MIND THE HEART – PSYCHOSOCIAL RISK FACTORS AND COGNITIVE FUNCTIONING IN CARDIOVASCULAR DISEASE

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MIND THE HEART – PSYCHOSOCIAL RISK FACTORS AND COGNITIVE FUNCTIONING IN CARDIOVASCULAR DISEASE

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EDITORIAL
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Editorial: Mind the Heart – Psychosocial Risk Factors and Cognitive Functioning in Cardiovascular Disease

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Editorial on the Research Topic

Mind the Heart – Psychosocial Risk Factors and Cognitive Functioning in Cardiovascular Disease

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Cardiovascular diseases (CVDs) are the leading cause of disability and premature death worldwide, and they contribute substantially to rising health care costs. Ameliorating cardiac risk factors is the most effective way of minimizing CVDs' negative physical and psychological ramifications World Health Organization (WHO, 2021). By targeting those people who are most predisposed to develop cardiac illness or whose risk factors prevent them from managing their illness as recommended, we might be able to minimize the vast global burden of this illness. The current topic for *Frontiers in Psychology* presents an effort to gain an integrated view of the role played by psychosocial and cognitive factors in the context of CVD.

The main variables analyzed in the current collection were anxiety, depression, and stress (Grech et al.; Murphy et al.; Callus et al.; Eisenberg et al.; Ely et al.; Heenan et al.). The main tools presented for measuring these construct were the DASS-21 (Grech et al.; Eisenberg et al.), the HADS (Murphy et al.; Heenan et al.), the PHQ-9 (Grech et al.; Callus et al.; Ely et al.), and the GAD-7 (Grech et al.; Callus et al.; Ely et al.). Less observed psychosocial variables were those capturing well-being, as measured by the PGWBI (Pietrabissa et al.) and the SF-36 (Heenan et al.), and those focusing on behaviors as nutritional behaviors, measured by the healthy heart score (Eisenberg et al.). In the rare occasions where patients' cognitive abilities were measured, the researchers applied the NAB (Neuropsychological Assessment Battery) (Byron-Alhassan et al.) or the Mini-Cog, a test used for memory evaluation (Ely et al.).

These psychosocial risk factors were found to be associated with CVD either directly or indirectly via unhealthy behaviors which are known to contribute to cardiac morbidity and mortality. For example, Murphy et al., detected anxiety and depression among 15–43% of their sample of 911 patients coping with acute myocardial infarction (AMI). Heenan et al. detected that cardiac patients' anxious attachment orientation has been associated with anxiety, depression, poorer physical and mental quality of life, and even fasting blood glucose, HbA1c, via greater levels of traumatic stress. In addition, psychological distress was associated with obesity among heart failure patients (Ely et al.), and psychological well-being was associated with exercise capacity-a well-established predictor of cardiovascular health (Pietrabissa et al.). Moderate (but not high) levels of anxiety were associated with consumption of sweetened drinks and white bread among a sample of women at cardiovascular risk (Eisenberg et al.). Somewhat surprisingly, a systematic review of case-control studies conducted by Galli et al. did not detect any consistent psychosocial risk factors associated with the emergence of Takotsubo syndrome.

Risk factors were explored in different CVD diagnoses, and different ages. Each population presented a unique picture of psychosocial and cognitive needs and difficulties. For example, Tye et al. revealed five themes of challenges adolescents with congenital heart defect face with: (1) emotional/psychological issues; (2) the progress of the illness; (3) relationship issues; (4) future preparation; and (5) school and community. Journiac et al. focused on young adults with congenital heart disease and showed that this age group copes with additional challenges as social isolation, identity changes and difficulties at work. On the other end of the spectrum, elderly cardiac patients cope with the additional burden of neuropsychological difficulties (Granata et al.). Indeed, Byron-Alhassan et al. detected regional atrophy in the brains of patient who underwent cardiac arrest and myocardial infarction, compared to a healthy control group. Overall, the current studies provide some useful insights for future research. First, in order to provide an adequate assessment of patient's emotional state, it is important to apply longitudinal designs as suggested in many of the current reports e.g., (Grech et al.). It is also recommended to prefer psychological interviewing over self-report questionnaires, due to the latter being much more susceptible to social desirability. Another advantage of applying an interview is the opportunity for the clinician who collects patient's information to also offer him/her with much needed support (Callus et al.; Granata et al.). There is also a need to launch broader, multicenter-based studies (national or international), integrating the biopsychosocial and the multidimensional approaches, and involving a more heterogeneous sample (Heenan et al.).

In the studies examined, attention was mainly paid to certain aspects of mental health, such as anxiety and depression, but future research should also consider aspects related to other diagnoses as post-traumatic stress disorder (Journiac et al.), as well as to patients' self-management acts as eating behavior (Eisenberg et al.) and physical exercise (Pietrabissa et al.). Finally, given the crucial role of early treatment in determining a better quality of life and less use of health services (Murphy et al.), it may be useful to focus on early identification of risk factors frequently present in CVD patients, so as to intervene in a timely manner.

To sum up, the accumulated data attest to the high prevalence of emotional distress among cardiac patients, which emerges as a consequence of cardiac illness and also plays a major role as risk factor for low adherence to health-promoting behaviors. Overall, cardiac patients seem to be caught in a vicious cycle in which negative psychological factors preceding the cardiac event or induced by it are associated with the emergence of additional risk factors, which down the road contribute to recurrence, and worse prognosis. Mapping and understanding patients' cognitive and emotional factors may be a valuable step in developing tailored primary and secondary cardiac prevention interventions. Overall, the assessment of psychological risk factors must be integrated into patients' health care routine during hospitalization, before discharge, and during convalescence, using designated tools and protocols.

AUTHOR CONTRIBUTIONS

EC produced the first draft. GP and NV reviewed the article. All authors contributed to the article and approved the submitted version.

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MINI REVIEW
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Traumatic Events, Personality and Psychopathology in Takotsubo Syndrome: A Systematic Review

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Objective: Takotsubo syndrome (TTS) is a transient heart disease that has been historically related to the occurrence of psychological (emotional) factors ("broken heart" syndrome). We aimed to conduct a systematic review analyzing the role of psychological factors in TTS.

Methods: All studies on TTS and psychological factors from January 1991 through April 2019 were scrutinized according to the Cochrane Collaboration and the PRISMA statements. Selected studies were additionally evaluated for the Risk of Bias according to the Newcastle-Ottawa Scale (NOS).

Results: Fifteen case-control studies (by Mayo Clinic criteria) were finally selected. Most studies analyzed stressful life-events or trauma, although with conflicting findings, while a likely role of long-lasting psychological distress seemed to be a homogenous result. Among life-time psychopathology, only anxiety appeared to have a significant role. Some studies outlined a likely role of personality, but findings are conflicting.

Conclusion: Our findings do not lead to any definitive assumption on the specific role of psychological factors in TTS, also for scant strong methodology of the most part of the studies. More studies with stronger research methodology are needed to better characterize psychological elements in TTS.

Keywords: Takotsubo syndrome, psychological factors, life-event, trauma, anxiety, depression, personality

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INTRODUCTION

Takotsubo syndrome (TTS) is a form of transient heart failure syndrome often mimicking acute myocardial infarction. It is also known as stress cardiomyopathy, broken heart syndrome, or apical ballooning syndrome, and was firstly described in 1990 (Dote et al., 1991), even if some Authors dated it earlier (Wittstein, 2008).

Takotsubo syndrome is characterized by acute, but reversible, left ventricular regional systolic dysfunction accompanied by electrocardiographic changes and cardiac biomarkers elevation in the absence of a significant pathological condition (Wittstein, 2008). The Position Statement from Heart Failure Association of the European Society of Cardiology has published new TTS diagnostic criteria (Parodi et al., 2014). The estimated prevalence of TTS is about 1–3% of all patients presenting with suspected acute coronary syndrome and up to 5–6% in female patients (Ghadri et al., 2018), indeed it is predominantly observed in postmenopausal women and elderly

(Templin et al., 2015). The pathophysiological mechanisms responsible for TTS are complex and may vary between patients (Agewall et al., 2017) The prognosis is generally good (Agewall et al., 2017).

Since the first descriptions of TTS, a role for psychological factors has been underscored in medical literature (Cebelin and Hirsch, 1980; Pavin et al., 1997; Prasad et al., 2008), as testified by the previously used terms "stress" cardiomyopathy or "broken-heart" syndrome to name TTS. Clarifying the role of psychological factors in TTS may add new framework issues and possibilities of intervention for these patients. The recent Consensus document on the diagnostic workup and management of TTS (Ghadri et al., 2018) outlines a specific role (diagnostic algorithm) of psychopathologic disorders and emotional stress for the diagnostic workflow of patients in the emergency department. However, evidence on the role of psychological factors in TTS are sparse, and mainly related to case-reports (Wang et al., 2015; Manfredini et al., 2018).

To the best of our knowledge, no systematic reviews have been realized analyzing the likely causative link between psychological factors and TTS, with the existing reviews detecting other factors (e.g., the role of drugs or pathophysiologic mechanisms). The objective of the present study was to systematically review all the studies on psychological factors (as antecedents) (traumatic/stressful events, psychopathology and personality) in patients with TTS diagnosis in order to understand their likely role in this syndrome.

METHODS

We conducted a systematic review of the literature on psychological factors (psychopathologic disorders, stressful life-events/psychological trauma, and personality characteristics) in TTS. All observational studies were included in the review by the ascertainment of a case-control study design, adequacy of the sample size, comparison, and outcome measures.

Search Strategy

To include the broadest range of relevant literature, electronic searches were conducted on the major databases in the field of health and social sciences: Pubmed, Scopus, Embase, PsycInfo, and Web of Science. The search was performed using Mesh terms OR Keywords (depending on the database) with the same search strategy: "Takotsubo " OR "Tako-Tsubo syndrome" OR "Stress – induced cardyomiopathy" OR "Takotsubo cardiomyopathy" "transient left ventricular ballooning syndrome" OR "apical ballooning syndrome" OR "ampulla cardiomyopathy" OR "broken heart syndrome" AND "Psychological distress" OR "Anxiety" OR "Depression" OR "Emotional distress/trigger" OR "acute stress" OR "Personality" OR "Psychiatric disorder" OR "Temperament" OR "Life-event". The selection of the search terms was based on the clinical experience and the literature topics on psychological factors involved in physical disorders (American Psychiatric Association [APA], 2013). The search was limited to English-written publications, and to the period from January 1991 to April 2019. An additional analysis of the reference list in each selected paper was also performed. When the full text was not retrievable, the study was excluded.

Selection Criteria

Inclusion Criteria

- Studies with an analytical study design as defined by Grimes and Schulz (2002) (i.e., an observational study with a comparison or control group Both retrospective and perspective studies have been included to consider the highest number of studies.
- Diagnosis of TTS by the Mayo Clinic criteria or by the new TTS criteria (Parodi et al., 2014; Lyon et al., 2016).
- Studies adopting standardized and validated tests.
- Studies written in English language.

Exclusion Criteria

- Studies with intra-group control (e.g., TTS with a pre-existing disorder or not).
- Case reports, reviews, Letters to the Editor, meeting abstracts, book chapters.
- Pharmacological and behavioral intervention trials, surgical protocols, or validation of measurement instruments.
- Number of subjects per group ≤ 5.

Data Extraction

Study selection was performed by two independent reviewers with research expertise in clinical psychology and cardiology (FG and FB) who assessed the relevance of the study for the objectives of this review. This first round of selection was based on the title, abstract, and keywords of each study. If the reviewers did not reach a consensus or the abstract did not contain sufficient information the full text was reviewed.

In the second phase (screening), full-text reports were evaluated to detect whether the studies met the inclusion criteria (**Figure 1**).

In the phase of eligibility, all full-texts were retrieved and a final check was made to exclude papers not responding to inclusion/exclusion criteria, and reaching the final consensus to decide the final number of studies to be selected.

A standardized data extraction form was prepared; data were independently extracted by two of the authors (FG and FB) and inserted in a study database. A process of discussion/consensus moderated by a third reviewer (SC) (Furlan et al., 2009) resolved discrepancies between reviewers.

Statistical Methods

A systematic analysis was conducted according to the Cochrane Collaboration guidelines (Higgins and Green, 2011) and the PRISMA Statement (Moher et al., 2009). Because the included studies were highly heterogeneous in terms of participants, variables, instruments, and outcomes, it considered inappropriate to undertake a meta-analysis (Higgins and Green, 2011). However, effect size computations were performed using Cohen's d (Cohen, 1988) and its 95% confidence interval for continuous variables for each outcome measure within each study (Borestein et al., 2011). The index was primarily calculated using descriptive statistics reported in the results section of each

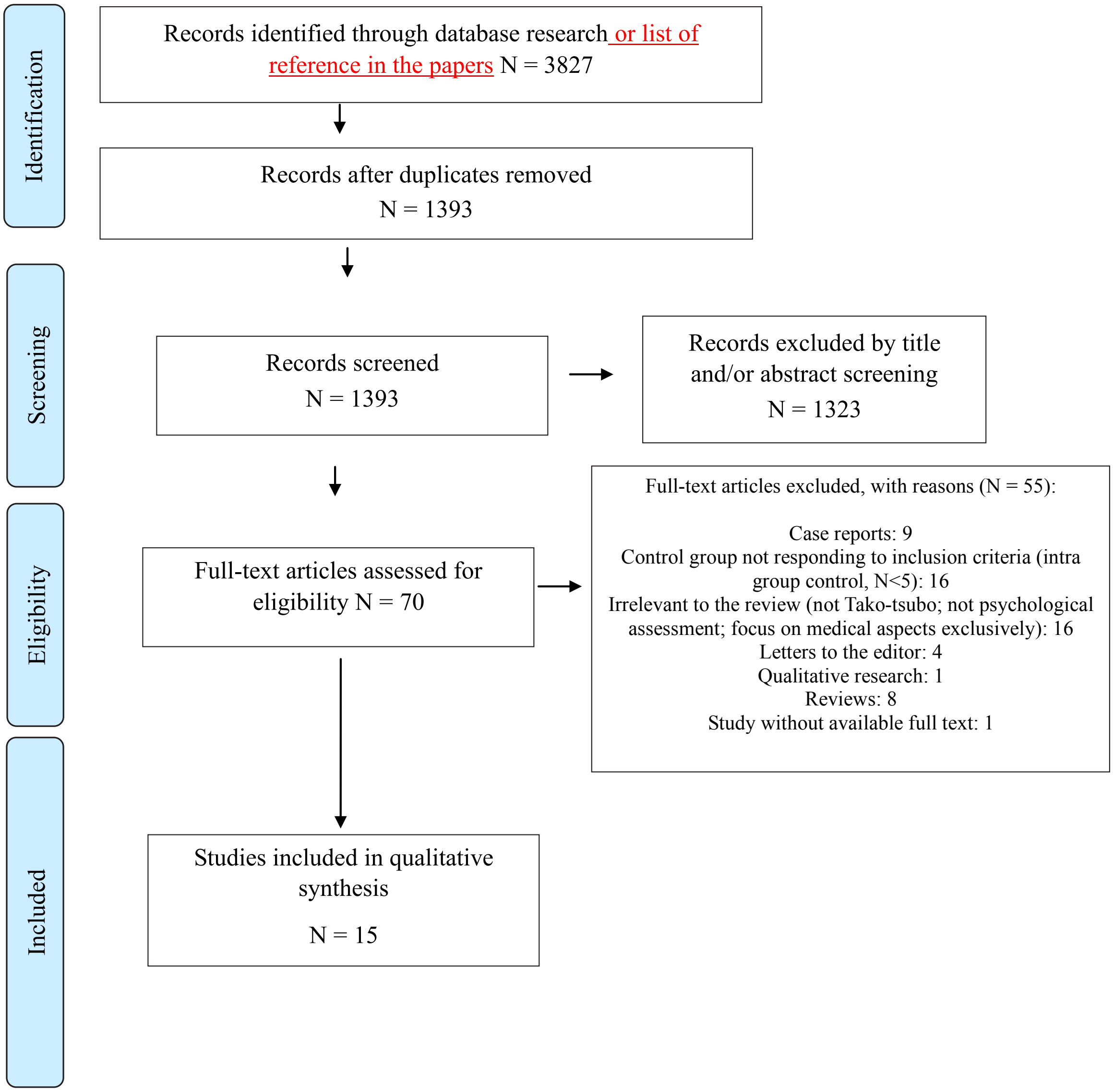

FIGURE 1 | PRISMA flow diagram of literature search and selection of publications.

study. When binary data was reported, we estimated the Odds Ratio with related estimates of confidence intervals (Borestein et al., 2011). Cohen's *d* values less than or equal to 0.20, 0.50, and 0.80 were interpreted as small, medium and large effect size, respectively (Cohen, 1988). For variables expressed as median and 25th–75th percentile it was not possible to calculate Cohen's *d*.

Risk of Bias

Quality assessment of each of the included studies was evaluated following the Newcastle-Ottawa Scale (NOS) for case-control studies on a 9-star model (Wells et al., 2014). Studies scoring above the median NOS value were considered as high quality (low risk of bias) and those scoring below the median value were considered as low quality (high risk of bias). In brief, two reviewers (FB and FG) independently extracted relevant information and data from all eligible reports that met the above inclusion criteria.

RESULTS

We found 15 studies meeting inclusion criteria (**Figure 1**), for a total of 2581 subjects (1152 TTS patients; 1069 other heart diseases; 360 healthy controls). The description of the samples, psychological variables, study design, psychometric scales (tests, interview or retrospective medical records analysis), key findings, Cohen's *d* or Odd ratios and 95% confidence intervals of selected studies are reported in **Table 1**.

TABLE 1 | Overview of the selected studies.

