly and directly correlated with brain 5HIAA overflow; $r = 0.86$, $P < 0.001$. To this point jugular venous sampling has not been performed during a panic attack.

Regionalized Brain 5HIAA Overflow in Panic Disorder

In those participants in whom the cerebral sinus venous scan demonstrated lateralized drainage into the internal jugular veins it was possible to compare 5HIAA overflow separately in cortical and subcortical regions. In panic disorder patients this was similarly increased (~4-fold) in cortical and subcortical brain regions. Cortical 5HIAA overflow (14 values in panic disorder, 10 in healthy subjects) was 863 pmol/min, SEM 131 in panic disorder patients and 225 pmol/min, SEM 73 in healthy volunteers ($P < 0.001$; student's *t*-test). Subcortical 5HIAA overflow (nine in panic disorder, seven values in healthy subjects) was 821 pmol/min, SEM 152 in panic disorder patients and 199 pmol/min, SEM 73 in healthy volunteers ($P = 0.005$; student's *t*-test).

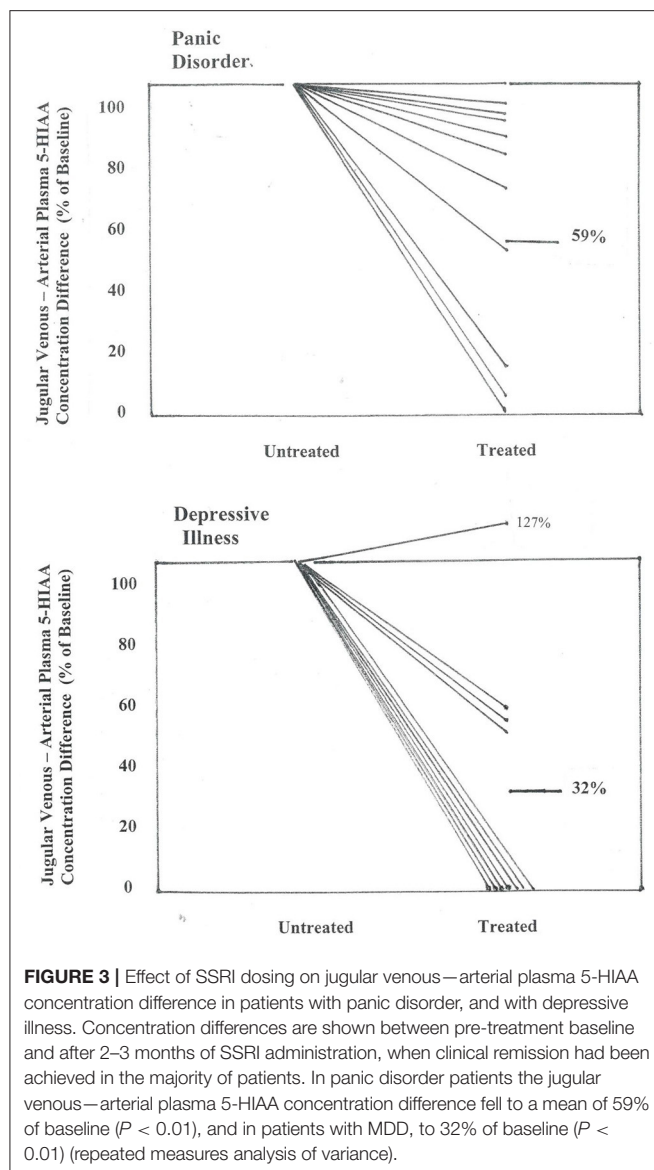
Depressive Illness

Patients with MDD were moderately to severely depressed with a HAM-D score of 25 (1), mean (SE). The BDI score was 29 (2). State anxiety score 57 (3) and trait anxiety score 62 (2) were also elevated. Seven of 21 MDD patients had comorbid (secondary) panic disorder.

In patients with depressive illness, the brain noradrenaline turnover biomarker, estimated from the internal jugular vein—arterial plasma concentration differences of MHPG and DHPG as for PD, was normal, almost identical with the concentration differences present in the healthy participants. The arterial 5-HIAA plasma concentration was similar in MDD and healthy participants, 46 (5) pmol/ml compared with 42 (4) pmol/ml (Table 2) (difference not statistically significant). The internal jugular vein—arterial plasma 5-HIAA plasma concentration difference was 4.4 (0.9) pmol/ml, compared with 1.6 (0.54) pmol/ml in healthy participants ($P = 0.003$), broadly indicative of a probable increase in brain serotonin turnover. The 5-HIAA concentration gradient in MDD was not quantitatively linked to the assessed risk of suicide ($P = 0.54$), or to the severity of depression based on the HAM-D rating ($P = 0.12$). The presence of comorbid, secondary panic disorder did not influence estimated brain serotonin turnover in MDD.

Effects of SSRI Dosing in PD and MDD

In the 10 patients with panic disorder studied before and during SSRI dosing with citalopram, the transcerebral 5-HIAA plasma concentration difference, which while untreated was



markedly higher than in normal volunteers, was reduced in the treatment phase, falling in nine of 10 patients, and into the normal range in 5 ($P < 0.01$) (Figure 3). This coincided with clinical improvement. Thermodilution jugular venous flow measurements were not available for the treatment group for direct measurement of brain metabolite overflow.

In the 11 patients with MDD where matching brain monoamine metabolite measurements were available after SSRI dosing, improvement in clinician- and patient-rated symptoms were noted. In this subgroup HAM-D fell to 7 (1), $P < 0.001$, and BDI to 9 (1), $P < 0.001$. The brain 5HIAA plasma concentration gradient was substantially reduced in all but one patient (Figure 3), with a fall from 6.0 (0.9) pmol/ml before treatment to 2.0 (0.7) following SSRI dosing ($P = 0.008$).

PANIC ATTACKS

Sympathetic Nervous Activation



FIGURE 4 | A spontaneous panic attack in the laboratory in an unmedicated patient was accompanied by a large increase in multiunit sympathetic burst size recorded in sympathetic fibers passing to the skeletal muscle vasculature of the leg, without an increase in sympathetic burst firing rate.

Relation of Estimated Brain Serotonin Turnover to Sympathetic Nervous System Activation in MDD and PD?

Could increased brain serotonin release be the driver of the sympathetic nervous system activation known to be present (26) in these two psychiatric disorders, persistent sympathetic activation in MDD (26, 27) and episodic sympathetic activation in PD, during panic attacks (27, 28)? We have been able to document that high level sympathetic nervous activation occurs during panic attacks (Figure 4), but we have not been able to test whether brain serotonergic activation is the mechanism. Persisting sympathetic activation is a characteristic of MDD. In this study population of patients with MDD, the increase in transcerebral 5HIAA plasma concentration gradient was found to be quantitatively unrelated to the ongoing sympathetic nervous system activation measured with whole body noradrenaline spillover methodology and nerve recording in the sympathetic outflow to the skeletal muscle vasculature (28).

DISCUSSION

With direct internal jugular venous sampling we found no abnormality in transcerebral noradrenaline plasma metabolite concentration gradient in depressive illness, in conflict with the Schildkraut CNS noradrenaline deficiency hypothesis (1). Similarly in panic disorder, overflow of brain noradrenaline metabolites was unremarkable in the absence of a panic attack. Perhaps the locus coeruleus and its noradrenergic projections are activated during a panic attack, but we were unable to test that.

The efficacy of SSRI drugs in MDD and PD has generated a *serotonin deficiency* hypothesis of both disorders (2), with serotonin reuptake-blockade after CNS release being imagined to correct a shortfall in neuronal serotonin release. This

heuristic is just that, an imagined formulation of CNS neurotransmitter abnormality without definitive sustaining scientific evidence. In reality, it is difficult to test for serotonin transmitter mechanisms of psychiatric illness because several brain serotonergic neuronal systems have actions unrelated to neuropsychiatry, including those linked to feeding and obesity, sunlight exposure, biorhythms and seasonality (15, 23–25). In the testing we did of brain serotonin turnover in MDD and PD, we attempted to avoid confounding by these extraneous factors through selection of the healthy comparator groups such as to be matched with the patient groups for body mass index (BMI) and sunlight hours exposure on the catheter testing day.

Good matching for BMI and sunlight hours on the testing day was actually achieved. The ~4-fold increase in brain 5HIAA overflow in PD, as we have noted previously (12) was unrelated to a genetic polymorphism impairing neuronal serotonin reuptake, was proportional to clinical indices of PD severity, and during SSRI dosing was often normalized in concert with patient clinical improvement (12). The reported finding of reduced capacity for serotonin ligand binding to brain serotonin receptors in PD (29, 30) is in harmony with our own observation, with presumed excess serotonin release in PD competing with the scanning ligand for receptor binding sites. Applying scanning methodology in parallel with the jugular venous technique would be instructive. PET and SPECT studies, ideally utilizing both 5-HT_{1A} and 5-HT_{1B} serotonergic ligands, should in the future provide regional measures of receptor occupancy which would be complementary to the measures of brain 5HIAA overflow based on jugular venous sampling. Scanning methodology should provide brain topography information further helping in the differentiation of brain serotonin neurons related to anxiety from those serotonergic neuronal pools related to seasonality and to feeding/satiety.

The finding of increased brain 5HIAA overflow in panic disorder is contrary to the commonly held view that brain serotonin release is diminished, but does fit well with some clinical and experimental observations. Common clinical experience is that these drugs can cause agitation and increased frequency of panic attacks as treatment is started (31). Clinical improvement occurs typically only after a few weeks of dosing. As panic disorder can be interpreted by our results as being characterized by increased brain neuronal serotonin release, this early clinical deterioration is as would be expected from a drug class increasing the synaptic concentration of serotonin. The phase of clinical improvement seen later possibly coincides with inhibition of firing of serotonergic neurons, by an extrasynaptic inhibitory action of serotonin on the neuronal cell body, although this interpretation does remain speculative.

A striking parallel was seen in MDD patients, where estimated brain 5HIAA overflow was increased ~4-fold, and typically normalized when illness remission was achieved with SSRI dosing. In MDD, however, depression severity was unrelated to this. Can we be sure that 5-HIAA, the serotonin metabolite we measure in the brain venous effluent, truly has a brain neuronal origin? Experimental studies indicate there is some potential for serotonin released by platelets into plasma to be taken up and

metabolized to 5-HIAA in both sympathetic nerves and vascular endothelium (32, 33), including within the cerebrovascular circulation. Human vascular preparations, however, have only minimal capacity to take up serotonin (34), so a brain neuronal origin of the excess 5-HIAA appears assured.

It is important to note that we assessed brain serotonin turnover from the measurement of brain 5HIAA overflow, and did not directly measure serotonin release. Serotonin turnover approximately equates with serotonin synthesis rate, which we inferred from the rate of 5-HIAA efflux from the brain, given that 5-HIAA is the predominant metabolite of the neurotransmitter (33). A substantial proportion of serotonin turnover derives from intra-neuronal transmitter vesicular escape, with subsequent metabolism by monoamine oxidase (11). Accordingly, serotonin turnover markedly exceeds the serotonin release rate. In the absence of a major disturbance in the stability of neuronal vesicular storage in MDD and PD, however, the estimated serotonin turnover increase in PD and MDD provides some information on neuronal serotonin release. Serotonin transporter genotyping demonstrates that the brain 5HIAA change we document in PD is not due to impaired serotonin reuptake (10), but most likely results from increased firing in midbrain raphe serotonergic neurons projecting to and releasing serotonin in the cerebral cortex and subcortical brain regions. Studies in experimental animals have demonstrated the importance of serotonergic raphe nuclei in anxiety responses (34). Beyond this probability, understanding the core significances of our findings does remain difficult. Why is brain 5HIAA overflow so increased in MDD also? MDD and PD are two distinct psychiatric conditions although, it is noted often mutually comorbid? And is the reduction in brain 5HIAA overflow during SSRI dosing the mechanism of therapeutic drug action?

MDD and PD are both characterized by sympathetic nervous system activation, persistent sympathetic activation in MDD (27, 28) and episodic sympathetic activation in PD, during panic attacks (35, 36). Chronic or recurring human sympathetic activation can be a lethality factor (37). A specific and noxious “toxic trifecta” of *activation of the cardiac sympathetic outflow*, coupled with *impaired sympathetic neural reuptake of noradrenaline*, and *firing of single sympathetic fibers in multiple salvos* within a cardiac cycle (38) exposes the heart to excessive noradrenaline concentrations and is demonstrably harmful (34). Both MDD and PD share these adverse sympathetic nervous system characteristics (28, 35–37). It is pertinent to emphasize this, in the present volume addressing mind-heart linkage, and further, to note that increased clinical cardiovascular risk is present in MDD (38) and PD (39, 40). In PD this is perhaps unexpected, but is proven. Could the CNS serotonergic activation we infer in MDD and PD, perhaps in the midbrain raphe, be the driver of this sympathetic activation? This is unlikely, as we have previously demonstrated that the dominant mechanism of activation of the human central sympathetic outflow in other pathophysiological contexts (hypertension, heart failure) is noradrenaline release in the hypothalamus and amygdala, from the projections of brainstem noradrenergic neurons (8, 41).

AUTHOR CONTRIBUTIONS

ME conceived the depressive illness and panic disorder studies, was primary supervisor of MA and DB in their thesis work, managed and funded the laboratory performing the research, and contributed to study design and data analysis. MA led the panic disorder project, as her primary Ph.D., thesis study, contributed to all levels of the panic disorder component of the work, including patient recruitment and diagnosis, and contributed to study design and data analysis. DB led the depressive illness project as his primary Ph.D., thesis study, contributed to all levels of the depressive illness component of the work, including patient recruitment and diagnosis, and contributed to study design and data analysis. GJ and DK led the invasive study day

and performed internal jugular catheterizations. LG contributed to neurochemical assays and interpretation of results. RS contributed to study design and diagnostic criteria. GL developed the brain monoamine turnover methodology and contributed to neurochemical assays. All authors contributed to interpretation of results and review of manuscript first draft.

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Evaluating Metacognitive Therapy to Improve Treatment of Anxiety and Depression in Cardiovascular Disease: The NIHR Funded PATHWAY Research Programme

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Background: Anxiety and depression contribute to poorer physical and mental health outcomes in cardiac patients. Psychological treatments are not routinely offered in cardiac care and have mixed and small effects. We conducted a series of studies under the PATHWAY research programme aimed at understanding and improving mental health outcomes for patients undergoing cardiac rehabilitation (CR) through provision of metacognitive therapy (MCT).

Methods: PATHWAY was a series of feasibility trials, single-blind, multicenter, randomized controlled trials (RCTs), qualitative, stated preferences for therapy and health economics studies.

Findings: Patients felt their psychological needs were not met in CR and their narratives of distress could be parsimoniously explained by the metacognitive model. Patients reported they would prefer therapy over no therapy as part of CR, which included delivery by a cardiac professional. Two feasibility studies demonstrated that RCTs of group-based and self-help MCT were acceptable, could be embedded in CR services, and that RCTs of these interventions were feasible. A definitive RCT of group-MCT within CR ($n = 332$) demonstrated significantly greater reductions in the severity of anxiety and depression, exceeding CR alone, with gains maintained at 12 month follow-up (SMD HADS total score = 0.52 at 4 months and 0.33 at 12 months). A definitive trial of self-help MCT is ongoing.

Conclusion: There is a need to better meet the psychological needs of CR patients. Embedding MCT into CR demonstrated high acceptability and improved efficacy on psychological outcomes. Results support roll-out of MCT in CR with evaluation of national implementation.

Registration: URL: NCT02420431; ISRCTN74643496; NCT03129282.

Keywords: metacognitive therapy, anxiety, depression, cardiac rehabilitation, qualitative, health economic, randomized control trial

INTRODUCTION

Cardiovascular disease (CVD) is the most common non-communicable disease and makes the largest contribution to morbidity and mortality worldwide (1). The psychological impacts of CVD are substantial and recognized as contributing to poorer prognosis (2). Specifically, anxiety and depression, which affect up to one-third of people with CVD, have been linked to increased future cardiac events, poorer quality of life, greater healthcare costs and poorer long-term psychological adjustment (3). Effective management of anxiety and depression in coronary care is crucial and a priority for policy makers and future clinical trials (4). Unfortunately, the quality of evidence supporting psychological treatments for anxiety and depression in CVD is generally low with small sample sizes impacting reliability of findings (5). The treatment effects have been found to be small to moderate (5).

Cardiac rehabilitation (CR) is offered routinely in a group setting to patients following a cardiac event, it reduces mortality and hospital readmissions, and improves quality of life (6, 7). CR consists of exercise sessions, education and stress management techniques directed at improving CVD risk profiles, physical fitness and psychological functioning (6). The psychological components are not standardized and vary by CR programme but may include counseling, relaxation, meditation, and cognitive challenging of negative thoughts. However, systematic reviews and meta-analyses suggest that the effects on anxiety and depression symptoms are small to moderate, and the quality of evidence is low suggesting major uncertainty over the effects reported. It is recommended that further studies be conducted to test the effectiveness of psychological therapies (5).

Metacognitive therapy (MCT) (8, 9) is a recent manualized treatment approach that may be particularly suited to addressing the psychological needs of CR patients. This is because MCT, unlike other therapies, does not require an in-depth analysis and challenging of the content of patients worries (e.g., “what if I suffer another heart attack”) that in the CR context are often realistic (10). In contrast, MCT focuses on regulating repetitive negative thinking cycles such as worry and rumination and other unhelpful behaviors that research shows maintain anxiety and depression.

MCT is based on a model where anxiety and depression are maintained by common factors involving difficult to control repetitive negative thinking and attention to threat. Feeding this thinking pattern are distorted beliefs (metacognitive beliefs) about thoughts concerning the usefulness of worrying (e.g.,

“Thinking the worst about symptoms will keep me safe”) and beliefs concerning the uncontrollability and danger of thinking (e.g., “I have lost control of worrying”). These beliefs interfere with the effective regulation of repetitive negative thinking patterns that maintain distress. For example, in response to a negative thought such as “what if I have another heart attack” the individual who believes that interpreting symptoms in the worst way possible will keep them safe engages in sustained negative thinking. Similarly, beliefs that worry cannot be controlled leads to diminished effort (or unhelpful strategies; e.g., alcohol) in controlling repetitive negative thinking. Such thinking persists leading to an escalating sense of threat and corresponding feelings of anxiety and sadness. MCT helps the person to consciously identify and change this thinking pattern by bringing worry, rumination and an excessive tendency to focus on threat (e.g., chest sensations) under control. A key therapeutic process in doing so is the challenging of metacognitive beliefs behind this thinking pattern. Results from randomized controlled trials in mental health settings and meta-analyses demonstrate that MCT is highly efficient and effective for anxiety and depression and may be more effective than various forms of cognitive behavior therapy (11). An important question concerns whether such positive effects might translate to the context of treating mental health symptoms in CR patients.

Given the limitations of existing treatments, there is a priority to implement effective psychological treatments in CR. Such a need led to the PATHWAY research programme, funded by the UK NIHR to examine the needs of patients and the effects of MCT. The PATHWAY program set out to address an important question; Can we improve psychological outcomes of CR patients? In doing so we explored the needs of patients, the feasibility of conducting a trial in the CR context and the effectiveness of adding MCT to usual CR. In the remainder of this paper, we summarize the results of the PATHWAY programme, which included the first large-scale trial of the effectiveness of adding Metacognitive Therapy for anxiety and depression in cardiovascular disease (CVD) patients.

IDENTIFYING PSYCHOLOGICAL NEEDS OF CR PATIENTS

Few studies have evaluated why the effects of psychological treatments are so limited in CVD. We aimed to explore: (1) how patients described their psychological distress, (2) if CR and routine care addressed their psychological needs, and (3) how two

different psychological treatment models might conceptualize patient problems.

To assess how patients described their psychological distress, we conducted semi-structured qualitative interviews with 46 CR patients with elevated symptoms of anxiety and/or depression. Data were analyzed using a constant comparative approach (10). Following the first four interviews commonalities and contrasts in patients accounts were noted and used to develop a preliminary thematic framework based on the research questions. Data continued to be analyzed into categories that described emerging elements of patients' accounts (10). Patients described low mood and diverse concerns and anxieties, not limited to fear of another cardiac event. Patients described worrying constantly, worrying about their worry, and feeling that worry was uncontrollable and harmful. Patients wanted to "get back to normal" but lacked any sense of how to achieve this. In fact, they reported that they were reluctant to discuss their worries with CR staff. They hoped to recover over time, meanwhile seeking reassurance that they were responding "normally." Patients were mostly dismissive of psychological techniques used in CR. We interpreted these results as suggesting that an acceptable psychological intervention for patients might be one that: (1) reduces a range of concerns that extend beyond a patient's cardiac event, (2) challenges beliefs about the uncontrollability and harmfulness of worry, (3) offers skills they could practice, (4) allows them to keep the content of worries private if they choose to.

These data appeared to support the choice of a transdiagnostic treatment such as MCT that targets the regulation of worry. Furthermore, patients' worry could be addressed with MCT without focussing on the content of those worries which seemed to be more consistent with the views expressed. The identification of patient concerns about needing to know if they were responding "normally" and their "worry about worry" were consistent with an MCT interpretation, which emphasizes developing and modifying unhelpful beliefs about thinking.

Subsequently, we explored whether the distress reported by 49 CR patients could be conceptualized parsimoniously within a MCT model of causal mechanisms (12) in contrast to the CBT model. Analysis of transcripts followed a stepwise approach. First inductive analysis followed a constant comparative approach whereby we identified commonalities and contrasts in how patients described and understood their distress. Patient transcripts were then re-examined from the perspectives of the CBT and MCT models using deductive and inductive elements. Inductive analysis allowed us to assess which model had the best fit with patients experience, with the primary criterion for fit being parsimony (i.e., how simply the models could be related to patients' accounts of their distress). Four patient transcripts reflecting diversity in the presentation and clinical context of distress were then selected for detailed analysis to illustrate the divergence between CBT and MCT models. When analyzing from the perspective of the CBT model, we focused on identifying distinct negative automatic thoughts, and then categorized the cognitive distortions apparent in these (13). When analyzing from the perspective of the MCT model, we focused on identifying talk showing perseverative negative

thinking (i.e., worry or rumination). When we saw possible underlying beliefs—negative beliefs from the perspective of CBT, or metacognitive beliefs from the perspective of MCT—these were coded and re-examined from the alternative perspective.

Patient talk showed multiple types of cognitive distortions, and required a distinction between realistic and unrealistic thoughts which proved difficult in the context of risk of future cardiac events. Understanding emotional distress from a CBT perspective presented multiple, diverse targets for treatment. In contrast, from the perspective of MCT, a single category of *perseverative negative thinking* was sufficient to understand all talk, irrespective of whether it contained realistic or unrealistic thoughts. MCT appeared to provide a more parsimonious account of emotional distress.

The data gained from our qualitative analyses supported the choice of MCT as a potential treatment approach for meeting the psychological needs of CR patients. However, we did not know if MCT was an acceptable treatment to patients or feasible to evaluate within CR.

A FEASIBILITY TRIAL OF GROUP-MCT (NCT02420431; ISRCTN74643496)

We assessed the acceptability and feasibility of implementing a randomized controlled trial of group MCT within CR services to support a subsequent definitive trial (14). We used the data from the study to estimate the required sample size, recruitment rates and site numbers, and should no modification to methods be required intended to use participants' data as an internal pilot in a subsequent full trial if deemed appropriate.

The evaluation of MCT was based on the implementation of a group-based treatment manual (15). The treatment consisted of six-sessions to explore and modify flexibility and control over patterns of extended negative thinking and to modify unhelpful metacognitive beliefs. At the end of treatment, each patient received their own "helpful behaviors" prescription summarizing what they had learned. Homework practice of certain techniques and behaviors was a feature throughout.

CR included 8 to 10 weeks of group exercise and educational sessions lasting 45 to 60 min. Exercise seminars focused on a range of topics including lifestyle and medical risk factor management. All sites included a psychological component within CR, however the content of these components varied. All sites delivered sessions on relaxation including breathing techniques and progressive muscle relaxation, however some sites provided further psychological components. For example, two sites incorporated cognitive therapy methods (i.e., challenging negative thoughts, worry decision tree), while one site delivered psychoeducational information on stress. In addition, one site offered a 4 week stress management course as part of CR which included generating and sharing a cognitive-behavioral case formulation, mindfulness techniques, and individual counseling with an occupational therapist.

Fifty-two patients with elevated anxiety and/or depression (Hospital Anxiety and Depression Scale (HADS) (16) > 8 on at least one subscale) were randomly allocated to group-MCT

plus usual CR (MCT+CR; $n = 23$) or usual CR alone ($n = 29$). Three NHS hospital sites participated across the North West of England. For further details on the study protocol see Wells et al. (17). Analysis of primary and secondary symptom outcomes was purely descriptive and based on the whole sample (not individual arms) as feasibility trials are not powered to detect differences and it was necessary to maintain the blinding of the research team if the data was to be combined with that of a larger subsequent trial. The assessment of feasibility and acceptability of adding group-MCT to CR was based on recruitment rates, withdrawal, and drop-out by the primary end-point of 4 months; number of MCT and CR sessions attended; completion of follow-up questionnaires; and ability of the outcome measures to discriminate between patients. The study was also used to re-estimate the required sample size for a full-scale trial. We also examined the extent by which non-mental health specialists (cardiac staff) adhered to the Group-MCT protocol.