Study	Population			Study characteristics			Significant findings (p)	*Cohen d* (95% CI)	Notes	Nos Score
	TTS (*N*, mean age, *SD*), *N* females (f)	Controls (*N*, mean age, *SD*), *N* females (f)	Control (diagnosis)	Assessment (time after diagnosis)	Outcome measures	Design				
Del Pace et al., 2011	50 (73 ± 9); 47f	50 (73 ± 9), 47f	STEMI	– Before hospital discharge	– STAI	Prospective case-control	– Stressful trigger event: TTS > STEMI ($p < 0.001$)	STAI $d = 0.08$ (−0.32–0.47) – Stressful trigger event OR 46.0 (13.38–158.09)	– High anxiety trait common to TTS and STEMI – Unclear how the antecedent stressful trigger event has been evaluated	5/9
Delmas et al., 2013	45 (72.7 ± 11.5); 41f	50 (72.9 ± 13.1); 47f	– ACS	– Within 48 h after admission	– Mini interrnational neuropsy-chiatric interview	Prospective case-control.	– ADD: TTS > ASC ($p < 0.001$) – Acute stressful event: 78% (TTS) vs. 18% (ACS) – Chronic psychological stress: TTS > ACS) ($p = 0.005$) – Current and/or past MDD: TTS > ACS ($p < 0.001$)	– TTS vs. ACS ADD OR 9.96 (3.87–25.63) – Acute stressful event OR 15.94 (5.82–43.65) – Chronic psychological stress OR 3.64 (1.44–9.24) – Current and/or past MDD OR 7.83 (3.13–19.52)	– ADD more common in TTS than ACS – Unclear as the acute stressful event and chronic psychological stress has been evaluated	4/9
Compare et al., 2013	37* (66 ± 12.8), 33f 38** (66 ± 11.1),34f	37 (66 ± 10.1), 33f	– AMI	– Within 48 h of symptoms (emotional symptoms assessment) – 3 months after symptoms (personality assessment)	– IRLE – PSI – DS14 questionnaire (Type D personality)	Cross-sectional, prospective case-contro.	– Type-D Social Inhibition sub-scale: TTS > AMI ($p < 0.001$)	– $d = 5.3$ (4.3–6.3) tTTS vs. nt TCC – $d = 5.05$ (4.1–6.1) tTTS vs. AMI	– No differences in emotional triggering events (TTS vs. AMI)	5/9
Compare et al., 2014	37 (55 ± 8), 33f	37 (57 ± 7), 33f	– AMI	– During first visit following admittance (by cardiologist) – 1-year follow-up (by clinical psychologist)	– IRLE – PSI – MacNew – PGWBI	Prospective case-control (1-year follow-up)	– Psychological distress TTS > AMI ($p = 0.001$) (1-year follow-up)	– Baseline TTS vs. AMI: PGWBI $d = 0.02$ (−0.44–0.49) – MacNew global $d = −0.20$ (−0.66–0.26) – 1 year TTS vs. AMI – PGWBI $d = 2.72$ (2.07–3.37); MacNew-global $d = 1.91$ (1.35–2.47)	– No patients with TTS had a “history of psychiatric illness” – The psychological distress in TTS tends to become more negative over time than in AMI	7/9

(Continued)

TABLE 1 | Continued

Study	Population			Study characteristics			Significant findings (p)	*Cohen d* (95% CI)	Notes	Nos Score
	TTS (*N*, mean age, *SD*), *N* females (f)	Controls (*N*, mean age, *SD*), *N* females (f)	Control (diagnosis)	Assessment (time after diagnosis)	Outcome measures	Design				
Kastaun et al., 2014	19 (61.1 ± 9.5)	20 (62.2 ± 10.0) 20 (58.4 ± 7.8)	– NSTEMI myocardial infarction – HV	– 18.4 (+8.5) months from TTS and NSTEMI acute event – Acute stressful event from medical record	– SCL-90 – FPI-R – TICS – MDMQ	Prospective case-control	– 2 (11%) TTS vs. 12 (60%) NSTEMI showed no acute trigger event (*p* = 0.014) – Life event inventory (physical/sexual abuse, traumatic experience): 8 TTS (42%) vs. 2 NSTEMI (10%) vs. 2 HV (10%) (*p* = 0.031) – TTS differed from controls for: FPI-R greater emotionality (*p* = 0.048); TICS chronic worrying (*p* = 0.030). – TTS: lower overall cortisol release (p < 0.05) – TTS felt significantly more nervous than controls at arrival (*p* < 0.01), post-stress (*p* < 0.05) and the end (<0.05) of examination	– No acute trigger OR 0.08 (0.01-0.44) TTS vs. NSTEMI – Life event inventory (physical/sexual abuse, traumatic experience): OR 6.54 (1.17-36.61) TTS vs. NSTEMI and HV.	– The psychological assessment and cortisol measure have been released 18 months after the cardiac event. – TTS showed lower cortisol release than controls. – No significant differences in SCL-90 scoring. – TTS showed more nervousness during stress situations, but they had lower cortisol level – Limited sample size	6/9

(Continued)

TABLE 1 | Continued

Study	Population			Study characteristics			Significant findings (p)	*Cohen d* (95% CI)	Notes	Nos Score
	TTS (*N*, mean age, *SD*), *N* females (f)	Controls (*N*, mean age, *SD*), *N* females (f)	Control (diagnosis)	Assessment (time after diagnosis)	Outcome measures	Design				
Lacey et al., 2014	31 sporadic TTS (sp-TTS) (66.7) 27 earthquake TTS (eq-TTS) (69.7)	26 (80.9)	HV	– In 12 months following the earthquake – From hospital records (2000–2012)	– EPQ-brief	Retrospective case-control	– Past experience of trauma connoted TTS (59% eq-TTS vs. 42% sp-TTS vs. 23% HV, $p < 0.05$) – EPQ neuroticism > in eq-TTS and sp-TTS vs. HV ($p < 0.01$)	– Past experience of trauma OR 4.84 (1.47–15.97) eq-TTS vs. HV OR 2.41 (0.76–7.67) sp-TTS vs. HV – EPQ extraversion $d = -0.25$ (−0.80–0.30) eq-TTS vs. HV; $d = -0.28$ (−0.81–0.25) spTTS vs. HV – EPQ neuroticism $d = 1.34$ (0.73–1.95), eq-TTS vs. HV; $d = 1.04$ (0.48–1.60) sp-TTS vs. HV	– The timing of assessment is very different in the three groups (also 10 years and more) – Antecedent psychiatric factors do not distinguish the three groups – Mean age of healthy volunteers is much higher than TTS – The semi-structured interview is not validated and the assessment criteria have not been described at all	7/9

(Continued)

TABLE 1 | Continued

Study	Population			Study characteristics			Significant findings (p)	*Cohen d* (95% CI)	Notes	Nos Score
	TTS (*N*, mean age, *SD*), *N* females (f)	Controls (*N*, mean age, *SD*), *N* females (f)	Control (diagnosis)	Assessment (time after diagnosis)	Outcome measures	Design				
Templin et al., 2015	455 (67.7 ± 12.5), 411f	455 (68.7 ± 12.3), 411f	– ACS	– Review of medical records (presumably during index hospitalization, but unspecified)	– DSM-IV	Multicentre retrospective case-control	– Acute, former or chronic neurologic *or* psychiatric diseases TTS > ACS ($p < 0.001$) – Total psychiatric disorders: TTS > 14.3% ($p < 0.001$) – Acute psychiatric disorders (12.6% TTS vs. 1.3% ACS) – Former or chronic psychiatric disorders TTS > ACS ($p < 0.001$); – Former or chronic affective disorders TTS > ACS ($p < 0.001$); – Acute affective disorders TTS > ACS ($p = 0.002$)	– Acute, former or chronic neurologic *or* psychiatric diseases OR 3.65 (2.75–4.83) – Total Psychiatric disorders OR 4.39 (3.17–6.07) – Acute psychiatric disorders OR = 10.6 (4.53–24.9); – Former or Chronic psychiatric disorders OR 3.66 (2.62–5.10) – Former or chronic affective disorders OR 3.05 (2.03–4.63); – Acute affective disorders OR 12.2 (1.58–94.15) – Former or chronic anxiety disorder OR 12.3 (4.39–34.51)	– Higher prevalence of psychiatric (*or* neurologic) disorders in TTS history – The psychiatric diagnosis has not been made by psychological test (it is presumably clinical according to DSM-IV criteria). – The distinction between former and chronic is not clear (not by DSM-IV criteria)	3/9

(Continued)

TABLE 1 | Continued

Study	Population			Study characteristics			Significant findings (p)	*Cohen d* (95% CI)	Notes	Nos Score
	TTS (*N*, mean age, *SD*), *N* females (f)	Controls (*N*, mean age, *SD*), *N* females (f)	Control (diagnosis)	Assessment (time after diagnosis)	Outcome measures	Design				
Christensen et al., 2016	45 (70)	95 (72) 90 (67)	– STEMI – HV randomly selected by Danish civil registry	– 24 months (min 8-max 36) for TTS – 26 months (min 2-max 32) for STEMI	– WHO-5 Well-Being Index – ENS – MDI – ASS (anxiety sub-scale)	Prospective case-control	– Anxiety score higher in TTS vs. STEMI (*p* = 0.007) – Compared to control group, TTS: less well-being (*p* = 0.02); higher neuroticism (*p* = 0.0002); more depression (*p* = 0.007); more anxiety (*p* = 0.0001) – Well-being: TTS < STEMI: (*p* = 0.0009); neuroticism TTS > STEMI(*p* = 0.01); depression: TTS > STEMI (*p* = 0.006); anxiety (ns)	Median values	– Only the level of anxiety differentiated TTS and STEMI – Tests mailed	5/9
Goh et al., 2016	73 (67.7 ± 9.8),71f	111 (68.2 ± 10.2), 109f	– ACS (with cardiac catherization)	– 33.8 months (TTS) – 36.3 months (ACS)	– HADS	Retrospective case-control.	– Anxiety HADS score: TTS vs. ACS (*p* = 0.06) – Emotional stress as trigger in 43%TTS vs. 23%.	– HADS *d* = 0.32 (0.02–0.61) – Emotional stress as a trigger OR 4.08 (2.04–8.17);	– The time range of HADS administration is very large – A role for anxiety may not be supported by data – Triggers in ACS group had not been detected.	5/9

(Continued)

TABLE 1 | Continued

Study	Population			Study characteristics			Significant findings (p)	*Cohen d* (95% CI)	Notes	Nos Score
	TTS (*N*, mean age, *SD*), *N* females (f)	Controls (*N*, mean age, *SD*), *N* females (f)	Control (diagnosis)	Assessment (time after diagnosis)	Outcome measures	Design				
Salmoirago-Blotcher et al., 2016	45 (62.4 ± 10.8)	32 (64.6 ± 15.3) 30 (55.9 ± 12.4)	– MI (24 STEMI and 8 NSTEMI) – HV	– 1 month after hospital discharge (telephone interview)	– HADS – PSS – IES – Cook-Medley hostility inventory – Life orientation test – DS14 questionnaire (Type D personality) – PERI Life (adapted)	Prospective case-control and cross-sectional design	– Psychiatric disorders: anxiety > TTS (24.4%) > MI(12.5%) > HV (0%) ($p = 0.01$) – Psychological distress (HADS): TTS vs. MI (ns); TTS > HV ($p < 0.05$) – PTSD: TTS > MI > HV ($p < 0.001$) – PSS: TTS > HV ($p < 0.05$) – Personality (negative affectivity): TTS > HV ($p < 0.05$) – Personality (social inhibition): TTS > HV ($p < 0.05$) – Stressful life events: TTS > HV ($p < 0.001$); TTS vs. MI (ns)	– Anxiety OR 2.27 (0.64-7.90) TTS vs. HV – HADS $d = 0.2$ (-0.26-0.67) TTS vs. MI, $d = 0.75$ (0.27-1.22) TTS vs. HV – PS score $d = 0.34$ (−0.12–0.80) TTS vs. MI, $d = 0.66$ (0.20–1.17) – IES score $d = 0.54$ ($d = 0.07$–1.00) TCC vs. MI $d = 1.00$ (0.51–1.50) TTS vs. HV – Type D personality negative affectivity $d = 0.11$ (−0.35–0.57) TTS vs. MI, $d = 0.64$ (0.16–1.12) TCC vs. HV – Type D personality social inhibition $d = 0.10$ (−0.35–0.57) TTS vs. MI $d = 0.66$ (0.18–1.13) – Stressful life event OR = 1.33 (0.45–3.94) vs. MI; OR = 4.57 (1.64–12.72) TCC vs. HV	– TTS: higher level of pre-discharge anxiety and post discharge psychological distress. – Personality did not differ comparing TTS and MI. -Data on psychiatric disorders have been drawn retrospectively from the medical records.	9/9
Smeijers et al., 2016	18, 14f (68.3 ± 11.7)	19, 13f (68.8 ± 10.1) 19 HV, 13f (60 ± 7.6)	– chronic HF – HV	– 23 months (+18)	– PHQ-9 – PSS – GAD-7 – Whiteley-7 scale (anxiety) – NEO-FFI	Prospective case-control.	– depression: TTS > HV ($p < 0.05$); – illness-related anxiety: TTS > HV ($p < 0.01$). – Level of openness: TTS < HV ($p = 0.021$).	– TTS vs. HV PHQ $d = 0.67$ (−0.02–1.36); – PSS $d = 0.61$ (−0.08–1.3); GAD $d = 0.52$ (−0.17–1.20); – Whiteley-7 scale $d = 0.92$ (0.21–1.65); – NEO FFI openness $d = -0.8$ (−1.50–0.99)	– TTS patients did not differ from HF for any of the psychological measures	5/9

(Continued)

TABLE 1 | Continued

Study	Population			Study characteristics			Significant findings (p)	*Cohen d* (95% CI)	Notes	Nos Score
	TTS (*N*, mean age, *SD*), *N* females (f)	Controls (*N*, mean age, *SD*), *N* females (f)	Control (diagnosis)	Assessment (time after diagnosis)	Outcome measures	Design				
Rosman et al., 2017	45 (62.4 ± 10.8)	32 (64.6 ± 15.3) 30 (55.9 ± 12.4)	– MI (24 STEMI and 8 NSTEMI) – HV	– 1 month after hospital discharge (telephone interview)	– PERI Life (adapted)	Prospective case-control.	– TOTAL number of events (along 6 months): TTS > MI > HV ($p < 0.001$). – anxiety: TTS > MI and HV ($p = 0.007$)	– Total N events *d* = 0.62 (0.15–1.10) TCC vs. MI, *d* = 1.21 (0.70–1.73) TCC vs. HV – Stressful event within 1 year prior to hospitalization OR = 0.89 (0.33–2.32) TTS vs. MI – Anxiety OR 3.12 (0.79–12.30)	– Not the event of the month before hospitalization, but the sum of multiple events during the last 6 months were linked to TTS	5/9
Saffari et al., 2017	94 (63.56 ± 7.48)	94 (62.8 ± 8.33) 94 (63.1 ± 6.45)	– AMI – HV	– Before discharge – 6 and 18-month follow-up	– FSFI – FSDS-R – Healt Related – HRQoL-SF-12 – HADS	Prospective case-control.	– Sexual distress, anxiety and depression: TTS > AMI > HV ($p < 0.05$) – Worse sexual functioning: TTS > AMI and HV (at 6 and 18 month follow-up) ($p < 0.001$)	– Baseline TTS vs. MI – FSDS-R *d* = 0.50 (0.21–0.79) – FSFI *d* = −0.037 (−0.32–0.24) – Depression HADS *d* = 0.04 (−0.25–0.32) – Anxiety HADS *d* = 0.34 (0.05–0.63) – HRQoL PCS *d* = −0.09 (−0.34–0.19) MCS *d* = −0.52 (−0.81 to −0.22) TTS vs. HV: – FSD-R *d* = 2.4 (2.05–2.81) – FSFI *d* = −1.75 (−2.09 to −1.41) -Depression HADS *d* = 0.64 (−0.243–0.93) – Anxiety *d* = 1.96 (1.61–2.31) – HRQoL: PCS *d* = −3.43 (−3.882.98); MCS *d* = −2.41 (−2.79–2.04)	– Worsening of sexual function and HRQoL across time	7/9

(Continued)

TABLE 1 | Continued

Study	Population			Study characteristics			Significant findings (p)	*Cohen d* (95% CI)	Notes	Nos Score
	TTS (*N*, mean age, *SD*), *N* females (f)	Controls (*N*, mean age, *SD*), *N* females (f)	Control (diagnosis)	Assessment (time after diagnosis)	Outcome measures	Design				
Compare et al., 2018	37* (66 ± 12.8), 33f 37** (66 ± 11.1),33f	37 (66 ± 10.1), 33f	– AMI*	– 3 months after symptoms	– TMMS – MCQ-30 – EPS – HAM-D	Cross-sectional	– HAM-D: TTS* vs. TTS** (*p* = 0.004); TTS* vs. AMI* (*p* = 0.021); – MCQ-30: TTS* > AMI and TTS** (*p* < 0.05); – TMMS: TTS* > AMI* (*p* < 0.05); – EPS: TTS* > AMI and TTS** (*p* < 0.05)	– NA	– Emotional competence more compromised in TTS* than TTS** and AMI*	5/9
Sancassiani et al., 2018	19 (63.26 ± 9.21), 17f	76 (63.26 ± 9.03), 68f	– HV	– 1 month after TTS	– ANTAS – SCID-I/NP	Prospective case-control.	– Any mood disorder: TTS > HV (*p* = 0.002)	– NA	– No evidence of association with anxiety disorders	5/9

*ADD, anxious-depressive disorder; AMI, acute myocardial infarction; ACS, acute coronary syndrome; ANTAS, advanced neuropsychiatric tools and assessment schedule; ASS, Hopkin's symptoms checklist; ENS, Eysenck's neuroticism scale; EPQ, Eysenck personality questionnaire; EPS, emotional processing scale; FPI-R, Freiburger personality inventory; FSDS-R, female sexual distress scale-revised; FSFI, female sexual function index; GAD, general anxiety disorder; HADS, hospital anxiety and depression scale; HF, heart failure; HAM-D, hamilton rating scale for depression; HRQoL-SF-12, health related quality of life [physical component summary (PCS) and mental component summary (MCS)]; HV, healthy volunteers; IES, impact of events scale-revised; IRLE, Italian version of the interview for recent life events; MacNew, MacNew heart disease health related quality of life; MCQ-30, meta-cognitions questionnaire; MDD, major depressive disorder; MDI, major depression inventory; MDMQ, multidimensional mood state questionnaire; MI, myocardial infarction; NEO-FFI, NEO five-factor inventory; NSTEMI, non-ST-segment elevation myocardial infarction; PGWBI, psychological general well-being index; PHQ-9, patient health questionnaire; PSI, Paykel stress index; PSS, perceived stress scale; PTSD, post-traumatic stress Disorder; SCID-I/NP, structured clinical interview for DSM-IV axis I disorders/No Patient version; SCL-90, symptom checklist-90; TICS, trier inventory for the assessment of chronic stress; TMMS, trait meta-mood scale; TTS, Takotsubo syndrome; WHO-5, WHO-5 well-being index; QoL, quality of life. *With emotional stress. **Without emotional stress. NOS score, New Ottawa Scale for case-control study. NB, distinction for gender was inserted when there was a mixed gender sample, otherwise is to be intended that it was a female sample.*

Life-Events and Psychological Trauma

Most studies investigated the likely role of concurrent stressful events in triggering TTS. The three studies (Compare et al., 2013; Salmoirago-Blotcher et al., 2016; Rosman et al., 2017) investigating the topic by means of psychometric scales did not find any differences between TTS and patients with other cardiac events. Conversely, the studies outlining a significant role of stressful events, collected data by patient interview at admission (Del Pace et al., 2011; Delmas et al., 2013; Compare et al., 2014) or retrospective review of medical records (Kastaun et al., 2014; Templin et al., 2015). One study found a greater impact of Post-Traumatic Stress Disorder (PTSD) after discharge (Salmoirago-Blotcher et al., 2016) in TTS compared to patients with myocardial infarction or healthy controls.

Of interest, the time elapsing between the cardiac event and the psychological assessment was extremely variable, ranging from hours (Delmas et al., 2013) to years (Goh et al., 2016).

History of long-lasting psychological distress not temporally related to the cardiac events was evidenced in four studies (Delmas et al., 2013; Kastaun et al., 2014; Lacey et al., 2014; Rosman et al., 2017).

Some studies differentiated emotional (27–38%) from physical (36–50%) triggers (Compare et al., 2014; Templin et al., 2015; Goh et al., 2016; Rosman et al., 2017), with 12–28% of patients with indeterminable reasons.

Psychopathology (Lifetime, by Medical Records)

Eight studies described psychopathology only recording data by clinical records (without psychometric tests) in a lifetime perspective (Del Pace et al., 2011; Delmas et al., 2013; Kastaun et al., 2014; Lacey et al., 2014; Templin et al., 2015; Goh et al., 2016; Salmoirago-Blotcher et al., 2016; Rosman et al., 2017). Six studies (Del Pace et al., 2011; Delmas et al., 2013; Kastaun et al., 2014; Lacey et al., 2014; Salmoirago-Blotcher et al., 2016; Rosman et al., 2017) aimed to detect whether a history of psychopathologic factors might be related to TTS. In four studies (Lacey et al., 2014; Templin et al., 2015; Salmoirago-Blotcher et al., 2016; Rosman et al., 2017) the psychopathologic diagnoses were made retrospectively by subsuming clinical data derived from medical records. Among these only one study found a significant association between mood *or* anxiety disorders and TTS (Templin et al., 2015). Two studies (Salmoirago-Blotcher et al., 2016; Rosman et al., 2017) found an association only with anxiety, while one study (Goh et al., 2016) did not find any significant associations.

Psychopathology (Current, by Standardized Measures)

Eight studies analyzed the presence of past psychopathologic diagnoses by means of psychometric tests after the occurrence of TTS (Del Pace et al., 2011; Delmas et al., 2013; Compare et al., 2014, 2018; Kastaun et al., 2014; Christensen et al., 2016; Smeijers et al., 2016; Sancassiani et al., 2018) with miscellaneous findings. Anxiety *and* depression seemed to be prevalent in the history of TTS in one study (Delmas et al., 2013), while two studies evidenced a role only for anxiety (Del Pace et al., 2011; Christensen et al., 2016). Two studies (Smeijers et al., 2016; Sancassiani et al., 2018) evidenced a role for depression (and not for general anxiety) if compared with healthy controls, but not if compared with patients with chronic heart failure (Smeijers et al., 2016). One study (Compare et al., 2018) compared the prevalence of depression in TTS with emotion triggers vs. acute myocardial infarction with emotion triggers vs. TTS without emotion trigger and found a significant prevalence only in the two groups with emotion triggers.

Other studies (Compare et al., 2014; Kastaun et al., 2014) did not find any role for psychopathology in the history of TTS patients.

Personality

Five studies (Compare et al., 2013; Kastaun et al., 2014; Lacey et al., 2014; Salmoirago-Blotcher et al., 2016; Smeijers et al., 2016) evaluated the role of personality in TTS. Three studies (Lacey et al., 2014; Salmoirago-Blotcher et al., 2016; Smeijers et al., 2016) found that TTS had pathological characteristics compared to healthy controls, but not if compared to patients with other cardiac events. The remaining studies (Compare et al., 2013; Kastaun et al., 2014) found a greater emotionality and a prevalence of Distressed personality (Type-D, mainly for Social Inhibition) in TTS compared with controls with myocardial infarction. Interestingly, one study (Compare et al., 2018) found a dysfunctional profile in emotional competence in patients with TTS.