Patient attendance at CR was high with 75% of participants across both arms attending usual CR, which is in line with national CR data (18). Group-MCT did not impact on attendance at usual care, as CR completion rates did not differ by study arm. In addition, attendance at group-MCT was high, with over half of patients attending at least four (the minimum pre-defined dose) out of six group-MCT sessions. At 4 month follow-up 72.4 and 69.6% of control and intervention group participants, respectively, returned follow up questionnaires. All outcome measures demonstrated a good range of observed scores, with little in the way of floor or ceiling effects.

We examined therapists' level of adherence to the treatment protocol since the treatment was to be administered by non-mental health specialists with no experience of delivering psychological treatments. An adherence checklist was used, where therapists indicated which aspects of the manual they had and had not implemented in each session. Checklist items were based on the key aspects of the manual that were to be implemented in each session. For example, in the first session adherence items included completing the case formulation, socializing patients to the model, practicing an attention control exercise called SpACE, and assigning homework. A total adherence score was created for each session by summing the total number of elements completed in session. Adherence was high across all three sites, with an overall adherence rating of 98.2%.

We estimated that a definitive randomized controlled trial would require a recruitment sample of 332 to have 90% power to detect a target 0.4 effect size (Cohen's d). This estimate took into account results from the internal pilot which indicated an attrition rate of 35%, over-time correlation of 0.5 (unchanged), mean group size of 3 and ICC of 0.05 (assumed).

ASSESSMENT OF PATIENT VIEWS OF MCT

Alongside the feasibility (and full-scale trial), we conducted a qualitative study of CR patients views of participating in group MCT (19). In-depth qualitative interviews with 24 purposively sampled CR patients following group MCT were conducted.

Data was analyzed using thematic analysis and revealed two main themes: (1) general therapy factors that were seen largely as beneficial, where patients highlighted interaction with other CR patients and CR staff delivery of treatment and their knowledge of cardiology; (2) MCT-specific factors that were seen as beneficial which included particular treatment techniques. All the patients who completed group MCT were positive about it and described self-perceived changes in their thinking and well-being. A minority of patients ($n = 4$) that were interviewed did not complete the intervention and two of them gave specific reasons for not finding the treatment helpful. They described how the staff delivering the intervention referred repeatedly to the treatment manual and this gave the impression that there was a lack of knowledge about the intervention being delivered.

FULL-SCALE TRIAL OF EFFECTIVENESS OF GROUP-MCT IN CR (NCT02420431; ISRCTN74643496)

As group-MCT appeared to be feasible and acceptable to deliver within CR, the next step was to evaluate the effectiveness of group-MCT plus CR in comparison to usual CR alone in a fully powered RCT (20).

The feasibility trial determined that a full trial required no changes to trial procedures, including recruitment and randomization processes, outcome measures, or the MCT manual or treatment delivery. We therefore regarded the 52 patients from the feasibility trial as a valid internal pilot to the full trial and recruited a further 280 CR patients –giving a total sample of 332—from five NHS hospitals across the North-West of England.

In total, 163 patients (49.1%) were randomly allocated to MCT+CR and 169 (50.9%) to usual CR alone. The primary outcome was the Hospital Anxiety and Depression Scale (HADS) total score after treatment (4 month follow-up). Secondary outcomes were the HADS anxiety and depression sub-scale scores, traumatic stress symptoms, and psychological mechanisms including metacognitive beliefs and repetitive negative thinking. Analysis was intention to treat. The adjusted group difference on the primary outcome, HADS total score at 4 months, significantly favored the MCT+CR arm (-3.24 [95% CI, -4.67 to -1.81], $p < 0.001$, standardized effect size 0.52 [95% CI 0.291 to 0.75]). The difference was smaller but remained significant at 12 months (-2.29 [95% CI -3.72 to -0.66] $p < 0.01$; standardized effect size 0.33 [95% CI 0.101 to 0.568]). The MCT intervention improved outcomes significantly for both anxiety and depression HADS subscales when assessed separately at 4 months and for anxiety but not depression at 12 months. Most secondary outcomes also favored MCT with medium to large effects observed and maintained up to 12 months. An incidental finding (though not statistically significant) was that the addition of MCT appeared to lower the risk of psychological deterioration during CR. No adverse treatment-related effects were reported. An economic evaluation is planned and will be published separately (21).

As part of the PATHWAY study a systematic review was conducted to evaluate the current cost-effectiveness literature for CR (7). The review identified that CR is cost-effective, however very little evidence focuses on psychological therapy in CR and this evidence has more mixed results. It found that more research is needed to determine the most cost-effective design of CR (inclusive of psychological intervention).

IMPROVING ACCESS: A FEASIBILITY AND ACCEPTABILITY TRIAL OF HOME-MCT (NCT03129282)

While CR offers home-based options, this has not been extended to psychological support which is typically offered in face-to-face formats (22). We therefore conducted a feasibility trial to evaluate the feasibility and acceptability of a home-based (i.e., self-help) version of the metacognitive therapy (23, 24). As with the feasibility trial of group-MCT, this trial was designed to also support a subsequent definitive trial (NCT03999359) (24) should the findings be favorable.

A multicenter randomized controlled trial with 4- and 12 month follow-up comparing self-help MCT plus usual CR (intervention) vs. usual CR alone (control) was conducted in two NHS hospitals in the North West of England. One-hundred and eight participants (69 males, 39 females) participated in a randomized, single-blind, parallel trial. Patients had a mean age of 59.9 years (SD = 9.7, range: 40–84).

Retention in both the intervention and control groups was high, with 52 (96.3%) patients in the control arm and 45 (83.3%) patients in the intervention arm returning questionnaires at 4 month follow up. This was maintained at 12 month follow up with 90.7% of control and 81.5% of intervention participants returning follow up data. All outcome measures demonstrated a wide range of observed scores, covering most of the possible range, with little in the way of floor or ceiling effects. Engagement with Home-MCT was high, 72.7% of patients who returned the end of study questionnaire completed four or more of the six modules. While most patients reported completing a module in 60 min, individual times varied, ranging from 40 to 105 min. Home-MCT demonstrated high credibility, with patients stating they found the manual easy to use and understand (median rating of 80 out of 100), that the homework was easy to follow (median rating of 85 out of 100), and that the exercise SpACE was easy to use (median rating of 90 out of 100).

Overall, Home-MCT was found to be an acceptable and feasible addition to CR. Home-MCT demonstrated no reported adverse events. The results support progression to a full scale randomized controlled trial to evaluate the efficacy of Home-MCT.

EXPLORING PATIENT PREFERENCES FOR TREATMENT

Discrete choice experiments (DCE) are used to understand preferences for healthcare interventions and services (25, 26), whereby participants are asked to choose between hypothetical

scenarios that vary by key attributes. A DCE was used to explore the preferences of participants who participated in the Home-MCT feasibility study for attributes of a psychological therapy intervention, relevant to home-based care. The aim was to evaluate the feasibility of conducting a full DCE, estimate the sample size needed for a full study and to explore preliminary preferences for included attributes.

Patient and public involvement feedback was sought to aid in selecting and defining attribute and levels (27). Thirty-five participants took part in the DCE. Participants stated that they disliked having no information about therapy before it started and favored lower costs to the NHS (28). Participants appeared to favor home-based therapy, with reduced waiting times and online or smartphone assisted therapy, though these results were not statistically significant. Significant positive constants for therapy options suggest that participants highly valued receiving therapy (compared to no therapy). It was estimated that a sample size of around 370 would be needed to identify significant coefficients for most attributes. The pilot study demonstrated the feasibility of a DCE in this group, it identified potential attributes and levels, and estimates the sample sizes needed for a full study.

GENERAL DISCUSSION

Current psychological support offered to CVD patients within cardiac services is limited in scope and in efficacy. It is imperative that new and more effective psychological therapies are offered that can be embedded within services.

In addressing this issue, we conducted a systematic research programme exploring the psychological needs of CR patients (10), the goodness of fit of metacognitive therapy to patient problems (12), the feasibility of MCT (14), the effectiveness of MCT (20), preferences for treatment attributes (28) and the feasibility and acceptability of a home-based self-help MCT manual and trial (23). We also examined preliminary health-economics data for the intervention.

Patients within CR feel that their psychological needs are not being effectively met by the components of CR, they have multiple concerns and are reluctant to talk about them in the CR context (10). The wide-ranging personal concerns expressed could be explained by a single construct; perseverative negative thinking, the reduction of which is a key target of MCT (12). The feasibility and acceptability of a RCT of MCT was supported by a feasibility trial (14).

A definitive RCT demonstrated that adding group-MCT to CR significantly reduced anxiety and depression and conferred advantages on a range of secondary psychological outcomes, with most gains sustained over 12 months (20). These results compared favorably against previous studies of psychological therapies (5). It was also shown that running group-MCT alongside usual CR did not interfere with CR attendance and engagement. We did not set out to test whether MCT is more effective than another specific psychological treatment but aimed to answer a more pragmatic question that could have immediate impact; can the addition of MCT to usual CR improve

psychological outcomes? It is possible that a different model of treatment (or simply more therapist contact) might also produce improved outcomes. Future studies are required that might assess the relative effectiveness of MCT vs. other therapeutic approaches when combined with CR. Results of studies from mental health settings are increasingly suggesting that MCT might outperform other evidence-based approaches (11, 29).

A test of a self-help version of MCT when added to CR was found to be a feasible and acceptable trial to pursue, potentially increasing patient choice (23). An investigation of patient preferences for therapy attributes showed that patients favored being offered a psychological therapy rather than no therapy at all, that they would prefer information about treatment before it was offered, and that they would prefer a home-based treatment option (28).

The results of the PATHWAY programme present implications for clinical practice and the development of more psychologically-oriented CR approaches. In particular, the results highlight the improvement in outcomes that could be achieved by using clinic-based group-metacognitive therapy. However, a home-based approach could offer more choice and is acceptable, but evidence of the effectiveness of self-help MCT needs to be determined by a full-scale RCT, a study which is currently in progress (NCT03999359). In order to realize the service-level potential of MCT, future studies

should examine implementation within healthcare services and cost-effectiveness.

AUTHOR CONTRIBUTIONS

AW and LC contributed to the first and subsequent drafts of the manuscript. All authors edited the manuscript and read and approved the final version.

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An Update on Postoperative Cognitive Dysfunction Following Cardiac Surgery

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Postoperative cognitive dysfunction is extremely prevalent following cardiac surgery. The increasing patient age and comorbidity profile increases their susceptibility to cognitive impairment. The underlying pathophysiological mechanisms leading to cognitive impairment are not clearly elucidated. Using the contemporary literature (2015–present), this narrative review has three aims. Firstly, to provide an overview of postoperative cognitive impairment. Secondly, to analyse the predominant pathophysiological mechanisms leading to cognitive dysfunction following cardiac surgery such as inflammation, cerebral hypoperfusion, cerebral microemboli, glycaemic control and anaesthesia induced neurotoxicity. Lastly, to assess the current therapeutic strategies of interest to address these pathophysiological mechanisms, including the administration of dexamethasone, the prevention of prolonged cerebral desaturations and the monitoring of cerebral perfusion using near-infrared spectroscopy, surgical management strategies to reduce the neurological effects of microemboli, intraoperative glycaemic control strategies, the effect of volatile vs. intravenous anaesthesia, and the efficacy of dexmedetomidine.

Keywords: postoperative cognitive dysfunction, inflammation, cerebral hypoperfusion, impaired autoregulation, anaesthesia induced neurotoxicity, glycaemic control, intra-operative blood pressure management, near-infrared spectroscopy

INTRODUCTION

Over two million cardiac surgeries are performed globally per annum. Patients requiring cardiac surgery are of increasing age and are likely to possess comorbidities such as hypertension and diabetes mellitus. Elderly patients are at increased risk of post-operative complications, morbidity and mortality (1). Neurological sequelae are among the most prevalent complications following

Abbreviations: CABG, coronary artery bypass graft; BBB, blood brain barrier; CPB, cardiopulmonary bypass; CAM, confusion assessment method; COX, cyclooxygenase; CST, Concept Shift Test; DAMP, damage associated molecular patterns; DSM-V, Diagnostic and Statistical Manual of Mental Disorders 5th edition; DWI, diffusion weighted imaging; GABA, γ -aminobutyric acid; GPT, Grooved Pegboard Test; HBA1C, Haemoglobin A1C; HITS, high intensity signals; HMGB1, high-mobility group 1; HVLIT, Hopkins Verbal Learning Test; IL, interleukin; MAP, mean arterial pressure; MMSE, mini-mental state examination; MMP, matrix metalloproteinases; MoCA, Montreal Cognitive Assessment Scale; NF-KB, nuclear factor kappa beta; NIRS, near-infrared spectroscopy; NMDA, N-methyl-D-aspartate; NCD, neurocognitive disorder; NSE, neuron specific enolase; POCD, post-operative cognitive dysfunction; POD, postoperative day; RAVLT, Rey Auditory Verbal Learning Test; RBANS, Repeatable Battery for the Assessment of Neuropsychological Status; rSO₂, regional cerebral oxygen saturation; TCD, transcranial doppler ultrasound; TNF-a, tumour necrosis factor a; TGF-B, transforming growth factor B; TMT, Trail Making Test; WMS, Wechsler Memory Scale.

cardiac surgery. The American College of Cardiology and American Heart Association have classified postoperative neurological defects following cardiac surgery into Type I and Type II neuronal injury. Type I defects describe well-defined, focal brain insults such as those occurring from transient ischaemic attacks and stroke. On the contrary, Type II neuronal injury describes poorly understood brain insults such as those resulting in delirium or postoperative cognitive impairment (2). This narrative review aims to provide an overview of postoperative cognitive impairment, analyse the predominant pathophysiological mechanisms leading to cognitive dysfunction and assess the current therapeutic strategies of interest using the contemporary literature (2015–present).

Definition

Postoperative cognitive dysfunction (POCD) is the most common neurological manifestation following cardiac surgery. Initially characterised by Bedford in 1955, POCD is generally defined as an impairment of cognitive functions such as executive function, attention, language, visuospatial interpretation, and motor skills (3, 4). Evered et al. (5) provided recommendations on the nomenclature of neurocognitive disorders (NCD) following surgery. These changes align with definitions in the Diagnostic and Statistical Manual of Mental Disorders 5th edition (DSM-5). NCDs are classified as mild or major in severity, with major NCDs resulting in significant cognitive impairment and disruptions to activities of daily living. The DSM-V criteria for the diagnosis of neurocognitive disorders are summarised below (6).

- a) Subjective evidence of cognitive impairment.
 - a. Either by the patient, clinician, or other informant.
- b) Objective cognitive impairment.
 - a. Mild: 1–2 standard deviations below average on neuropsychological batteries.
 - b. Major: >2 standard deviations below average on neuropsychological batteries.
- c) Disruptions to activities of daily living.
 - a. Mild: No major disruption to capacity to perform activities of daily living.
 - b. Major: Major disruption to capacity to perform activities of daily living.
- d) The cognitive defects do not occur exclusively in the context of delirium.
- e) Cognitive deficit is not better explained by another mental disorder.

Evered et al. (5) suggested that ‘perioperative NCDs’ should be used as an overarching term to include pre-existing cognitive impairment prior to surgery, acute events such as post-operative delirium, delayed neurocognitive recovery and post-operative mild/major (POCD) NCD. Delayed neurocognitive recovery is defined as cognitive impairment lasting up to 30 days post-operatively, even if the DSM-V criteria for a neurocognitive disorder are met. In contrast, post-operative mild/major NCD

is defined as cognitive impairment persisting between 30 days and 1 year post-operatively. To reduce heterogeneity in future studies, POCD should refer to the definition of post-operative mild/major NCD as per Evered et al. (5). Lastly, cognitive impairment which persists for greater than 1 year following surgery lose the ‘postoperative’ specifier and are termed mild or major neurocognitive disorders as the impairment is unlikely to be linked to the occurrence of surgery (5). The distinction between delayed neurocognitive recovery and postoperative mild/major NCD (or POCD) manifest because recovery from the stressors of hospitalisation such as procedural insult, anaesthesia, sleep disturbance, medication side-effects largely occur within the 30 days (5). The distinction between postoperative delirium and POCD is difficult. It is not known whether they are entirely separate entities or lie on the same spectrum. Postoperative delirium is largely a clinical characterised by confusion and inattention. However, the diagnosis of postoperative delirium may be aided using the confusion assessment method (CAM). Conversely, POCD is characterised by changes to higher cognitive functioning, and its diagnosis requires the comparison of pre-operative and post-operative scores from neuropsychological testing (7, 8). This review will utilise the loose, clinical definition of POCD given that the nomenclature has not been widely adopted and the reviewed literature predominantly use this definition.

Epidemiology

The incidence of POCD is unclear due to the wide range of criteria used to define cognitive dysfunction. Postoperative cognitive impairment affects between 10–40% of patients in the sixth postoperative week following cardiac surgery. Only around 45% of patients fully recover from cognitive impairment after 1 year post cardiac surgery (9). Furthermore, the presence of early cognitive impairment following surgery predicts the incidence and severity of cognitive dysfunction at 5 years following cardiac surgery (10).

Risk Factors

The risk factors for POCD can be divided into pre-operative and intra-operative risk factors. The preoperative risk factors for POCD include advanced age (11–13), lower educational levels (12), pre-existing cognitive impairment (12, 14), APOE4 genotype carriers (15), depression (13), and diabetes (13, 16). The intraoperative risk factors include the surgical approach, use of cardiopulmonary bypass (CPB) (17), duration of surgery (13, 18) and anaesthesia (12, 13, 19), arterial pressure management (20), glycaemic management (21) and intraoperative haemoglobin concentration (18).

Assessment of Postoperative Cognitive Dysfunction

The detection of POCD involves comparing pre-operative and post-operative neuropsychological test results (22). Due to variability in the tests used to detect POCD, a “Statement of Consensus” was produced to outline ideal conditions for measuring neuro-behavioural outcomes following cardiac

surgery. The recommended core neuropsychological battery to assess for POCD is summarised in **Table 1** (23). These tests were selected as they are easily administered, sensitive in detecting cognitive changes and can be standardised against normative data. Following cardiac surgery, memory, psychomotor speed function and attention are likely to be impacted and hence cognitive tests should be powered to detect these changes (24). Studies have also recommended the inclusion of mood assessment tools such as the Depression, Anxiety, and Stress Scale due to a potential association between mood and cognition (25). Despite the recommendations by the 1995 “Statement of Consensus,” a recent systematic review has found that those neuropsychological tests were performed in less than half of the sixty-two identified studies (26). Investigators select several neuropsychological tests which they believe to best examine the cognitive domains of interest. In several studies, investigators do not select a sufficient number of neuropsychological tests, or do not test all of the cognitive domains. Unfortunately, this practice has contributed to the heterogenous literature and impairs the robust comparison of studies examining POCD following cardiac surgery. The follow-up period for neuropsychological testing is also extremely variable between studies. This period is generally dictated by when the investigators believe they are likely to capture most cognitive impairment cases. The follow up period for these tests is also potentially limited by time, staffing, and financial constraints. Given the recent recommendations by Evered et al. (5), the follow up period in future studies should be up to a month post-operatively to detect cases of delayed neurocognitive recovery, and a year to detect postoperative mild/major neurocognitive disorders.

There are numerous neuropsychological tests which are used in assessing POCD.

Mini-Mental State Examination

The Mini-Mental State Examination (MMSE) is the most commonly used test in these studies, acting as a global test of cognition and a screening test for dementia. The test includes 30 questions, assessing attention, orientation, memory, language and visual-spatial skills. Importantly, the MMSE was not designed to detect POCD and should be used in conjunction with other neuropsychological tests. Scored between 0–30, a lower score indicates poorer performance. Traditionally, a score of 23 or 24 out of 30 is used as the cut-off score to define cognitive impairment, but this has not been validated (27).

Montreal Cognitive Assessment

The Montreal Cognitive Assessment (MoCA) is another commonly used bedside cognitive test, testing similar domains as the MMSE. The maximum test score is 30. A score of 26 and above is considered normal, whilst anything below this is considered cognitive impairment (28).

Rey Auditory Verbal Learning Test

The Rey Auditory Verbal Learning Test (RAVLT) assesses the ability to encode, store and retrieve verbal memory. In this test, a series of meaningful words are presented for five rounds. At

TABLE 1 | Neuropsychological battery recommended by the 1995 “Statement of Consensus” for the assessment of POCD following cardiac surgery (23).

Neuropsychological Battery	Cognitive Domain Assessed
Trail Making Tests A	Attention and concentration
Trail Making Tests B	Executive functioning
Rey Auditory Verbal Learning Test	Verbal learning and memory
Grooved Pegboard	Motor skills

the end of each round, immediate recall is tested by asking the participants to retrieve as many words as possible. Additionally, following the final round, delayed recall is tested by asking the patients to wait a period such as 20 min and attempt to retrieve as many words as possible (29).

Hopkins Verbal Learning Test

The Hopkins Verbal Learning Test (HVLT) assesses short term memory, verbal learning and delayed recall. The examiner reads twelve words aloud and asks the patient to recall as many as possible immediately afterwards. This is repeated three times. Subsequently, 20–25 min later, delayed recall is tested by asking the patient to recall as many as possible (30).

Trail Making Test

The Trail Making Test A (TMT-A) analyses psychomotor speed and attention by asking the patients to draw a trail, connecting numbered circles in ascending order without lifting their pencil off the paper. The Trail Making Test B (TMT-B) is similar to the TMT-A, but requires the patients to alternate between numbers and letters in ascending order. This added complexity assesses for executive functioning (31).

Concept Shift Test

The Concept Shift Test (CST) is similar to the TMT-A and TMT-B, assessing the patients’ ability to shift attention between stimuli. They are required to quickly cross out empty circles, or letters, numbers or a combination (32).

Wechsler Memory Scale

The Wechsler Memory Scale (WMS) has three subtests including the Visual memory Span, Digit Span Forwards and Digit Span backwards. The Visual Memory Span subtest assesses visual and short-term memory by showing patients three shapes for 10 s, taking them away and subsequently asking the patients to draw them. The Digit Span Forwards and backwards tests assess attention and short-term memory. The Digit Span Forwards subtest requires the participant to repeat a sequence of numbers read aloud by the investigator in the same order, whereas the Digit Span Backwards Subtest requires participants to repeat a sequence of numbers read aloud by the investigator in the reverse order (33).

Stroop Colour and Word Test

The Stroop Colour and Word test (SCWT) assesses the patients’ ability to inhibit cognitive interference during the processing of incongruent stimuli. A common example in practice involves giving the patient a list of words of names of colours. However,

the list of words are printed in a colour which is different to the word itself. The examiner records the time spent reading the lists and the number of errors (34).

Grooved Pegboard Test

The Grooved Pegboard Test (GPT) is a complex manual dexterity test which assesses hand-eye coordination and psychomotor speed. The pegboard is a square apparatus containing 25 holes. Patients are required to pick up keyhole shaped pegs and manipulate them to fit into the holes. The time required for completion is recorded by the examiner. The patient may be asked to use only their dominant hand, non-dominant hand, or both (35).

Neuropsychological Testing Limitations

Firstly, performing neuropsychological tests on unwell patients is difficult. Post-operatively, patients are recovering from surgical trauma, the effects of anaesthesia or medications, and complications are, therefore, unlikely to be able to cooperate with clinicians (25). Secondly, given the limited number of neuropsychologists available, clinicians often assess cognition using quick bedside tests such as the MMSE or MoCA (36). Whilst the use of these tests is acceptable, they should be complemented by other validated neuropsychological tests. Thirdly, neuropsychological tests should be adaptable to different languages as cultural differences and language barriers may impair the understanding of the test questions (37). Additionally, the MMSE and MoCA also require training of personnel to administer the neuropsychological tests. Moreover, since 2001, the use of the MMSE has been hindered by the implementation of copyright and usage fees (38). Furthermore, patients are often subjected to many neuropsychological tests. This may result in a patient becoming mentally fatigued throughout the tasks and performing more poorly in the later tasks. Conversely, patients undergoing neuropsychological testing may perform better during subsequent attempts due to the learning effect, where patients answer the test based on their previous experiences (39). Lastly, the neuropsychological test battery recommended by the “statement of consensus” are not universally adhered to according to Rudolph et al. (26). This impairs the ability to collate studies and perform meta-analyses which provide definitive conclusions.

Statistical Assessment of Postoperative Cognitive Dysfunction

Numerous statistical methods have been used to assess POCD, contributing to the heterogeneous literature. The analytic criteria used to define POCD include standard deviation (SD) changes, percentile changes, Z score changes, factor analysis and consensus of experts. Firstly, Standard deviation is typically used to measure the dispersion of data from the mean. Studies have defined POCD by a post-operative neuropsychological test result of 1 standard deviation below their baseline result. Results with an SD of 1.5 and 2 below the mean are defined as moderate and severe cognitive impairment respectively (40, 41). Secondly, Z scores are used to determine how far a score is from the mean. POCD can be defined as by a Z score greater than -1.96 . The individual Z score

is calculated by subtracting the mean score change between the pre-operative and post-operative tests in the control group from the difference in performance in the same tests in the surgical group. Then, this result is subsequently divided by the standard deviation of the mean score change in the control group (36, 42, 43). Thirdly, the percentile change criteria identify patients with POCD based on a specific decrease in the patients' pre-operative and post-operative neuropsychological test scores. Ho et al. (44) and Keizer et al. (45) defined POCD as a decline of greater than 20% compared to their preoperative test results (44, 45). Moreover, the factor analysis technique utilises the standard deviation approach on a group of data derived from neuropsychological tests intending to analyse similar cognitive domains. Lastly, as the name suggests, the consensus of experts' approach involves experienced clinicians determining whether a patient has POCD based on test results and clinical features.

Implications of Postoperative Cognitive Dysfunction

Patients with POCD are more likely to have a slower recovery time, and an increased duration of hospital admission compared to patients without POCD (46). Additionally, these patients have an increased mortality rate in the year following their surgery (46). POCD is also associated with reduced adherence to rehabilitation programmes, potentially contributing to earlier retirement, increased morbidity and mortality. A 5-year prospective study revealed that neurocognitive function is strongly associated with quality of life and a patients' perception of their own health. This is corroborated by evidence which suggests that postoperative cognitive changes following cardiac surgery predict cognitive deterioration 6 years following surgery (47–49). Furthermore, patients with higher cognitive function scores are more likely to productively contribute to society and maintain fulltime work (50). Evidence suggests that POCD may be associated with development of Alzheimer's Dementia as anaesthesia may induce deposition of B-amyloid in the brain (51, 52). Thus, it is crucial to monitor and to optimise the pre- and post-operative management of cardiac surgery patients to reduce the likelihood of developing POCD and the potential long-term implications.

METHOD

A literature search using OVID Medline and Embase was performed for this narrative review. To reflect the contemporary literature, the included studies were published between 2015 and present. However, for background and contextual information, this limit was removed. Additional relevant articles, such as novel pre-clinical studies examining pathophysiological mechanisms leading to POCD, were obtained using references from the identified articles. Keywords for POCD included POCD; postoperative cognitive dysfunction; cognitive impairment; neuronal injury; neuroinflammation; neurocognitive test; neurocognitive battery; rey auditory verbal learning test; grooved pegboard; trail making test; neuropsych*; neurocog*; cognitive test; cognitive performance and cognitive dysfunct*.

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. As mentioned previously, the loose/old definition of POCD is used given that minimal studies have adopted the 2018 nomenclature recommendations.

The identification and selection of studies is depicted in **Figure 1**. Study designs of interest included cohort studies, randomised controlled trials and systematic reviews. Systematic reviews were not included in the table of studies to avoid duplication with other studies. However, they were discussed in the main text given they are a high level of evidence. Forty studies were discussed in this narrative review. This comprises 4 studies on dexamethasone, 4 studies on autoregulation/intraoperative blood pressure management, 10 studies on the use of NIRS to detect cerebral desaturations, 5 studies on micro-emboli, 5 on intra-operative glycaemic control, 6 studies on anaesthesia induced- neurotoxicity and 6 studies on dexmedetomidine.

PATHOPHYSIOLOGY OF POSTOPERATIVE COGNITIVE DYSFUNCTION FOLLOWING CARDIAC SURGERY

It was previously thought that POCD following cardiac surgery was predominantly driven by an inflammatory response due to cardiopulmonary bypass. However, off-pump cardiac surgery studies have yet to convincingly demonstrate a reduction of cognitive impairment compared to traditional on-pump cardiac surgery (53, 54). Consequently, there is significant interest in understanding the underlying mechanisms contributing to POCD. There are numerous proposed pathophysiological mechanisms leading to the development of POCD. This review will focus on several main theories, including systemic and neuroinflammation, cerebral hypoperfusion and cerebrovascular autoregulation impairment, cerebral microemboli, impaired glycaemic control and anaesthesia induced neurotoxicity. A summary diagram of the mechanisms leading to POCD, and the resulting implications of POCD is depicted in **Figure 2**.

Inflammation

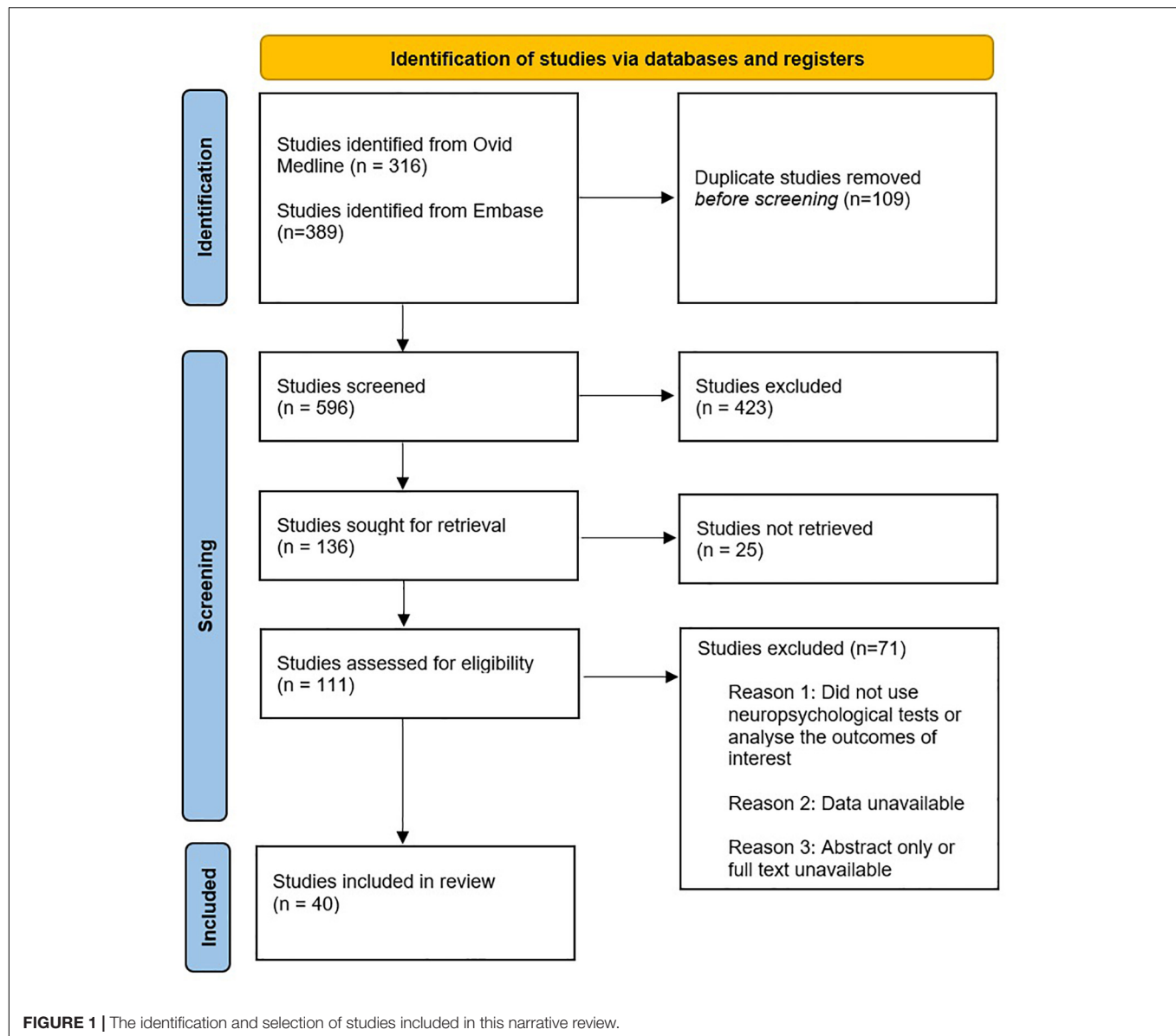
Systemic and Neuroinflammation

The link between inflammation and POCD is complex. There are several activators of the inflammatory response in cardiac surgery including surgical trauma, blood surface interactions with CPB circuitry and ischaemic reperfusion injury (55). Firstly, surgical trauma results in the release of danger associated molecular patterns (DAMPs) such as high-mobility group 1 (HMGB1) and S100A8. HMGB1 is associated with parenchymal neuroinflammation and neurocognitive impairment (56, 57). This is supported by the reduction in POCD and memory defects following the use of HMGB1 inhibitors in rodent models

following liver surgery (58). In contrast, S100A8 is associated with macrophage migration into the brain and is likely to play a key role in POCD. Pre-operative administration of an S100A8 inhibitor in mice improved cognitive functioning 24 h following surgery and inhibited hippocampal gliosis (59). DAMPs bind to pattern recognition receptors on the endothelium to activate the transcription factor nuclear factor kappa beta (NF- κ B), triggering a pro-inflammatory cascade. The pro-inflammatory cascade involves the release of cytokines such as interleukin-1, interleukin-6, and tumour necrosis factor- α (TNF- α), and upregulates the expression of cyclooxygenase-2 (COX2). COX2 is implicated in the disruption of the blood brain barrier (BBB) by upregulating the expression of matrix metalloproteinases (MMP), contributing to neuroinflammation (60). Secondly, blood exposure to the CPB circuitry causes systemic inflammation, involving both the humoral and cellular response (61). Adsorption of the C3 complement protein to the circuitry activates the alternative complement pathway. The formation of heparin-protamine complexes at the completion of surgery activates the classical complement pathway (55). Increased inflammatory markers within the periphery or CNS are associated with the development of POCD (62–67). Furthermore, Zhu et al. (65) demonstrated a significant association between increased TNF- α levels and decreased executive functioning (65). However, Nemeth et al. did not detect an association between magnitude of the inflammatory response and incidence of POCD (68).

Blood Brain Barrier Disruption

The blood brain barrier consists of endothelial cells, basement membrane and glial cells, functioning to limit the entry of deleterious substances into the brain (69). Cardiac surgery has been implicated in the development of BBB disruption, with the extent of the disruption correlating with the magnitude of POCD (70). BBB dysfunction leads to potential exposure to toxic and pro-inflammatory substrates. One theory explaining this disruption suggests that microembolisation triggers an interaction with the vascular endothelium, impairing the BBB (71). However, as previously stated, it is believed that the pro-inflammatory response triggers the activation of MMPs which proteolytically degrade the BBB (72, 73). The use of CPB in porcine models increases the permeability of the BBB (74). Merino et al. (75) demonstrated that following human cardiac surgery, BBB disruption is most prevalent within the first 24 h post-operatively (75). Abrahamov et al. (76) demonstrated a relationship between on-pump CABG and BBB disruption. MRI studies demonstrated that the BBB disruption was predominantly localised to the frontal region of the brain. This disruption correlates with a significant decrease in attention and executive functioning postoperatively (76). Similarly, Danielson et al. (71) showed that on-pump CABG triggers BBB dysfunction as well as systemic and neuroinflammation (71). Following the disruption of the BBB, pro-inflammatory cytokines such as TNF- α pass through the BBB, and there is an upregulation of chemokines such as MCP-1 which recruit bone marrow derived macrophages into the CNS (77, 78). Subsequently, the bone-marrow derived macrophages secrete further pro-inflammatory

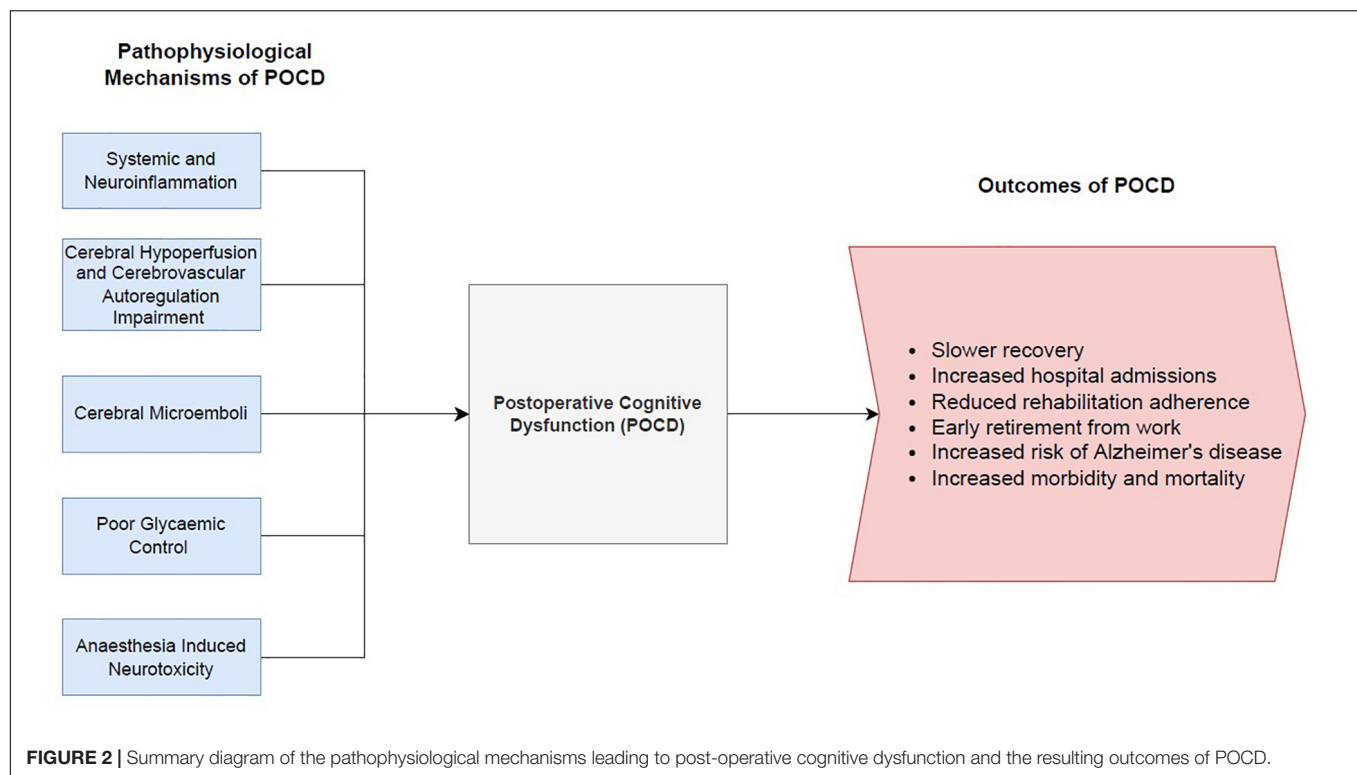


cytokines, reactive oxygen species, and activate microglia cells (79). Microglial cells may adopt an inflammatory phenotype which further contributes to neuroinflammation and cognitive impairment (80).

Dexamethasone to Attenuate the Inflammatory Response

Given the link between inflammation and POCD, the use of glucocorticoids such as dexamethasone to attenuate the inflammatory response has been proposed. Dexamethasone has a long duration of action and may reduce neuroinflammation and cerebral oedema (81). However, prolonged use of dexamethasone is itself associated with cognitive impairment (82). Results from recent studies are conflicting and are summarised in **Table 2**. Four studies were identified. Glumac et al. (63) found that 0.1 mg/kg of dexamethasone reduced the incidence of POCD within the

first 6 days compared to placebo (RR: 0.43; 95% CI: 0.21–0.89; $p = 0.02$) (63). Glumac and colleagues also demonstrated that patients receiving dexamethasone performed significantly better in the MMSE, symbol digit modality test and simple reaction time tests compared to the placebo group at POD6. This suggests that dexamethasone may preserve global cognition and positively influence psychomotor processing speed. That was also the first study to confirm that the systemic inflammatory response is inhibited by dexamethasone based on inflammatory markers ($p < 0.001$). In a follow-up from their 2017 study, Glumac et al. (83) observed that dexamethasone reduced the incidence of cognitive impairment over 4 years. However, this finding narrowly failed to reach significance (RR: 0.459; 95% CI: 0.192–1.100; $p = 0.068$) (83). This study was the first long-term study to assess the effect of dexamethasone on cognitive outcomes following cardiac surgery. The 4-year timepoint for



post-operative follow up was chosen as it was likely to truly reflect the long-term effect of dexamethasone prior to surgery. An earlier post-operative follow-up point, such as at 1 year postoperatively, was not chosen because it was unlikely to reflect the long-term effect of dexamethasone. Conversely, follow up after 5 years postoperatively may also not reflect the effects of dexamethasone, as the results may be confounded by age related cognitive decline, the development or progression of new cardiovascular or cerebrovascular disease, and the development of dementia. Glumac et al. (83) also investigated whether cognitive impairment at POD6 influenced the development of cognitive impairment at 4 years. Thirteen patients who did not have POCD at POD6, had POCD detected at 4 years post-operatively. Ten of these thirteen patients were in the placebo group. These results reveal that dexamethasone may attenuate the inflammatory response and potentially prevent long term cognitive impairment.

The results of Sauer et al. (84) and Li et al. (85) did not support the use of dexamethasone to reduce cognitive impairment. Sauer et al. demonstrated that the intraoperative administration of 1 mg/kg dexamethasone did not reduce delirium during the first four postoperative days (84). Similarly, a meta-analysis by Li et al. (85) involving 1460 patients did not support the use of dexamethasone compared to placebo to reduce POCD (RR: 1.00; 95% CI: 0.51–1.96). A subgroup analysis of cardiac surgeries was also non-supportive (RR: 0.90; 95% CI: 0.21–3.77) (85). These conflicting results may be caused by variation in the dose of dexamethasone used. As previously mentioned, high doses of dexamethasone, such as those used by Sauer, may contribute to cognitive impairment as the hippocampus has

a high concentration of glucocorticoid receptors, and hence yield negative results. Moreover, heterogeneity in the timing of dexamethasone administration may cause conflicting results. Glumac, who demonstrated positive benefits, administered dexamethasone 10 h prior to surgery as they believed this would allow sufficient time for the anti-inflammatory properties to work (63). In contrast, the negative studies administered dexamethasone at the induction of anaesthesia (84, 85). Further studies are required before a definitive conclusion can be made regarding the efficacy of dexamethasone on cognitive impairment following cardiac surgery.

Cerebral Hypoperfusion Cerebrovascular Autoregulation

Cerebrovascular autoregulation refers to the ability of the brain to maintain stable cerebral perfusion *via* myogenic, neurogenic, and metabolic mechanisms despite changes in cerebral perfusion pressure (86). The cerebral perfusion pressure is calculated as the difference between mean arterial pressure (MAP) and the larger of either central venous pressure or intracranial pressure. It is generally accepted that this autoregulatory mechanism functions optimally between a MAP of 60–160 mmHg (87). If the MAP is above the higher limit of the autoregulation zone, there is excessive cerebral blood flow, leading to oedema and capillary damage. Conversely, if the MAP is below the lower limit of the autoregulatory zone, cerebral ischaemia ensues (88). Fluctuations in cerebral perfusion are common during cardiac surgery and may fall below levels necessary to maintain autoregulation (89, 90).

TABLE 2 | The effect of dexamethasone on POCD.

Study	Aim	Surgery Type	Study Type	Patient number	Definition of POCD	T1 Cognitive Assessment	T2 Cognitive Assessment	Psychological Assessment Tool	Findings
Sauer et al. (84)	To determine whether the intraoperative administration of high dose dexamethasone would reduce delirium during the first 4 postoperative days	On-pump cardiac surgery	RCT Dexamethasone 1 mg/kg vs. placebo administer at the induction of anaesthesia	737 Dexamethasone ($n = 367$) Placebo ($n = 370$)	Not specified	Not specified	POD1-4	CAM	Intraoperative administration of dexamethasone did not significantly reduce the incidence of delirium (OR: 0.85, 95% CI: 0.55–1.31) Incidence of delirium in dexamethasone vs. placebo group: 14.2 vs. 14.9%
Glumac et al. (63)	To determine whether prophylactic dexamethasone reduces POCD	Cardiac surgery	RCT Dexamethasone (0.1 mg/kg) vs. placebo administered 10 h prior to surgery	161 Dexamethasone ($n = 80$) Placebo ($n = 81$)	$RCI \leq 1.96$ on at least one test	Two days before surgery	POD 6	MMSE RAVLT WMS (Involving subtest of Visual Memory Span, Digit Span Forward, Digit Span Backward) SDMT PsychE	The dexamethasone group had a reduced incidence of POCD compared to placebo (RR: 0.43, 95% CI: 0.21–0.89, $p = 0.02$). Patients in the dexamethasone group performed significantly better in the MMSE, Symbol digit modality test and simple reaction times compared to placebo group at day six ($p < 0.05$). Dexamethasone also reduced systemic inflammatory response compared to placebo (30 vs. 58%; $p < 0.001$).
Glumac et al. (83)	Four years follow study to determine whether prophylactic dexamethasone reduced POCD	Cardiac surgery	Follow up of previous RCT Dexamethasone (0.1 mg/kg) vs. placebo administered 10 h prior to surgery	116 Dexamethasone ($n = 54$) Placebo ($n = 62$)	$RCI \leq 1.96$ on at least one test	Two days before surgery	POD 6 and 4 years postoperatively	MMSE RAVLT WMS PsychE	Dexamethasone did not significantly reduce POCD at 6 days (RR: 0.510; 95% CI: 0.241–1.079; $p = 0.067$) Dexamethasone did not significantly reduce POCD at 4 years (RR: 0.459; 95% CI: 0.192–1.100; $p = 0.068$)

CABG, Coronary Artery Bypass Graft; CAM, confusion assessment method; MMSE, mini mental state exam; POCD, postoperative cognitive dysfunction; RAVLT, rey auditory verbal learning test; RCT, randomised control trial; SDMT, symbol digit modalities test; T1, pre-operative timepoint for neurocognitive testing; T2, post-operative timepoint for neurocognitive testing; WMS, wechsler memory scale test.

TABLE 3 | Intraoperative blood pressure management and cerebrovascular autoregulation.

Study	Aim	Surgery Type	Study Type	Patient Number	Definition of POCD	T1 Cognitive Assessment	T2 Cognitive Assessment	Psychological Assessment Tool	Findings
Vedel et al. (93)	To determine the effect of a higher vs. lower blood pressure target as titrated using noradrenaline during on-pump cardiac surgery on cerebral injury	On-pump CABG and/or left sided heart valve surgery	RCT (PPCI Trial) Higher MAP Target (70–80 mmHg) Lower MAP Target (40–50 mmHg)	169 High target (n = 98) Low target (n = 99)	Combined Z score > 1.96 from neuropsychological tests	Day before surgery	At discharge from hospital or 1 week (whichever was earlier) Second follow up was between 2–4 months postoperatively	VLT CST SCWI PPMST LDC Four boxes test	Targetting higher blood pressures during on-pump surgery did not affect the volume or number of cerebral infarcts detected by diffusion weighted MRI. Brain lesions were present in 52.8 and 55.7% of patients in the low and high MAP target group respectively No difference in the incidence of POCD between the low and high MAP groups at discharge (OR = 1.76, 95% CI: 0.90–3.47, $p = 0.12$) No difference in the incidence of POCD between low and high MAP groups at second follow up (OR = 0.72, 95% CI = 0.23–2.31, $p = 0.77$). Median time for second follow up was 92 days post-operatively
Kumpaitiene et al. (91)	To detect episodes of impaired cerebrovascular autoregulation and the association between this impairment and POCD	On-pump CABG	Prospective observational study Cerebrovascular autoregulation assessed using non-invasive ultrasonic monitor (Vittamed 505 monitor)	59	Patients' combined score > 2, or at least two scores for separate tests were > 2 Combined scores were calculated by dividing the sum of all individual scores by the SD of the mean sum of all the patients' scores	Day before surgery	POD10	MMSE RAVLT WAIS (Digit Span and Digit Symbol Substitution) Schulte table	Incidence of POCD was 37% (22 patients) All patients experienced impaired cerebrovascular autoregulation Mean duration of cerebrovascular autoregulatory impairment was 4.9 min Duration of the single longest cerebrovascular autoregulation impairment was associated with the incidence of POCD. Mean duration of the longest cerebrovascular autoregulatory impairment episode was significantly longer in the POCD group (6.38 min) compared to non-POCD group (4.22 min) ($p = 0.001$).

(Continued)

TABLE 3 | (Continued)

Study	Aim	Surgery Type	Study Type	Patient Number	Definition of POCD	T1 Cognitive Assessment	T2 Cognitive Assessment	Psychological Assessment Tool	Findings
Larsen et al. (95)	As a follow up study to the PPCI trial, they investigated whether patients allocated to a higher MAP target had a higher long term mortality at 3 years follow up	On-pump CABG and/or left sided heart valve surgery	Follow up observational study to PPCI trial Higher MAP Target (70–80 mmHg) Lower MAP Target (40–50 mmHg)	113 patients followed up High target (n = 55) Low target (n = 58)	Combined Z score > 1.96 from neuropsychological tests	Day before surgery	At discharge from hospital or 1 week (whichever was earlier) Second follow up was between 2–4 months postoperatively Final follow up was at 3 years	VLT CST SCWI PPMST LDC Four boxes test	No difference in mortality over a median follow up period of 3.4 years between the high and low MAP target groups (HR = 1.23, 95% CI: [0.33–3.12], $p = 0.65$) No difference in the development of POCD between the high and low MAP target groups (OR = 1.01, 95% CI: [0.33–3.12])

CABG, coronary artery bypass graft; CST, concept shifting test; LDC, letter digital coding; MAP, mean arterial pressure; MoCA, montreal cognitive assessment; MMSE, mini mental state exam; POCD, postoperative cognitive dysfunction; POD, postoperative day; PPCI, perfusion pressure cerebral infarct; PPMST, paper and pencil memory scanning test; RAVLT, rey auditory verbal learning test; RCT, randomised control trial; SCWI, stroop colour word interference; SDMT, symbol digit modalities test; T1, pre-operative timepoint for neurocognitive testing; T2, post-operative timepoint for neurocognitive testing; VLT, verbal learning test; WMS, wechsler memory scale test.