Risk of Bias

Half of the studies reflected the median value ($\mu = 5$), four were above it and three below (**Table 2**). Four studies were quoted as high quality (low risk of bias) by NOS (see **Table 2**).

DISCUSSION

Although the role of psychological factors has been extensively studied in TTS, only fifteen studies fulfilled the criteria to perform a systematic review. Consequently, we could not perform a meta-analysis, as originally planned, because of the small number of selected studies and the heterogeneous methodology used for the psychological assessment (no studies shared the same psychological assessment tools).

Most studies attempted to understand if stressful events (or trauma) could have a role (trigger) in TTS, but findings are conflicting. As suggested by the recent Expert Consensus Document on TTS (Jelena-Rima et al., 2018), one of the key questions to answer is which role triggering factors have in the stress response of the heart. Nevertheless, the etymology of "stress" cardiomyopathy requires specific attention for the role of psychological stressor as possible etiological factor. Unfortunately, our review does not allow any conclusion by this side. The first point that warrants attention is the difference between studies drawing data from standardized psychometric tools or from retrospective assessment of medical records. Among studies based on standardized tests, none allowed any

TABLE 2 | Ottawa-Newcastle risk of bias for case-control studies.

Authors	Selection				Comparability[1]	Outcome (psychological tests)			Total NOS score
	Adequate case definition	Represen-tativeness	Selection of controls	Definition of controls		Ascertainment	Same Ascertainment for case/control	Non-response rate	
Del Pace et al., 2011	*	*	–	*	*	–	*	–	5/9
Delmas et al., 2013	*	*	–	–	*	–	*	–	4/9
Compare et al., 2013, 2018	*	*	–	*	*	*	–	–	5/9
Compare et al., 2014	*	*	–	*	**	*	*	–	7/9
Kastaun et al., 2014	*	–	*	–	**	–	*	*	6/9
Lacey et al., 2014	*	–	–	*	*	–	–	*	4/9
Templin et al., 2015	*	*	–	–	*	–	–	–	3/9
Christensen et al., 2016	–	*	*	–	*	–	*	*	5/9
Goh et al., 2016	*	*	–	–	**	–	–	*	5/9
Salmoirago-Blotcher et al., 2016	*	*	*	*	**	*	*	*	9/9
Smeijers et al., 2016	*	–	*	*	*	–	*	–	5/9
Rosman et al., 2017	*	*	*	–	*	*	–	–	5/9
Saffari et al., 2017	*	*	*	*	*	–	*	*	7/9
Sancassiani et al., 2018	*	*	–	*	*	–	*	–	5/9

**The criterion is reflected in the study.* [1]*Two stars were assigned when the control was matched not only for age and gender, but for the index event date as well.*

conclusion toward a role for psychological trigger events in comparison to other cardiac events (control group). On the other hand, all studies that draw data from medical records (usually based on clinical interview at admission) evidenced a role for psychological trigger events compared to controls. Obviously, this opens both to methodological and clinical considerations. From a methodological side, the use of standardized measures of assessment would lead to strongest conclusions, but in a direction making questionable the evidence of a role of psychological factors closely involved in the etiology of TTS. On the other hand, homogenous clinical observations by medical records suggest implementing further case-control studies to support the role of psychological triggers in TTS.

Some studies differentiated between "emotional" and "physical" traumas preceding TTS. Distinguishing between "emotional" or "physical" dimensions may be a critical matter, as it is very difficult to imagine any physical trauma not burdening on the emotional side. Life-threatening illnesses such as myocardial infarction or TTS may cause PTSD symptoms (Edmondson et al., 2012; Salmoirago-Blotcher et al., 2016) to testify the mutual interplay between mind and body. The unanswered question is why a person develops TTS and another one other disorders.

Summing up the various findings, we cannot prove or refute a role for psychological trigger events, differentiating what happens in patients with TTS versus those with other cardiac diseases. The role of stress in the genesis of coronary heart disease is known and relates to the sympathetic system and hypothalamic – pituitary – adrenal axis leading to increased levels of catecholamines and cortisol with a cascade of events predisposing to cardiac disease (Ndrepepa, 2017). Not finding any differences between TTS and myocardial infarction as regards to psychological triggers may delineate at some level the involvement of similar mechanisms.

Furthermore, homogeneous (albeit still limited) findings are driven from the analysis of studies evidencing a role for long-lasting psychological distress. A role for early traumatic psychological experience has been evidenced as predisposing factor for patients with cardiovascular diseases (Thurston et al., 2014, 2017; Bomhof-Roordink et al., 2015; Winning et al., 2016), and deserves more attention in future studies.

Personality was examined in a small number of studies, which consequently do not allow any clear conclusion. Personality may have a role in influencing cardiac activity, because it is related to the way people usually cope with and respond to daily stressful situations. The so-called type-A personality (described as ambitious, rigidly organized, sensitive, impatient, anxious, and concerned with time management) coined in cardiologic field (Friedman and Rosenman, 1959), continues to be a central construct in current psychosomatic practice (Fava et al., 2016) and in medical research (Lohse et al., 2017). More recently, the Type-D (distressed personality characterized by negative affectivity and social inhibition) has been associated with cardiovascular disorders (Denollet, 2000). This condition is defined by two dimensions: negative affectivity and social inhibition. Our review shows conflicting results for a role of Type-D personality, with one study (Compare et al., 2013) indicating a role for social inhibition subscale in TTS (selected according to the presence of emotional triggers) and another one (Salmoirago-Blotcher et al., 2016) evidencing a similar pattern in TTS and myocardial infarction patients. Noteworthy, we have to outline that about personality types (A, D, etc.), the existing literature is still controversial (for example, these types are not even considered in the DSM-5) and more research is further warranted in this direction. Moreover, a role for specific emotional regulation patterns in TTS patients or other cardiac events needs further research as previously speculated (Bahremand et al., 2016).

Finally, we analyzed the role of psychopathologic disorders in TTS Several selected studies tried to detect if a previous (lifetime) history of psychopathology could be predictive of TTS. Even though there were methodological disparities in the way data were collected (retrospective data by review of medical records vs. prospective assessment by standardized questionnaire at hospitalization), life-time anxiety disorders might be hypothesized to have a role in TTS. Interestingly, a recent study (Lazzeroni et al., 2018) found that only patients with pre-existing anxiety disorders were at risk of TTS triggered by emotional stressful events. This finding may help to explain why only some patients experience a stressful event as trigger of TTS.

Depression and anxiety have been associated not only with TTS (Nayeri et al., 2018), but also with elevated risk of developing other cardiac diseases (Janszky et al., 2007; Kendler et al., 2009; Gustad et al., 2014; Galli et al., 2017). A recent retrospective cohort study (Nayeri et al., 2018) found that pre-existing psychopathologic disorders (anxiety, mood disorders, and schizophrenia) were associated with an increased risk of recurrent TTS, but not to survival. It is well recognized that the comorbidity of anxiety and depression is more the rule than the exception in many chronic disorders (Fava et al., 2012; Nayeri et al., 2017) including cardiac diseases (Bahremand et al., 2016). In our opinion, the comorbid occurrence of anxiety and depression should be considered as non-specific of TTS, but a more general risk factor.

A final note on the unique study (Saffari et al., 2017) evidencing worsening of the quality of life and sexuality in TTS, aspects that merit further studies.

As the main limitation of our study, there is the impossibility to make a meta-analysis, as it was in our first intention. Unfortunately, the small number of studies and the differences in the psychometric tools, timing of observation and different design among different studies did not allow to pursuit the initial aim. As stated above, some studies adopted constructs (e.g., A or D personality) not totally supported by strong evidence (not included in DSM 5), so that any sound conclusion on this topic is not allowed and further research need to be addressed on this topic. However, the rigor of methodology we relied on (Cochrane Collaboration and the PRISMA statements) allowed to get strong results and conclusion.

In synthesis, on the basis of our systematic review we cannot evidence a clear-cut role for psychological trauma preceding TTS onset, but a possible role of long-lasting emotional distress. From the side of psychopathology, we can suggest a role for life-time anxiety disorders (more than depression), but studies are needed to clarify if differences exist with other cardiac events. For personality, we cannot conclude in the direction of specific patterns differentiating TTS from other cardiac disorders.

We need studies with stronger methodology addressing the involvement of emotional events by structured interviews conducted shortly after the onset of TTS. The timing of interviewing patients should be carefully delineated (no more than 6 months) to avoid recall bias. Furthermore, multicentre studies are warranted to recruit a large number of patients and increase sample size for this relatively rare entity. The choice of an adequate control groups needs attention, because one of the main questions is whether TTS actually differs from other cardiac disorders, as regards to personality and comorbid psychopathologic disorders.

Finally, we stress the importance of a multidisciplinary approach to TTS; such an approach should involve a collaborative process between cardiologists and clinical psychologists from the diagnosis to treatment. Evidence are accumulating on the efficacy of psychological interventions for cardiac diseases (Richards et al., 2018).

AUTHOR CONTRIBUTIONS

FG, FB, and SC contributed to the conception and design of the study. FG organized the database and wrote the first draft of the manuscript. FG and FB made the bibliographic research and selected papers for the systematic review (in case of doubt made confirmation with SC). FB performed the statistical analysis. FB and SC read and approved the submitted version of the manuscript. All authors contributed to the manuscript revision, read, and approved the submitted version.

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Identifying the Internalizing Disorder Clusters Among Recently Hospitalized Cardiovascular Disease Patients: A Receiver Operating Characteristics Study

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Depression and anxiety disorders are common among cardiovascular disease (CVD) populations, leading several cardiology societies to recommend routine screening to streamline psychological interventions. However, it remains poorly understood whether routine screening in CVD populations identifies the broader groups of disorders that cluster together within individuals, known as anxious-misery and fear. This study examines the screening utility of four anxiety and depression questionnaires to identify the two internalizing disorder clusters; anxious-misery and fear. Patients with a recent hospital admission for CVD (n = 85, 69.4% males) underwent a structured clinical interview with the MINI International Neuropsychiatric Interview. The participants also completed the Patient Health Questionnaire (PHQ-9), Generalized Anxiety Disorder (GAD-7) scale, Overall Anxiety Severity Impairment Scale (OASIS), and the stress subscale of the Depression Anxiety Stress Scale (DASS). The PHQ-9 and the GAD-7 yielded appropriate screening properties to detect three different iterations of the anxious-misery cluster (sensitivity >80.95% and specificity >82.81%). The GAD-7 was the only instrument to display favorable screening properties to detect a fear cluster omitting post-traumatic stress disorder (PTSD) but including obsessive-compulsive disorder (OCD; sensitivity 81.25%, specificity 76.81%). These findings indicate that the PHQ-9 and GAD-7 could be implemented to reliably screen for anxious-misery disorders among CVD in-patients, however, the receiver operating characteristics (ROC) to detect fear disorders were contingent on the placement of PTSD and OCD within clusters. The findings are discussed in relation to routine screening guidelines in CVD populations and contemporary understandings of the internalizing disorders.

Keywords: depression, anxiety, internalizing disorders, receiver operating characteristics, cardiovascular disease, post-traumatic stress disorder

INTRODUCTION

Depression and anxiety disorders are prevalent in between 15 and 20% of cardiovascular disease (CVD) patients, representing a substantial morbidity burden globally (Rutledge et al., 2006; Thombs et al., 2008; Magyar-Russell et al., 2011; Tully et al., 2014). The presence of depression and anxiety disorders results in substantial individual, societal and economic cost worldwide, disability, and a reduction in quality of life (Scott et al., 2009; Dickens et al., 2012; Vos et al., 2012; Baumeister et al., 2015; Chisholm et al., 2016). Moreover, depression and anxiety portend a poorer cardiovascular prognosis as independent (Rutledge et al., 2006; Thombs et al., 2008; Roest et al., 2010; Tully et al., 2014) and additive or comorbid psychiatric risk factors (Phillips et al., 2009; Watkins et al., 2013). The high prevalence of depression and anxiety disorders, coupled with adverse cardiovascular prognosis, led several cardiology societies to recommend routine screening in order to better identify and streamline psychological treatments in CVD populations in the United States (Lichtman et al., 2008), Germany (Ladwig et al., 2014), Italy (Sommaruga et al., 2018), Australia (Colquhoun et al., 2013), and Europe (Albus et al., 2004).

The identification of psychiatric disorders in CVD populations is typically based on screening for depression (Thombs et al., 2013), with less attention paid to anxiety disorders and the comorbidity between depression and anxiety disorders. One limitation of this approach is that depression and anxiety disorders are comorbid in up to 50% of patients (Kessler et al., 2005, 2012; Slade and Watson, 2006; Beesdo-Baum et al., 2009) including among CVD populations (Serber et al., 2009; Tully et al., 2014). In fact, a robust body of empirical research indicates that common mental disorders tend to cluster together, evidenced by the higher than chance comorbidity patterns observed across the lifespan (Kessler et al., 2011). In particular, the depression and anxiety disorders cluster together under a higher-order internalizing domain, which is distinct from the externalizing domain reflecting the antisocial and substance use disorders (Krueger, 1999). Subsequent research demonstrates that the internalizing domain can bifurcate into two lower order groups characterized by anxious-misery [e.g., Major Depressive Disorder, Dysthymia, Generalized Anxiety Disorder (GAD), and Post Traumatic Stress Disorder (PTSD)], or, by fear [e.g., Panic Disorder, Agoraphobia, Specific Phobia, Social Anxiety Disorder, and Obsessive-Compulsive Disorder (OCD)] (Slade et al., 2009; Watson, 2009; Eaton et al., 2013; Waszczuk et al., 2017). Notably, GAD is considered to be a part of the anxious-misery cluster compared to the other anxiety disorders subsumed under fear, which are generally characterized by phobias and somatic arousal (Watson, 2005).

Evidence indicates that the arrangement of disorders into anxious-misery and fear, in contrast to disorder-specific models, informs the prediction of CVD and other health outcomes (Eaton et al., 2013; Tully et al., 2015b; Roest et al., 2017). However, this framework is lesser utilized to inform screening procedures in health settings such as cardiology where routine depression screening is recommended. Given that comorbidity between disorders is the norm rather than the exception, it may be inappropriate to limit assessment and mental health triage to single disorders (Tully et al., 2015a). Indeed, disorder-specific screening in CVD populations omits a substantial number of persons that are candidates for intervention (Bunevicius et al., 2013). It is therefore likely that enquiries about single disorders are less meaningful when the primary goal is to detect clinically relevant psychological distress and streamline patients into clinical supports or treatments. Due to the high likelihood of comorbidity and shift toward transdiagnostic treatment approaches (Barlow et al., 2017), grouping disorders into clusters may aid screening efforts in CVD populations by cutting across discrete single-disorder categories. The current study aims to evaluate the receiver operating characteristics (ROC) of four common clinical tools for the screening of the emotional disorders in a CVD population.

We theorized that the measures designed to capture depression and GAD would have higher ROCs to detect the anxious-misery cluster than measures designed to capture phobia and avoidance. Conversely, we theorized that the measures designed to capture phobia and avoidance would have higher ROCs to detect the fear cluster than measures designed to capture depression and GAD. Measures with a high negative affectivity component were theorized to equally predict anxious-misery and fear clusters.

MATERIALS AND METHODS

Participants

Data for this study were obtained from a single-blind randomized control trial to evaluate the feasibility of the unified protocol for the transdiagnostic treatment of emotional disorders in patients recently hospitalized for CVD (Tully et al., 2016). Participant recruitment took place from January 2016 until March 2017 at the Queen Elizabeth Hospital, a tertiary hospital in the Western urban area of Adelaide, South Australia. Eligibility criteria were: a primary hospital admission for CVD specified by relevant International Classification of Disease codes (myocardial infarction, heart failure, atrial fibrillation or other ventricular or atrial arrhythmia, coronary revascularization intervention; symptomatic coronary heart disease including unstable angina pectoris, or heart valve disease); spent two or more nights admitted to the Department of Cardiology; $\geq$18 years of age, and proficiency in the English language. Ineligible participants had: a known or observed cognitive impairment or dementia; a medical condition likely to be fatal within 1 year; or a neurodegenerative condition such as Parkinson's or Multiple Sclerosis (Flow chart in **Figure 1**). Patients with psychosis, bi-polar disorder, substance or alcohol dependence/abuse, or high suicide risk were excluded from the main trial but included in the current analyses. The rationale is that undocumented severe psychiatric disorders would be a related or incidental finding from depression and anxiety screening. The Human Research Ethics Committee from the Queen Elizabeth Hospital gave approval for the study (approval #HREC/15/TQEH47).

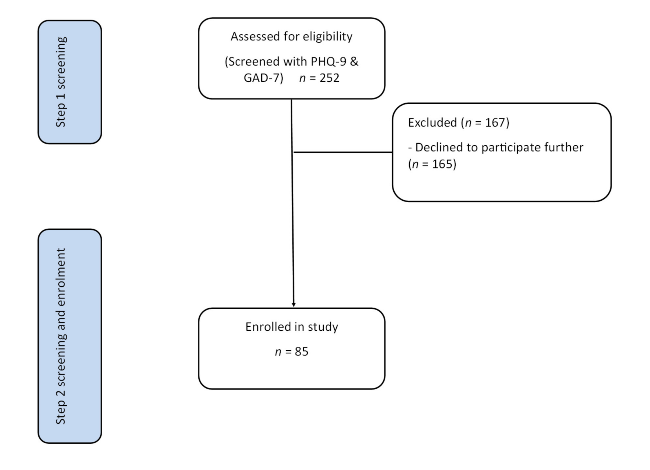

FIGURE 1 | A flow chart of participant eligibility through the study. Step 1 screening was performed in hospital. Step 2 screening was performed 2 weeks after the index CVD admission. CVD, cardiovascular disease; GAD-7, Generalized Anxiety Disorder scale-7; PHQ-9, Patient Health Questionnaire scale-9.

Measures

Psychiatric Diagnosis

All participants underwent a structured diagnostic interview with a graduate from a 4th year psychology degree to determine disorder status. The assessor was trained, and supervised, in all aspects of clinical assessments. The MINI International Neuropsychiatric Interview (MINI) version 5.0.0 served as the gold standard. Analysis of previous MINI versions suggested high sensitivity and specificity to detect the emotional disorders specified by Diagnostic and Statistical Manual of Mental Disorders (DSM), and good inter-rater agreement (κ = 0.86–0.96) (Lecrubier et al., 1997; Sheehan et al., 1997, 1998; Amorim et al., 1998). The MINI modules utilized in this study covered: Major Depressive Disorder; Major Depressive Disorder with Melancholic Features, Dysthymia, Hypomanic and Manic Episode (Bipolar I and II), Panic Disorder, Agoraphobia, Social Anxiety 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. The modules relating to anorexia and bulimia nervosa were omitted for brevity.

Disorder Arrangement Into Clusters

Because of uncertainty in the optimal placement of certain disorders within the anxious-misery and fear clusters, several models were arranged and tested. Specifically, discrepant findings have been reported for the placement of OCD, PTSD, and social anxiety disorder in cross-sectional and longitudinal evaluations (Watson, 2009; Naragon-Gainey et al., 2016; Forbes et al., 2017; Kotov et al., 2017; Waszczuk et al., 2017; Conway and Brown, 2018).

Model^{a}: Anxious-misery^{a} – major depressive disorder, dysthymia, GAD, PTSD, and bi-polar disorder; fear^{a} – panic disorder, agoraphobia, social anxiety disorder, and OCD.

Model^{b}: This model was a variant of Model^{a} whereby PTSD was included in each cluster, with OCD included only in anxious-misery. Anxious-misery^{b} – major depressive disorder, dysthymia, GAD, major depressive disorder with melancholic features, PTSD, bi-polar disorder, and OCD; fear^{b} – panic disorder, agoraphobia, social anxiety disorder, and PTSD.

Model^{c}: This model was a variant of Model^{a} and Model^{b} whereby PTSD and OCD were excluded from all clusters, in accordance with DSM-5 arrangement of PTSD and OCD as separate disorders from anxiety. Anxious-misery^{c} – major depressive disorder, dysthymia, GAD, and major depressive disorder with melancholic features; fear^{c} – panic disorder, agoraphobia, and social anxiety disorder.

Self-Reported Distress Scales

Participants completed a battery of self-report measures consisting of four depression and anxiety questionnaires. The GAD-7 approximates DSM-5 criteria for GAD (Spitzer et al., 2006). The GAD-7 is scored on a scale of 0 to 3 (not at all, several days, more days than half the days, and nearly every day). The GAD-7 is considered a psychometrically sound measure to use in primary care settings for detection of anxiety disorders as the measure does not contain any items tapping into somatic symptoms (Spitzer et al., 2006).

The PHQ-9 is a standardized instrument that approximates DSM-5 major depression criteria (Kroenke et al., 2001). 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 (Kroenke et al., 2001). The PHQ-9 is recommended for depression screening in CVD populations because of its specificity to detect depression and sensitivity to clinical change (Lichtman et al., 2008; Colquhoun et al., 2013; Ladwig et al., 2014).

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 (Norman et al., 2006; Campbell-Sills et al., 2009). Participants respond to the items that best describe their experience on a five-point scale (0, little or none; 1, mild; 2, moderate; 3, severe; 4, extreme). The OASIS psychometric properties were evaluated in primary care settings and psychiatric samples and the measure is commonly utilized for clinical trials (Campbell-Sills et al., 2009).

Stress was measured using the stress subscale of the Depression, Anxiety and Stress Scales (DASS-21). The DASS-21 is a commonly utilized measure and validated in adults aged to 90 years (Lovibond, 1998). Scores range from 0 to 21 for the stress subscale. The DASS-21 factor structure approximates a tripartite structure (Clark and Watson, 1991), with stress broadly indicative of negative affectivity (Brown et al., 1997).

Procedure

The assessment of depression and anxiety was based on a two-stage screening process as recommended by the American Heart Association (Lichtman et al., 2008) to confirm elevated symptoms of anxiety and depression after hospitalization.

During the CVD hospital admission, each participant completed the PHQ-9 and the GAD-7 in the cardiology department. All patients were followed-up for a repeat screening approximately 2 weeks later with the PHQ-9, GAD-7, OASIS, DASS-stress, and the MINI. Patients with a PHQ-9 total score ≥10 and/or GAD-7 total score ≥7 on both occasions, and a MINI depression or anxiety disorder, were deemed eligible for the feasibility study (Tully et al., 2016). Otherwise, participants were included in a non-distressed control group. The current study utilizes only the measurements obtained 2 weeks after the CVD admission, which took place in the outpatient setting.

Statistical Analysis

Statistical analyses were performed using MedCalc Statistical Software version, 18.5 (MedCalc Software, Ostend, Belgium). The MINI diagnosis (yes/no) constituted the criterion standard for the presence or absence of disorders. Scores on the screening measures (PHQ-9, GAD-7, OASIS, and DASS-stress), were used to detect clusters arranged into anxious-misery and fear in three iterations (denoted[a,b,c]). The ROCs were modeled to identify the true positive rate (sensitivity) plotted against the false positive rate (1-specificity) for all possible cut off points. The area under the curve (AUC) is the percentage of randomly drawn pairs for which the screening measures correctly classifies affected and non-affected cases and represents the diagnostic power of the test. An AUC of 1.0 indicates the measure has perfect diagnostic detection properties and an AUC of 0.5 indicates that the screening measure is no better than chance. Interpretation of the AUC values were as follows: 0.5 – <0.7 mildly accurate, 0.7 – 0.9 moderately accurate, and 0.9 – <1 highly accurate (Hanley and Mcneil, 1982). The screening measures cut off points were reported for AUC $p < 0.05$ and were determined by the maximal Youden Index (sensitivity + specificity – 100). The positive predictive value (PPV) is the likelihood that there is a cluster present given a positive test result, and the negative predictive value (NPV) is the likelihood that a cluster is not present given a negative test result. High sensitivity at the expense of low specificity results in an inordinate number of diagnostic interviews for false positives and therefore, a specificity of >75% is desirable for clinical purposes (Hanley and Mcneil, 1982). The AUCs between measures were compared statistically using the methods of Delong et al. (1988). Sensitivity analyses were performed excluding persons receiving psychotropic drugs or psychiatrist or psychologist care. The rationale was that depression and anxiety screening intends to identify new and previously unidentified cases.

In all analyses a p-value < 0.05 was considered as statistically significant, and no adjustment was made for multiple comparisons based on the recommendations of Rothman (1990). The rationale was that the study hypotheses are well defined, and secondly, that the study is exploratory in nature where the risk of Type II error is greater than the risk of Type I error. A sample size of 46 patients per group (i.e., yes/no for anxious-misery or fear) would provide 80% power to detect a $\theta = 0.20$ difference between ROCs at $\alpha < 0.05$.

RESULTS

A total of $n = 85$ patients were included in the current analyses. The most common CVD-cause admissions were for angina pectoris (34.1%), followed by arrhythmia (25.9%), and heart failure (22.4%) (**Table 1**). The number of patients diagnosed with discrete internalizing disorders on the MINI were as follows: major depressive disorder ($n = 20$, 23.5%), major depressive disorder with melancholic features ($n = 11$), GAD ($n = 7$, 8.2%), agoraphobia ($n = 9$, 10.6%), panic disorder ($n = 6$, 7.1%), bipolar depression ($n = 4$, 4.7%), social phobia ($n = 2$, 2.4%), PTSD ($n = 2$, 2.4%), OCD ($n = 1$, 1.2%). There were no dysthymia cases due to hierarchal exclusion rules ($n = 0$). In regards to comorbidity, the number of patients with comorbid affective disorders were as follows: no disorder ($n = 57$, 67.1%), one disorder ($n = 12$,

TABLE 1 | Descriptive and medical comorbidity data.

Descriptive variables	N (%)
Male sex	59 (69.4)
Age in years, M ± SD	63.3 ± 11.6
Employment status	
Working	44 (51.8)
Retired	22 (25.9)
Unemployed	2 (2.4)
Primary CVD admission cause	
Acute myocardial infarction	11 (12.9)
Heart failure	19 (22.4)
Arrhythmia	22 (25.9)
Revascularization	2 (2.4)
Angina pectoris with CAD	29 (34.1)
Other CVD	2 (2.4)
CVD comorbidities	
Past myocardial infarction	18 (21.2)
Past revascularization	10 (11.8)
Valve disease	8 (9.4)
Biventricular pacemaker	5 (5.9)
Implantable cardioverter defibrillator	7 (8.2)
Stroke or cerebrovascular accident	8 (9.4)
Lung disease	9 (10.6)
Renal disease	8 (9.4)
Diabetes	22 (25.9)
Hypertension	56 (65.9)
Hypercholesterolemia	48 (56.5)
Tobacco smoking (current)	5 (5.9)
Sleep apnea	14 (16.5)
Chronic pain	20 (23.5)
Psychiatric treatment	
Using SSRI or SNRI	2 (2.4)
Using TCA	2 (2.4)
Using anxiolytic	1 (1.2)
Current psychiatrist care	1 (1.2)
Current psychologist care	–

CAD, coronary artery disease; CVD, cardiovascular disease; SNRI, serotonin and norepinephrine reuptake inhibitors; SSRI, selective serotonin reuptake inhibitors; TCA, tricyclic antidepressants.

14.1%), two disorders ($n = 4$, 4.7%), three disorders ($n = 7$, 8.2%), four disorders ($n = 3$, 3.5%), six disorders ($n = 1$, 1.2%), and seven disorders ($n = 1$, 1.2%). The number of patients diagnosed with discrete externalizing disorders on the MINI were as follows: manic episode ($n = 2$, 2.4%), hypomanic episode ($n = 3$, 3.5%), alcohol dependence ($n = 3$, 3.5%), alcohol abuse ($n = 1$, 1.2%), psychotic disorder ($n = 1$, 1.2%), mood disorder with psychotic features ($n = 1$, 1.2%). No patients met criteria for substance abuse or dependence. On the MINI, suicide risk was rated as moderate for nine patients (10.6%) and high for four patients (4.7%).

Receiver Operating Characteristics

Anxious-misery cluster[a] ($n = 21$, 24.7%): The ROCs are presented in **Table 2**. The AUC was greatest for the PHQ-9, followed by the GAD-7, the DASS-stress, and the OASIS. Using a cut-point of six, the PHQ-9 showed favorable sensitivity (85.71%) and specificity (82.94%). Employing a cut point of 4, the GAD-7 yielded comparable sensitivity (85.71%) and specificity (82.81%). The DASS-stress scale and OASIS sensitivity and specificity rates were suboptimal for screening purposes to detect the anxious-misery[a] cluster. When AUCs were compared, the PHQ-9 ($p = 0.049$) and the GAD-7 ($p = 0.048$) had significantly higher AUCs than the OASIS (**Figure 2**).

Anxious-misery cluster[b] ($n = 21$, 24.70%): Employing a cut off of 7 the PHQ-9 showed desirable sensitivity (80.95%) and specificity (94.12%), while the GAD-7 required a cut point of four for a sensitivity of 85.71% and specificity of 84.31%. The DASS-stress scale and the OASIS, again, demonstrated suboptimal screening properties in the detection of anxious-misery[b]. *Post hoc* tests revealed that the GAD-7 ($p = 0.031$) and PHQ-9 ($p = 0.031$) AUCs were both statistically different from the OASIS.

TABLE 2 | Receiver operating characteristics of depression and anxiety screening measures to detect anxious-misery and fear clusters.

Clusters	AUC (SE)	95% CI	Cut-off	Sensitivity true +	Specificity true −	Youden index	PPV	NPV
Anxious-misery[a] ($n = 21$)								
GAD-7[1]	0.856 (0.060)	0.763–0.923	4	85.71	82.81	68.53	55.5	95.9
PHQ-9[2]	0.873 (0.058)	0.783–0.935	6	85.71	85.94	71.65	66.7	94.8
OASIS	0.692 (0.72)	0.582–0.787	2	52.38	84.37	36.75	52.4	84.4
DASS	0.732 (0.60)	0.625–0.822	2	80.95	57.81	38.76	38.6	90.2
Anxious-misery[b] ($n = 21$)								
GAD-7[1]	0.860 (0.060)	0.758–0.930	4	85.71	84.31	70.03	57.5	95.8
PHQ-9[2]	0.879 (0.057)	0.780–0.944	7	80.95	94.12	75.07	77.5	95.2
OASIS	0.680 (0.074)	0.560–0.785	3	47.62	88.24	35.85	50.3	87.1
DASS	0.747 (0.061)	0.631–0.842	2	80.95	62.75	43.70	35.2	92.9
Anxious-misery[c] ($n = 21$)								
GAD-7[1]	0.856 (0.060)	0.763–0.923	4	85.71	82.81	68.53	55.5	95.9
PHQ-9[2]	0.873 (0.058)	0.783–0.935	6	85.71	85.94	71.65	60.4	96.0
OASIS	0.692 (0.072)	0.582–0.787	2	52.38	84.37	36.76	45.6	87.6
DASS	0.732 (0.060)	0.625–0.822	2	80.95	57.81	38.76	32.4	92.4
Fear[a] ($n = 17$)								
GAD-7[3]	0.776 (0.076)	0.673–0.860	4	81.25	76.81	58.06	38.2	95.9
PHQ-9	0.719 (0.082)	0.611–0.811	7	68.75	82.61	51.36	41.1	93.7
OASIS	0.673 (0.073)	0.563–0.771	0	75.00	57.97	32.97	29.3	90.9
DASS	0.626 (0.077)	0.474–0.777	2	75.00	53.62	28.62	22.2	92.4
Fear[b] ($n = 16$)								
GAD-7	0.787 (0.077)	0.684–0.868	7	68.75	91.30	60.05	58.3	94.3
PHQ-9	0.732 (0.084)	0.625–0.823	7	68.75	82.61	51.36	41.1	93.7
OASIS	0.669 (0.072)	0.559–0.768	0	75.00	57.97	32.97	23.9	92.9
DASS	0.621 (0.074)	0.510–0.724	2	75.00	53.62	28.62	22.2	92.4
Fear[c] ($n = 15$)								
GAD-7[3]	0.768 (0.080)	0.663–0.852	7	66.67	90.00	56.67	54.1	93.9
PHQ-9	0.710 (0.087)	0.601–0.803	7	66.67	81.43	48.10	38.8	93.3
OASIS	0.642 (0.074)	0.531–0.743	0	73.33	57.14	30.48	23.2	92.4
DASS	0.592 (0.075)	0.480–0.698	2	73.33	52.86	26.19	21.5	91.8

AUC, area under the curve; CI, confidence interval; NPV, negative predictive value; PPV, positive predictive value; SE, standard error; GAD-7, Generalized Anxiety Disorder-7 scale; PHQ-9, Patient Health Questionnaire-9 scale; OASIS, Overall Anxiety Severity Impairment Scale; DASS, Depression Anxiety Stress Scale – Stress subscale. Anxious-misery[a] – major depression, dysthymia, generalized anxiety disorder, depression melancholic, post-traumatic stress, and bi-polar; Fear[a] – panic disorder, agoraphobia, social anxiety disorder, and obsessive-compulsive disorder. Anxious-misery[b] – major depression, dysthymia, generalized anxiety disorder, depression melancholic, bi-polar and obsessive-compulsive disorder; Fear[b] – disorder, agoraphobia, social anxiety disorder, and post-traumatic stress disorder. Anxious-misery[c] – major depression, dysthymia, generalized anxiety disorder, and depression melancholic; Fear[c] – panic disorder, agoraphobia, and social anxiety disorder. 1 – The GAD-7 was significantly different ($p < 0.05$) from the OASIS; 2 – The PHQ-9 was significantly different ($p < 0.05$) from the OASIS; 3– The GAD-7 was significantly different ($p < 0.05$) from the DASS-stress.

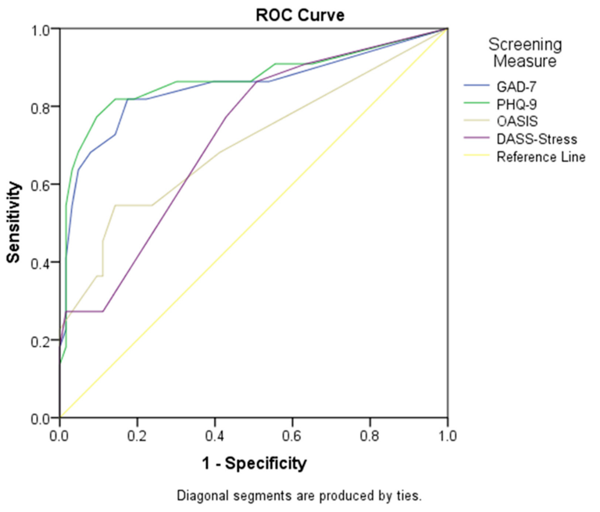

FIGURE 2 | Screening measure AUC to detect anxious-misery disorders. Graph showing the AUC (sensitivity and 1- specificity) for the GAD-7, PHQ-9, OASIS, and DASS-stress scales to detect the anxious-misery[a] cluster (major depressive disorder, dysthymia, generalized anxiety disorder, post-traumatic stress disorder, bipolar disorder). AUC, area under the curve; DASS-stress, Depression, Anxiety and Stress Scales-stress subscale; GAD-7, Generalized Anxiety Disorder 7 item scale; OASIS, Overall Anxiety Severity and Impairment Scale; PHQ-9, Patient Health Questionnaire scale 9 item scale.

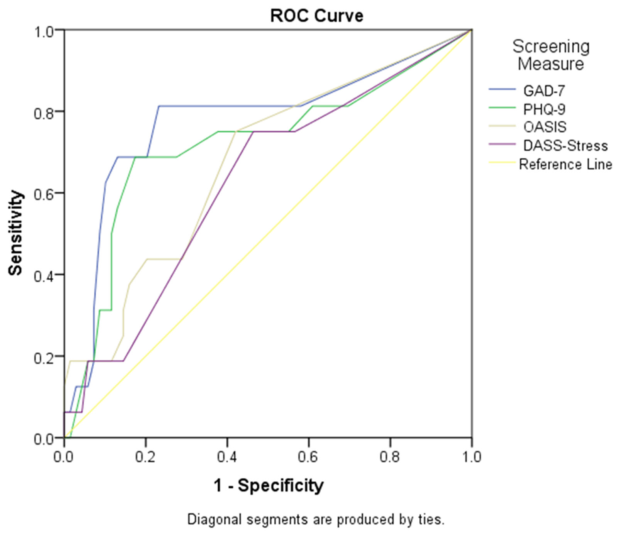

FIGURE 3 | Screening measure AUC to detect fear disorders. Graph showing the AUC (sensitivity and 1- specificity) for the GAD-7, PHO-9, OASIS, and DASS-stress scales to detect the fear[a] cluster (panic disorder, agoraphobia, social anxiety disorder, obsessive-compulsive disorder). AUC, area under the curve; DASS-stress, Depression, Anxiety and Stress Scales-stress subscale; GAD-7, Generalized Anxiety Disorder 7 item scale; OASIS, Overall Anxiety Severity and Impairment Scale.

Anxious-misery cluster[c] (n = 21, 24.70%): Again, the PHQ-9 showed favorable sensitivity (85.71%) and specificity (82.94%). Employing a cut point of 4 the GAD-7 also yielded a highly favorable sensitivity of 80.95% and a specificity of 94.12%. The GAD-7 ($p = 0.048$) and PHQ-9 ($p = 0.049$) AUCs were statistically significant when compared to the AUC of the OASIS.

Fear cluster[a] (n = 17, 21.52%): The GAD-7 was the only measure to demonstrate suitable sensitivity and specificity values for the fear[a] cluster. The AUC was greatest for the GAD-7 employing a cut of four, with favorable sensitivity (81.25%) and specificity (76.81%). A cut-point of seven on the PHQ-9 showed a sensitivity of 68.75% and a specificity of 82.61% and therefore, considered unfavorable for screening purposes. Further, the OASIS and the DASS-stress yield matching sensitivity scores (75%) but unfavorable specificity values (57.97% and 53.62%, respectively). The GAD-7 AUC was statistically significantly different from the DASS-stress scale ($p = 0.046$) (**Figure 3**).

Fear cluster[b] (n = 16, 18.82%): The GAD-7 was no longer considered to be an appropriate screener for fear cluster[b] due to low sensitivity (68.75%), though the GAD-7 was statistically different from the DASS-stress scale ($p = 0.027$). Irrespective, no measure was considered appropriate for detection of fear cluster[b].

Fear cluster[c] (n = 15, 17.6%): Both the GAD-7 and the PHQ-9 yielded unfavorable sensitivity scores (sensitivity, 66.67%), while the OASIS and the DASS-stress scale had specificity values considered to be suboptimal (specificity, <70). The GAD-7 was considered to be diagnostically more accurate than the DASS-stress scale in fear cluster[c] disorders ($p = 0.024$). Despite this finding, no measures in this cluster had suitable screening properties when evaluating the sensitivity and specificity values.

Sensitivity Analysis

After excluding persons receiving current psychiatric treatment, similar findings were observed for detecting the anxious-misery cluster (**Table 3**). The PHQ-9 and GAD-7 revealed favorable sensitivity (82.35% and 70.59%, respectively) and specificity (90.32% and 95.16%, respectively). The AUC for the PHQ-9 (p = 0.043) was significantly different from the DASS-stress scale indicating further screening benefits of the PHQ-9. The GAD-7 was the only screening measure from the fear[a] cluster with favorable diagnostic qualities (sensitivity, 78.57%; specificity, 78.46%). Comparison of ROC curves did not yield any statistically significant differences between the screening measures suggesting similar screening accuracy across outcomes.

DISCUSSION

The GAD-7 and the PHQ-9 both had favorable ROCs for screening of the anxious-misery disorders, irrespective of cluster variations. The ROCs were generally suboptimal for the detection of fear disorders, with only the GAD-7 yielding sufficient sensitivity and specificity values to detect the fear[a] cluster. However, the ability to detect fear disorders was dependent on inclusion of OCD and the exclusion of PTSD from the fear cluster. The OASIS yielded unsuitable ROCs

TABLE 3 | Receiver operating characteristics from sensitivity analyses excluding persons receiving current psychiatric treatment.

Clusters	AUC (SE)	95% CI	Cut-off	Sensitivity true +	Specificity true −	Youden index	PPV	NPV
Anxious-misery[a] (*n* = 17)								
GAD-7	0.836 (0.719)	0.736–0.910	7	70.59	95.16	65.75	78.5	92.8
PHQ-9[1]	0.856 (0.070)	0.759–0.925	7	82.35	90.32	72.68	68.0	95.3
OASIS	0.647 (0.080)	0.531–0.751	2	47.06	87.10	34.16	47.7	86.8
DASS	0.679 (0.068)	0.565–0.780	2	76.47	56.45	32.92	28.5	91.6
Fear[a] (*n* = 14)								
GAD-7	0.762 (0.084)	0.653–0.851	4	78.57	78.46	57.03	39.2	95.4
PHQ-9	0.701 (0.090)	0.588–0.799	7	64.29	83.08	47.36	40.1	92.9
OASIS	0.675 (0.077)	0.561–0.776	0	71.43	61.54	32.97	24.7	92.4
DASS	0.605 (0.081)	0.489–0.713	2	71.43	53.85	25.27	21.5	91.4

AUC, area under the curve; CI, confidence interval; NPV, negative predictive value; PPV, positive predictive value; SE, standard error; GAD-7, Generalized Anxiety Disorder-7 scale; PHQ-9, Patient Health Questionnaire-9 scale; OASIS, Overall Anxiety Severity Impairment Scale; DASS, Depression Anxiety Stress Scale – Stress subscale. 1 – The PHQ-9 was significantly different ($p < 0.05$) from DASS-stress.

for screening purposes, thus not supporting our hypotheses. Taken together, the results here obtained 2 weeks after a CVD admission are promising given that the aim of screening is to distinguish patients with transient or short-term distress from those with clinically relevant disorders requiring mental health treatment.