Kumpaitiene et al. (91) aimed to detect episodes of impaired cerebrovascular autoregulation and determine whether there was an association with POCD following cardiac surgery. They assessed cerebrovascular autoregulation using a novel, non-invasive ultrasonic monitor known as the 'Vittamed 505 Monitor.' POCD was present in twenty-two patients (37%), with a significant difference between the groups in the attention test ($p = 0.0016$), Rey Auditory Visual Learning Test ($p = 0.04$) and digit symbol substitution test ($p = 0.005$). Impaired cerebrovascular autoregulation was detected in all 59 patients, with a mean duration of autoregulatory impairment being 4.9 min. Building on this, they found that the mean duration of the longest cerebrovascular episode was significantly longer in patients experiencing POCD (6.38 min) compared to patients without POCD (4.22 min, $p = 0.001$). Furthermore, Kumpaitiene and colleagues determined that 15 of their patients had a lower cerebrovascular autoregulatory limit between 61.4–69.5 mmHg (91). Traditionally, cardiac surgeons have maintained an intraoperative MAP between 50–60 mmHg as it was believed that this was the lower autoregulatory limit (92). Hence, aiming for a low intraoperative blood pressure in these patients may cause end-organ damage and cognitive impairment. Thus, it is ideal that future studies confirm the association between cerebrovascular autoregulation impairment and POCD with larger multi-centred studies and consider integrating the identification of patient specific cerebrovascular autoregulatory limits into clinical practice.

Intraoperative Blood Pressure Management

Two randomised controlled trials and a meta-analysis was identified examining the effect of high vs. low intraoperative blood pressure management on post-operative cognitive impairment following cardiac surgery (Table 3). Overall, there is conflicting evidence on the best target for MAP to reduce POCD following cardiac surgery. Vedel et al. (93) conducted the Perfusion Pressure Cerebral Infarcts trial to determine the effect of a higher vs. lower blood pressure target by titrating using noradrenaline during on-pump cardiac surgery on cerebral injury. Patients were allocated to either a higher MAP target (70–80 mmHg), or a lower MAP target (40–50 mmHg) (93). They detected the number and volume of new cerebral lesions using diffusion weighted MRI. Vedel and colleagues found that targetting higher blood pressures during on-pump surgery did not affect the volume of new cerebral lesions as detected by diffusion weighted MRI. The low MAP target group had a median cerebral infarct volume of 25 mm³ (Interquartile Range: 0–118), whilst the high MAP target group had a median cerebral infarct volume of 29 mm³ (Interquartile Range: 0–143). New brain lesions were present in 52.8 and 55.7% of patients in the low and high MAP target group respectively. There was no difference in the incidence of POCD between the low and high MAP groups at discharge (OR = 1.76, 95% CI: 0.90–3.47, $p = 0.12$). Additionally, there was no difference in the incidence of POCD between low and high MAP groups at the second post-operative follow up (OR = 0.72, 95% CI = 0.23–2.31, $p = 0.77$), with a median follow up time of 3 months. Notably, there was a trend towards significance in the occurrence of

strokes in the higher MAP group compared to the low MAP group (6 vs. 1.1%, $p = 0.06$). This study has strongly contributed to the 2019 guidelines released by the European Association for Cardio-Thoracic Surgery which currently recommend targeting an intraoperative MAP between 50–80 mmHg (94). Moreover, this study highlights the potential of using diffusion weighted MRI to supplement baseline cognitive testing. Larsen et al. (95) conducted a 3-year follow-up study of the Perfusion Pressure Cerebral Infarcts trial (95). They found no difference in mortality over a median follow up period of 3.4 years between the high and low MAP target groups (HR = 1.23, 95%CI: (0.33–3.12), $p = 0.65$). Furthermore, there was no difference in the development of POCD between the high and low MAP target groups [OR = 1.01, 95% CI: (0.33–3.12)]. Kiabi et al. (96) performed a meta-analysis to determine the effect of intraoperative low vs. high MAP on the development of POCD following on-pump CABG. They identified three studies which were not previously examined in this review, including Gold et al. (97), Charlson et al. (98) and Siepe et al. (99). From a patient population of 731, the intraoperative maintenance of low MAP did not reduce the incidence of POCD compared to a higher intra-operative MAP (RR = 1.012, 95% CI: [0.277–3.688], $p = 0.986$). However, it was noted that a shorter cardiopulmonary bypass time was associated with a lower incidence of POCD, regardless of which group the patients were allocated to (RR-logarithmic form = -0.519 , 95% CI: [-0.949 , -0.089], $p = 0.017$) (96). These results suggest that perhaps the longer bypass time did potential benefits of a low intraoperative MAP on post-operative cognitive function to be observed.

Monitoring of Cerebral Perfusion via Near-Infrared Spectroscopy

The monitoring of cerebral perfusion is an area of interest to reduce POCD. Regional cerebral oxygenation may be non-invasively monitored using near-infrared spectroscopy (NIRS). This involves attaching probes, one transmitter and two sensors, onto the skin of the patients' forehead (100). One sensor detects the absorption of infrared light from superficial tissue, whilst the other detects infrared light from deeper tissue (100). Subsequently, the transmitter emits infrared light, which is absorbed by haemoglobin. Oxygenated and deoxygenated haemoglobin absorb infrared light differently, allowing real-time monitoring of regional cerebral oxygenation by comparing the balance between cerebral oxygen consumption and supply (101, 102). NIRS does not distinguish between arterial and venous blood but reflect the overall regional balance of oxygen supply and demand. This is known as regional cerebral oxygen saturation (rSO₂). In contrast, pulse oximetry aims to determine the saturation of oxygen in arterial blood (103). Monitoring of rSO₂ with NIRS allows for a rapid correction of cerebral desaturations using a standardised protocol. This involves reducing mechanical obstruction to cerebral flow by repositioning of the head or venous canulae, increasing cerebral oxygen delivery (increasing FiO₂, pCO₂ or PaCO₂, red blood cell transfusions or pump flow rate), or reducing oxygen consumption (increasing depth of anaesthesia or hypothermia) (104).

The efficacy of detecting cerebral desaturations using NIRS to prevent POCD following cardiac surgery is unclear. Ten studies were identified, with the results summarised in **Table 4**. Five studies supported the use of NIRS for the early detection of cerebral desaturations to prevent POCD. Kara et al. (105) demonstrated that the use of NIRS during cardiac surgery to detect desaturations of rSO₂ > 20% is associated with an increase in MoCA scores post-operatively ($p < 0.001$) (105). The standardised protocol mentioned previously was applied when cerebral desaturations were greater than 20%. Mild cognitive impairment was present in 16.3% of patients in the NIRS group, whilst it was present in 44.4% of the non-NIRS group. The use of NIRS as a cerebral oximeter was also correlated with an increase in MoCA scores ($r = 0.59$, $p < 0.001$). Similarly, Colak et al. (106) demonstrated that the incidence of POCD was significantly less in the NIRS group compared to the control group ($p = 0.02$). Additionally, they found that prolonged rSO₂ desaturations were the strongest predictor of cognitive decline (106). Zorilla et al. conducted a meta-analysis and found that the use of intraoperative NIRS is associated with a significant reduction in POCD at 1 week postoperatively (RR 0.55; 95% CI 0.36–0.86; $p = 0.009$) (107). Uysal et al. (108) used intraoperative NIRS monitoring to detect episodes of rSO₂ < 60% for more than 60 s. Upon reaching this threshold, the previously mentioned standard intervention was applied to increase rSO₂ until it was at least 60% on both probes. They found that patients allocated to the NIRS group had significantly better memory scores at the 6-month post-operative follow up compared to the control group (0.60 vs. -0.17 ; $p = 0.008$). However, there was no difference in response speed, processing speed or attention at the 6 month follow up. They also did not find an association between the duration of and severity of the cerebral desaturations with the development of POCD (108). Furthermore, Soenarto et al. (103) conducted a cohort study and demonstrated that the episodes of cerebral desaturation of >20% were significantly longer in patients with POCD ($p = 0.007$) (103). However, the magnitude of rSO₂ desaturations was not associated with POCD.

Five studies did not show the clear benefit of detecting cerebral desaturations with NIRS and providing early intervention in preventing POCD following cardiac surgery. In a study of 59 patients, Kumpaitiene et al. (109) aimed to demonstrate an association between a reduction in rSO₂, POCD and the level of brain injury markers. They defined cerebral desaturation as a decrease in decrease in rSO₂ $\geq 20\%$ from baseline or an absolute rSO₂ of $\leq 45\%$. They detected POCD in 37% of patients and cerebral desaturations in 35% of the patients. However, short reductions in rSO₂ during surgery is not associated with the incidence of POCD. With regards to the brain injury markers, there were no significant changes in the level of glial fibrillary acidic protein following surgery. This may be explained by a reduced susceptibility of glial cells to ischaemia. On the contrary, there was an elevation in Neuron-Specific enolase in 49% of patients following surgery, but there was no association with POCD. As neuron-specific enolase is also found in erythrocytes and platelets, this elevation may be attributed to haemolysis as a result of blood surface interactions during

TABLE 4 | Studies examining the efficacy of NIRS to detect cerebral desaturations in preventing POCD following cardiac surgery.

Study	Aim	Surgery Type	Study Type	Patient number	Definition of POCD	T1 Cognitive Assessment	T2 Cognitive Assessment	Psychological Assessment Tool	Findings
Kara et al. (105)	To investigate whether intraoperative cerebral oximetry using NIRS should be used to prevent POCD following CABG	On-pump CABG	RCT NIRS vs. No NIRS A standardised desaturation algorithm was commenced when rSO ₂ value dropped by more than 20% compared to baseline	79 NIRS (<i>n</i> = 43) No NIRS (<i>n</i> = 36)	MoCA Score: <26 Mild cognitive impairment: 19–25 Serious cognitive impairment: <19	Before surgery	Not specified	MoCA	The NIRS group had 16.3% patients with mild cognitive impairment, whilst 44.4% of non-NIRS group had mild cognitive impairment ($p = 0.01$). Use of NIRS is with a correlated increase in MoCA score ($r = 0.59$, $p < 0.001$) Post-operative MoCA score in NIRS group was 26.8 ± 1.9 , whilst non-NIRS group was 23.6 ± 2.5 , $p < 0.001$. Statistically significant decrease in mean postoperative MoCA score compared to baseline in no NIRS group
Colak et al. (106)	To determine whether cerebral oximetry monitoring (INVOS) can decrease POCD following CABG	On-pump CABG	RCT NIRS vs. control Intervention group maintained rSO ₂ > 80% of baseline or >50% absolute value. If rSO ₂ decreased below these values, standardised protocol commenced	200	Decrease in performance on at least one test	Day before surgery	POD7	MMSE CTT1 GPT	POCD Incidence: 40.3% POCD incidence was significantly less in the INVOS NIRS group (28%) compared to control group (52%; $p = 0.02$) at POD7. Prolonged rSO ₂ desaturation was the strongest predictor of cognitive decline in INVOS group
Dubovoy et al. (49)	To determine whether management of cerebral oximetry desaturations is associated with improved cognitive outcomes	Aortic reconstruction under deep hypothermic circulatory arrest	Retrospective analysis	17	Decrease in summed normalised score from neuropsychological battery compared to baseline	Not specified	3 months postoperatively	HVLT leaning/delay/discrimination index COWAT BVMT delay/recognition discrimination	POCD in 17 (41%) of patients No association between baseline cerebral oximetry and cognitive dysfunction “POCD is associated with loss of complexity of the time series as shown by a decrease in FwFn”

(Continued)

TABLE 4 | (Continued)

Study	Aim	Surgery Type	Study Type	Patient number	Definition of POCD	T1 Cognitive Assessment	T2 Cognitive Assessment	Psychological Assessment Tool	Findings
Rogers et al. (113)	To assess whether personalised optimisation of cerebral perfusion using NIRS would reduce perioperative brain, kidney and heart injury.	Combined on-pump CABG+ valve surgery, isolated valve surgery.	RCT Personalised vs. generic algorithms for optimising tissue oxygenation The generic algorithm optimised tissue oxygenation using measures of oxygen utilisation and a predefined intraoperative haematocrit transfusion threshold of 23% NIRS algorithm aimed to maintain an absolute rSO ₂ value >50%, or >70% compared to baseline. A restrictive intraoperative haematocrit transfusion threshold of 18% was applied	204 Patient specific algorithm (<i>n</i> = 98) Generic Algorithm (<i>n</i> = 106)	Not specified	Pre-operatively	POD4-7, 3 months	TMT A + B RAVLT WIAS (Digit Symbol Test) COWAT GPT MMSE Anxiety/depression	NIRS group performed better for verbal fluency (non-core cognitive domain; mean difference 3.73; 95% CI: 1.50, 5.96) No difference between groups for core cognitive domains (attention, verbal memory, motor coordination) and non-core cognitive domains (psychomotor speed and visuospatial skills)
Kumpaitiene et al. (109)	To determine the correlation between decreased rSO ₂ saturation, POCD and blood levels of brain injury markers following cardiac surgery	On-pump CABG	Prospective observational trial Cerebral desaturation was defined as a decrease in rSO ₂ ≥ 20% from baseline or an absolute rSO ₂ of ≤45%	59	Sum of Z score > 2, or at least two Z scores for separate tests > 2	Eve of surgery	POD7-10	MMSE RAVLT TMT A + B WIAS (Digit Span and Digit Symbol Substitution Test) Schulte table	POCD in 22 (37%) patients Decreased rSO ₂ in 21 (35%) patients Short term episodes of decreased rSO ₂ during surgery is not correlated with incidence of cognitive impairment No significant changes in the level of glial fibrillary acidic protein following surgery. Neuron-specific enolase increased in 29 (49%) of patients following surgery, but there was no association with POCD

(Continued)

TABLE 4 | (Continued)

Study	Aim	Surgery Type	Study Type	Patient number	Definition of POCD	T1 Cognitive Assessment	T2 Cognitive Assessment	Psychological Assessment Tool	Findings
Holmgaard et al. (111)	To identify whether longer cumulative times of $rSO_2 > 10\%$ below baseline as detected using NIRS is associated with POCD	On-pump CABG	Secondary analysis of parallel group randomised trial	148	Sum of Z score > 2 , or at least two Z scores for separate tests > 2	Day before surgery	First follow up was day before discharge or POD8, whichever came first Second follow up was 3 months later	ISPOCD battery (VLT, CST, SCWI, and LDC)	44 (29%) of patients had POCD at discharge, 12 (8%) of patients had POCD at 3 months The median time of $rSO_2 > 10\%$ below baseline did not differ between patients with or without POCD at discharge (Difference = 0.0 min, 95% CI: $(-3.11, 1.47)$, $p = 0.88$) No significant association between any neuropsychological test outcomes and POCD No significant association between intra-operative rO_2 and incidence of POCD
Uysal et al. (108)	Assess whether optimising cerebral oxygenation using intraoperative NIRS is associated with better neurocognitive outcomes compared to current care	On-pump cardiac CABG or valve surgery	RCT NIRS intervention vs. control Intraoperative $rSO_2 < 60\%$ for more than 60 s triggered intervention Intervention protocol initiated until rSO_2 was restored to at least 60% on both probes	125 NIRS Group ($n = 59$) Control group ($n = 66$)	Change in 4 cognitive factor scores from preoperative to postoperative time points	> 24 h before surgery	3 and 6 months postoperatively	Cognitive Stability Index Battery (10 subtests which analyse response speed, processing speed, attention and memory)	Intraoperative NIRS triggering early intervention resulted in significantly better memory scores at the 6-month postoperative follow up (0.60 vs. -0.17 ; $p = 0.008$). No difference in response speed, processing speed, or attention at 6 months. However, duration and severity of desaturation was not associated with cognitive impairment.
Bennett et al. (101)	To determine whether their NIRS protocol would improve neurological outcomes postoperatively prior to discharge and at 6 months postoperatively	Cardiac surgery with CPB	Double blinded RCT Intervention initiated if rSO_2 dropped below baseline on room air	182 NIRS Group ($n = 91$) Conventional management group ($n = 91$)	Not specified	Day before surgery	POD3-5 and 6 months	MMSE HVLIT TMT A/B Anti-saccadic eye test	Significant improvement in self-reported 6-month general functioning in the NIRS group ($p = 0.016$) No difference between groups in neurocognitive tests ($p = 0.498$) and neurological dysfunction ($p = 0.600$) postoperatively Duration of ICU stay was significantly shorter in NIRS group ($p = 0.026$)

(Continued)

TABLE 4 | (Continued)

Study	Aim	Surgery Type	Study Type	Patient number	Definition of POCD	T1 Cognitive Assessment	T2 Cognitive Assessment	Psychological Assessment Tool	Findings
Semrau et al. (114)	To determine the relationship between rSO ₂ and postoperative neurological function	On-pump CABG	Prospective observational trial	40	Z score > 1.96	Day before surgery	3 months following surgery	RBANS and KINARM (robotic technologies)	Pre-operative cognitive impairment accounted for 82.2% of variance in post-operative performance
Soenarto et al. (103)	To determine the relationship between POCD and rSO ₂ using NIRS	Cardiac surgery with CPB	Prospective observational trial Desaturation defined as >20% decrease on NIRS compared to baseline	70	>20% drop from baseline on at least 2 cognitive tests	Day before surgery	POD5	RAVLT TMT Digit Span (forwards and backwards)	POCD incidence: 51.7% (31 patients) Total cerebral desaturation was significantly longer in patients with POCD ($p = 0.007$) Absolute value of rSO ₂ was not associated with POCD but a drop in rSO ₂ > 20% from baseline may be associated with POCD

BVMT, brief verbal memory test; CABG, coronary artery bypass graft; COWAT, controlled oral word association test; CST, concept shifting test; CTT1, colour trail test 1; GPT, grooved pegboard test; HVLIT, Hopkins verbal learning test; LDC, letter digit coding; MMSE, mini-mental state examination; MoCA, montreal cognitive assessment scale; NIRS, near infrared spectroscopy; POCD, postoperative cognitive dysfunction; POD, postoperative day; RAVLT, rey auditory verbal learning test; RCT, randomised control trial; SCWI, stroop colour word interference; rSO₂, regional cerebral oxygen saturation; T1, pre-operative timepoint for neurocognitive testing; T2, post-operative timepoint for neurocognitive testing; TMT, trail making test; VLT, verbal learning test; WIAS, wechsler adult intelligence scale.

on-pump cardiac surgery (109, 110). Similarly, in a secondary analysis of 148 patients, Holmgaard et al. (111) did not detect an association between the duration or extent of rSO₂ desaturations >10% compared to baseline with the incidence of POCD at discharge, or 3 months post-operatively. The median time of rSO₂ > 10% below baseline did not differ between patients with or without POCD at discharge [Difference = 0.0 min, 95% CI: (−3.11, 1.47), $p = 0.88$]. There was no significant association between any neuropsychological test outcomes and the development of POCD. However, a potential confounder may be the more frequent use of noradrenaline in patients with POCD, given noradrenaline is associated with decreased rSO₂ (111, 112). Rogers et al. (113) aimed to determine whether a maintaining an absolute rSO₂ of >50% or >70% compared to baseline would reduce peri-operative end-organ damage. However, there was no difference in neuropsychological performance in the cognitive domains including attention, verbal memory, motor coordination, psychomotor speed and visuospatial skill. The NIRS group performed better in the verbal fluency test compared to the generic algorithm group (Mean difference 3.73, 95% CI: 1.50–5.96). There was no difference between the groups in regard to the time to intensive care unit discharge, time to hospital discharge, brain injury markers (S100), myocardial injury markers (serum troponin T) or kidney injury markers (113). Furthermore, Semrau et al. (114) demonstrated that pre-operative cognitive impairment is a stronger predictor of POCD compared to intraoperative rSO₂ desaturations. They measured neuropsychological function using a standardised assessment known as the Repeatable Battery for Assessment of Neuropsychological Status (RBANS) and the KINARM Standard Tests on the KINARM Endpoint robot. The KINARM robotic test provides quantitative information about cognitive domains, sensory and motor function by asking patients to move the handles and complete visually stimulated tasks. From the RBANS test, there were non-significant impairments in immediate (10 vs. 10%, $p = 1.00$) and delayed memory (12.5 vs. 17.1%, $p = 0.727$), visuospatial (12.5 vs. 9.75%, $p = 1.00$) and language (2.5 vs. 0%, $p = 1.00$) when comparing pre-operative and post-operative results. Similarly, from the KINARM test, there were non-significant impairments on the reverse visually guided reaching task, object hit and avoid tasks, ball on bar tasks and arm positioning match tasks. Notably, pre-operative cognitive performance accounted for 82.2% of variance in post-operative performance (114). Bennett et al. found that their NIRS protocol (commencing intervention when rSO₂ dropped below baseline on room air) did not reduce neurocognitive dysfunction post-operatively prior to discharge or at 6 months. However, the length of the ICU stay was significantly shorter in the NIRS group ($p = 0.026$) (101).

Benefits of Near-Infrared Spectroscopy

Near-infrared spectroscopy is a cost-effective monitoring modality compared to electroencephalogram and transcranial doppler. These alternatives modalities require additional technical support, specifically for setup and interpretation of the results (49). Secondly, NIRS allows for monitoring of

haemodynamic trends, identifying patients at risk of developing POCD, and consequently implementing interventions prior to the occurrence of prolonged or significant cerebral desaturations. This is particularly important in the elderly, as cognitive function naturally declines with age and cardiac surgery may exacerbate this cognitive decline (49, 90, 115). Interventions have included increasing inspired oxygen concentration, altering carbon dioxide levels, increasing mean arterial pressure, and increasing anaesthesia (100). Additionally, the positioning of the NIRS probes over watershed areas such as the anterior and middle cerebral arteries may prevent watershed strokes (116, 117). Furthermore, cerebral desaturations have been associated with greater length of hospital stays and additional financial strains. Fischer et al. demonstrated that a perioperative regional cerebral oxygenation of under 60% for greater than 30 min was associated with an additional 4 days in the hospital, costing an extra \$8300 (118).

Limitations of Near-Infrared Spectroscopy

Firstly, the cerebral oximetry algorithm assumes that the venous: arterial ratio within the tissue is 70/30. However, this is altered during heart failure and consequently the cerebral oximetry reading may not be accurate. Furthermore, the algorithm also assumes that infrared light travels the same distance in each patient. Hence, in patients with oedema, the infrared light may not reach the vasculature and detect hypoxia in the frontal lobes (49). This is naturally compounded by the inability to detect ischaemia in unmonitored regions such as the posterior circulation. Additionally, false positives have been recorded, with patients being neurologically normal despite periods of cerebral desaturations (119). However, this may reflect optimal intervention shortening the period of intraoperative desaturations. Despite these limitations, to facilitate the integration of NIRS into clinical practice, rSO₂ values should be regularly inputted into a patient's medical records. Furthermore, having a bedside monitor which displays live rSO₂ values may allow for pre-emptive interventions on the wards to reduce cognitive impairment (90). Lastly, future studies should aim to use standardised intervention parameters when determining when to reverse cerebral desaturations to allow for more robust clinical data.

Cerebral Microemboli

Source of Microemboli

Emboli may cause adverse neurological outcomes through cerebral inflammation, ischaemia, and infarction (120). Microemboli may contribute to POCD by occluding smaller arteries, arterioles and capillaries, whilst macroemboli are thought to contribute to strokes by occluding flow in vessels larger than 200 μ m in diameter (121, 122). Emboli may be in the form of thrombi, fat or gas. Lipid emboli are derived from plaque release following aortic manipulation such as cross clamping or cannulation/decannulation, or from the cardiectomy suction. Emboli returned through the arterial canula will travel through the aortic arch, reaching sites such as the cerebral vessels (123, 124). In contrast, gaseous emboli may be derived from inadequate deairing of open chamber procedures, introduction by perfusion

interventions such as drug delivery or the entrapment of air within the cardiectomy suction (88, 125).

Detection of Microemboli

Microemboli are predominantly detected using transcranial doppler ultrasound (TCD) (126). TCD detects high-intensity signals (HITS), a surrogate marker for the number of microemboli (123). HITS are generally detected within the middle cerebral arteries. Currently, TCD cannot determine the composition of the emboli or detect extremely small emboli (<3 mm) (88). Diffuse weighted imaging MRI is the gold standard for detecting ischaemic lesions, but is more costly. However, the use of MRI is limited by several factors. Firstly, MRI cannot provide real-time intraoperative monitoring, whilst a transcranial doppler ultrasound can be used intraoperatively. Moreover, MRI is limited by the logistical and timing requirements, as they cannot be performed perioperatively in contrast to transcranial doppler ultrasounds. Lastly, MRIs are unable to be performed in all patient groups due to contraindications such as having a pacemaker *in situ* (127).

Recent Literature

Recent studies have examined the relationship between the embolic load or embolic size and POCD (Table 5). Patel et al. used a novel bubble sizing algorithm to determine the size and volume of bubbles released during cardiac surgery. The number of bubbles and emboli detected were not associated with POCD ($p = 0.49$) (128). The main limitation of this study was the inability to distinguish between the types of emboli. Historically, studies have suggested that reduced embolic load is associated with less POCD (129–131). These conflicting results perhaps suggest that the composition and site of emboli are more important factors in the development of POCD. This supports the notion of “strategic infarcts,” where small lesions or emboli in key brain regions which control cognitive and behaviour may result in more significant cognitive impairment compared to insults in other regions (132). In Wiberg's study, patients were randomised to low MAP (40–50 mmHg) or high MAP (70–80 mmHg) targets during cardiac surgery. However, there was no relationship between the number of gaseous microemboli and the development of POCD (133). This does not support the washout theory, which states that higher MAP targets during surgery facilitate the clearance of emboli (134).

Modification of surgical techniques have been explored to minimise microemboli. Halkos et al. investigated the effect of different aortic clamping strategies on the development of cerebral emboli and POCD. They had four groups: off-pump with partial clamp, off-pump with a clampless facilitating device, on-pump with single or double clamp. There was no association between clamping strategies and POCD. They detected more embolic events using TCD in the off-pump group with the clampless facilitating device. There were no differences in embolic events for the on-pump group (123). Bozhinovska et al. (120) explored the difference between mini-sternotomy and mini-thoracotomy for aortic valve replacement on the development of neurological complications. There was no difference in microembolic load between the groups

TABLE 5 | Studies analysing microemboli and POCD.

Study	Aim	Surgery Type	Study Type	Patient number	Definition of POCD	T1 Cognitive Assessment	T2 Cognitive Assessment	Psychological Assessment Tool	Findings
Halkos et al. (123)	To investigate different operative strategies (aortic clamping) on developing of cerebral emboli as detected with transcranial doppler ultrasound	On-pump or Off-pump CABG	Randomised control trial Off pump group: partial clamp or clampless facilitating device On pump group: single or double clamp	142 Off-pump CABG with partial clamp ($n = 36$) Off-pump CABG with clampless facilitating device ($n = 36$) On-pump CABG with single clamp ($n = 34$) On-pump CABG with double clamp ($n = 36$)	Not specified	Preoperatively	POD30	CNS-VS	No association between cerebral microembolisation and POCD “No difference in cerebral embolic events between on-pump patients undergoing a single clamp-technique and those undergoing a double clamp technique” “More cerebral embolic events occurred in off pump patients when clamp less facilitating device was used compared with partial clamp technique”
Patel et al. (128)	To determine whether high volumes of macrobubbles ($> 100 \mu\text{M}$) entering the brain is associated with an increased risk of cerebral microbleeds or POCD	CABG, valve surgery	Prospective, observational trial	46	Not specified	1–2 weeks before surgery	6–8 weeks postoperatively	TMT A/B GPT WMS WIAS	Total number of emboli ($p = 0.49$) and CPB duration ($p = 0.99$) is not associated with POCD Odds of developing POCD increased by 11% for every year after 64 years of age ($p = 0.01$)
Wiberg et al. (133)	To investigate the association between total number of gaseous micro-emboli in the CPB circuitry and the development of POCD or cerebral infarcts	Cardiac surgery with CPB	Secondary analysis of parallel group randomised trial (PPCI trial) Patients randomised to low MAP (40–50 mmHg) or high MAP target (70–80 mmHg) Number and volume of gaseous micro-emboli passing through inflow CPB canula detected by doppler ultrasound (Bubble Counter Clinical 200) Cerebral infarcts detected by diffusion weighted MRI.	143	Sum of Z score > 1.96 , or at least two Z scores for separate tests > 1.96	Day before surgery	Before POD7 or discharge	ISPOCD battery (VLT, CST, SCW, and LDC)	No significant association between number of gaseous microemboli and the development of POCD or cerebral infarctions Significant association between cerebral infarcts and development of POCD 36 (28%) of patients developed POCD and 66 (46%) of patients had cerebral infarctions after 7 days

(Continued)

TABLE 5 | (Continued)

Study	Aim	Surgery Type	Study Type	Patient number	Definition of POCD	T1 Cognitive Assessment	T2 Cognitive Assessment	Psychological Assessment Tool	Findings
Bozhinovska et al. (120)	To assess the difference in neurological complications such as POCD following mini-sternotomy vs. mini-thoracotomy using microembolic signals	Aortic valve replacement	Prospective, observational trial Middle cerebral arteries monitored via trans-cranial doppler ultrasound	52 Mini-sternotomy (n = 25) Mini-thoracotomy (n = 27)	Not specified	Day before surgery	Up to 30 days post-operatively	ACE-R	Microembolic signals were not associated with POCD following mini-thoracotomy or mini-sternotomy. Hence, both techniques are comparable. No difference in ACE-R scores between groups (p = 0.630).

ACE-R, addenbrooke's cognitive examination revised; CABG, coronary artery bypass graft; CNS VS, cns vital signs; CST, concept shifting test; GPT, grooved pegboard test; LDC, letter digit coding; MAP, mean arterial pressure; POCD, postoperative cognitive dysfunction; POD, postoperative day; SCW, stroop colour word interference; T1, pre-operative timepoint for neurocognitive testing; T2, post-operative timepoint for neurocognitive testing; TMT, trail making test; VLT, verbal learning test; WASI, wechsler adult intelligence scale; WMS, wechsler memory test.

and no association with POCD as detected using TCD. The Addenbrooke's Cognitive Examination Revised Test score decreased in both groups following surgery (Mini-sternotomy: 85.2 ± 9.6 vs. 82.9 ± 11.4 , $p = 0.012$; Mini-thoracotomy: 85.2 ± 9.6 vs. 81.3 ± 8.8 , $p = 0.001$). This suggests that the less-invasive mini-thoracotomy approach may be a safe alternative. The main limitation of the mini-thoracotomy approach arises from the possibility of incomplete cardiac deairing at the conclusion of the procedure. The total intraoperative micro-embolic load was associated with the duration of cardiopulmonary bypass.

Issitt et al. demonstrated that a new lipid filtration technique prevents entry of lipid microemboli from the pericardial suction into systemic circulation using a syphon mechanism ($p < 0.001$). This overcomes the current limitations of fat deformability, which allows fats to pass through the CPB filters. The effective filtration of lipid microemboli attenuates the release of neuron-specific enolase, a biomarker for neuronal injury ($p = 0.013$) (135, 136).

Glycaemic Control
Importance of Glycaemic Control During Cardiac Surgery

Optimisation of peri-operative glycaemic control is crucial in cardiac surgery for improving clinical outcomes. Hyperglycaemia is both a cause and consequence of inflammation. Chronic and intraoperative hyperglycaemia is associated with adverse outcomes. Chronic hyperglycaemia increases the risk of developing age related cognitive impairment and dementia (137). This predisposition to neurocognitive impairment may be attributed to a reaction between glycated end-products caused by hyperglycaemia, with the vascular endothelium (138). Conversely, intraoperative hyperglycaemia is associated with arrhythmias, low cardiac output states, postoperative infections, postoperative neurocognitive dysfunctions, and increased mortality in both cardiac surgery patients and critically ill patients in the intensive care unit (139–141). Intraoperative hyperglycaemia may occur due to a stress hyperglycaemic response, which refers to a transient elevation of blood glucose levels in response to illness or injury. Within the cardiac surgery setting, stress hyperglycaemia may occur due to hypothermia, the administration of glucose containing cardioplegia and the administration of heparin (142, 143). Certain physiological processes such as increased substrate availability and renal reabsorption of glucose are enhanced during cardiac surgery, exacerbating the stress hyperglycaemia response (144).

Pathophysiological Mechanism

The pathophysiological mechanism linking hyperglycaemia and postoperative cognitive impairment has yet to be fully elucidated. Hyperglycaemia may disrupt the blood brain barrier by damaging pericytes embedded in the basement membrane of blood vessels and increase the susceptibility of these vessels to oxidative stress (145). Disruption of the blood brain barrier facilitates the development of the cerebral oedema, which worsens neurological functioning (146). Additionally, there is an increase in anaerobic glycolysis as a response to activation of the hypothalamic

pituitary axis and stress hyperglycaemia during cardiac surgery. This leads to a rise in the concentration of acidic metabolites such as lactate, which contributes to intracellular acidosis. Lactate may cross the disrupted blood brain barrier and contribute to neurocognitive impairment *via* excess increases in intracellular calcium concentration, mitochondrial dysfunction, and protein denaturation (147, 148). Lastly, hyperglycaemia may disrupt the autonomic regulation of cerebral vasculature, delaying neurocognitive recovery following cardiac surgery (148).

Association Between Glycaemic Control and Postoperative Cognitive Impairment

Three studies examined the association between glycaemic control and postoperative cognitive impairment following cardiac surgery (Table 6). Kotfis et al. performed a retrospective cohort study to determine whether pre-operative elevation of Haemoglobin A1C (HBA1C) or diabetes was associated with post-operative delirium following cardiac surgery. In an analysis, of 3178 patients, preoperative HBA1C was elevated above 6% in more delirious patients compared to non-delirious patients (44.54 vs. 33.04%; $p < 0.001$). Additionally, patients with delirium were more likely to be diabetic than non-diabetic (42.03 vs. 29.86%; $p < 0.001$) (149). From this, it appears that elevated pre-operative HBA1C and diabetes are risk factors for post-operative delirium following cardiac surgery. However, given the retrospective nature of the study, a causal relationship cannot be established. To overcome this limitation, prospective trials should be performed in the future. Additionally, Zhou et al. conducted an observational trial to examine the effect of impaired fasting glucose on brain injury in patients undergoing on-pump CABG surgery. Patients were followed up based on their pre-operative fasting glucose levels. They found that there were no differences in MMSE scores between the impaired fasting glucose and control groups at 7 days ($p = 0.704$). However, Neuron Specific Enolase (NSE) and S100B concentrations were significantly higher in the impaired fasting glucose group immediately following the termination of CPB, 2 h after the termination of CPB and 24 h postoperatively (148). This suggests that while overt neurocognitive deterioration and postoperative cognitive dysfunction was minimally observed in the impaired fasting glucose group, subclinical manifestations of brain injury may have been present. Scrimgeour et al. (150) conducted a similar observational study, aiming to determine whether perioperative glycaemic control improves neurocognitive decline following cardiac surgery. Patients were followed up based on their pre-operative HBA1C levels (<7 or $>7\%$). Scrimgeour and colleagues found that preoperative elevated HBA1C was not associated with neurocognitive impairment on POD4 ($p = 0.973$). Elevated fasting glucose levels (>126 mg/dL or 7 mmol/L) on the morning of surgery was not associated with neurocognitive impairment on POD4 ($p = 0.910$). This may be potentially explained by a minimal duration of time with metabolic derangements. Scrimgeour et al. also observed that 73% of patients within the trial had a reduction in neurocognitive functioning on POD4 (150). This large incidence of postoperative neurocognitive

decline may be attributed to the use of the 'Repeatable Battery Assessment of Neuropsychological Status,' which is sensitive in detecting any minor neurocognitive impairment. Scrimgeour and colleagues also compared changes in genetic expression in patients with neurocognitive decline, and without neurocognitive decline following cardiac surgery. They detected an upregulation in anti-inflammatory genes such as Annexin A1 and transforming growth factor B (TGF-B) in patients without neurocognitive dysfunction following surgery. Annexin A1 has anti-inflammatory properties, inhibiting neutrophil migration and inducing the conversion of macrophages into an anti-inflammatory M2 phenotype. Similarly, TGF-B increases the expression of anti-inflammatory cytokine IL-10 and facilitates the conversion of macrophages into an anti-inflammatory M2 phenotype. Future studies should examine whether these gene expression changes are indeed a causative factor in the development of postoperative cognitive dysfunction and whether therapeutic strategies can be developed to target this mechanism.

Degree of Glycaemic Control and Postoperative Cognitive Impairment

Two studies examined whether tight intra-operative control of blood glucose levels during cardiac surgery may prevent post-operative cognitive impairment (Table 6). Saager et al. (151) compared the effect of tight intra-operative glucose control using a hyperinsulinemic-normoglycemic clamp and standard blood glucose management on postoperative delirium following cardiac surgery. The tightly controlled blood glucose group targetted an intraoperative blood glucose level of 80–110 mg/dL or 4.4–6.1 mmol/L. This was achieved with a constant infusion of insulin and concomitant infusion of 20% dextrose. The standard blood glucose control group targetted an intraoperative blood glucose level less than 150 mg/dL or 8.3 mmol/L, which was achieved *via* conventional insulin administration. Saager et al. observed that patients in the tight intraoperative glucose control were 1.89× more likely of developing delirium compared to the standard therapy group (RR 1.96; 95% CI: 1.06–3.37; $p = 0.03$). The incidence of delirium was also double in the tight glucose control group compared to the standard therapy group (28 vs. 14%) (151). Kurnaz et al. also compared tight and liberal control of intraoperative glucose levels. For the tightly controlled blood glucose group, an insulin infusion was started when blood glucose levels exceeded 120 mg/dL or 6.7 mmol/L. For the liberally controlled blood glucose group, an insulin infusion was started when blood glucose levels exceeded 180 mg/dL or 10 mmol/L. Kurnaz and colleagues observed that the incidence of POCD between the two groups during the first week postoperatively were similar. Additionally, they found that persistent POCD was observed in 5 patients (25%) in the tight glucose control group, while no POCD was observed in the liberal control group at 3 months ($p = 0.047$). This suggests tight intra-operative glycaemic control may prevent persistent cognitive impairment following cardiac surgery (21). However, future studies should aim to use standardised interventions and definitions of tight glycaemic control to establish the most effective method of peri-operative glycaemic control following cardiac surgery.

TABLE 6 | Studies assessing the effect of glycaemic control on post-operative cognitive impairment following cardiac surgery.

Study	Aim	Surgery Type	Study Type	Patient Number	Definition of POCD	T1 Cognitive Assessment	T2 Cognitive Assessment	Psychological Assessment Tool	Findings
Saager et al. (151)	To determine the effect of tight intraoperative glucose control using hyperinsulinemic-normoglycemic clamp on postoperative delirium following cardiac surgery	Cardiac surgery	Double blind RCT Tight intraoperative glucose control with hyperinsulinemic-normoglycemic clamp (target BSL 80–110 mg/dl or 4.4–6.1 mmol/L). Achieved with constant infusion of insulin and concomitant infusion of 20% dextrose Standard therapy (conventional insulin administration with BSL target <150 mg/dl or 8.3 mmol/L)	198 Hyperinsulinemic clamp ($n = 93$) Standard therapy ($n = 108$)	Not specified	Preoperatively	Not specified	CAM MDAS	Patients in the tight intraoperative glucose control group were 1.89× more likely of developing delirium compared to standard therapy group (RR 1.96; 95% CI: 1.06–3.37; $p = 0.03$) Incidence of delirium was 28% in tight glucose control group and 14% in standard therapy group
Kurnaz et al. (21)	To determine the effect of tightly controlled blood glucose levels during cardiac surgery	On-pump CABG	Double blind RCT Tight glucose control group-maintained blood glucose between 80–120 mg/dl or 4.4–6.7 mmol/L. Liberal control group maintained blood glucose between 80–180 mg/dl or 4.4–10 mmol/L	40 Tight control group ($n = 20$) Liberal control group ($n = 20$)	Drop of one SD from baseline on two or more tests	Day before surgery	1 and 12 week following surgery	Weschler Memory Scale Logical Memory Subtest Clock drawing test Word list generation test Digit span subtest Visuospatial skills test	Tight perioperative glycaemic control following cardiac surgery may prevent persisting cognitive impairment. Incidence of POCD during the first week following surgery was similar between the groups. Persistent POCD was observed in 5 patients (25%) in the tight glucose control group, while no POCD was observed in the liberal control group at 3 months ($p = 0.047$).
Kotfis et al. (149)	To determine whether postoperative delirium following cardiac surgery is associated with diabetes or elevated HBA1C	Major cardiac surgery	Retrospective observational cohort study	3178	Not specified	Not specified	Not specified	CAM	15.8% of patients (502) were diagnosed with postoperative delirium Patients with delirium were more likely to be diabetic (42.03 vs. 29.86%, $p < 0.001$). Preoperative HBA1C was elevated above 6% in more delirious than non-delirious patients (44.54 vs. 33.04%; $p < 0.001$). Risk factors for delirium include older age (> 70), ischaemic heart disease, diabetes, arterial hypertension, NYHA3/4, ejection fraction $< 30\%$ ($p < 0.01$)

(Continued)

TABLE 6 | (Continued)

Study	Aim	Surgery Type	Study Type	Patient Number	Definition of POCD	T1 Cognitive Assessment	T2 Cognitive Assessment	Psychological Assessment Tool	Findings
Zhou et al. (148)	To determine the effect of impaired fasting glucose on brain injury in patients undergoing cardiac surgery	On-pump CABG	Prospective observational trial Patients divided based on their preoperative fasting glucose levels	50 Impaired fasting glucose ($n = 25$) Control ($n = 25$)	MMSE < 24	Day before surgery	POD7	MMSE	No differences in MMSE scores between the impaired fasting glucose and control groups at 7 days ($p = 0.704$) NSE and S100B concentrations were significantly higher in the impaired fasting glucose group immediately following the termination of CPB, 2 h after the termination of CPB and 24 h postoperatively. Cerebral oxygen extraction ratio and lactic acid expression were significantly higher in the impaired glucose
Scrimgeour et al. (150)	To determine whether perioperative glycaemic control improves neurocognitive decline following cardiac surgery	On-pump CABG or valvular surgery	Prospective observational trial Patients followed up based on their pre-operative HBA1C levels (<7 or >7%)	30	Reduction from baseline	Day before surgery	POD4	RBANS	73% of patients had decrease neurocognitive function at POD4. Preoperative elevated HBA1C was not associated with neurocognitive impairment on POD4 ($p = 0.973$) Elevated fasting glucose levels (> 126 mg/dL or 7 mmol/l) on the morning of surgery was not associated with neurocognitive impairment on POD4 ($p = 0.910$) No difference in postoperative neurocognitive function in patients with higher maximum blood glucose levels during CPB (> 180 mg/dL or > 10 mmol/L; $p = 0.252$) or average glucose levels (> 160 mg/dL or > 8.9 mmol/l; $p = 0.639$)

CABG, coronary artery bypass graft; CAM, confusion assessment method; CPB, cardiopulmonary bypass; MDAS, memorial delirium assessment scale; MMSE, mini mental state examination; NSE, neuron-specific enolase; POCD, postoperative cognitive dysfunction; POD, postoperative day; RBANS, repeatable battery assessment of neuropsychological status; RCT, randomised controlled trial; T1, pre-operative timepoint for neurocognitive testing; T2, post-operative timepoint for neurocognitive testing; WMS, wechsler memory test.

Anaesthesia Induced Neurotoxicity

Anaesthesia during cardiac surgery may be induced using intravenous anaesthesia, or as a combination of intravenous and inhalational anaesthesia. Anaesthesia is essential for reducing sensation and inhibiting motor responses during the procedures. This section will discuss the types of anaesthesia agents used in clinical practice, their mechanism of actions, benefits and disadvantages and review the contemporary literature regarding their effect on post-operative cognitive impairment.

Volatile Anaesthetic Agents

Volatile anaesthetics exist in the liquid state at room temperature, before being vaporised into gas for absorption and distribution through the alveoli and pulmonary circulation. There are three main groups of volatile anaesthetics including halogenic ethers, alkanes, and gaseous agents. The halogenic ethers include isoflurane, sevoflurane, enflurane and desflurane. This group is the most common used in cardiac surgery. Secondly, the main alkane volatile anaesthesia agent is halothane. Halothane is the main non-ether anaesthetic in use today in modern clinical practice. Lastly, the gaseous volatile anaesthetic agents include nitrous oxide and xenon (152, 153). The specific mechanism of action of inhaled anaesthetic agents is unknown. However, it is known that they broadly potentiate the inhibitory, type A Gamma-aminobutyric acid (GABA_A) receptors within the central nervous system and two pore domain K⁺ channels to modulate neurotransmission. Additionally, the gaseous inhaled agents function by inhibiting the N-methyl-D-aspartate (NMDA) receptors (152, 154).

The use of inhaled halogenic ether anaesthetic agents such as isoflurane and sevoflurane have been demonstrated to be cardioprotective during cardiac surgery. Sevoflurane enhances the post-operative recovery of the stunned myocardial contractility, reduces myocardial ischaemia and the extent of reperfusion injury by scavenging oxygen free radicals (155, 156). These beneficial effects are a result of alterations in intracellular signalling pathways such as *via* the G-protein coupled-receptors, changes in mitochondrial function as well as potassium channel functioning (157). Recent studies and meta-analyses have reported conflicting evidence on the renal and hepatoprotective properties of volatile anaesthetics (158–160). Further human studies are required to elucidate the potential beneficial effects of volatile anaesthetics on other organ systems.

Whilst inhaled anaesthetic agents are essential for cardiac surgery, their use have been implicated the development in post-operative complications such as POCD and the development of Alzheimer's Dementia. There are numerous speculated molecular mechanisms regarding their potential neurotoxic nature. Pre-clinical studies from cell cultures and animal models have demonstrated that volatile anaesthesia may be cytotoxic, alter neuronal morphology, and increase caspase-3 expression, culminating in neuronal apoptosis. Additionally, there may be formation, oligomerisation and deposition of amyloid in response to anaesthesia (161). However, the literature has not shown a clear association between the exposure to general anaesthesia and the development of Alzheimer's disease (162).

Intravenous Anaesthesia

Intravenous anaesthesia can be used for both the induction and maintenance of general anaesthesia. Examples of intravenous anaesthesia includes propofol, dexmedetomidine, ketamine, barbiturates, and benzodiazepine (163). There has been significant research interest in the use of propofol and dexmedetomidine during cardiac surgery within the last few years. Propofol is a phenol compound with a rapid onset and short duration of action. Mechanistically, it primarily functions by potentiating the inhibitory GABA_A neurotransmitter response. Propofol also inhibits NMDA receptors, which prevents calcium ion influx and consequently reduces the likelihood of cytotoxic intracellular calcium overload. Furthermore, propofol may inhibit neuronal apoptosis through the modulation of cell survival and apoptotic proteins such as Bcl-2 and inhibits caspase-3. The use of propofol is associated with benefits such as ease of patient waking with minimal secretions, and anti-emetic properties. However, care must be taken when using propofol to prevent dose dependent hypotension and respiratory depression (164, 165). Dexmedetomidine is a selective α -2 adrenergic receptor agonist, which has been increasingly used. Section 3.6 provides a detailed discussion on the use of dexmedetomidine to reduce postoperative cognitive impairment.

Volatile Anaesthesia vs. Intravenous Anaesthesia

The European Association for Cardio-Thoracic Surgery as well as the American College of Cardiology and American Heart Association have recently released their guidelines stating a preference for using volatile anaesthesia during coronary artery bypass graft surgery (166, 167). However, the superiority of volatile anaesthesia over total intravenous anaesthesia for reducing poor outcomes is unclear. Four trials and two systematic reviews were identified comparing volatile and intravenous anaesthesia (Table 7).

Chen et al. conducted the first systematic review and meta-analysis to compare the neuroprotective effects of inhalational anaesthesia compared to total intravenous anaesthesia (such as propofol and sodium thiopental) in cardiac surgery with cardiopulmonary bypass (168). The inhalational anaesthesia included within the systematic review consisted of isoflurane, sevoflurane and desflurane. Conversely, the intravenous anaesthesia included within the study consisted of propofol, thiopental, midazolam, and ketamine. From six studies involving 230 patients, the serum level of S100B (Weighted Mean Difference; 95% CI) was significantly lower in the inhalational anaesthesia group compared to the total intravenous anaesthesia following cardiopulmonary bypass (−0.41, 95% CI [−0.81, −0.01], $p = 0.05$) and 24 h post-operatively (−0.32, 95% CI [−0.59, −0.05], $p = 0.02$). Additionally, from three studies involving 110 patients, the MMSE score (Weighted Mean Difference; 95% CI) was significantly higher in the inhalational anaesthesia group compared to the total intravenous anaesthesia group at 24 h post-operatively (1.87, 95% CI [0.82, 2.92], $p = 0.002$). These results highlight the potential superiority of inhalational anaesthesia compared to total intravenous anaesthesia for neuroprotection in patients undergoing cardiac

TABLE 7 | Studies assessing the effect of anaesthesia on cognitive impairment following cardiac surgery.