Our results offer new information beyond studies primarily focusing on depression screening in CVDs. A systematic review of depression measures indicated favorable ROCs for most depression questionnaires to detect major and minor depression in coronary heart disease populations (Thombs et al., 2008). The current work extends beyond these previous studies by arranging disorders into theorized anxious-misery and fear clusters. The overall performance of the PHQ-9 and GAD-7 were remarkably similar in detection of the anxious-misery disorders and cluster iterations[a,b,c]. Thus, the PHQ-9 and GAD-7 ROCs were largely unrelated to the placement of PTSD and OCD within or excluded from anxious-misery. One explanation for the similarities in screening properties is that the PHQ-9 and GAD-7 cover the core symptoms of major depressive disorder and GAD and may capture a negative affectivity component related more strongly to anxious-misery (Bohnke et al., 2014).

Anxiety disorder screening in CVD populations is less common and has proven challenging to identify suitable screening measures. Bunevicius et al. (2013) showed that the Hospital Anxiety and DepressionScale-Anxiety (HADS-A), the Spielberger State-Trait Anxiety Inventory, and the Spielberger State Anxiety Inventory yielded high false positive rates for anxiety disorder screening in CVD populations. Likewise, screening measures based on a tripartite structure of depression and anxiety yielded unsuitable ROCs to detect fear disorders (Tully and Penninx, 2012). Here the only diagnostically accurate screening tool for the fear cluster was the GAD-7 and this was limited to fear[a] (i.e., panic, agoraphobia, social anxiety, and OCD). Recently, it was suggested that worry, the hallmark feature of GAD, may be best modeled at a broad structural level, rather than an indicator of fear or anxious-misery clusters (Naragon-Gainey et al., 2016). This provides a potential explanation for the ability of the GAD-7 to screen both fear and anxious-misery clusters (Naragon-Gainey et al., 2016). Intriguingly, the removal of OCD (n = 1) made GAD-7 screening inadequate for fear[c] cluster. The increase in the sensitivity of fear[a] cluster as a result of including OCD may simply be due to some overlap in the symptoms of OCD and those captured by the GAD-7 (e.g., feeling anxious or on edge, trouble relaxing, and feeling afraid something awful might happen). In addition, worries can also be present in individuals with OCD (Abramowitz and Foa, 1998), and obsessions might be understood or subjectively perceived by patients as worries. A recent review and meta-analysis indicated that further studies are required in primary care to determine if the GAD-7 is proficient in detecting fear disorders including OCD (Plummer et al., 2016).

The finding that the OASIS screening properties were unfavorable for the detection of fear disorders did not support our hypothesis. Other work suggests that the AUC is fair for the OASIS when applied to anxiety disorders (Ito et al., 2015). An explanation for the low sensitivity and AUC produced by the OASIS here is that the measure was designed to tap the behavioral (i.e., avoidance) and functional aspects (i.e., impairment in work, or, interpersonal relationships) of disorder severity. The GAD-7 and PHQ-9 are likely affected by the frequency of cognitive-affective and/or somatic aspects of anxiety or depression (Ito et al., 2015). The symptoms experienced by CVD patients might be different and more somatically driven than the avoidance or functional impairment symptoms captured by the OASIS and those considered as hallmark features of the fear cluster (Mineka and Zinbarg, 2006). Moreover, patients with CVDs tend to experience less health-related and heart-focused anxiety by comparison to chest-pain patients without known cardiac disease (Marker et al., 2008; Robertson et al., 2008).

The hypotheses that the DASS-stress measure would be associated with both the anxious-misery and fear clusters was partially supported, albeit that the ROCs were suboptimal. The AUC was moderately accurate at detecting the fear clusters and moderately accurate at detecting the anxious-misery clusters. There is some debate over whether the DASS-stress measures a construct that is similar but not the same as depression and anxiety, since it nestles itself under the umbrella of the higher order negative affectivity factor (Norton, 2007). In the current study, the DASS-stress appeared to be more sensitive to the anxious-misery cluster than the fear cluster indicating some differences in the way the DASS-stress performs in regards to two clusters. One explanation is the close association between stress and worry. For example, there is evidence to suggest that individuals with non-clinical levels of frequent and uncontrollable worry also experience a high level of stress as measured by the DASS-stress (Szabo, 2011).

The high specificities and PPVs, and high sensitivities and NPVs, for the PHQ-9 and GAD-7 to detect anxious-misery indicate that screening will appropriately exclude persons without an anxious-misery disorder when adopting the recommended cut-points. Moreover, positive screens are likely to have an anxious-misery disorder requiring clinical intervention, despite lack of confirmation of a specific diagnosis. Parallel work suggests the HADS has suitable screening ROCs to detect any diagnosis of depression and anxiety from the Clinical Interview Schedule-Revised, with 85.78% sensitivity and 82.55% specificity, while the NPV was 97.63% (Palacios et al., 2016). Such work indicates that short questionnaire batteries sufficiently screen both anxiety and depression disorders in cardiovascular populations.

The results of this study should be interpreted recognizing several limitations including that the hierarchical structure of mental disorders is debated (Beesdo-Baum et al., 2009) and not always supported (Conway and Brown, 2018). This uncertainty is partly reflected in the number of cluster iterations tested here. Moreover, interpretation of the ROCs for screening purposes is closely tied to the empirical validity of such disorder structures, which have not been validated in CVD populations. A related limitation is that the current study did not include the externalizing disorder cluster (Forbes et al., 2017; Kotov et al., 2017). Since clinical trials in CVD populations typically exclude patients with externalizing disorders (e.g., alcohol/substance use disorders), the significance of these disorders, their prevalence, and prognosis are lesser known and largely examined only in epidemiological surveys (Scott et al., 2013). Moreover, the rates of externalizing disorders such as abuse and dependence were lower here than previous studies of comparable sample size (Fraguas et al., 2000). Concerning comorbidity, the MINI utilizes hierarchical exclusion rules which may lessen specific disorder comorbidity combination rates (e.g., dysthymia and major depressive disorder). The MINI has no module for specific phobias, which are less prevalent in CVD populations (Tully et al., 2014) than community estimates (Kessler et al., 2005). Given that there was a small number of OCD, PTSD, and bipolar disorder diagnoses in the current study, further investigation in diverse and larger samples of CVD patients is justified to reproduce the current findings. The timing of the assessment near an index CVD admission may spuriously inflate symptoms, particularly somatic symptoms that are commonly experienced during hospitalization and partially overlap with some mental disorders. It could also be important to test the ROCs for the PRIME-MD somatization module (Spitzer et al., 1994) against somatoform disorders. The somatoform disorders are especially prevalent in primary care populations (Piontek et al., 2018) and at least 5% of cardiac patients (Rafanelli et al., 2006). Lastly, this was a single-center design from a public hospital in Australia. Therefore, our results may not generalize to other geographic regions with diverse demographics nor to private hospitals and those serving veterans whom have a higher likelihood of PTSD (Scherrer et al., 2010).

In summary, the GAD-7 and PHQ-9 self-report scales provided sufficient ROCs to identify the anxious-misery cluster in patients recently hospitalized for CVD. The GAD-7 has additional psychometric properties making it suitable to screen for a fear cluster inclusive of OCD. Given the high likelihood of disorder comorbidity, there are potential advantages in shifting away from traditional disorder based taxonomies to an emphasis on the commonalities between disorders for screening purposes. Given that this is one of the first studies to evaluate the screening utility against internalizing disorders in patients recently hospitalized for CVD, future research should validate self-report measures against the anxious-misery and fear clusters in other larger samples.

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DATA AVAILABILITY STATEMENT

The datasets for this manuscript are not publicly available because of data management and confidentiality constraints imposed by local laws, the governing institution, and human research ethics committee. Requests to access the datasets should be directed to PT, phillip.tully@adelaide.edu.au.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Human Research Ethics Committee from the Queen Elizabeth Hospital (approval #HREC/15/TQEH47). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

PT and GW: study design. PT, GW, and MG: data acquisition. MG: data analysis. MG, DT, and PT: write up. MG, DT, GW, and PT: editing the final manuscript.

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Traumatic Stress, Attachment Style, and Health Outcomes in Cardiac Rehabilitation Patients

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Objective: Research on psychosocial risk factors in cardiovascular disease (CVD) has identified traumatic stress and attachment style as independent risk factors for the development of CVD and poor prognosis for those with established CVD. Exploring the interrelationships between these variables will inform psychosocial risk factor modeling and potential avenues for intervention. Therefore, the hypothesis that attachment style is related to health outcomes among CR patients and that traumatic stress mediates this relationship was tested.

Methods: Patients in a cardiac rehabilitation program (n = 201) completed validated self-report measures of traumatic stress and attachment style at baseline (program intake). Health outcomes were assessed at baseline and 3 months, including anxiety, depression, quality of life, fasting blood glucose, glycated hemoglobin (HbA1c), and cholesterol (HDL ratio). Multivariate structural equation modeling was used to fit the data.

Results: Of the 201 participants, 42 (21%) had trauma scores indicating the probable presence of posttraumatic stress disorder. Via greater levels of traumatic stress, greater attachment anxiety at baseline was indirectly related to greater anxiety, depression, fasting blood glucose, and HbA1c, and poorer physical and mental quality of life. There were no significant indirect effects on HDL ratios.

Conclusion: Greater attachment anxiety predicted greater traumatic stress; this, in turn, predicted poorer health outcomes. Screening and treatment for these constructs in CVD patients is warranted.

Keywords: cardiovascular disease, attachment anxiety, traumatic stress, health outcomes, attachment avoidance

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Abbreviations: CABG, coronary artery bypass grafting; CFI, Comparative Fit Index; CR, cardiac rehabilitation; CVD, cardiovascular disease; ECR-R, Experiences in Close Relationships – Revised; HADS, Hospital Anxiety and Depression Scale; HbA1c, glycated hemoglobin; HDL, high-density lipoprotein; ICD, implantable cardioverter defibrillator; IES-R, Impact of Event Scale – Revised; IL-6, cytokine interleukin 6; MANOVA, multivariate analysis of variance; MCAR, Missing Completely at Random; PCI, percutaneous coronary intervention; PTSD, posttraumatic stress disorder; RMSEA, root mean square error of approximation; SEM, structural equation modeling; SF-36, 36-Item Short Form Survey; UOHI, University of Ottawa Heart Institute.

INTRODUCTION

Cardiovascular disease (CVD) includes a host of different disorders of the heart and blood vessels, such as coronary artery disease and hypertension, and symptoms typically manifest only after the disease has progressed to an advanced stage (Perk et al., 2012). Prevalence rates of CVD in the United States (Mozaffarian et al., 2015) and Canada (Government of Canada, 2019) are very high (6.2 and 7.8%, respectively), especially for an ostensibly preventable disease (Mozaffarian et al., 2015), and these rates are associated with a significant societal financial burden (Trogdon et al., 2007; Mozaffarian et al., 2015). As the population of people with CVD in developed countries continues to increase, so does the need for preventative medicine (Yazdanyar and Newman, 2009).

The promotion of health behavior change is central to CVD prevention efforts. These changes focus on reducing or moderating specific risk factors; these can be behavioral in nature, such as managing weight loss, quitting smoking, or eating healthier (Mozaffarian et al., 2015), they can be physiological, such as targeting specific CVD markers like hypertension, high cholesterol, or lack of exercise (Lee et al., 2012), or, these risk factors can psychological, such as elevated anxiety and depression (Rothenbacher et al., 2007; Whalley et al., 2014; Blumenthal et al., 2016), insecure attachment (Maunder and Hunter, 2001), and lower levels of psychological well-being (Boehm and Kubzansky, 2012).

Interest in attenuating psychological risk factors has grown in recent years, as some targeted psychosocial interventions have proven effective in reducing cardiac events (Whalley et al., 2014; Blumenthal et al., 2016; Richards et al., 2018), which is positive, as individuals with CVD are known to have elevated rates of anxiety (Frasure-Smith and Lespérance, 2008; Bunevicius et al., 2013) and depression (Frasure-Smith and Lespérance, 2008; Lichtman et al., 2008). Stress and depression directly contribute to poorer cardiovascular health by increasing blood pressure (Rothenbacher et al., 2007), vascular inflammation, and endothelial dysfunction (Williams and Steptoe, 2007). Indirectly, greater anxiety and depression promote other unhealthy behaviors (e.g., sedentary behavior, smoking) that exacerbate CVD risk.

Insecure Attachment as a Psychosocial Risk Factor for CVD

One potential psychosocial risk factor for CVD that has not yet been fully explored is insecure attachment, a construct that has been associated with increased prevalence of illness and disease (Maunder and Hunter, 2001; McWilliams and Bailey, 2010; Pietromonaco et al., 2013; Pietromonaco and Collins, 2017). Attachment was first described in the literature over four decades ago; it is defined as the tendency for human beings to develop strong emotional bonds with significant people in their lives, referred to as "attachment figures," as a principal means of emotion regulation in the face of stress or potential danger (Bowlby, 1958, 2005; Ainsworth and Bell, 1970). Secure attachment refers to the tendency to seek out emotional support and comfort from an attachment figure in situations of stress or emotional pain. Securely attached individuals perceive others as safe and trustworthy (Bowlby, 1980); thus, they are able to receive comfort and reassurance when they need it to reduce stress. Insecure attachment, however, is characterized by the tendency to either avoid seeking out emotional support and closeness from others (i.e., avoidant attachment) or exist in a near-constant state of reassurance-seeking that often leaves one feeling distressed and vulnerable, rather can calm and safe (i.e., anxious attachment; Bartholomew and Horowitz, 1991; Simpson and Rholes, 2017).

Instead of deriving reassurance and comfort from their relationships with attachment figures, people who are insecurely attached are more likely to worry and to feel uneasy about these relationships. This is highly stressful and is thought to contribute to the onset and course of chronic disease (Maunder and Hunter, 2001; McWilliams and Bailey, 2010; Pietromonaco et al., 2013; Pietromonaco and Collins, 2017). More specifically, the theorized mechanisms by which insecure attachment relates to increased disease risk include higher cortisol levels during times of stress (Luecken, 1998; Quirin et al., 2008; Pierrehumbert et al., 2012), augmented blood pressure during social interactions (Gallo and Matthews, 2006), and heavier reliance on external regulators for emotions, including alcohol and tobacco (Maunder and Hunter, 2001).

Although there is a known link between a lack of social relationships and increased mortality in general (Cerhan and Wallace, 1997; Holt-Lunstad et al., 2010; Barger, 2013), only a handful of studies have examined the impact of attachment style on heart health (Vilchinsky et al., 2010; Pietromonaco et al., 2013; Peleg et al., 2017; Pietromonaco and Collins, 2017). This may indicate an important gap in the literature, as the studies that have been conducted suggest a connection between insecure attachment and poor health (West et al., 1995; Bohachick et al., 2002; McWilliams and Bailey, 2010; Pietromonaco and Collins, 2017). For example, in one sample of the general population (N = 5645), insecure attachment was identified as a risk factor for the development of chronic illness, especially conditions related to the cardiovascular system (McWilliams and Bailey, 2010). Likewise, a follow-up study of heart transplant patients revealed that those with insecure attachment had worse functional outcomes 6 months after the procedure than did patients with secure attachment (Bohachick et al., 2002). A recent investigation found similar results; the researchers found insecure attachment styles were significantly more prevalent among people with coronary artery disease compared to healthy controls (Oladi and Dargahi, 2018).

There are known mechanistic links between attachment and CVD risk factors; for example, inflammation has been identified as a major contributor to the onset of heart disease, and there is evidence that both avoidant and anxious attachment are related to the production of the IL-6 in stressful situations such as conflict discussions between spouses and even CABG surgery (Kidd et al., 2014; Ehrlich, 2019). Despite some anti-inflammatory properties that have been noted, IL-6 is generally considered atherogenic, to the point where some researchers have suggested targeting it as a treatment for atherosclerosis (Reiss et al., 2017). Cardiovascular reactivity is another risk factor that researchers have linked to attachment and the development of CVD. Compared to when doing a cold pressor task alone, securely attached participants had significantly reduced systolic and diastolic blood pressure when their primary attachment figures were present or when they were instructed to think about them (Bourassa et al., 2019). Greater reductions in heart rate variability have also been detected during this stress task among participants with high levels of attachment avoidance (Bryant and Hutanamon, 2018). Once again, greater attachment security was related to less cardiovascular risk, and vice versa. Lastly, attachment insecurity has also been linked to primary hypertension. One group of researchers observed that 88% of hypertensive patients presented as insecurely attached, as compared to 50% in non-clinical populations (Balint et al., 2016).

Attachment, Psychological Functioning, and the Heart

Insecure attachment throughout the lifespan is also a robust predictor of psychopathology. For example, Stovall-McClough and Dozier (2016) noted in a comprehensive review of the literature that anxious, avoidant, and disorganized (i.e., sometimes anxious, sometimes avoidant) attachment styles detected during childhood play a key role in the development of major depression, anxiety disorders, dissociative disorders, and personality disorders later in life. The findings of more recent studies corroborate these results; insecure attachment (anxious and avoidant) has been linked to major depression comorbid with generalized anxiety disorder (GAD), panic disorder, and PTSD in adults (Huang et al., 2019), whereas fear of rejection by romantic partners and fearful attachment in general has also predicted the presence of mental-health problems among adults (Alonso et al., 2018). Taken together, these findings suggest that the subjective sense of loneliness typical of people with insecure attachment styles might contribute to the onset and course of psychological problems. This makes sense considering that, according to attachment theory, the perceived emotional unavailability of an attachment figure, especially in times of stress, is inherently traumatizing for human beings (Johnson, 2020), with all of the physical and psychological implications that the experience of trauma can have.

Symptoms of traumatic stress can also occur following a cardiac event; in fact, a systematic review of PTSD induced by a cardiac event revealed an average prevalence of about 12% of cardiac samples across 150 studies and noted that pre-existing psychological risk factors were important predictors in developing PTSD in this manner (Vilchinsky et al., 2017). Symptoms of PTSD, generally, include intrusive thoughts or images (flashbacks, nightmares), avoidance of triggering stimuli, emotional numbing, hyperarousal, sleep difficulties, and negative cognitions and mood (American Psychiatric Association, 2013). A diagnosis of PTSD is made when symptoms of traumatic stress are significant enough to disrupt an individual's functioning or to cause them clinically significant distress. A recent systematic review of 21 studies of attachment and post-traumatic stress in the general population revealed that insecure attachment consistently had mediating and moderating effects on the link between the experience of a traumatic stressor and the onset of symptoms of post-traumatic stress (Barazzone et al., 2019). The more insecurely attached a person is, the more likely he or she appears to develop PTSD in the face of a traumatic event. Potential reasons for this correlation might be that people with insecure attachment perceive a lack of emotional support and are therefore less resilient to trauma. Those with anxious attachment also report greater distress than do those with secure or avoidant attachment, indicating that they may be more focused on, and sensitive to, threatening stimuli.

With respect to cardiovascular functioning, chronic traumatic stress is detrimental to the heart; it is linked to increased heart rate, blood pressure, and substance abuse (Bedi and Arora, 2007; Coughlin, 2011); as well as greater risk of developing CVD (Kubzansky et al., 2007, 2009; Boscarino, 2008) and negative physical and mental health outcomes in patients with CVD (Whitehead et al., 2006; Edmondson and Cohen, 2013; Ginzburg et al., 2016). In one study of over 1000 patients with CVD followed over 7.5 years, exposure to traumatic events throughout the lifespan predicted greater mortality and a greater number of adverse cardiovascular events (Hendrickson et al., 2013). Moreover, the experience of potentially fatal cardiovascular events (e.g., myocardial infarction) has been shown to induce PTSD in some patients (Spindler and Pedersen, 2005; Edmondson et al., 2011, 2012; Edmondson and Cohen, 2013), and PTSD symptoms after such an event, in turn, are linked to subsequent cardiac health problems (Wikman et al., 2008; Edmondson et al., 2011) and all-cause mortality (Edmondson et al., 2011). To our knowledge, no one has yet examined the role of both attachment insecurity and traumatic stress in a CVD population, despite the potential for attachment insecurity to explain some of the well-documented effects of trauma on the heart.