Study	Aim	Surgery Type	Study Type	Patient Number	Definition of POCD	T1 Cognitive Assessment	T2 Cognitive Assessment	Psychological Assessment Tool	Findings
Tang et al. (171)	To compare the effect of propofol vs. sevoflurane on cognitive impairment following on-pump cardiac surgery	On-pump cardiac surgery	RCT Sevoflurane administered to maintain end expiratory and end-effluent concentrations of 1–3% Propofol was infused to reach a serum concentration of 0.5–2.0 ug/kg/min with a BIS index of 40–55 intraoperatively	110 Propofol ($n = 55$) Sevoflurane ($n = 55$)	Not specified in study	Day before surgery	12 and 24 h postoperatively	MMSE	MMSE scores (Mean $\pm$ SD) were higher in the propofol group compared to the sevoflurane group when measured 24 h post-operatively (28.74 ± 4.53 vs. 24.30 ± 3.77 ; $p < 0.05$) Serum levels of NSE, S100B and MMP-9 were lower in the propofol group compared to the sevoflurane group at 6, 12, and 24 h post-operatively ($p < 0.05$) Incidence of POCD was significantly lower at 12 and 24 h postoperatively in the propofol group compared to the sevoflurane group ($p < 0.05$). POCD incidence in Sevoflurane group at 12 h: 12 patients (21.82%) POCD incidence in propofol group at 12 h: 5 patients (9.09%) POCD incidence in sevoflurane group at 24 h: 14 patients (25.45%) POCD incidence in propofol group at 24 h: 6 patients (10.91%)
Shi et al. (169)	To compare the effects of different maintenance methods on postoperative outcomes, inflammation, and haemodynamic stability	Off-pump CABG	RCT Control group (propofol 3 mg/kg/hr and fentanyl 5 ug/kg/hr for maintenance of anaesthesia) Observation group (Sevoflurane 3–4% concentration titrated to a BIS value for maintenance of anaesthesia)	94 Control group ($n = 47$) Observation group ($n = 47$)	Reduce in score compared to baseline	Day before surgery	Day after surgery	MMSE MoCA	A reduction in MMSE and MoCA scores postoperatively was lower in the observation group (sevoflurane) compared to the control group ($p < 0.005$). Larger increase in inflammatory markers (CRP, TNF- α , IL-6) in the control group compared to the observational group following surgery ($p < 0.05$) No significant difference in haemodynamic parameters including heart rate, mean arterial pressure, systemic vascular resistance index and cardiac index between the groups ($p > 0.05$) Intraoperative serum levels (Mean $\pm$ SD) of Malondialdehyde were lower in the observational group compared to the control group (3.48 ± 1.02 vs. 6.24 ± 1.07 ; $p < 0.001$) No difference in the incidence of adverse drug reactions between the groups including nausea/vomiting, hypoxaemia, postoperative agitation or delay in waking ($p > 0.05$)

(Continued)

TABLE 7 | (Continued)

Study	Aim	Surgery Type	Study Type	Patient Number	Definition of POCD	T1 Cognitive Assessment	T2 Cognitive Assessment	Psychological Assessment Tool	Findings
Landoni et al. (172)	To determine whether volatile anaesthesia vs. total intravenous anaesthesia for cardiac surgery would improve clinical outcomes	Both on-pump and off-pump CABG	RCT Volatile vs. total intravenous anaesthesia	5400 Volatile anaesthesia ($n = 2709$) Total intravenous anaesthesia ($n = 2691$)	"Cognitive deterioration that exceeds a 'normal' age- and time-attributed cognitive decline and which is caused by negative consequences of peri-operative condition" Statistical definition not specified	Not specified	Not specified	Not specified	No significant difference between the volatile and total intravenous anaesthesia groups with respect to all-cause mortality at 1 year ($RR = 0.94$, 95% CI: [0.69–1.29], $p = 0.71$) No difference in the incidence of post-operative cognitive impairment between the groups (Volatile: 1.1%, total intravenous: 1.2, 95% CI: 0.56–1.48)
Wang et al. (174)	To compare the effect of propofol vs. sevoflurane on chronic post-surgical pain and cognitive function after cardiac surgery in Chinese patients > 65 years old	On-pump CABG	RCT Propofol infused at 3–8 mg/kg/h Sevoflurane administered to achieve end tidal concentration of 0.5–2	220 Sevoflurane ($n = 110$) Propofol ($n = 110$)	Not specified in study	Day before surgery	Not specified in study	MMSE	Patients who received propofol had a smaller reduction in MMSE scores (Mean score) following cardiac surgery compared to patients who received sevoflurane (64 vs. 59, respectively). However, significance was not achieved

BIS, bispectral index; CABG, coronary artery bypass graft; IL-6, Interleukin-6; MMSE, mini mental state examination; MOCA, montreal cognitive assessment; MMP-9, matrix metalloproteinase 9; NSE, neuron specific enolase; POCD, postoperative cognitive dysfunction; POD, postoperative day; RCT, randomised controlled trial; T1, pre-operative timepoint for neurocognitive testing; T2, post-operative timepoint for neurocognitive testing; TMT, trail making test; TNF- α , tumour necrosis factor- α ; WAIS, wechsler adult intelligence scale; 6-CIT, six-item cognitive impairment test.

surgery. Shi et al. (169) compared the combination of propofol and fentanyl to sevoflurane for maintenance of anaesthesia in off-pump CABG. The reduction in MMSE and MoCA scores postoperatively was lower in the sevoflurane group compared to the propofol/fentanyl group ($p < 0.005$). Additionally, there was a larger increase in inflammatory markers (CRP, TNF- α , IL-6) in the propofol/fentanyl group compared to the sevoflurane group following surgery ($p < 0.05$). These results indicate that sevoflurane, compared to propofol/fentanyl attenuates the inflammatory response during cardiac surgery. This may have contributed to a lower reduction in MMSE and MoCA scores post-operatively in the sevoflurane group. Furthermore, the intraoperative serum levels (Mean $\pm$ SD) of Malondialdehyde were lower in the sevoflurane group compared to the propofol/fentanyl group (3.48 ± 1.02 vs. 6.24 ± 1.07 ; $p < 0.001$) (169). Malondialdehyde is a metabolite within the oxidative stress pathway and reflects the level of oxidative stress (170). The lower levels of intraoperative malondialdehyde within the sevoflurane group reaffirms the current mechanistic understanding that volatile anaesthetics can scavenge free oxygen radical and attenuate oxidative stress.

Tang et al. compared the effect of sevoflurane vs. propofol on cognitive impairment following on-pump cardiac surgery (171). Sevoflurane was administered to maintain end expiratory and end-effluent concentrations of 1–3%, whilst propofol was infused to reach a serum concentration of 0.5–2.0 $\mu\text{g/kg/min}$ with a BIS index of 40–55 intraoperatively. They observed a lower incidence of POCD at 12 and 24 h post-operatively in the propofol group compared to the sevoflurane group. The incidence of POCD was significantly lower at 12 and 24 h postoperatively in the propofol group compared to the sevoflurane group ($p < 0.05$). At 12 h, the incidence of POCD in the sevoflurane group was 21.82%, whilst it was 9.09% in the propofol group. At 24 h, the incidence of POCD in the sevoflurane group was 25.45%, whilst it was 10.91% in the propofol group. Additionally, the MMSE scores (Mean $\pm$ SD) was higher in the propofol group compared to the sevoflurane group when measured 24 h post-operatively (28.74 ± 4.53 vs. 24.30 ± 3.77 ; $p < 0.05$). Furthermore, serum levels of NSE, S100B and MMP-9 were lower in the propofol group compared to the sevoflurane group at 6, 12, and 24 h post-operatively ($p < 0.05$). Taken together, this study depicts a strong case for the use of propofol over volatile anaesthesia to reduce the incidence of POCD following during cardiac surgery.

Landoni et al. (172) conducted the MYRIAD trial, a multi-centred RCT spanning 36 centres in 13 countries to compare the clinical outcomes in patients receiving volatile anaesthesia or total intravenous anaesthesia undergoing CABG surgery. Whilst there was no strict inhalational anaesthesia protocol, the authors had recommended the use of cardioprotective strategies for patients receiving volatile anaesthesia, including achieving a minimum alveolar concentration of one for at least 30 min, the wash out of volatile anaesthesia prior to initiating CPB and performing at least three wash in/wash out periods. At least one of these cardioprotective strategy was applied in 97.4% of patients receiving volatile anaesthesia, whilst all three strategies were applied in 9.9% of patients receiving volatile anaesthesia. With a sample size of 5400 patients, there was no significant

difference in all-cause mortality at 1 year postoperatively between the volatile and total intravenous anaesthesia groups (RR = 0.94, 95% CI: [0.69–1.29], $p = 0.71$). Whilst Landoni and colleagues did not specifically provide a statistical definition for POCD or state how they measured POCD, they did not find a difference in the incidence of POCD between the groups (Volatile Anaesthesia: 1.1% incidence, Total Intravenous Anaesthesia: 1.2% Incidence, 95% CI [0.56–1.48]) (172). It should be noted that some investigators decided to co-administer propofol during the induction of anaesthesia. Studies have shown that the co-administration of propofol may reduce the beneficial effect of volatile anaesthesia, which may explain the observed non-significant result (173). Future studies should aim to use a standardised anaesthesia protocol which reflect clinical practices. Wang et al. (174) compared the effect of sevoflurane and propofol on chronic post-surgical pain following cardiac surgery in Chinese patients aged >65 years. Propofol was infused at 3–8 mg/kg/hr , whilst sevoflurane was administered to achieve an end tidal concentration of 0.5–2. They found that patients who received propofol had a smaller reduction in MMSE scores (Mean score) following cardiac surgery compared to patients who received sevoflurane (64 vs. 59, respectively). However, significance was not achieved (174). Jiao et al. (175) conducted a systematic review and meta-analysis to compare the effect of volatile anaesthetics and total intravenous anaesthesia in patients undergoing coronary artery bypass grafting. A total of 89 studies comprising of 14,387 patients were included in the meta-analysis. From the eight studies within the meta-analysis reporting on post-operative cognitive impairment, there was no significant difference between volatile anaesthesia and total intravenous anaesthesia (RR = 1.20, 95% CI: 0.74–1.94, $p = 0.46$). It should be noted that quality of the studies included for this outcome were rated as low by the authors. From the forty-four studies which examined operative mortality, there was no significant difference between volatile anaesthesia and total intravenous anaesthesia (RR = 0.92, 95% CI: 0.68–1.24, $p = 0.59$). Five studies did not find a significant difference in mortality at 1 year when comparing volatile and total intravenous anaesthesia (RR = 0.64, 95% CI: 0.32–1.26, $p = 0.19$). Forty-three studies demonstrated that the length of stay in the intensive care unit was significantly shorter in the volatile anaesthesia group compared to the total intravenous anaesthesia group (Mean Difference = -4.14 h, 95% CI: -5.63 – -2.66 , $p < 0.00001$). Similarly, thirty-four studies revealed that the length of stay in hospital was also shorter in the volatile anaesthesia group compared to the total intravenous anaesthesia group (Mean Difference = 0.122 days, 95% CI: -1.81 – -0.62 days, $p < 0.0001$) (175).

Dexmedetomidine

Dexmedetomidine is frequently used for anaesthesia and within the intensive care setting, acting as a selective α -2 adrenergic receptor agonist. There has been significant interest in dexmedetomidine as it may reduce POCD following cardiac surgery. Dexmedetomidine has numerous therapeutic uses, acting as a sedative, anxiolytic, anti-inflammatory, and analgesic. It has also been shown to inhibit sympathetic outflow and provide neuroprotection (176). Firstly, the anti-inflammatory

TABLE 8 | Studies analysing the effect of dexmedetomidine on postoperative cognitive functioning following cardiac surgery.

Study	Aim	Surgery Type	Study Type	Patient Number	Definition of POCD	T1 Cognitive Assessment	T2 Cognitive Assessment	Psychological Assessment Tool	Findings
Gong et al. (178)	To determine the effect of dexmedetomidine on postoperative cognitive function in patients undergoing CABG	On-pump CABG	RCT Dexmedetomidine vs. placebo (saline) Dexmedetomidine 1 ug/kg administered during first 10 min, followed by 0.2 ug/kg infusion until the end of the procedure	80	MMSE < 27 MoCA < 26	Preoperatively	POD 1, 3, 7	MMSE MoCA	MMSE and MOCA scores in the dexmedetomidine group were significantly higher than the scores in the control group ($p < 0.05$ and $p < 0.01$ respectively) Quicker anaesthesia recovery time and lower duration of mechanical ventilation time in the dexmedetomidine group compared to the control group ($p < 0.001$) Lower levels of cortisol, adrenaline and noradrenaline in the dexmedetomidine group compared to the control group at the end of surgery ($p < 0.001$)
Rajaei et al. (185)	To compare the effects of dexmedetomidine and midazolam on postoperative cognitive impairment following CABG	On-pump CABG	Double Blind RCT Midazolam (0.05–0.1 mg/kg) vs. Dexmedetomidine (1 ug/kg) administered as induction of anaesthesia	42	Not specified	Day before surgery	POD 5 and POD30	MMSE WMS	Midazolam group had lower WMS scores (Mean $\pm$ SD; 87.6 ± 14.30) and increased cognitive impairment compared to dexmedetomidine group (103.53 ± 19.93 ; $p = 0.05$) 30 days following surgery. No difference in MMSE scores between the groups postoperatively ($p = 0.394$).
Metry et al. (189)	To compare the effect of dexmedetomidine vs. propofol on postoperative cognitive impairment and rSO2 following cardiac surgery	On-pump CABG	Double blind RCT Propofol (0.3–4 mg/kg/hr) vs. dexmedetomidine (0.2–0.7 mcg/kg/h) infusion following cannulation to the CPB. Drugs ceased when off pump.	50	Decrease in MMSE by 2 or more points compared to pre-operative scores	Day before surgery	1 h following extubation and POD7	MMSE	Pre-operative mean MMSE in both groups: 30 Non-significant decrease in MMSE scores in both groups 1 h post extubation (Mean $\pm$ SD; Propofol 23.3 ± 0.408 ; Dexmedetomidine 23.2 ± 0.41). MMSE performance normalised by POD7 (Propofol 30; Dexmedetomidine 30) Comparison between the groups was not conducted.

(Continued)

TABLE 8 | (Continued)

Study	Aim	Surgery Type	Study Type	Patient Number	Definition of POCD	T1 Cognitive Assessment	T2 Cognitive Assessment	Psychological Assessment Tool	Findings
Kang et al. (186)	To compare the effect of dexmedetomidine + isoflurane vs. isoflurane anaesthesia on brain injury	On-pump valve replacement surgery	Single blind RCT Dexmedetomidine given as bolus infusion at 0.6 ug/kg, then as a continuous 0.2 ug/kg/h following intubation. Isoflurane given through oxygenator of CPB, targetting BIS of 40–50	97 Dexmedetomidine + Isoflurane (<i>n</i> = 50) Isoflurane (<i>n</i> = 47)	Decrease of scores more than 30% compared to pre-operative scores	Day before surgery	POD7	ASEM	No significant difference in ASEM score (Mean ± SD) between intervention and control group following surgery (13.69 ± 6.8 vs. 14.0 ± 6.5; <i>p</i> = 0.714). Dexmedetomidine group had significantly lower levels of GFAP than isoflurane alone group following CPB off (0.70 ± 0.05 vs. 0.81 ± 0.04; <i>p</i> = 0.033). Dexmedetomidine group had significantly lower levels of MMP-9 than isoflurane alone group following CPB off (90.5 ± 15.3 vs. 118.2 ± 17.1; <i>p</i> = 0.007) and on POD1 (87.2 ± 12.2 vs. 102.9 ± 11.5; <i>p</i> = 0.036)
Gao et al. (183)	To determine the effect of dexmedetomidine on postoperative cognitive function and neuroglobin expression following minimally invasive CABG	Minimally invasive off-pump CABG	RCT Dexmedetomidine vs. control (normal saline) Dexmedetomidine given as bolus infusion at 0.6 ug/kg 15 min prior to induction of anaesthesia, then as a continuous 0.2 ug/kg/h until the end of intubation	40 Dexmedetomidine (<i>n</i> = 20) Control (<i>n</i> = 20)	MMSE < 27	Day before surgery	POD7, POD30, POD90	MMSE	POCD incidence significantly lower in the dexmedetomidine group at POD7 and POD 30 (<i>p</i> < 0.05) MMSE scores (Mean ± SD) of dexmedetomidine group significantly higher compared to control group at POD7 (24.8 ± 1.3 vs. 20.5 ± 1.4; <i>p</i> < 0.001) and POD30 (28.3 ± 1.5 vs. 24.2 ± 1.2; <i>p</i> < 0.001) NgB expression significantly higher in the dexmedetomidine group compared to the control group at 6 h post single lung ventilation and at POD1 (<i>p</i> < 0.01).

ASEM, anti-saccadic eye movement test; BIS, bispectral index; CABG, coronary artery bypass graft; CAM, confusion assessment method; CRT, choice reaction test; GFAP, glial fibrillary acidic protein; MMSE, mini mental state examination; MOCA, montreal cognitive assessment; MMP-9, matrix metalloproteinase 9; NgB, Neuroglobin B; NSE, neuron specific enolase; POCD, Postoperative cognitive dysfunction; POD, postoperative day; PRM, pattern recognition memory test; rSO₂, regional cerebral oxygen saturation; RCT, randomised controlled trial; SCWI, stroop colour word interference; SSP, spatial span test; SRM, spatial recognition memory test; T1, pre-operative timepoint for neurocognitive testing; T2, post-operative timepoint for neurocognitive testing; VLT, verbal learning and retention test; WMS, wechsler memory scale.

properties of dexmedetomidine are reflected by a significant decrease of serum cytokines IL-6, IL-8, and TNF- α following major surgery in humans (177, 178). This may be attributed to a downregulation of TLR receptors, as observed in an aged mice model (179). Dexmedetomidine also increases the transcription of brain derived neurotrophic factors, anti-apoptotic proteins and decrease nerve sensitivity to glutamate. These gene expression changes, in combination with the previously mentioned anti-inflammatory effects, produce a neuroprotective effect (176).

The analgesic properties arise from the inhibition of substance p and activation of α -2B adrenoceptors within the dorsal horn. These analgesic effects are achieved with minimal concerns of respiratory depression, unlike traditional opioids (180). On the contrary, the activation of α -2A adrenoceptors inhibits central sympathetic outflow from the locus coeruleus, culminating in a reduction of catecholamine release (181). This in turn reduces the heart rate and systemic vascular resistance. Additionally, the sedative and anxiolytic effects also arise from interactions within the locus coeruleus. These therapeutic effects have stirred significant interest into the potential use of dexmedetomidine for reducing postoperative cognitive impairment following cardiac surgery.

Six recent studies analysed the effect of dexmedetomidine on postoperative cognitive functioning following cardiac surgery (Table 8). Three studies supported the use of dexmedetomidine. Gong et al. demonstrated that MMSE and MoCA scores were significantly higher in the dexmedetomidine group compared to the control group ($p < 0.05$ and $p < 0.01$, respectively) at 1 day postoperatively following on-pump CABG. They also observed that the use of dexmedetomidine is associated with a quicker anaesthesia recovery time, and a reduced duration of mechanical ventilation compared to the control group ($p < 0.001$) (178). Gao et al. examined the effect of dexmedetomidine vs. control on postoperative cognitive function and neuroglobin expression following minimally invasive off-pump CABG. It should be noted that off pump CABG is prone to intra-operative oxygen desaturation and associated with POCD, given the requirement for single lung ventilation (182, 183). The use of dexmedetomidine was associated with a lower incidence of POCD at POD7 and POD30 ($p < 0.05$) and higher MMSE scores (Mean $\pm$ SD) at POD7 (24.8 ± 1.3 vs. 20.5 ± 1.4 ; $p < 0.001$) and POD30 (28.3 ± 1.5 vs. 24.2 ± 1.2 ; $p < 0.001$). They also detected an association between dexmedetomidine and increased expression of neuroglobin at 6 h post single lung ventilation and POD1 ($p < 0.01$). Neuroglobin is a hypoxia inducible protein which is highly expressed in the frontal lobes and hypothalamus. It has a high affinity for oxygen, increasing oxygen delivery to the brain (183, 184). These results suggest that neuroglobin may be neuroprotective for postoperative cognitive impairment. While the current literature surrounding the role of neuroglobin is conflicting, these promising results suggest further study into dexmedetomidine and neuroglobin is warranted (184). Rajaei et al. compared the effects of dexmedetomidine and midazolam on postoperative cognitive functioning following on-pump CABG. The use of midazolam was associated with significantly lower WMS scores (Mean $\pm$ SD) compared to dexmedetomidine at POD30 (87.6 ± 14.30 vs. 103.53 ± 19.93 ;

$p < 0.05$). However, there was no difference in MMSE scores ($p = 0.394$) (185).

Two studies had conflicting results regarding the use of dexmedetomidine for postoperative cognitive impairment. Kang et al. examined whether the effect of dexmedetomidine and isoflurane compared to isoflurane alone on brain functioning in patients undergoing on-pump valve replacement surgery. There was no difference in ASEM score (Mean $\pm$ SD) between intervention and control group following surgery (13.69 ± 6.8 vs. 14.0 ± 6.5 ; $p = 0.714$). However, the group with dexmedetomidine had significantly lower levels of glial fibrillary acidic protein (GFAP) and MMP-9 following surgery compared to the control group ($p = 0.033$ and $p = 0.036$, respectively) (186). GFAP is a brain specific intermediate protein. Serum levels of GFAP > 0.49 ng/mL are considered pathological and may be indicative of ischaemic or haemorrhagic brain injury. Conversely, MMP-9 expression is increased following brain injury and ischaemia (187). Therefore, these results suggest that dexmedetomidine may reduce the extent of brain insult following cardiac surgery. Xiong et al. (188) conducted a systematic review on the effects of dexmedetomidine on perioperative neurocognitive disorders. With data from 3610 patients collated from 24 studies, they detected no significant difference in the incidence of POCD between dexmedetomidine and the control group (OR: 0.47, 95% CI: 0.22–1.03, $p = 0.060$). It should be noted that numerous studies may have used an insufficient maintenance dose of dexmedetomidine, ranging between 0.2–0.5 μ g/kg/hr of dexmedetomidine. In contrast, there was a significant reduction in the incidence of postoperative delirium in the dexmedetomidine group compared to the control group (OR: 0.59, 95% CI: 0.43–0.82, $p = 0.001$) (188).

One study did not support the use of dexmedetomidine for postoperative cognitive dysfunction. Metry et al. examined the effect of dexmedetomidine compared to propofol on postoperative cognitive impairment following cardiac surgery (189). They reported a non-significant reduction in MMSE scores in both groups 1 h following extubation (Mean $\pm$ SD; Propofol 23.3 ± 0.408 ; Dexmedetomidine 23.2 ± 0.41). A direct comparison between the groups was not performed.

FUTURE DIRECTIONS

Large, multi-centred, double blinded randomised controlled trials are required to produce higher level evidence in order to evaluate the effectiveness of interventions in reducing POCD. Many trials within the literature have shown benefits for interventions, but the sample sizes were extremely small and within a specific population. This has reduced external validity. Currently, investigators are assessing POCD with a battery of neuropsychological tests which they believe most effectively analyse the cognitive domain of interest. However, this may lead to extensive testing and a drop in concentration or dis-engagement. Thus, the development of a validated neuropsychological battery specifically assessing for POCD following cardiac surgery is necessary. To reduce the learning effect from multiple follow ups, alternative forms of the

neuropsychological tests should be used at each encounter. Additionally, there is little consensus on the statistical assessment of POCD. This must be addressed to reduce the heterogeneity in the detection of POCD. Given the recent nomenclature recommendations by Evered et al. (5), future studies should adopt the terms delayed neurocognitive recovery (for cognitive impairment up to 30 days post-operatively) and post-operative mild/major neurocognitive disorders (for cognitive impairment up to 1 year post-operatively). Studies should also adopt follow up times which reflect the duration of these cognitive impairment episodes (i.e., 30 days and 1 year). The combination of a standardised neuropsychological battery for cardiac surgery, a consistent statistical definition for POCD and similar follow-up times between studies will hopefully lead to a more accurate rate of detecting POCD.

Patient risk factors for POCD should be recorded prior to surgery. The strongest risk factors have been shown to be advanced age and lower education attainment. This would allow clinicians to identify patients most at risk of POCD and monitor them closely. The PPCI trial by Vedel et al. (93) has suggested that patients may potentially receive diffusion weighted MRI scans prior to surgery and receive scans post-operatively to identify the development of new cerebral lesions. Given this is a relatively novel technique, more data is required before it can be introduced into clinical practice. Transcranial doppler may also be used for intra-operative monitoring of cerebral blood flow and autoregulation. This has been introduced in several centres already.

There is significant interest in identifying effective therapeutic strategies to attenuate the pathophysiological mechanisms leading to POCD following cardiac surgery. Given the use of low dose dexamethasone (0.1 mg/kg) may be effective in reducing POCD in the long term, future studies assessing the efficacy of dexamethasone should use this dose as their intervention to confirm or refute the finding. Studies on intra-operative blood pressure management appear to be inconclusive. The use of NIRS to detect cerebral desaturations and enable quick intervention is promising. Whilst the evidence is conflicting, the use of NIRS is cost-effective and can be feasibly integrated into clinical practice if further positive data emerges. Additionally,

there is limited data on intra-operative glycaemic control during cardiac surgery and suggest there should be some focus on this area. Furthermore, there are limited human studies assessing the mechanism of anaesthesia induced neurotoxicity. Of particular interest is understanding whether anaesthesia truly accelerates the Alzheimer's pathophysiological process and how anaesthesia ties into POCD. This may potentially alter anaesthetic practice if agents are identified which strongly contribute to POCD.