OBJECTIVES

The main objective of this study was to test a model predicting health outcomes measured at 3 months in a CR population using baseline measures of attachment style and traumatic stress. Multivariate SEM was used to test the following hypotheses: (1) insecure attachment (i.e., avoidant or anxious attachment) would be associated with greater traumatic stress symptoms, (2) elevated traumatic stress and insecure attachment would each be independently associated with poorer cardiac-related physical and mental health outcomes, and (3) traumatic stress would mediate the relationship between insecure attachment and poorer physical and mental health outcomes.

MATERIALS AND METHODS

Participants

Patients enrolled in the cardiac rehabilitation program (CR) at the UOHI were assessed at baseline (program intake) and 3 months (end-of-program). The CR program consists of exercise, education, and allied health services (e.g., nurses, physiotherapists, vocational rehabilitation). Patients are automatically referred to CR following discharge from hospital

(Tiller et al., 2013). Only those who were unable to speak/read in English or French were excluded from the study. This study was approved by the Ottawa Health Science Network Research Ethics Board.

A power analysis was conducted using the software G*Power 3 (Faul et al., 2007) in order to calculate the minimum sample size required to achieve sufficient power for the statistical analyses involved. With a power level a 0.80 and an alpha of 0.05, it was estimated that a sample size of 200 would be required. This is also in keeping with the minimum suggested sample size for SEM (i.e., $N = 200$), suggested by Kline (2011).

Procedures

Individuals participating in the CR program at the UOHI were recruited at the patient's standard intake into the program. A healthcare professional in the prospective participant's circle of care provided an overview of the study and obtained consent for research staff to approach the patient. Research personnel obtained written informed consent and administered baseline questionnaires on-site. Physiological variables [fasting blood glucose concentration (mmol/L), glycated hemoglobin (HbA1c;%), HDL cholesterol ratios] were assessed at baseline by CR staff as part of standard intake procedure and then again at 3 months when participants returned for on-site follow-up appointments as part of standard care at the CR program. With respect to psychosocial variables, anxiety, depression, and quality of life were assessed at baseline and 3 months, while attachment and traumatic stress were assessed at baseline only. For those variables measured at 3 months, follow-up questionnaires (3 months) were mailed to participants along with a prepaid return envelope so that participants could mail back completed questionnaires.

Measures

Demographic and Clinical Information

At baseline, participants reported their age, sex, ethnicity, and marital status (see **Table 1**). Compliance with CR was calculated as the percentage of prescribed CR appointments patients attended. Participants' cardiac diagnoses and relevant cardiac procedures are also provided in **Table 1**.

TABLE 1 | Demographic characteristics of sample.

***N* = 201**		***n* (%)**
Sex	Male	160 (79.6)
	Female	41 (20.4)
Marital Status	Single	23 (11.4)
	Married/Common Law	150 (74.6)
	Divorced/Separated	15 (7.5)
	Widowed	13 (6.5)
Race	Caucasian	189 (94.0)
	Black	3 (1.5)
	Other	9 (4.5)
Education	Less than High School	23 (11.4)
	High School	47 (23.4)
	University	131 (65.2)
Cardiac Diagnoses or Event	Angina	56 (27.9)
	Heart Failure	22 (11)
	Congenital Heart Problem	6 (3.0)
	Myocardial Infarction	88 (43.8)
	Valvular Heart Disease	29 (14.4)
Cardiac Procedure	PCI	97 (48.3)
	ICD/Pacemaker	8 (4.0)
	Transplant	1 (0.5)
	Valve Procedure	3 (1.5)
	CABG	53 (26.4)
	None	39 (19.4)

CABG, coronary artery bypass grafting; PCI, percutaneous coronary intervention; ICD, implantable cardioverter defibrillator.

Experiences in Close Relationships-Revised

Attachment style was measured using the validated (Fraley et al., 2000) and reliable (Sibley et al., 2005) Experiences in Close Relationships-Revised (ECR-R). The ECR-R has 36 items designed to measure two individual factors of attachment: attachment anxiety (i.e., the degree to which a person worries their attachment figures will not be available or supportive when they need them) and attachment avoidance (i.e., the degree to which a person distrusts their attachment figures and achieves self-assurance by maintaining emotional distance). Each item consists of a statement regarding how the respondent feels in emotionally intimate relationships. Responses are indicated on a 7-point Likert-type scale (1 = *Strongly Disagree*; 7 = *Strongly Agree*) and the summed total of all items in each attachment style represents the score for that attachment style. Higher values indicate stronger affiliation with a particular attachment style.

Impact of Event Scale-Revised

Traumatic stress was measured using the validated (Horowitz et al., 1979) and reliable (Rash et al., 2008), 22-item Impact of Event Scale-Revised (IES-R). On the IES-R, respondents are asked questions about how they have been feeling over the last week with reference to their traumatic event (participants were asked specifically to refer to their cardiac event). Responses are indicated on a 5-point Likert-type scale (0 = *Not at All*; 4 = *Extremely*) and the summed total of all items serves as the total score. Higher scores indicate greater traumatic stress and scores of 33 or higher are indicative of a probable diagnosis of PTSD. The IES-R has been previously validated in a CVD population (Eslami, 2017).

Anxiety and Depression

The HADS (Zigmond and Snaith, 1983) is a 14-item self-report measure of anxiety (seven items) and depression (seven items) that has been used often in clinical populations, including with cardiac patients (Tulloch et al., 2018; Lemay et al., 2019). The HADS examines a range of anxious (e.g., muscle tension, panic-like symptoms, constantly worrying) and depressive (e.g., decreased mood, loss of interest, lack of motivation) symptoms. Symptoms statements are rated on a scale from 0 to 3. The HADS produces separate total scores for anxiety and depression (scores range from 0 to 21), with higher scores indicating greater levels of anxiety or depression; scores of 5 (depression) and 7 (anxiety) or greater are considered the cut-offs for clinical screening (Singer et al., 2009). The validity (Bjelland et al., 2002) and reliability (Boxley et al., 2016) of this measure has been demonstrated.

Quality of Life

Physical and mental quality of life was measured using the Short Form Health Survey Questionnaire, Version 1 (SF-36, V.1; Ware and Sherbourne, 1992), a self-report questionnaire containing 36 items. For the physical health (i.e., summed total of scale scores for "physical functioning," "physical role functioning," "bodily pain," and "general health perceptions") and mental health (i.e., summed total of scale scores for "vitality," "emotional role functioning," "social role functioning," and "mental health") total scores, higher values indicate better perceived physical or mental quality of life, respectively. This measure has been validated previously in a CVD population (Muller-Nordhorn, 2004) and has demonstrated reliability (Bunevicius, 2017).

Physiological Health Outcomes

Blood samples were drawn to assess physiological health outcomes, including fasting blood glucose concentration (mmol/L), glycated hemoglobin (HbA1c;%), and cholesterol information, including HDL ratios (total cholesterol/HDL), which have been shown to be superior predictors of poor cardiovascular health than other indicators of cholesterol (Lemieux et al., 2001); higher cholesterol is a risk factor for CVD as it indicates greater risk of arterial plaque deposits. Greater fasting blood glucose or HbA1c are indicative or greater risk of CVD, and can indicate prediabetes or diabetes.

Data Analyses

Missing data were evaluated following the procedures outlined by Tabachnick and Fidell (2007), and were imputed using multiple imputation (i.e., missing values replaced with means of 5 repeated imputations; Rubin, 1996). The effect of participating in the CR program on all dependent variables was assessed using a repeated-measures MANOVA. For the multivariate SEM analyses, the following parameters were used to determine excellent model fit: non-significant χ^2, CFI $\geq$ 0.95, RMSEA $<$ 0.07, and values ranging from 2 to 3 for CMIN/df (Hooper et al., 2008). Modification indices were examined to identify instances where variables and error terms were highly correlated; these relationships were allowed to covary within the model to improve fit. The main theoretical model consisted of baseline attachment anxiety and attachment avoidance, predicting traumatic stress, with traumatic stress in turn predicting all end-of-intervention health outcomes (see **Figure 1**). Compliance and baseline measures of health outcome variables were included in the model as controls. For all standardized indirect coefficients, the bias-corrected percentile method of generating two tailed significance values was used. Indirect effects were calculated using 2000 bootstrap samples.

RESULTS

Preliminary Analyses

All variables were normally distributed. For baseline data, 9 and 10% of the data were missing for attachment anxiety and attachment avoidance subscales respectively, while 8% of the data were missing for the IES-R. Regarding information collected at baseline and 3 months, HADS scores were missing 1 and 23%, respectively, SF-36 scores were missing 0 and 33%, fasting blood glucose values were missing 2 and 21%, glycated hemoglobin (HbA1c) values were missing 4 and 29%, and HDL ratio values were missing 1 and 20%. Compliance data were missing 10%. Missing values were found to be missing at random, Little's MCAR (747) = 42.87, p = 0.999.

Sample Characteristics

We approached 410 patients for the study. Of those, 409 were eligible (1 was not eligible due to language barrier), 288 agreed to participate (70% of eligible patients), and 201 completed the baseline questionnaires (70% of consented patients). Between baseline and follow-up, 2 patients died, 2 were out of the country, 9 dropped out of the study (2 said they felt it was not relevant to them, 2 had insufficient time, and 5 stated they were no longer interested), and 23 were unreachable, leaving 165 participants (82%) with completed 3-month data.

A demographic summary is presented in **Table 1**. The participants (n = 201) ranged in age from 24 to 89 years (M = 62.08, SD = 10.87) and were predominately male (n = 160, 80%), white (n = 189, 94%), and married (n = 150, 75%). Regarding traumatic stress, 42 (21%) scored above 33 on the IES-R, suggesting the probable presence of PTSD. On the HADS at baseline, a minority of individuals with scores above the cut-offs on anxiety (n = 86, 43%) and depression (n = 75, 37%); at 3 months, the number of those who scored high on the anxiety subscale had dropped moderately (n = 55, 27%) while those above the depression cut-off dropped off to a lesser degree (n = 61, 30%). The sample mean for fasting blood glucose concentration was above the normal range of 3.9 – 5.6 mmol/L (The Emerging Risk Factors Collaboration, 2010) at both baseline and 3 months and the sample mean for HbA1c was above the normal range of 3.8–5.9% (Cavalot et al., 2006) at both baseline and 3 months. The sample mean for HDL ratio was below the highest risk cut-off of 5 at both baseline (M = 3.25, SD = 0.96) and 3 months (M = 2.99, SD = 0.79) (Manninen et al., 1992). Compliance was high (M = 82.42%, SD = 25.17); about a third of participants attended every session (n = 73, 36.3%).

Effects of the Cardiac Rehabilitation Program

A repeated measures MANOVA on all dependent variables was significant, $F(7,194) = 29.78$, $p < 0.001$, Wilk's $\lambda = 0.48$, partial $\eta^2 = 0.52$. Depression (p = 0.003), anxiety ($p < 0.001$), and HDL ratio ($p < 0.001$), were all significantly lower at 3 months compared to baseline; physical quality of life ($p < 0.001$) and mental quality of life ($p < 0.001$) were significantly higher at 3 months compared to baseline. There was no significant change

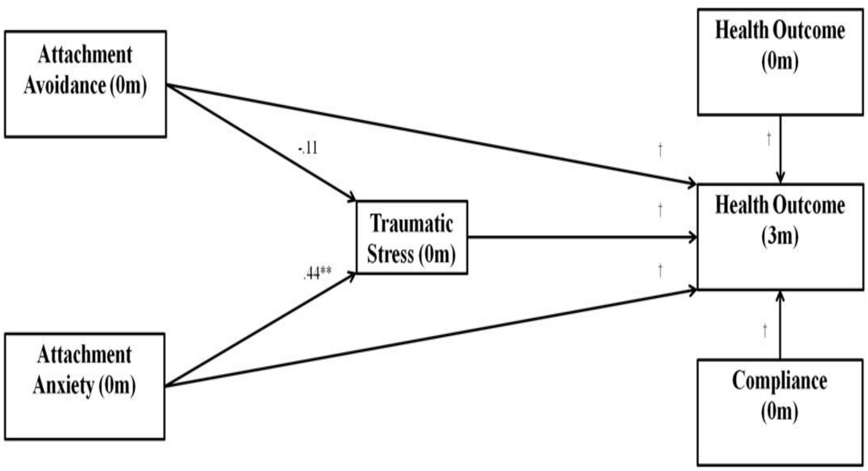

FIGURE 1 | Multivariate structural equation model used for path analysis. Hypothesized pathways included attachment anxiety and avoidance having indirect effects on health outcome variables through traumatic stress. m, months.

in fasting blood glucose or HbA1c values between baseline and 3 months. See **Table 2** for all means, standard deviations, and zero-order correlations between variables.

Structural Equation Modeling

The multivariate SEM model (with standardized estimates) can be found in **Figure 2**. The model fit statistics indicated the hypothesized model was a good fit of the data; the chi-square test was not significant [$\chi^2(74) = 91.30$, $p = 0.084$], and the measures of approximate fit were: RMSEA = 0.03 ($CI_{90\%}$ = 0.00,0.06), CFI = 0.99, CMIN/df = 1.23.

The results of the path analysis were that baseline attachment anxiety had a significant, positive indirect effect (via traumatic stress) on depression, anxiety, fasting blood glucose, and HbA1c, and a significant, negative indirect effect on mental quality of life and physical quality of life (see direct effects in **Table 3** and indirect effects in **Table 4**). The indirect effect of baseline attachment anxiety on HDL ratio was not significant; however, greater baseline attachment anxiety directly predicted significantly greater HDL ratios. There were no significant indirect effects of baseline attachment avoidance on any outcome variable.

DISCUSSION

The purpose of the present study was to test a model predicting physical and mental health outcomes in CVD patients using measures of attachment style and traumatic stress. To this end, CR patients were assessed at baseline (program intake) and 3-month follow-up (end-of-program) on a variety of outcomes.

Hypothesis 1

The first hypothesis was that insecure attachment (i.e., attachment anxiety or avoidance) would be positively associated with traumatic stress. In support of this, the zero-order correlations (see **Table 2**) between attachment anxiety, attachment avoidance, and traumatic stress were all significant and positive. The SEM results, however, supported this hypothesis only for attachment anxiety; attachment avoidance did not significantly predict traumatic stress (see **Figure 2**).

Attachment Anxiety and Trauma

One reason why attachment anxiety might associate with greater traumatic stress is that individuals with anxious attachment appear to be more sensitive to detecting threatening stimuli (Barazzone et al., 2019). This focus on potential threat, coupled with generally less perceived social support compared to securely attached individuals, may make those with anxious attachment less resilient to trauma. Perceived social support is known to be among the most important buffers against symptoms of PTSD (e.g., Guay et al., 2006; Stanley et al., 2018). It follows logically that insecurely attached people would be more susceptible to the effects of trauma than would securely attached people.

It has also been proposed that traumatic experiences, such as an acute cardiac event, activate the attachment system. Although both securely attached and anxiously attached individuals are likely to seek out reassurance and comfort from their attachment figures, those who are anxiously attached are less likely to perceive and to integrate the emotional support that is offered. This drives them to persist in their bids for reassurance, which might strain their close relationships and add additional barriers against processing trauma effectively (Mikulincer et al., 2007, 2015).

Attachment Avoidance and Trauma

Alternatively, our finding that attachment avoidance did not significantly predict traumatic stress is not without precedent. For example, in one meta-analysis, there was no relationship between attachment avoidance and traumatic stress, though the authors noted that this may have been due to the tendency to underreport, especially when completing self-report measures (Woodhouse et al., 2015). Psychophysiological measures that tap into adrenocortical activity, skin conductance, and heart rate,

TABLE 2 | Means, standard deviations, and correlations for all study variables.

	Variables	*M* (*SD*)	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
1	IES-R (0m)	20.03 (16.79)	–																
2	ECR-Avd (0 m)	44.63 (20.64)	0.14*	–															
3	ECR-Anx (0 m)	36.93 (16.82)	0.43**	0.52**	–														
4	HADS-Anx (0 m)	5.98 (3.91)	0.57**	0.22**	0.39**	–													
5	HADS-Dep (0 m)	3.91 (3.09)	0.48**	0.25**	0.40**	0.56**	–												
6	HADS-Anx (3 m)	4.68 (3.47)	0.52**	0.21**	0.35**	0.66**	0.42**	–											
7	HADS-Dep (3 m)	3.36 (3.09)	0.46**	0.25**	0.38**	0.43	0.66**	0.60**	–										
8	SF-36 Phys (0 m)	52.71 (20.75)	−0.29**	−0.13	−0.20**	−0.32**	−0.52**	−0.24**	−0.35**	–									
9	SF-36 Ment (0 m)	61.31 (20.86)	−0.48**	−0.26**	−0.39**	−0.56**	−0.64**	−0.35**	−0.48**	0.65**	–								
10	SF-36 Phys (3 m)	67.65 (22.69)	−0.34**	−0.17*	−0.22**	−0.43**	−0.55**	−0.47**	−0.64**	0.65**	0.45**	–							
11	SF-36 Ment (3 m)	72.82 (20.15)	−0.50**	−0.31**	−0.44**	−0.54**	−0.62**	−0.71**	−0.79**	0.45**	0.56**	0.74**	–						
12	FBG (0 m)	5.76 (1.28)	0.04	0.03	0.08	−0.02	0.06	−0.01	0.09	−0.24**	−0.06	−0.16*	−0.08	–					
13	FBG (3 m)	5.83 (1.31)	0.16*	0.12	0.09	0.01	0.09	0.03	0.15*	−0.26**	−0.08	−0.21**	−0.14*	0.82**	–				
14	HbA1c (0 m)	6.04 (0.88)	−0.03	0.13	0.02	−0.10	0.02	−0.04	0.03	−0.09	0.03	−0.04	−0.03	0.57**	0.69**	–			
15	HbA1c (3 m)	6.06 (0.76)	0.12	0.09	−0.01	−0.11	0.03	−0.06	0.05	−0.20**	−0.02	−0.13	−0.11	0.69**	0.84**	0.80**	–		
16	HDL Ratio (0 m)	3.25 (0.96)	−0.05	0.04	0.08	−0.01	0.12	0.03	0.15*	−0.08	−0.08	−0.14*	−0.14*	0.09	0.12	−0.02	0.06	–	
17	HDL Ratio (3 m)	2.99 (0.79)	−0.03	0.01	0.14*	0.01	0.07	0.06	0.09	−0.02	−0.05	−0.09	−0.13	0.15*	0.26**	0.11	0.21**	0.74**	
18	Compliance	82.43 (25.17)	−0.02	−0.02	0.04	0.09	0.11	0.11	0.13	−0.15*	−0.14*	−0.16*	−0.13	0.13	0.00	−0.18*	−0.05	−0.01	−0.09

**p* < 0.05, ***p* < 0.01, *M*, *means; SD, standard deviation; m, months; Avd, avoidance subscale; Anx, anxious subscale; Dep, depression subscale; Phys, physical health subscale; Ment, mental health subscale; FBG, fasting blood glucose.*

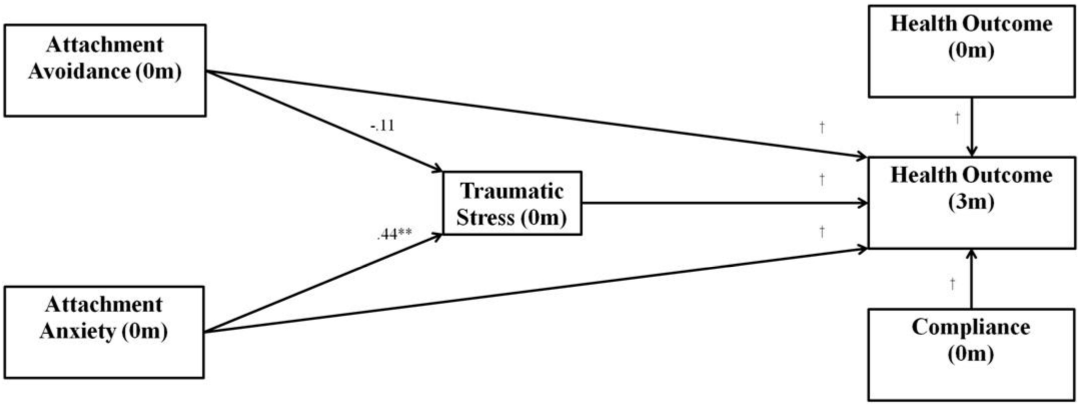

FIGURE 2 | Multivariate structural equation model used for path analysis with values representing standardized regression coefficients. The hypothesized pathways include attachment anxiety and avoidance having indirect effects on health outcome variables through traumatic stress. $^{**}p < 0.01$, m, months, †values are presented in **Table 2**. Indirect effects for model are shown in **Table 3**.

TABLE 3 | Standardized direct effects and R^2 values for multivariate structural equation model.

		Direct Effects on Outcome Measures (3 m)					
		Attachment Avoidance (0 m)	Attachment Anxiety (0 m)	Traumatic Stress (0 m)	Baseline Health Outcome (0 m)	Compliance (0 m)	R^2
Psychosocial Measures	HADS Anxiety	0.04	0.05	0.23**	0.46**	0.08	0.44
	HADS Depression	0.07	0.08	0.23**	0.45**	0.09	0.44
	SF-36 Physical QOL	−0.04	0.02	−0.13*	0.60**	−0.08	0.40
	SF-36 Mental QOL	−0.07	−0.17*	−0.16*	0.32**	−0.09	0.31
Physical Health Measures	FBG	0.12*	−0.05	0.11**	0.82**	−0.10*	0.68
	HbA1c	0.02	−0.12*	0.14**	0.81**	0.10	0.66
	HDL Ratio	−0.08	0.14*	−0.05	0.72**	−0.08	0.55

$^{*}p < 0.05$, $^{**}p < 0.01$, m, months; HADS, Hospital Anxiety and Depression Scale; SF-36, Short Form Health Survey – 36 Item Form; FBG, Fasting Blood Glucose; HbA1c, Glycated Hemoglobin; HDL, High-density Lipoprotein.

TABLE 4 | Standardized indirect effects for multivariate structural equation model.

		Indirect Effects on Outcome Measures (3 m) via Traumatic Stress	
		Attachment Avoidance (0 m)	Attachment Anxiety (0 m)
Psychosocial Measures	HADS Anxiety	−0.02	0.10**
	HADS Depression	−0.02	0.10**
	SF-36 Physical QOL	0.01	−0.06*
	SF-36 Mental QOL	0.02	−0.07*
Physical Health Measures	Fasting Blood Glucose	−0.01	0.05**
	HbA1c	−0.02	0.06**
	HDL Ratio	0.01	−0.02

$^{*}p < 0.05$, $^{**}p < 0.01$, m, months; HADS, Hospital Anxiety and Depression Scale; SF-36, Short Form Health Survey – 36 Item Form; HbA1c, Glycated Hemoglobin; HDL, High-density Lipoprotein.

are generally more sensitive indicators of stress among people with avoidant attachment styles (Gander and Buchheim, 2015). For this reason, it is likely that the lack of a link between attachment avoidance and traumatic stress may be more related to a lack of reporting than to true resilience against trauma. Individuals with an avoidant attachment style tend to dismiss or compartmentalize trauma without seeking support from others, which seems to disrupt the ability to process trauma effectively (Mikulincer et al., 2007). In addition, there is some evidence that individuals with avoidant attachment express fewer positive and negative psychological symptoms, tending to experience psychological symptoms that are negative to neutral (Kerr et al., 2003). In accordance with this, almost all zero-order correlations in the present study between attachment scores and outcome variables were greater for anxious attachment than they were for avoidant attachment. Future research is required to fully understand the relationships between trauma and both types of insecure attachment; however, it is possible our theoretical model is only appropriate for those with anxious attachment.

Hypothesis 2

Second, it was hypothesized that insecure attachment (i.e., greater attachment anxiety and avoidance) and greater traumatic stress would each independently predict poorer health outcomes. Again, this hypothesis was partially supported (see **Table 3**).

Attachment Anxiety, Attachment Avoidance, and Health

While greater attachment anxiety directly predicted several poorer health outcomes, attachment avoidance predicted significantly higher fasting blood glucose values only. This, as well as the finding that attachment anxiety had significant indirect effects on many outcome variables and attachment avoidance had none (see **Table 4**), suggests that attachment anxiety, not avoidance, may drive the previously observed relationship between insecure attachment and poorer health (Maunder and Hunter, 2001).

Hypothesis 3

The third hypothesis was that traumatic stress would mediate the relationship between insecure attachment and poorer physical and mental health outcomes. The results of the multivariate SEM supported this hypothesis for attachment anxiety only.

Traumatic Stress as a Mediator of the Effects of Attachment on Physical and Mental Health Outcomes

Greater baseline attachment anxiety was indirectly related to greater anxiety, depression, fasting blood glucose, and HbA1c levels at 3 months, and poorer physical and mental quality of life at 3 months. There were no significant indirect effects of attachment avoidance on any outcome measure; however, our findings are the first evidence that attachment anxiety is associated with poorer health outcomes in CVD patients via the experience of traumatic stress, which is an important finding. It is the first substantial empirical evidence of the notion that people with an anxious attachment style may be so preoccupied with their attachment relationships that it puts their health at risk.

Attachment Anxiety

In previous research, attachment anxiety has been linked to greater cortisol levels in times of stress (Quirin et al., 2008), and augmented diastolic and systolic blood pressure during social interactions (Gallo and Matthews, 2006). Our findings complement these and demonstrate that attachment anxiety is highly predictive of negative outcomes in people with heart disease. People with an anxious attachment style experience a great deal of interpersonal stress throughout most of their lives (Simpson and Rholes, 2017); their intense fear of losing meaningful attachment relationships and the accompanying hyperactivation of the attachment system might reach chronic levels similar to the hypervigilance that characterizes PTSD, with all of the health risks this can pose.

Attachment Avoidance

Although attachment anxiety was directly and indirectly linked to poor physical and mental health outcomes, attachment avoidance was not. The only finding related to CVD risk factors that was observed for attachment avoidance was that greater attachment avoidance at baseline was directly related to greater fasting blood glucose levels at 3 months. Regarding relationships with mediating factors in the SEM model, greater attachment avoidance predicted significantly lower levels of traumatic stress, which is at odds with previous findings (Clark and Owens, 2012). One possibility is that attachment avoidance may provide some measure of protection or resiliency against traumatic stress, but at the cost of fewer people who could potentially provide positive support. Alternatively, those who score higher in attachment avoidance tend to have less insight into and ability to express their own emotional experiences, otherwise known as alexithymia (Fantini-Hauwel et al., 2012). They might underreport traumatic stress, which may be the more plausible interpretation of this finding.

Limitations

The present study is not without limitations. Our CR patients were diverse in terms of cardiac diagnoses (see **Table 1**), meaning our relatively small sample size (N = 201) precluded diagnosis-based analyses of our data. Furthermore, we lacked some important variables (e.g., length of time since cardiac event, duration of hospitalization, etc.) that are important in the context of understanding the nature of traumatic stress. In many ways, our sample may be considered a relatively small subsample of the overall cardiac population; larger cohort studies could provide additional evidence regarding the relationship between attachment style and traumatic stress in specific cardiac subgroups. Understanding whether there are differences in terms of cardiac diagnoses would inform screening and treatment considerations in these groups.

Although diverse in terms of CVD, our sample was quite homogenous in other ways, further limiting the degree to which our findings may generalize to other settings. Our group of participants were mainly white, married, and highly educated; while this reflects the nature of who attends CR in our clinical setting and thus has clinical validity here, it makes examining relationships between study variables and sample variables (e.g., ethnicity) very difficult with a sample this size, disqualifying some potentially interesting analyses.

Finally, future studies could conduct longer-term follow up (i.e., compared to the 3 months presented here), and more thorough data collection (e.g., length of time since cardiac event, as listed above). The design of the present study was made with the structure of the current CR program in mind; alternative studies in a less clinical setting could prioritize more rigorous follow-up procedures, longer-term data-collection window, and greater control over the type of data collected from participants.

CONCLUSION

In the present sample of patients participating in a CR program, greater attachment anxiety predicted greater traumatic stress; this, in turn, predicted poorer physical and mental health outcomes. Via traumatic stress, baseline attachment anxiety was indirectly linked with a host of negative outcomes at 3 months, including greater anxiety, depression, fasting blood glucose, and HbA1c levels. Stated differently, people who tend to fear emotional abandonment and loss appear to be more susceptible to traumatic stress in the context of heart disease, which in turn seems to have negative effects on their mental and physical health, itself known to further worsen CVD (e.g., Williams and Steptoe, 2007).

Screening and interventions designed to target elevated attachment anxiety and traumatic stress should be considered for future study. Attachment-focused therapies such as Emotionally Focused Individual Therapy (EFIT; Johnson, 2019), Emotionally Focused Therapy (EFT) for couples (Johnson, 2020), or interpersonal psychodynamic approaches (Yalom, 1995) are interventions that might be particularly effective with the CVD population, due to their emphasis on helping clients develop and maintain secure attachment bonds to the most significant people in their lives. Another program that has shown promise among people with heart disease and their partner is Healing Hearts Together (Tulloch et al., 2016, 2017), which is heavily based on the principles of attachment theory and EFT. Whatever the intervention, our findings suggest that a key component ought to be the strength and quality of the personal relationships of patients with heart disease.

DATA AVAILABILITY STATEMENT

The datasets generated for this study are available on request to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ottawa Health Science Network Research Ethics Board. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

All authors contributed to the writing and conceptualization of the manuscript. AH and HT completed the statistical analyses.

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Psychological Well-Being as an Independent Predictor of Exercise Capacity in Cardiac Rehabilitation Patients With Obesity

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Objective: Exercise capacity (EC) is a well-established predictor of cardiovascular health. It is notoriously influenced by several factors, but the independent effect of psychological well-being (PWB) on EC has not yet been explored. The present study aims to investigate (1) whether PWB is an independent predictor of EC over and above selected demographic, behavioral, and biomedical parameters in a sample of CR patients with obesity and (2) whether PWB is a stronger predictor of EC than the other variables.

Methods: Data from 1968 patients were collected at the time of their inclusion in a cardiac rehabilitation (CR) program and retrospectively analyzed in a cross-sectional study. Since cardiorespiratory parameters defined in normal weight populations differ from those of their obese counterparts, an *ad hoc* validated formula taking body mass index (BMI) into consideration was used to predict EC.

Results: A multiple regression analysis revealed left ventricular eject fraction (LVEF) to be the strongest predictor of EC, followed by PWB, type 2 diabetes (DM), smoking status, atrial fibrillation (AF), and education. Bayesian evaluation of informative hypotheses corroborated LVEF as the best predictor of EC, and confirmed the superiority of PWB over and above DM and smoking status in influencing EC.

Conclusion: These findings strengthen the link between psychological and physical health, suggesting a better PWB is associated with greater EC. Prompt screening of a patient's mood and readiness to perform an active lifestyle would therefore enhance the long-term health benefits of CR.

Keywords: physical activity, exercise capacity, psychological well-being, cardiac rehabilitation, obesity

INTRODUCTION

Cardiovascular disease (CVD) is a leading cause of disability and premature death, globally, and substantially contributes to the escalating costs of healthcare (Roth et al., 2017). The American Heart Association (AHA) has established a sedentary lifestyle as a major modifiable risk factor for CVD (Thompson et al., 2003). However, despite overwhelming evidence promoting an active lifestyle in both primary prevention and formal cardiac rehabilitation (CR), evidence suggests that patients with CVD often fail to maintain physical activity (PA) recommendations (Dontje et al., 2014; Yates et al., 2017).

Still, a low level of PA increases the risk of developing other chronic conditions including diabetes, hypertension, obesity (Wing and Hill, 2001), and depression (Pollock, 2001; Dibben et al., 2018). Findings from a meta-analysis of 63 randomized studies evaluating the efficacy of different CR programs–with and without exercise–in patients with documented ischemic heart disease (IHD) showed that exercise alone produced a significant reduction in diverse causes of mortality (Clark et al., 2005). Thus, exercise capacity (EC) is a valuable measure for the control and treatment of CVD, and its assessment provides important information to guide exercise prescription (Demers et al., 2001; Banerjee et al., 2012). Assessment includes subjective evaluation of an individual's exercise tolerance and objective exercise test (ET) results.

Besides the well-known effect of age and gender, which continue to be the basis of the equation most frequently used to calculate exercise intensity (Ahmadian et al., 2013), evidence exists for the influence of body mass index (BMI, kg/m^2) on EC (Gondoni et al., 2010; Gong et al., 2013). Obesity is constantly increasing in prevalence (Pietrabissa et al., 2012; Holmgren et al., 2017) and the cardiovascular benefits obtained from increasing PA are greater than those from dietary control to lose weight.

Sufficient information is also found in the medical literature on the role of atrial fibrillation (AF) (Osbak et al., 2012; Zakeri et al., 2014), left ventricular ejection fraction (LVEF) (Wong and Yeo, 2010), type 2 diabetes (DM) (Awotidebe et al., 2014), smoking status (Mesquita et al., 2015), and educational level (Witham et al., 2006) in predicting aerobic capacity in patients with CVD.

Although evidence exists for the negative impact of impaired EC on perceived psychological well-being (PWB) in the cardiac population (Wang, 2018), the role of psychosocial domains on EC remains unclear (Chiala et al., 2018). Also, to our knowledge, no study has yet tested the independent effect of PWB in determining the maximum amount of physical exertion that a patient with both CVD and obesity can sustain. Understanding this effect could assist in the design of tailored assessments and intervention procedures in CR.

The present cross-sectional study aims to investigate (1) whether PWB is an independent predictor of EC over and above a series of selected demographic, behavioral, and biomedical parameters in a sample of patients with CVD and obesity, and (2) whether PWB is a stronger predictor of EC than the other selected variables.

MATERIALS AND METHODS

Participants

From January 2012 to June 2019, relevant data were collected from 1968 consecutive patients (1348 males) with CVD and obesity who were referred to a single clinical center (Istituto Auxologico Italiano IRCCS, San Giuseppe Hospital, Verbania, Italy) to attend a comprehensive cardiac and nutritional rehabilitation program (duration 25 ± 3 days).

Inclusion criteria for participating in the study were (1) being 18 or over; (2) presenting a diagnosis of IHD, defined as a history of at least one of the following: myocardial infarction, coronary artery bypass grafting, or percutaneous transluminal coronary angioplasty; (3) presenting a history of congestive heart failure (CHF) with either reduced or preserved EF; (4) having BMI $\geq$ 30; and (5) having undergone symptom-limited exercise stress testing to define their effort tolerance for exercise.

Patients (1) with recent (less than 2 months) myocardial infarction, coronary artery bypass, or coronary angioplasty or (2) who were unable to perform ET were excluded from the study.

All patients were clinically stable, and none had clinically evident heart failure according to the Framingham criteria (McKee et al., 1971).

The study conformed with the principles outlined in the Declaration of Helsinki and complied with APA ethical standards.

Measures

At the time of inclusion for CR, all subjects underwent a comprehensive routine assessment, including clinical history, physical examination, laboratory tests, and echocardiogram for the calculation of LVEF–which is the percentage of the diastolic left ventricular volume that is pumped out during systole–and exercise stress test. Also, demographic (i.e., age, gender, education) and behavioral (smoking status) parameters were collected at baseline.

Exercise Test Protocol

A Marquette series 2000 motorized treadmill and Marquette Max Personal electrocardiography (ECG) instrumentation (Marquette Medical Systems, Milwaukee, WI, United States) were used to assess patients' EC for treadmill speed and grade. EC is defined as the maximal oxygen intake for a stated workload, and it is commonly measured in metabolic equivalents (METs).

The test was tailored to patients' characteristics, and a ramp protocol was used. ET was conducted in the morning, at least 2 h after breakfast and while taking regular medication.

Patients were encouraged to continue exercising until symptoms prevented them from continuing, even after reaching 85% of their maximum predicted heart rate. Reasons for test termination were limiting symptoms (i.e., fatigue, angina, dyspnea, and muscular pain), abnormal ECG, abnormal blood pressure, or choice of the patient.

Since cardiorespiratory parameters defined in normal weight populations differ from those of patients with obesity, the following *ad hoc* validated formula that takes into account BMI along with other variables (i.e., height, age, and gender) was used to predict EC: Predicted *EC (METs)* $= 14.53 - (0.12 \times \text{age in years}) - (0.17 \times \text{BM in kg/m}^2\text{I}) + (3.16 \times \text{height in meters}) (+ 0.71 \text{ for male patients})$ (Gondoni et al., 2006). The ratio between measured and predicted values was calculated.

Psychological Assessment

The Italian version of the *psychological general well-being index (PGWBI)* was used to investigate the patients' self-evaluation of their perceived PWB. The score is derived from the summary score of six dimensions through 22 items: anxiety, depressed mood, positive well-being, self-control, general health, and vitality (Grossi et al., 2006). The PGWBI has been translated and culturally adapted into several languages across diverse populations of chronic patients and displays high values of Cronbach's alpha coefficients (range 0.80–0.94). The majority of applications have been in studies involving patients with CVD (Croog et al., 1986). The overall reliability index for the present sample was 0.87. Data were obtained retrospectively from the patients' medical records by a research assistant.

For the aims of the present study, literature-based selected predictors of EC were perceived PWB, education, LVEF, DM, AF, and smoking status.

Since BMI, height, age, and gender are parameters already included in the equation used to predict EC, these variables were excluded from the analysis.

Statistical Analysis

Data were examined prior to hypothesis testing for identification of any missing data and normality, revealing no missing data that was normally distributed.

Descriptive statistics were performed to summarize the characteristics of the sample.

A multiple regression analysis was performed to evaluate whether DM, LVEF, AF, smoking status, education, and the PGWBI total score were significant and independent predictors of EC. The model was fitted by a forward stepwise method. Parametric assumptions, possible outliers, and influential cases were assessed by inspection of diagnostic plots and calculation of *ad hoc* statistics. Critical alpha was set at 0.05, if not otherwise specified, and p-values $\leq$ 0.05 were considered as statistically significant.

A Bayesian method for the evaluation of informative hypotheses on regression coefficients was also used to compare the predictors for statistical differences and identify the most influential ones (Kluytmans et al., 2012).

Descriptive statistics and regression analysis were completed with SPSS 20.0 for windows (Release 20.0.0, SPSS Inc.), while the BIEMS free software package (Mulder et al., 2009) was used to perform Bayesian analysis.

RESULTS

Of 1968 patients, 620 were female (31.5%) and 1348 were male (68.5%). The mean age of the sample was 62.2 (SD = 9.5), and the average BMI was 38.8 (SD = 5.4) (**Table 1**).

TABLE 1 | Descriptive statistics of the sample.

	Total sample = 1968	
	Mean (Min–Max)	***SD***
Age (years)	62.2 (19.7–84.7)	9.5
Body mass index–BMI (kg/m^2)*	38.8 (30–61.9)	5.4
Left ventricular eject fraction–LVEF (%)	0.6 (0.15–0.8)	0.1
Exercise capacity–EC (METs)	5.76 (2–16.8)	2.5
EC measured/predicted (METs)	93.03 (24–232.8)	32.5
Psychological general well-being–PGWBI total score	69.39 (6–136)	19.9
Gender (*n*;%)		
Male	1348	68.5
Female	620	31.5
Smoking status (*n*;%)		
Active	341	17.3
Past	1113	56.6
Never	517	26.1
Education** (*n*;%)		
Low	565	28.7
Middle	780	39.6
High	623	31.7
Coronary artery disease, CAD Ischemic heart disease, IHD (*n*;%)	1400	71.1
Chronic heart failure, CHF, with either reduced or preserved eject fraction, EF (*n*;%)	932	47.4
Type 2 diabetes–DM (*n*;%)	927	47.1
Atrial fibrillation–AF (*n*;%)	260	13.2

**Obesity levels: Class I obesity: 496 (25%), Class II obesity: 803 (41%), Class III obesity: 669 (34%). **Education was coded as follows: 5 years or less = low; 6 to 12 years = middle; >12 (i.e., high school or university) = high.*

Predictors of EC

The stepwise multiple regression analysis stopped at step 6 and the final model included LVEF, PGWBI, DM, smoking, AF, and education as significant and independent predictors of EC [F(6.1961) = 38.53; p < 0.001]. The multiple correlation coefficient was 0.32, indicating that approximately 10.5% of the variance of EC could be explained by the included variables.

Diagnostic statistics showed no collinearity among the predictors (VIF values were all well below 4 and the tolerance statistics all well above 0.2) (Hair et al., 2010), and the P–P plot, as well as the histogram, suggested normality of residuals. However, a relatively random display of points in the scatterplot of standardized residuals against standardized predicted values did not provide evidence of homogeneity of variance.

The Durbin-Watson statistic was also computed to evaluate independence of errors; the result was equal to 0.21, which was not considered acceptable.

Inspection of standardized residuals revealed that heteroskedasticity did not concern the LVEF and AF variables. With respect to outliers and influential cases, no more than 5% of cases were shown to have absolute standardized residuals above 2 (3.6%; n = 71). Still, 15 cases (0.76%) had standardized residuals equal to or above 3 and could thus be considered as outliers. However, neither the Mahalanobis and Cook distances, nor the DFBeta values, showed any case significantly influencing the estimation of the model parameters.