CONCLUSION

This review provides a contemporary overview on postoperative cognitive impairment following cardiac surgery and examines the main pathophysiology mechanisms contributing to such including inflammation, cerebral hypoperfusion, cerebral microemboli, glycaemic control and anaesthesia induced neurotoxicity. Therapeutic areas of interest targetting these mechanisms were examined. The efficacy of dexamethasone in attenuating the inflammatory response is currently questionable. The use of NIRS to monitor for cerebral desaturations and cerebral perfusion appears to be beneficial by allowing clinicians to correct desaturations. However, further studies using similar thresholds for initiating interventions are required. Recent studies demonstrated that emboli size and a higher target MAP during cardiac surgery were not associated with cognitive impairment. Nevertheless, the modification of surgical techniques to reduce the occurrence of emboli and POCD have been promising.

AUTHOR CONTRIBUTIONS

TV and JS conceptualised and designed the study. TV collected and analysed the data and produced the first draft of the manuscript. Both 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.

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Depressive Symptoms and Quality of Life in Patients With Heart Failure and an Implantable Cardioverter-Defibrillator

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Background: Heart failure (HF) is associated with development of depressive symptoms and reduced quality of life (QoL). Patients with HF and an implantable cardioverter-defibrillator (ICD) were evaluated regarding depressive symptoms and QoL.

Methods: The present study included 446 patients with HF and an ICD. Depressive symptoms were assessed using the Patient Health Questionnaire 9 (PHQ-9), QoL was evaluated using the Minnesota Living with Heart Failure Questionnaire (MLHFQ). Functional ability and exercise tolerance were assessed at inclusion and after 6 months with help of the 6-min walking test (6MWT).

Results: Patients included in the study had a mean age of 65.8 years and were predominantly male (83.6%), with mostly ischemic ($n = 277$; 62.1%) or dilated ($n = 150$; 33.6%) cardiomyopathy. One hundred ninety-three (43.2%) patients had depressive symptoms, of whom 75 patients (16.8%) were classified as moderate to severe depression according to the PHQ-9 at baseline. Depressive symptoms were associated with low QoL independent of NYHA functional class. High NYHA functional class, high PHQ-9 score, age and body mass index (BMI) were associated with a lower 6MWT at enrollment, while depressive symptoms (expressed as higher PHQ-9 score) and age were associated with a lower 6MWT after 6 months. Patients with history of smoking and a higher BMI showed higher PHQ-9 scores after 6 months. Patients under antidepressant medication showed improved PHQ-9 score after 6 months, indicating controlled/treated depression. However, patients with low QoL at inclusion remained with low QoL after 6 months.

Conclusion: Depressive symptoms correlate with low QoL and lower long-term functional status in patients with HF and an ICD. Depressive symptoms are associated with smoking and obesity, which themselves are risk factors for a poor prognosis in HF. Only a small fraction of patients with HF and ICD showing depressive symptoms receives appropriate treatment. Assessing depressive symptoms and lifestyle factors should be part of a multimodal treatment plan in patients with HF and an ICD.

Keywords: heart failure, implantable cardioverter-defibrillator, depression, quality of life, PHQ-9

INTRODUCTION

Heart failure (HF) is a leading cause of morbidity and mortality worldwide (1–3). HF is associated with high risk for sudden cardiac death and recurrent hospitalizations (4). In recent years, development of new therapeutic agents has led to significantly better outcomes in patients with HF (5). Nevertheless, progression of the underlying disease has significant impact on the physical and psychosocial status of patients with HF (6). Implantation of an implantable cardioverter-defibrillator (ICD) for primary prevention of sudden cardiac death (SCD) is indicated in patients with reduced left ventricular function ($LVEF \leq 35\%$) or for secondary prevention after hemodynamically not tolerable ventricular tachycardia or aborted SCD (5, 7–9). Patients with HF (10) and/or an ICD (11, 12) frequently report depressive symptoms. Patients with HF exhibit depressive symptoms in as high as 41.9% of cases, with 28.1% showing moderate to severe depression (10). Depressive symptoms can be detected by self-rating questionnaires such as the Patient Health Questionnaire 9 (PHQ-9), and high PHQ-9 scores have been associated with low quality of life (QoL) and high risk of hospitalization (13). HF is also associated with reduced QoL and supportive care interventions have been shown to ameliorate the QoL of patients with HF (14).

In the present study, patients with HF and an ICD were prospectively evaluated regarding depressive symptoms and QoL with the intention to elucidate the prevalence of depressive symptoms in this patient cohort and to assess how QoL evolves in the course of the underlying disease. Aim of the analysis is to identify patients in need for antidepressive treatment such as psychotherapy and/or antidepressant medication.

METHODS

Four hundred forty-six patients presenting with HF and an ICD at Hannover Heart Rhythm Center of the Department of Cardiology and Angiology at Hannover Medical School were included between 2012 and 2014. Patients had a mean age of 65.8 ± 12.1 years at inclusion, were predominantly (83.6%) male, and were evaluated at inclusion and after 6 months in a prospective non-randomized manner. The study protocol complied with the Declaration of Helsinki and was approved by the local ethics committee. All patients gave written informed consent prior to study inclusion. Baseline parameters and medical history were retrieved through hospital records. Functional ability and exercise tolerance were evaluated at inclusion and after 6 months with the 6-min walking test (6MWT) (15). Symptoms of depression were assessed using the PHQ-9 screening tool (16). PHQ-9 scores of 0–4 were classified as none to minimal depressive symptoms, PHQ-9 scores of 5–9 as mild depressive symptoms and PHQ-9 scores of 10–27 as moderate to severe depressive symptoms (16). QoL was evaluated using the Minnesota Living with Heart Failure Questionnaire (MLHFQ) (17).

A standard 12-lead ECG was performed in all patients. ECG was performed in accordance with international standards (18). Baseline parameters were recorded including underlying disease, left ventricular ejection fraction (LVEF) and body mass index (BMI) among others. Medication at time of inclusion was documented by the treating physician after looking through the patient's charts and current list of medication.

Statistical Analysis

Statistical analysis was conducted using SPSS version 26 (IBM, Armonk, NY, USA). Categorical variables are presented as numbers and percentages and were compared among subgroups using Chi square test. For comparison of continuous variables, the two-sided *T*-test was used. ANOVA was used to compare patient groups with none-minimal, mild, and moderate-to-severe depression. Regression analysis (BACKWARD method) was used to analyze potential predictors of low functional cardiac status. We used the 6MWT at inclusion as dependent variable, and PHQ-9 sum score, LVEF, BMI, NYHA functional class, age, and gender as potential predictors. Similarly, we analyzed potential predictors of 6MWT at 6 months follow up. Data are presented as mean $\pm$ standard deviation. Values of $p < 0.05$ were considered statistically significant.

RESULTS

Baseline characteristics of the patients included in the study are shown in **Table 1**. **Table 2** shows the specific device-related characteristics as well as medication at time of enrollment. Of note, a high percentage of patients (39.9%) had a cardiac resynchronization therapy (CRT) device.

Depressive Symptoms and Quality of Life

One hundred ninety-three patients (43.2%) showed at least mild depressive symptoms: 75 patients (16.8%) had moderate to severe depressive symptoms at baseline and 118 patients (26.5%) had mild depressive symptoms at baseline. Three groups were formed, patients with no or minimal depressive symptoms ($n = 253$), patients with mild symptoms ($n = 118$), and patients with moderate to severe symptoms ($n = 75$). **Table 3** shows the assessed clinical factors examined between the three groups according to the severity of depressive symptoms.

Depressive symptoms at inclusion were associated with low QoL at inclusion ($p < 0.001$) and after 6 months ($p < 0.001$) independent of NYHA functional class (**Figure 1**).

Regression analysis (BACKWARD method) with 6MWT at inclusion as dependent variable and PHQ-9, LVEF, BMI, NYHA functional class, age, and gender as potential predictors revealed that 6MWT was predicted by PHQ-9 sum score ($p = 0.01$), NYHA functional class ($p = 0.008$), age ($p < 0.001$), and BMI ($p < 0.001$). Regression analysis (BACKWARD method) with 6MWT after 6 months as dependent variable, and PHQ-9, LVEF, BMI, NYHA functional class, age, and gender as potential predictors revealed that 6MWT was predicted by PHQ-9 sum score ($p = 0.02$) and age ($p < 0.001$) (**Table 4**).

TABLE 1 | Baseline patient characteristics (*n* = 446).

Parameter	<i>n</i> = 446
Age (y)	65.8 ± 12.1
Male (<i>n</i> , %)	373 (83.6%)
Underlying disease (<i>n</i>, %)	
Ischemic cardiomyopathy	277 (62.1%)
Dilated cardiomyopathy	150 (33.6%)
Hypertrophic cardiomyopathy	8 (1.8%)
Other	11 (2.5%)
LVEF (%)	30.5 ± 6.9
NYHA functional class (<i>n</i>, %)	
I	25 (5.6%)
II	255 (57.2%)
III	164 (36.8%)
IV	2 (0.4%)
Body mass index (kg/m ²)	28.9 ± 5.1
Arterial hypertension (<i>n</i> , %)	311 (69.7%)
Type 2 diabetes mellitus (<i>n</i> , %)	118 (26.5%)
Hyperlipoproteinemia (<i>n</i> , %)	257 (57.6%)
Peripheral vascular disease (<i>n</i> , %)	51 (11.4%)
Chronic kidney disease (<i>n</i> , %)	106 (23.8%)
History of smoking (pack years)	34.2 ± 24.2
COPD (<i>n</i> , %)	53 (11.9%)
Creatinine (μmol/L)	114.6 ± 70.0
CRP (mg/L)	4.7 ± 8.5
NTproBNP (ng/mL)	2005.7 ± 6104.1
6-minute walking test (m)	438.7 ± 110.2
PHQ-9 (points) at inclusion	5.1 ± 4.9
MLWHF (points) at inclusion	27.0 ± 21.1
ECG parameters	
Atrial rhythm (<i>n</i>, %)	
Sinus rhythm	318 (71.3%)
Atrial fibrillation	106 (23.8%)
Other	22 (4.9%)
Heart rate (bpm)	67.9 ± 12.9
QTc interval (ms)	450.4 ± 44.4

LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; PHQ-9, Patient Health Questionnaire; MLWHF, Minnesota Living With Heart Failure questionnaire.

Depressive Symptoms After 6 Months

Patients with high PHQ-9 score at inclusion displayed high PHQ-9 score also after 6 months (**Figure 2**). Patients under antidepressant medication (*n* = 27, 6.1%) showed lower PHQ-9 score after 6 months, with 12 patients showing no or minimal symptoms, 9 patients exhibiting mild symptoms and 6 patients had moderate to severe depressive symptoms. However, patients with low QoL at inclusion remained with low QoL also after 6 months. Further analysis revealed that patients with history of smoking (*p* = 0.048), a higher BMI (*p* = 0.042), low QoL at inclusion (*p* < 0.001), and low QoL after 6 months (*p* < 0.001) showed higher PHQ-9 scores after 6 months (data not shown). Furthermore, patients with a higher PHQ-9 score had a higher heart rate (*p* = 0.036).

TABLE 2 | Basic ICD characteristics and medication.

ICD characteristics	
Indication (<i>n</i>, %)	
Primary prevention	335 (75.1%)
Secondary prevention	108 (24.2%)
Unknown	3 (0.7%)
Type of ICD (<i>n</i>, %)	
Single chamber	145 (32.5%)
Dual chamber	122 (27.4%)
Cardiac resynchronization therapy	178 (39.9%)
Subcutaneous ICD	1 (0.2%)
Medication	
ACEI or ARB	415 (93.0%)
Beta-blockers	409 (91.7%)
Mineralocorticoid receptor antagonists	258 (57.8%)
Digitalis	77 (17.3%)
Calcium antagonists	59 (13.2%)
Sotalol	10 (2.2%)
Amiodarone	53 (11.9%)
Statin	307 (68.8%)
Antidepressant agents	27 (6.1%)

ACE, Angiotensin-converting enzyme inhibitor; ARB, Angiotensin II receptor blocker.

DISCUSSION

The present study demonstrates the prevalence of depressive symptoms and the association with QoL in a large cohort of patients with HF and an implanted ICD. The main findings of the present study include:

1. 43.2% of patients with HF and an ICD showed mild to severe depressive symptoms. In 75 patients (16.8%), depressive symptoms were moderate to severe.
2. Depressive symptoms in patients with HF and an ICD were associated with low QoL and reduced 6MWT.
3. PHQ-9, NYHA functional class, age and BMI were predictors of low current functional ability, and PHQ-9, age, and BMI by trend were predictors of low follow-up functional ability after 6 months.
4. History of smoking, high BMI and low QoL were associated with depressive symptoms after 6 months.

These results are in accordance with data from the literature, showing high depression burden in patients with HF and ICD, and in adults with congenital heart disease (19). In a recent meta-analysis including 305,407 patients with HF, Moradi et al. reported a prevalence of 28.1% of moderate to severe depressive symptoms in this patient cohort (10). The different results between our study and the meta-analysis by Moradi et al. may be explained by the heterogeneity of the sample in the meta-analysis. Moradi et al. included HF samples from all over the world, including the EMRO region, and from countries with a lower socioeconomic level. One result of the study is that depression rates are higher in countries of the EMRO region, and in countries with lower socioeconomic level. In contrast,

TABLE 3 | Baseline characteristics according to the severity of depressive symptoms.

	Depressive symptoms			p-value
	None-minimal (n = 253)	Mild (n = 118)	Moderate-severe (n = 75)	
Age (y)	66.2 ± 11.2	66.0 ± 13.1	63.8 ± 13.1	n.s.
Body mass index(kg/m ²)	28.8 ± 4.7	28.9 ± 5.4	29.4 ± 5.9	n.s.
Heart rate (bpm)	65.5 ± 10.6	67.2 ± 10.0	74.8 ± 62.6	n.s.
6-Min-Walking Test (m)	455.7 ± 100.1	420.1 ± 112.9	407.8 ± 128.6 ¹	0.042
Corrected QT intervall (ms)	448.8 ± 44.0	454.2 ± 46.9	450.1 ± 41.6	n.s.
Kreatinin (μmol/L)	110.0 ± 70.8	125.0 ± 68.7	113.9 ± 68.7	n.s.
CRP (mg/L)	4.3 ± 6.1	4.7 ± 6.6	6.3 ± 15.4	n.s.
NTproBNP (ng/mL)	2063.5 ± 7575.1	2073.5 ± 3733.6	1703.7 ± 2548.9	n.s.
PHQ-9 (points) at inclusion	1.8 ± 1.4	6.7 ± 1.4	13.9 ± 3.4 ^{1,2}	<0.001
MLWHF total score at inclusion	15.3 ± 13.2	34.9 ± 17.8	53.5 ± 17.3 ^{1,2}	<0.001
Smoking (pack years)	36.7 ± 24.7	29.2 ± 17.2	33.4 ± 30.1	n.s.

The 6-Min-Walking test (6MWT) and quality of life, assessed with the Minnesota living with heart failure scale (MLWHF) were significantly different between the groups. Particularly patients with moderate to severe depressive symptoms had a lower 6MWT compared to patients with none to minimal depressive symptoms, and reduced quality of life compared to both other groups.

A p-value < 0.05 was considered significant.

^a means a significant difference between patients with moderate to severe depressive symptoms compared to patients with none to minimal depressive symptoms.

^b means a significant difference between patients with moderate to severe depressive symptoms compared to patients with none to mild to moderate depressive symptoms.

CRP, C-reactive protein; PHQ-9, Physical Health Questionnaire; MLWHF, Minnesota Living With Heart Failure questionnaire.

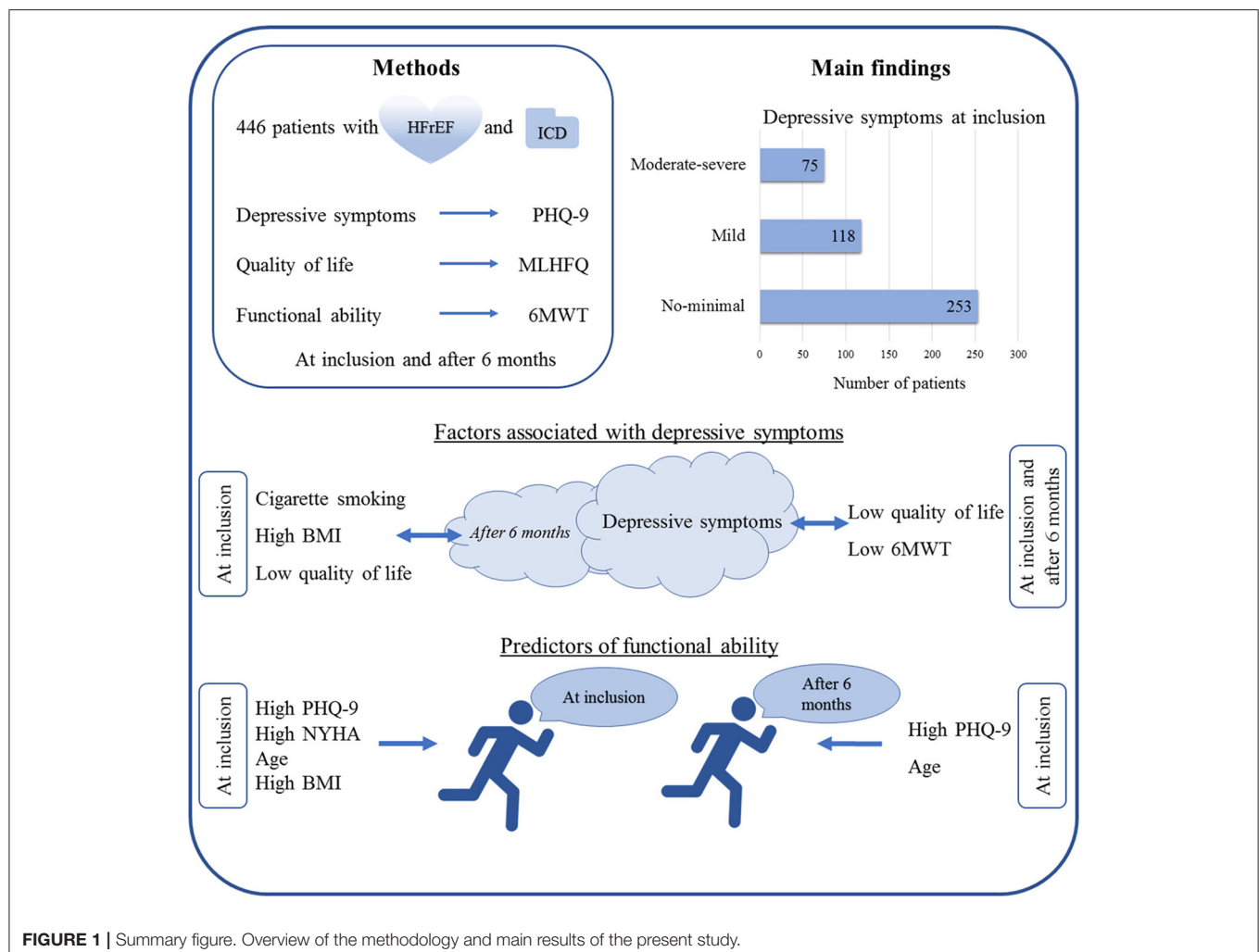
**FIGURE 1 |** Summary figure. Overview of the methodology and main results of the present study.

TABLE 4 | Overview of the results of regression analysis (BACKWARD method) regarding 6-min walking test.

	Regression coefficient β	SD	Beta	T	p
Predictors of 6-min walking test at enrollment					
Body mass index	−4.5	1.2	−0.210	−3.8	<0.001
Age (years)	−2.4	0.5	−0.274	−4.9	<0.001
NYHA functional class	−26.2	10.1	−0.142	−2.6	0.01
PHQ-9	−4.1	1.3	−0.180	−3.3	0.001
Predictors of 6-min walking test after 6 months					
Body mass index	−2.5	1.3	−0.112	−1.8	0.076
Age (years)	−2.7	0.5	−0.298	−4.7	<0.001
PHQ-9 (points)	−3.1	1.3	−0.146	−2.4	0.02

PHQ-9, Physical Health Questionnaire; SD, standard deviation.

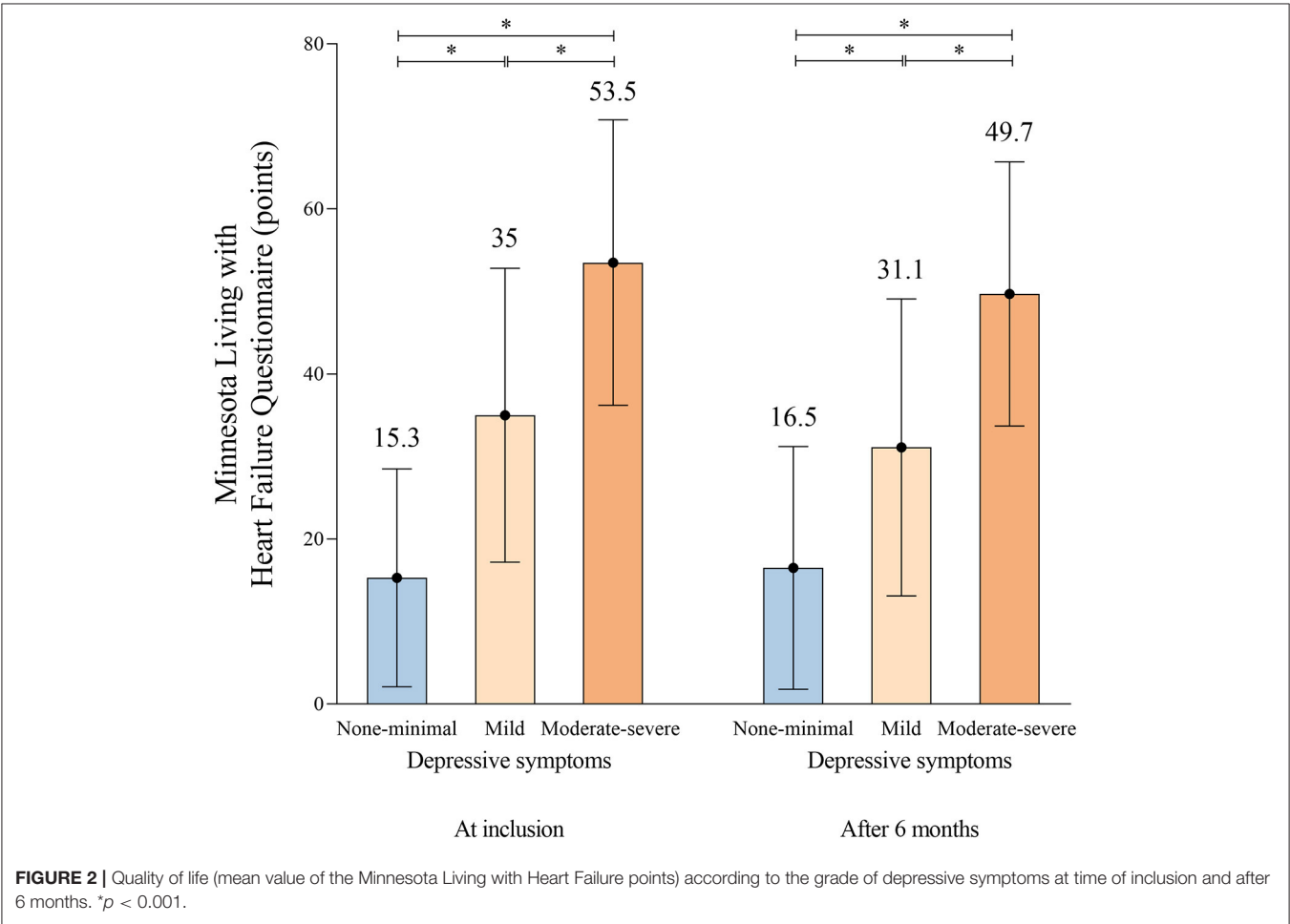


FIGURE 2 | Quality of life (mean value of the Minnesota Living with Heart Failure points) according to the grade of depressive symptoms at time of inclusion and after 6 months. * $p < 0.001$.

our study group consisted of patients from a German referral center and depression rates in our study are similar to those observed by Moradi et al. in Sweden and Italy. Bhatt et al. also reported depression rates of 26% up to 50.7% in 308 patients with HF. In the present study, 43.2% of the patients had at least mild depressive symptoms while 16.8% of HF patients presented with moderate to severe depressive symptoms. Twenty-seven patients (6.1%) were under antidepressant medication, which could partially explain the slightly reduced rates of depressive

symptoms compared to previous published studies. Furthermore, patients with multiple comorbidities, such as obesity and smoking, were more likely to exhibit depressive symptoms, a fact that has not been reported in most of the studies including patients with HF (20). Prevalence of depression also differs according to the socioeconomic level of the country in which a study is conducted (21). In general, the significant discrepancies in the reported rates of depression in patients with HF ranging from 9 to 43% (11) could be also attributed to the different

instruments utilized to evaluate presence of depressive symptoms (PHQ-9, HADS etc.).

Previous studies have shown that patients with ICD show high rates (23.6%) of depressive symptoms (11), especially in case of ICD shocks. Delivery of shock therapy has an adverse impact on depression and vice versa (22, 23). Thus, therapy of depressive symptoms should be an essential part of the therapeutic strategy in patients with HF and/or ICD. In the present study, patients under antidepressant medication showed low PHQ-9 score possibly indicating controlled or treated depression. A recent work from Peng et al. could demonstrate that cognitive behavioral therapy significantly ameliorates depressive symptoms in 480 patients with HF (24).

In the present study, a high percentage of patients ($n = 178$, 39.9%) were implanted with a CRT device. CRT can improve psycho-cognitive performance in patients with HF (12). Depressive symptoms at follow-up were associated with smoking and high BMI at time of enrollment. These findings are in line with previously published data. Smoking is a well-known risk factor for depression, although patients with a genetic predisposition to depression also show higher smoking rates (25). Thus, there seems to be a bidirectional correlation between smoking and depression. Similarly, patients with a higher BMI are at high risk to develop depressive symptoms (26).

HF is associated with reduced QoL (14, 27). Also, patients with a high PHQ-9 score often show a low QoL, highlighting the impact of depressive symptoms in QoL (13). In our study, depressive symptoms were the main driver of worse QoL in patients with HF and ICD independent of NYHA functional class.

Physical and emotional support significantly improve outcomes in patients with HF (14). Nevertheless, cognitive behavioral therapy as therapeutic approach against depression did not show substantial impact on the QoL and 6MWT distance for HF (24). In the present study, depressive symptoms in ICD patients with HF were associated with low QoL. Moreover, patients with low QoL at time of inclusion remained with low QoL after 6 months. These data implicate a lack of intervention in the studied patient cohort regarding depressive symptoms and consequently QoL, although it remains unclear to which extent a therapeutic approach could impact outcomes in patients with HF. Regarding ICD and QoL, numerous studies have demonstrated that shock therapy is associated with higher morbidity and mortality (28).

Limitations

The present study has several limitations. Since the study included patients from a single academic hospital of an urban area, it is unclear to which extent the reported depression rates allow generalizability. To which extent the duration of heart failure plays a role in depressive symptoms is unclear, since time

point of first diagnosis of heart failure data were not available for most of the patients. Since patients were included between 2012 and 2014, the impact of more recent therapeutic agents such as Angiotensin-Receptor-Neprilysin inhibitors (ARNI) and Sodium/glucose cotransporter type 2 inhibitors could not be evaluated. Moreover, assessment of depressive symptoms and QoL was performed at time of enrollment and after 6 months without longer follow-ups. In this period, we observed very few major clinical events, making a correlation between depressive symptoms or QoL and major endpoints impossible. Future studies with longer follow-ups and thus more clinical events could elucidate a possible association. Depressive symptoms were evaluated with help of the PHQ-9, which represents a screening tool and should not misinterpreted as diagnostic method for depression.

CONCLUSION

Patients with HF and an ICD presenting depressive symptoms have a lower QoL as well as a lower functional status according to 6MWT. Smoking, obesity and low QoL are predictors of depressive symptoms in this patient cohort. Only few patients with HF and ICD exhibiting depressive symptoms receive appropriate treatment. Thus, evaluation of depressive symptoms and lifestyle factors should be part of a multimodal treatment plan in patients with HF and an ICD.

DATA AVAILABILITY STATEMENT

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

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

CZ and KK contributed equally in conducting the analysis and writing the manuscript. DD designed the study, collected the data, conducted the analyses, supervised the statistical analyses, and wrote the manuscript. All authors made substantial contributions to the conception or design of the work, the acquisition, interpretation of data for the work, drafting the work or revising it, and approved the final version to be accountable for all aspects of the work.

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Fear of Recurrence of Atrial Fibrillation: Translating a Cancer Fear Model to the Atrial Fibrillation Patient Experience

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Background: Atrial fibrillation occurs when rapid and disorganized electrical signals cause the atria in the heart to beat irregularly and is associated with an increased risk for stroke. Despite medical advancements, first and second line atrial fibrillation treatments exhibit significant recurrence rates. Because of this, atrial fibrillation patients often experience disease-specific fears that are not routinely assessed and targeted in clinical management. Fear of recurrence models in cancer research and other cardiac-specific fears have paved the way for a patient-centric approach to disease intervention.

Purpose: Clinical assessment focused solely on the taxonomy of anxiety disorders may miss key components unique to the atrial fibrillation patient experience. An anxiety disorder diagnosis in the presence of an arrhythmia could be misleading and ultimately fail to address patient needs. Modeled from the cancer literature, providers may benefit from a broader disease specific conceptualization for AF patients that differs from a general DSM-5 diagnosis.

Aims: The objectives of this paper are: (1) to review the medical aspects of atrial fibrillation, (2) to examine the comparability of fear of recurrence concept from cancer literature to the atrial fibrillation patient, and (3) to suggest considerations of these novel concepts in patient care.

Future Directions: Increased understanding of fear of recurrence among atrial fibrillation patients aims to define and assess fear of recurrence components, determine treatment targets, and ultimately improve patient outcomes.

Keywords: atrial fibrillation, cardiac electrophysiology, cardiac psychology, fear of recurrence, health anxiety

INTRODUCTION

Consultation liaison psychiatrists and psychologists are often called to the bedside or clinic room of a medical patient coping with multiple health challenges. The use of the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition [DSM-5, (1)] provides the blueprint for examining psychological disorders and making diagnoses. As the evidence base grows for the psychological aspects of chronic diseases, mental health professionals are faced with

evaluating patients with significant anxieties that are either consistent with, or part of, the disease process. This scenario presents a significant challenge for providers as the manifestations of disease-specific fears may be difficult to diagnose and, therefore, unresponsive to traditional treatment recommendations for DSM-5-defined anxiety disorders. Even so, illness-related anxieties surrounding fears of symptoms or conditions worsening are common for individuals with chronic conditions (2). Patients presenting with cardiac arrhythmias may experience spontaneous palpitations, shortness of breath, exercise intolerance, and other discomforts that mimic anxiety disorders. Nonetheless, the diagnosis of an anxiety disorder in the presence of an arrhythmia with similar symptoms could be misleading.

Psycho-oncology literature has rapidly deployed cancer-specific constructs in an effort to understand the patient experience of the unique aspects of living with cancer. The juxtaposition of cancer and cardiac disease constructs to describe the disease experience may provide complementary insights, as both conditions have significant impacts on perceived health and longevity, disease burden, life interruption, multiple treatment modalities, and recurrent follow-up care. Both disease states have disease-specific fears that involve patients navigating the health care system, while feeling poorly, and managing future threats. As a result, perceptions and expectations of the future become an important aspect for both disease states—specifically around the phenomenon of fear of recurrence (FoR).

Consulting psychiatrists and psychologists may increasingly be referred patients with AF. The purposes of this paper are: 1) to review the medical aspects of atrial fibrillation, 2) to examine the comparability of FoR concept from cancer literature to the AF patient, and 3) to apply these novel concepts in patient care.

MEDICAL ASPECTS OF AF

Atrial fibrillation (AF) occurs when rapid and disorganized electrical signals cause the atria in the heart to irregularly beat, restricting blood flow from the atria to the ventricles (3). Over time, AF can decrease the heart's pumping ability which can lead to heart failure and is also associated with an increased risk of stroke or systemic embolism (4). In the United States alone, roughly 3 to 6 million people are impacted by AF with domestic and global prevalence expected to increase to 12.1 million by 2030 and up to 17.9 million by 2050 in Europe (5–7). Individuals aged 65 years and older are most likely to be diagnosed with AF, however, it can occur among younger patients especially if precipitated by other cardiac risk factors (e.g., hypertension, premorbid cardiovascular conditions, lifestyle and behavioral risk factors) or familial predisposition (8). Before the age of 75, men are more often diagnosed with AF compared to women (9), although women exhibit elevated risk of adverse events and AF incidence and burden (10–12). Similar patterns are demonstrated among Black and Brown patient populations with lower overall AF prevalence,

but greater risk for heightened symptom burden and adverse events (13).

Presentation of AF can also vary significantly among individuals, and the presentations are categorized as paroxysmal AF (e.g., AF episodes occur spontaneously for less than a week and are often responsive to first- or second-line treatments), persistent AF (e.g., episodes occur for longer than a week and require additional intervention), and permanent AF (e.g., chronic irregular heart rhythm often unresponsive to repeated interventions). Typical symptoms reported by AF patients across all presentations include heart palpitations, lightheadedness/dizziness, tiredness/fatigue, shortness of breath, and chest pain (14). Interestingly, as much as 39% of AF patients report never having experienced any AF symptoms (15). Irrespective of symptom reporting, worsened disease progression (e.g., moving from paroxysmal to persistent to permanent presentations) can occur among AF patients with poorly managed co-morbid conditions, significant psychological distress, and behavioral risk factors among the most vulnerable (10).

The comprehensive treatment of atrial fibrillation requires multidisciplinary collaboration and includes primordial anti-arrhythmic and rate control agents, catheter ablation, and lifestyle management (16). The first-line treatment option for patients requires consideration of risk factors, duration of atrial fibrillation, left atrial fibrosis, and other individual factors (17, 18). Further, the introduction of direct oral anticoagulants and the addition of left atrial appendage occlusion devices have increased the effectiveness and safety profile of stroke prophylaxis in AF. Recurrence of atrial fibrillation while taking antiarrhythmic agents is close to 40–70%, compared to 20–50% with ablation (18, 19). Initial antiarrhythmic drug therapy can reduce recurrent AF episodes for some patients; however, catheter ablation interventions have demonstrated effectiveness at reducing recurrence risk (19, 20). Even so, ablative interventions do not significantly reduce risk of adverse events when compared to pharmacological treatments (20), and in 1 year following ablation and cardioversion, up to 40% of people can still have recurrence [despite anti-arrhythmic medications (21)].

Despite all of the advancements in the treatment paradigm of atrial fibrillation, some patients can remain focused on AF recurrence with each of these approaches (22, 23). While some patients may never experience recurrence of an AF episode after the initial treatment, variables such as obesity, thyroid abnormalities, alcohol consumption and obstructive sleep apnea have all been closely linked to increased probability of recurrence of AF (24). Given the notable probability for recurrent AF episodes following first and second-line treatments and the behavioral link, identifying the role of recurrence possibility for patients is critical. Thus, contemporary management of atrial fibrillation is multi-pronged: reduction of stroke risk, prevention of AF incidents with medical, surgical, or electrical means, and reduction of recurrence to promote comprehensive symptom relief with aggressive risk factor modifications (16, 19, 22).

FEAR OF RECURRENCE: PSYCHOLOGICAL AND BEHAVIORAL ASPECTS

FoR refers to specific anxiety among medical patients with episodic disease bouts of varying intensity and causality that are resistant to forecast. In the US, cancer accounted for nearly 10 million deaths in 2020 (25) compared to approximately 26,000 caused by AF (26). Despite this difference in mortality, the possibility for adverse events (e.g., stroke and premature death) is also prominent in AF patient populations (5), and, as such, it appears that the emotional dimensions and behavioral implications of these conditions share some similarities. Similar to cancer patients in remission, AF patients may exhibit significant fears related to the possibility of recurrence. Specifically, AF symptoms and recurring episodes due to high rates of AF recurrence are anticipated by patients (27).

While this concept has yet to be translated to understanding the AF patient experience, both FoR models in cancer research and prior research regarding other well-defined cardiac-specific fears (e.g., ICD shock anxiety) have taken a two-factor approach to understanding patient fears—examining both *fear of antecedents and consequences* (28, 29). Similarly, (30) have recently utilized a cancer model as a framework for understanding recurrence fears among patients following acute coronary syndromes (ACS). Birk and colleagues are currently examining its impact on medication adherence and physical activity engagement in a randomized trial targeting patients fears vs. usual care. While this work will help better inform the feasibility of transferring cancer-informed ideas about FoR to cardiac populations and how to treat it, conceptualization of AF patient fears maybe more specific and centered around the AF patient experience. Clinical care of FoR among cancer patients spans reliable assessment, psychoeducation, signs and symptoms, and cognitive behavioral therapy (CBT) strategies for risk reduction and follow-up (31). Similar action-oriented interventions can be integrated into AF patient care to better target specific fears and produce considerable patient benefit.

Fear of Recurrence Among Cancer Patients

Within populations of cancer survivors, it is estimated that roughly 30–70% of patients endorse having moderate to severe levels of recurrence fears that can persist for years following diagnosis (32). Models of FoR generally involve antecedent and consequence-focused specific fears of cancer relapse. These models have proposed that patient perception of physical sensations and identification of symptoms often serve as a trigger for elevated fears that can result in increased symptom reporting, significant psychological distress, feelings of hopelessness, and diminished quality of life (32, 33). In addition, FoR among cancer survivors has been linked to increased depressive symptoms, frequent rumination, and impairment in functioning (34). Fear of recurrence has also been associated with heightened death anxiety and intrusive and threatening thoughts about death and dying (35, 36). Patients who have experienced disease recurrence

exhibit heightened fear of disease progression and fear of loss of autonomy and related emotional distress (37).

Behavioral impacts of FoR generally occur on a spectrum—with some patients becoming hypervigilant about their health (i.e., over-utilization of health care, constantly monitoring symptoms and displaying control-seeking behaviors), while others become avoidant [i.e., missing routine appointments, avoiding necessary testing, non-adherence to medications and treatment regimens; (32, 34, 38)]. Differences in FoR in cancer survivors have also emerged in regard to gender with women experiencing FoR at higher rates than men (39). In addition, patients with lower education, decreased income, and younger age are also more likely to experience FoR following cancer remission. Even so, a pattern exists between high FoR and diminished engagement in health behaviors, such as physical activities like walking or running (40). The body of literature for cancer patients is substantial, and many of these specific fears (and manifestations) are mirrored in the AF patient experience.

Fear of Recurrence in Atrial Fibrillation Patients

FoR in AF populations can also be understood as a two-factor concept-composed of both patient fears around antecedents (e.g., fear of activities that could trigger an AF episode) and consequences (e.g., fear of what may happen if an AF episode occurs). In other words, specific to this population, FoR can be conceptualized as cognitions and behaviors associated with either fear of triggering an AF episode or fear of the potential consequences of AF recurrence. Interestingly, recent research has demonstrated that only alcohol use was a reliable trigger in a study utilizing patient selected triggers for AF (41), suggesting that commonly held ideas about the triggers of caffeine, reduced sleep, exercise, lying on the left side, dehydration, large meals, and other customized triggers were not associated with the occurrence of AF.

While the concept of FoR can be theorized into two distinct components, it is important to recognize that FoR is multidimensional and encompasses patient-perceived possible triggers, emotions, thoughts, behavioral reactions, and coping strategies (see **Table 1**). Additional value or utility of FoR includes that cardiac providers would likely be comfortable reviewing the chances and the impact of AF recurrence. Identifying patients with high FoR for AF would allow for more targeted patient education, whereas addressing more general anxiety would likely not be as responsive to patient education. Moreover, recent constructs, such as confidence in living with AF (42), provide cardiac clinics with other patient centered metrics to evaluate positive or desirable aspects of the patient experience as well. Taken together, increased theory and metrics of the AF patient experience can address both fears and the initiation of empowerment.

Commonalities of Patient Psychological Responses in AF to Cancer

The patient experience of AF symptoms has long included a curious component with a significant portion of patients

TABLE 1 | Signs, symptoms, and steps for identifying and targeting AF patient fears.

Components of fear of recurrence	Manifestations (avoidance, catastrophizing, hypervigilance)	Assessment/Recommendations
Fear of physical activity (exercise, sexual activity, emotional reactivity)	◇ Avoidance of normal activities ◇ Body listening ◇ Decreased emotions ◇ Relationship difficulties ◇ Worsened medical severity	◇ Cardiac rehab is a safe and manageable option for AF patients. It may increase comfort and has been proven to decrease arrhythmic burden for some AF patients (43). ◇ Psychoeducation on the importance of physical activity may be necessary. ◇ AF patients often have unique fears regarding physical activity. Stress management techniques may be beneficial to reduce anxiety and gain confidence. ◇ Some AF patients become deconditioned as they resign from typical activities. It may be helpful to schedule pleasant activities to boost mood and aid in re-engagement.
Fear of death	◇ Increased healthcare utilization ◇ Catastrophizing ◇ Withdrawal/avoidance (e.g., missing routine appointments, non-adherence) ◇ Decreased QOL	◇ Psychoeducation on one's prognosis may alleviate some distorted beliefs and provide reassurance. ◇ Reducing catastrophizing thinking through CBT techniques can decrease distress and improve QOL (44).
Fear of stroke (loss of independence, burden, subsequent death)	◇ Increased health-specific anxiety ◇ Caregiver concerns	◇ Education around the importance of anticoagulant therapy could better inform patients about risk of stroke (e.g., significantly lowered if patients are adherent). ◇ Taking a shared-decision making approach to discussing anticoagulant therapy (and AF-specific treatment plans) could help the patient feel as if they are in the driver's seat of their health decisions (and possibly re-establish patient confidence and reduce worry around loss of independence).
Fear of medical consequences (finances, procedures, medical severity)	◇ Financial Stress ◇ Apprehension ◇ Avoidance of seeking healthcare to save money ◇ Non-compliance	◇ Reviewing social determinants of health and financial support to ensure equitable healthcare delivery. ◇ Utilization of payment assistance programs to offset costs of copayments and/or prescription medications (45).

(approximately 39%) reporting that they were asymptomatic (15). Objective metrics of the presence of AF allow for examination of both the objective and subjective components of AF symptoms. This research suggested that negative emotions were more strongly associated with AF symptom score than the presence of device-detected AF (46). More recently, observational studies using serial assessment of AF patients in a specialty clinic demonstrated that depression and anxiety were the best predictors of AF symptom severity and that symptom severity was associated with increased costs and healthcare utilization (47). These data further necessitate understanding the psychological aspects of AF symptom reporting and the AF patient experience.

Approximately 28–38% of AF patients experience significant depressive or anxious symptoms (11, 48), and the interrelationships between these symptoms and AF are multidimensional and complex (49). Those patients taking the anti-coagulant, warfarin, as a method for stroke prevention are also at an increased risk of depressive symptoms and dementia (50). These high rates of emotional reactivity may be attributed to AF specific fears, consequences, and demanded psychological adjustment (51). The combination of uncertainties regarding the cause, symptom presentation, treatment options, and outcomes of AF can be overwhelming for patients (52). AF on its own is not typically life threatening, however, AF increases the

risk of stroke by nearly five times and is the most commonly reported fear by AF patients, and for good reason (53, 54). Those patients with both AF and history of stroke experience increased rates of medical and neurological complications and are more likely to face consequences such as disability and even death when compared to stroke patients without AF (55–57). The current assessment of fear of stroke revolves largely around physical functioning (e.g., mobility, memory and thinking, communication, etc.) and emotional impacts following the event rather than future, stroke-related fears (58). In addition to fear of stroke, death anxiety is a salient fear in those with chronic conditions such as AF (59, 60) and refers to feelings of discomfort, worry, or fear that may follow becoming aware of one's own mortality (61). Death anxiety in patients has been shown to be negatively related to quality of life; that is, those with higher levels of death anxiety often experience poorer quality of life (62). Collectively, psychological well-being can strongly impact AF symptom severity and patient healthcare utilization (63).

Similar patterns in individual and group differences identified in research regarding FoR in cancer populations may also be reflected in AF patient populations. For instance, women living with AF consistently exhibit higher rates of depression and anxiety, increased incidence of physical AF symptoms and symptom burden, and decreased quality of life when compared

to their male counterparts (11, 44, 64–66). In addition, younger AF patients (i.e., <60 years old) are seemingly more impacted by health-related stress and experience depression and anxiety at higher rates than older patients (65). Patients with lower SES and diminished access to resources are at increased risk for elevated AF symptom burden and adverse events [e.g., premature death, heart failure, MI, and stroke; (67)]. Interestingly, although female patients have demonstrated diminished quality of life and worse symptoms, they are less likely to seek secondary AF treatment such as catheter ablations (68), and as such, may be particularly vulnerable to continued psychological concerns. Moreover, it is likely that women, patients of lower SES (and lower access to resources and health literacy), and younger age are also at increased risk for developing AF-specific fears contributing to worse outcomes—a notion echoed in cancer FoR literature.

Behavioral Changes and Response in AF Patients

The importance of patient understanding and adherence to the medical regimen is common across chronic diseases and can prompt a set of changes spanning behavioral, emotional, and medical challenges (69).

For the AF patient, ongoing clinical care includes the management of the risk factors of AF, such as adherence to medical management (e.g., rate control, rhythm control, blood pressure control, and stroke prophylaxis) and engagement in risk reduction behaviors (e.g., weight management, abstinence from smoking, avoiding or minimizing alcohol consumption, and participation in regular physical activity) (70).

Even a quick review of these risk behaviors would indicate that many of these changes are indicated as part of a healthy lifestyle for all patients. The progression of AF can be associated with the presence and combination of behavioral risk factors, and young-onset individuals may even have risk factors that are maintaining their condition (71). However, the challenges for AF patients are multiplicative because existing research in both China and in Europe suggest that as few as 4% of AF patients are engaged in a fully “healthy lifestyle” (72). Some modifiable risk factors have been shown to have distinct associations with atrial fibrillation (e.g., alcohol consumption, being overweight/obese, smoking) and the cumulative impact poses significant risk for these patients [Di (73)]. Successes and failures at making these lifestyle changes often chip away at patients’ perceptions of control, daily planning to engage in valued activities, and life itself (74). Many patients fear that physical activity may trigger an AF episode which initiates a behavioral avoidance pattern to exercise/exertion (75). Finding meaning in AF symptoms, trying to “stay clear” of AF episodes, and managing unpredictable and functional limits are also common behavioral responses that can translate into increased distress and worsened quality of life (76).

DIAGNOSTIC CONSIDERATIONS

A common goal of AF patient care among psychiatrists and psychologists typically involves determining if an anxiety disorder diagnosis is warranted and then providing typical

recommendations or a referral for the treatment of an anxiety disorder. Considering the specificity of AF patient experiences, it may not be ideal to pursue general anxiety disorders for these patients. Although some symptoms may overlap, patient concerns are often specifically related to AF symptoms and risk factors. Moreover, a simple phobia diagnosis also does not fit the phenomena well. Many AF patients “approach” the fear of irregular heartbeat constantly by seeking information and diagnostics in an attempt to detect AF. Similar to routine care among cancer patients, psychiatrists and psychologists can assess for FoR, provide adequate medical information, discuss signs and symptoms of recurrence, normalize patient fears, implement strategies, and provide a plan for follow-up (31). AF patients could likely benefit from a similar action-oriented plan encompassing their individual fears and providing specific treatment plans as needed for the future. The activation of therapeutic interventions, such as exercise programs, alcohol reduction, and OSA management, would be expected to be exceedingly more beneficial than a diagnosis alone.

Each AF patient likely has a unique combination of the established components of FoR in AF. It is common for AF patients to experience a spectrum of disease-specific fears such as fear of exercise, fear of death, fear of stroke, and fear of other medical consequences. **Table 1** consists of these components of fear of recurrence, manifestations of those fears, and recommendations for each.

Specific action plans that can be efficiently established during regularly scheduled appointments can improve patient outcomes, improve rapport, and decrease healthcare utilization for AF patients.

CONCLUSION AND FUTURE DIRECTIONS

The FoR model in AF is proposed to give consultation liaison psychiatrists and psychologists a broader disease-specific conceptualization related to the AF patient experience, beyond traditional anxiety disorders in AF patients in hopes to improve patient outcomes. The FoR concept in cancer has proven useful for targeting and reducing disease-specific fears among cancer patients. A similar model for AF patients may also provide utility for consultation liaison psychiatrists and psychologists to recognize and address similar fears in the AF patient. In turn, the aim is to help advance provider assessment of FoR components, possible presentations and manifestations, and specific fears that can be targeted in AF management plans. The importance of this work is highlighted in that many patients may feel misunderstood or disregarded when their fears are not recognized by providers and instead receive anxiety disorder diagnoses that are not representative of their experience (77). Overall, FoR assessment can help normalize the patient experience and provide education around rationality of fears. In addition, it can help patients balance the risk and benefits of engaging in previously feared behaviors necessary for proper AF management (e.g., physical activity). It is our belief that AF patient care involves a commitment to understanding unique patient fears outside of what can be defined by the DSM-5. We

can borrow from cancer FoR assessment strategies to inform AF care by addressing disease-specific fears.

Tailored treatment therapies from FoR in cancer should also be further evaluated for applicability to help target AF patients' shared experiences. A growing number of therapeutic interventions have demonstrated effectiveness in managing FoR among cancer patients (31). Psychological interventions (e.g., CBT interventions) have been identified as efficacious treatments for alleviating FoR among cancer survivors with effects immediately following intervention and at follow-up periods. Of note, contemporary CBT interventions have demonstrated greater efficacy in treating FoR than traditional CBT interventions, indicating that treatments aimed at altering how individuals relate to inner experiences (e.g., worry, rumination, etc.) are especially advantageous (34). Similar strategies spanning behavioral, psychological, and cognitive

concerns can be translated into AF-specific clinical care to improve patient outcomes. As a first step to targeted target, we are currently developing and testing a measure assessing AF FoR informed by the model presented in the current paper. This model intends to provide a blueprint for further assessment and future treatments in hopes to improve the AF experience.

AUTHOR CONTRIBUTIONS

SA contributed to the conceptualization with support from SS, RH, CM, SK, TH, and AN. SS, SA, and RH contributed to visualization. SS, SA, RH, CM, TH, and SK contributed to the writing—original draft. SA, SS, RH, TH, SK, and AN contributed to writing—review and editing. SS supervised the writing of this article. All authors contributed to the article and approved the submitted version.

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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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