Bayesian Analysis

Standardized regression coefficients (βs) showed LVEF to be the strongest predictor of EC in the study sample, followed by the PGWBI total score, DM, smoking status, and AF (**Table 2**).

TABLE 2 | Summary of stepwise regression analyses for variables predicting exercise capacity (n = 1968).

	B	SE	β	t	Sig.
(Constant)	48.32	4.65		10.39	0.000
LVEF	62.80	6.25	0.21	10.05	0.000
PGWBI	0.23	0.35	0.14	6.58	0.000
Diabetes	−6.17	1.40	−0.95	−4.41	0.000
Smoking	−5.35	1.08	−0.11	−4.96	0.000
AF	−8.95	2.09	−0.09	−4.28	0.000
Education	2.53	0.91	0.06	2.79	0.005
R^2			0.10		
F			38.53*		

*$p < 0.01$.

However, this ranking is purely descriptive and provides no statistical evidence about the superiority of LVEF over PWB, or of PWB over the other determinants in predicting EC in the present population. Three informative hypotheses were thus formulated: (1) $\beta_{LVEF} > \beta_{PWB}$, (2) $\beta_{PWB} > \beta_{DM}$, and (3) $\beta_{PWB} > \beta_{Smoking}$.

BIEMS generated a default prior and calculated a Bayes Factor for each hypothesis versus its unconstrained alternative (both βs are free to vary from minus to plus infinity).

For the first hypothesis, a Bayes factor of 1.96 was found. This means that the hypothesis stating that LVEF is more important for predicting EC than the PGWBI received almost two times more support from the data than the unconstrained hypothesis.

The second hypothesis received a Bayes factor of 2.00 and the third one received a value of 2.01, indicating that the data supported the superiority of PGWBI over both DM and smoking status in predicting EC.

DISCUSSION

This study targeted a large representative sample of patients with CVD and comorbid obesity referred for CR and revealed PWB to be a strong predictor of EC, second only to LVEF. Indeed, left ventricular dysfunction has been shown to have a largely demonstrated negative impact on exercise performance (von Roeder et al., 2017; Sacre et al., 2018), especially in obese patients (Benge et al., 1980). Moreover, DM, smoking status, AF, and education were significant predictors of EC in the present sample, although to a lesser extent than the subjective well-being.

Consistently, previous studies showed reduced EC in individuals without CVD who had DM (Choe et al., 2018), and a lower improvement of exercise tolerance in CR patients with diabetes compared with their non-diabetic counterparts–independently from their BMI (Verges et al., 2004; Kim et al., 2015).

These findings might be explained by the strong association between subjective well-being and lifestyle habits in people with DM. Diabetes is a chronic disease that affects both health and PWB (Moreno and Pearson, 2011). In fact, diet and exercise are the foundation of most therapies for diabetes (Tonetto et al., 2019), and people with DM often feel challenged by their disease-related features and complications and its day-to-day management demands (Thapa et al., 2019). Fears about the reality of complications (i.e., obesity, CVD, renal failure, etc.) also prevent people from exercising (Stryker, 2016) and are responsible for impaired PWB in persons with DM (Jing et al., 2018). At the same time, feeling good and staying healthy would give a further boost to the subjective well-being of the sufferers and their health-related outcomes. Accurate lifestyle analysis of patients suffering from CVD and other chronic conditions is, therefore, important for a comprehensive assessment in CR and the promotion of disease prevention strategies (Ceccarini et al., 2015; Pietrabissa et al., 2017b). This includes the screening of smoking habits and of socioeconomic status (SES) of the person.

In fact, cigarette smoking is a powerful independent risk factor for CVD and has a significant negative impact on EC (Asthana et al., 2012) and other cardiovascular parameters (Unverdorben et al., 2008). Still, most smokers gain weight after quitting due to increased energy intake and reduced energy expenditure. In order to prevent or reduce the onset of further complications, such as diabetes or obesity, actions for smoking cessation should, therefore, be combined with weight control interventions. These must be tailored for home-based care that would consider social disparities and meet the varying needs (and limitations) of the patients (Favoccia et al., 2014).

In fact, previous research has found inverse relationships between SES–including household income, education, housing status, and occupation–and unhealthy behaviors (Lantz et al., 2001; Pampel et al., 2010). In fact, socioeconomically challenged individuals confront more barriers (e.g., access, cost) to modifying risk behaviors over time such as quitting smoking, improving diet, increasing PA, and adhering to medications (Chandrasekhar, 2019). In particular, low education levels might affect the individuals' ability to interpret and to comply with health recommendations and to interface effectively with healthcare professionals (Kavanagh et al., 2010; Stringhini et al., 2010; Prag and Subramanian, 2017; Andrade and Mehta, 2018; Vonneilich et al., 2019), therefore constituting a risk factor for adherence to PA programs and functional EC (Anderson et al., 1997; Shishehbor et al., 2006).

Strengths and Limitation of the Study

The strengths of this study include its large sample size and the use of the Bayesian approach, which provides the most theoretically defensible framework that can be used to address probabilistic questions.

However, this work must be considered in light of several potential limitations. Firstly, absence of a comprehensive screening of mental health problems [e.g., eating disorders (Faulconbridge et al., 2012) and depression (Alizai et al., 2015; González-Castro et al., 2019)], readiness to change, and perceived self-efficacy of the participants prevented us from clarifying the role played by emotional factors in influencing the amount of physical effort that an individual with obesity and cardiac complication can sustain. Adaptation to living with CVD may, in fact, differ for each individual, and further studies should also investigate the role played by disease severity/typology (i.e., coronary artery disease–CAD, ischemic heart disease–IHD, or chronic heart failure–CHF) in the relation between PWB and patient-reported EC. Moreover, obesity might affect CR in many ways, but the absence of a control condition did not allow us to investigate the specific impact of PWB on EC during CR in both obese and non-obese people with CVD. It is also possible that other unmeasured modifiable and non-modifiable variables might account for these results, including family history, blood pressure, pulmonary functions, the skeletal muscle status, or the individuals' perceived social support. Lastly, the use of self-report methods in the assessment of the individuals' PWB and the absence of a proper cognitive screening in CR might limit the reliability of the research findings. Socially desirable responding, difficulties in assessing themselves accurately or misunderstanding of the meaning of the questions cannot, therefore, be excluded. Still, self-reports represent an inexpensive tool that allows the collection of a large amount of data in a relatively short amount of time and, therefore, are a particularly useful approach in assisting the assessment of CR patients in research and in everyday practice.

CONCLUSION

The present study showed for the first time the independent impact of PWB on exercise intolerance over and above a series of selected physical and social components in a representative sample of patients with obesity and CVD enrolled in a CR program.

Exercise capacity is a key outcome of CR, and these results highlight the importance for healthcare professionals to properly assess the psychosocial status of the patient in order to promptly address potentially modifiable barriers to PA other than the biomedical ones (Baldasseroni et al., 2016; Cattivelli et al., 2018). Indeed, many patients with obesity and CVD fail to meet recommended daily PA levels (Balady and McInnis, 1996; Ghashghaei et al., 2012), and effective personalized actions aimed at increasing long-term behavioral change should be promoted (Pietrabissa et al., 2013, 2015, 2017a,b; Ceccarini et al., 2015).

Maintenance of healthy behaviors (i.e., PA, smoking, alcohol use, diet) would also increase cardiovascular parameters and reduce severity of comorbid illnesses (i.e., obesity, diabetes, etc.), thus preventing these conditions from further affecting the individuals' exercise tolerance.

Still, longitudinal studies are needed to examine the mediating effect of health behaviors in the relationship between emotional status and the main clinical parameters of cardiac patients–with and without obesity. Findings from this study should be further explored in investigations targeting different populations. In fact, a research gap still exists in understanding the predictors and barriers to PA adherence in samples with varying background, ethnicity, or SES.

DATA AVAILABILITY STATEMENT

The datasets generated for this study are available on request to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Istituto Auxologico Italiano, IRCCS. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

LG conceived the original idea. GP planned and supervised the work, collected the experimental data, and wrote the manuscript with support from GC and RC. GM performed the analysis. EM supervised the findings of this work. All authors discussed the results and contributed to the final manuscript.

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Anxiety and Depression After a Cardiac Event: Prevalence and Predictors

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Introduction: Patients who are anxious or depressed after an acute cardiac event are at increased risk of a subsequent event and premature death. It is therefore important to identify these patients early in order to initiate supportive or even preventive measures. In the present study, we report on the prevalence of anxiety and depression during the first 12 months after an acute cardiac event, and the patient characteristics predictive of increased anxiety and depression risk in early and late convalescence.

Methods: We recruited a sample of 911 patients with acute myocardial infarction (AMI), acute coronary syndrome (ACS), and/or unstable angina (UA), and/or undergoing coronary artery bypass graft surgery (CABGS). Patients completed the Hospital Anxiety and Depression Scale (HADS) close to the time of their event, and again during early (2–4 months post-event) and late (6–12 months post-event) convalescence. Using HADS-A and HADS-D cut-offs of 8+, prevalence rates for anxiety, depression, and comorbid anxiety and depression were determined for each timepoint. Chi-square tests and odds ratios were used to identify baseline patient characteristics associated with increased anxiety and depression risk over 12 months.

Results: Anxiety rates were 43, 28, and 27% at the time of the event, early, and late convalescence. Depression rates were 22, 17, and 15%, respectively. Factors consistently associated with increased anxiety and depression risk were history of depression, financial strain, poor self-rated health, low socioeconomic status, younger age (<55 years), and smoking. Obesity, diabetes, and social isolation (living alone or being unpartnered) were identified as important albeit less significant risk factors. Neither sex nor event type were predictive of anxiety or depression.

Conclusion: This large patient sample provided the opportunity to identify rates of anxiety and depression during the 12 months after a cardiac event and key patient characteristics for increased risk. These risk factors are easily identifiable at the time of the event, and could be used to guide the targeting of support programs for patients at risk.

Keywords: psychosocial risk factors, heart disease, anxiety, depression, heart attack

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INTRODUCTION

Anxiety and depression are both common after an acute cardiac event, such as acute myocardial infarction (AMI) or coronary artery bypass graft surgery (CABGS). It is generally agreed that around one in five patients meet diagnostic criteria for depression while hospitalized for a cardiac event (Thombs et al., 2006; Lichtman et al., 2008; Colquhoun et al., 2013; Murphy et al., 2016), and up to one in three experience severe anxiety (Andrew et al., 2000; Tully and Baker, 2012; Murphy et al., 2016). While relatively few studies have reported rates of anxiety and depression at later points during patients' convalescence, there is evidence that early symptoms resolve for many patients during the first few months after hospital discharge (Murphy et al., 2008a, 2013, 2016).

Patients who are anxious or depressed after an acute cardiac event are at increased risk of a subsequent event and premature death (Strik et al., 2003; Barth et al., 2004; van Melle et al., 2004; Tully et al., 2013). The negative health impacts appear to surface or increase when anxiety or depressive symptoms persist or emerge after hospital discharge during convalescence (Blumenthal et al., 2003; Murphy et al., 2013; Worcester et al., 2019; Kim et al., 2020). In a 12-year follow-up study of 170 female AMI and CABGS patients, we found that the mortality rate was highest in those whose depression symptoms worsened in the 2 months after hospital discharge, and lowest in those whose in-hospital symptoms remitted by 2 months (Murphy et al., 2013). Others have reported similar findings (Blumenthal et al., 2003). Anxiety at one to 2 months post-event has been found to confer a 2.3 to 2.8-fold increased risk of adverse cardiac events (Strik et al., 2003; Frasure-Smith and Lesperance, 2008). For this reason, it is important to identify patients at risk of symptoms of anxiety or depression that emerge later or persist into convalescence, rather than identifying only those with symptoms present in hospital (Murphy et al., 2016). Moreover, it is important to identify patient characteristics other than early anxious or depressive symptoms, given that these cannot be regarded as a good indicator of later mental health status (Murphy et al., 2008a, 2013, 2016).

Mechanisms for the associations between CHD and mental health have been well documented in several reviews published in recent years. These include hypothalamic pituitary adrenal axis dysregulation, platelet activation, and inflammation (Brydon et al., 2006; Smith and Blumenthal, 2011; Goldstein et al., 2015). It has been suggested that CHD and anxiety and depression share several biological mechanisms. Patients with depression, for example, have higher levels of biomarkers that promote atherosclerosis; in anxiety and depression, we see reduced heart rate variability suggesting decreased parasympathetic activity; altered serotonergic pathways; altered platelet aggregability; and increased C-reactive protein, an indicator of increased inflammatory response. The process can be summarized in the following way (Brydon et al., 2006): atherosclerosis, the disorder underlying this disease, is an inflammatory process in which leukocytes interact with structurally intact but dysfunctional endothelium of the arteries. Platelets bind to leukocytes and promote their recruitment to the endothelium. Platelet-leukocyte interactions also stimulate the release of pro-inflammatory and pro-thrombotic factors which promote atherosclerosis (Brydon et al., 2006). Another mechanism involves impaired cardiac neuronal reuptake of noradrenaline across the heart in patients with anxiety and depression (Alvarenga et al., 2006); such an abnormality magnifies sympathetically mediated responses, particularly emotionally driven responses in the heart where noradrenaline inactivation is so dependent on neuronal reuptake, potentially causing sensitization to cardiac symptom development. Augmentation of the sympathetic neural signal in the heart, by impairment of neuronal noradrenaline reuptake, additionally could increase cardiac risk, predisposing to the development of cardiac tachyarrhythmia (Alvarenga et al., 2006).

Several effective evidence-based supports are available to assist patients to manage anxiety and depression, underscoring the importance of early identification of at-risk patients. Cognitive behaviour therapy (CBT) has been shown to be effective in reducing anxiety and depression in cardiac patients (Ski et al., 2016; Tully et al., 2017), as has cost-effective short term psychotherapy (Pristipino et al., 2019) and low intensity collaborative care (Huffman et al., 2014). Selective serotonin reuptake inhibitors (SSRIs) are effective for cardiac patients with depression, both for remission of depressive symptoms (Thombs et al., 2008; Pizzi et al., 2011; Kim et al., 2018) and reduced incidents of re-events and death (Taylor et al., 2005; Kim et al., 2018). Physical activity has been shown to be effective in reducing symptoms of mild to moderate depression in patients generally (Wegner et al., 2014), and in older patients with chronic disease (Blumenthal et al., 1999).

If patients at risk of anxiety and/or depression during convalescence after an acute event are identified at the time of their event, supportive or even preventive measures can be initiated. Therefore, it is important to identify baseline characteristics – or risk factors – for anxiety and depression during convalescence.

Aims of the Study

The present study has two primary aims. First, the study aims to report the prevalence of anxiety and depression at the time of the acute cardiac event, and again at early and late convalescence during the first year after hospital discharge. Second, the study aims to identify the patient characteristics associated with increased risk of anxiety and depression during early and late convalescence.

MATERIALS AND METHODS

Sample

Eligible patients were those admitted to hospital after AMI, acute coronary syndrome (ACS) or unstable angina (UA), and those on the waiting list for elective CABGS. Admissions were to four hospitals in metropolitan Melbourne, Victoria, and two hospitals in regional Victoria, Australia. Patients with a current episode of severe psychiatric illness, those with intellectual disability, and those who did not have sufficient English language to complete the questionnaires were excluded.

Procedure

Eligible patients were identified by medical or nursing staff from relevant admission records and waiting lists and were then approached by the researcher who explained the study and provided an introductory letter and consent form. All participating patients provided signed consent. All patients completed a baseline self-report questionnaire (while in hospital after admission for AMI, ACS, and UA, and prior to hospital admission for elective CABGS patients), and again during early convalescence (2–4 months post-event) and late convalescence (6–12 months post-event). Baseline questionnaires were completed and collected by the researcher, while follow-up questionnaires to re-assess anxiety and depression were mailed to patients' homes, with completed questionnaires being returned by patients in reply paid envelopes. Approval was obtained from the Human Research Ethics Committees of the participating hospitals.

Measures

The 14-item *Hospital Anxiety and Depression Scale* (HADS) was used to assess anxiety (HADS-A) and depression (HADS-D) at each of the three timepoints (Snaith and Zigmond, 1994). The HADS has been shown to be psychometrically sound for use in cardiac populations (Roberts et al., 2001). The generic cut offs for mild to moderate symptoms are HADS-A $>$ 8 for anxiety and HADS-D $>$ 8 for depression. It was necessary to dichotomize HADS scores in this way in order to report on prevalence rates for anxiety and depression, as per the first aim of the study.

Socio-demographic information was collected at baseline by self-report questionnaire, and included age, sex (male vs. female), partner status (partnered vs. unpartnered), living arrangements (alone vs. with other), current or last occupation (non-manual vs. manual), and private health cover (insured vs. uninsured). Age was dichotomized as under 55 vs. 55 or over. In Australia, having private health cover is associated with outright home ownership, luxury vehicle ownership and a six-figure income (Muggli et al., 2006), hence its relevance as an indicator of financial security. Manual occupation and not having private health cover were combined to create a variable for socioeconomic status (SES), with patients classified as manual workers and having no health cover being classified as low SES. *Financial strain* was assessed by asking patients to rate their level of financial strain, as either extreme, considerable, moderate, slight or none. For the dichotomous variable, ratings of extreme and considerable were combined to indicate financial strain.

Clinical information was also collected at baseline by self-report questionnaire, and included admission event (AMI, CABGS, ACS, and UA), diabetes mellitus, height, and weight (for calculating body mass index; dichotomized as obese vs. not obese) and smoking status (current, past or never-smoked, dichotomized as current vs. non-smoker). While there is inevitable overlap between the diagnostic categories of AMI, CABGS, ACS, and UA, patients' diagnoses were allocated based on their index event at the time of hospital admission. *Self-rated health* was assessed on a 5-point scale, indicated as poor, fair, good, very good, and excellent (Bosworth et al., 1999). Responses were re-classified as poor vs. not poor for the dichotomous variable. *History of depression* was assessed by asking patients "Have you ever been depressed in the past, prior to your cardiac event?" and were classified as yes or no.

Data Analysis

The prevalence of anxiety and depression was calculated for each of the three timepoints: at the time of the event, early convalescence and late convalescence. The chi-square statistic, crude odds ratios and 95% confidence intervals were used to identify baseline factors significantly associated with increased risk of anxiety, depression and comorbid anxiety/depression at either early or late convalescence. We identified the variables that might be clinically significant and show an association or borderline association with clinical anxiety or depression, with variables $p < 0.10$ reserved for inclusion in the multivariate analysis. We included comorbid anxiety/depression as an outcome in this level of the analysis given its clinical importance as a predictor of poorer outcomes than either disorder alone (Coplan et al., 2015).

We used decision-tree analysis using Chi-square automatic interaction detection (CHAID) (Kass, 1980) to determine clinically relevant predictors of anxiety or depression at late convalescence. We chose anxiety OR depression as the outcome at this level of the analysis in order to capture the largest number of patients with any mental health condition and therefore maximize the statistical power of the analysis. Moreover, from a clinical perspective, it is useful to identify predictors for *either* mental health condition in order to best identify at-risk patients, be they those at risk of anxiety or those at risk of depression. We chose to present the CHAID analysis only for predicting anxiety or depression at late convalescence since this is a period when most of the adverse effects of surgery and treatment have stabilized and any ongoing elevated anxiety and depression is likely to be of clinical significance (Milani et al., 1996; Worcester et al., 2007). We chose the CHAID method since it is intended to work with discrete targets and does not require the data to be normally distributed (Song and Lu, 2015). The CHAID algorithm also has the advantage of including missing values as part of the analysis. Based on the smallest p value, the algorithm decides whether to merge the missing category with its most similar category or to keep the missing category as a separate category. The classification tree starts with identifying the target variable (anxiety or depression) which would be considered the root. CHAID analysis then splits the target into two or more categories (initial parent nodes). Using Bonferroni correction as a splitting criterion, these nodes are then split into child nodes. In this CHAID analysis tree, the variable that is a major influence on anxiety or depression appears first in the tree (initial node) and the less influential variables come last (terminal nodes). In order to preserve statistical power, the number of splits was limited to three and number of patients in child nodes was restricted to 20 and above, thereby restricting the number of levels. Similar criteria have been used in previous decision tree analyses involving similar size samples (Reges et al., 2014). To validate resultant decision-trees a 5-fold cross-validation procedure was applied with misclassification risk estimate, overall accuracy percentage and cross-validation risk estimate calculated.

All analyses were conducted using IBM SPSS Statistics V.26 (IBM Corporation, Armonk, NY, United States).

RESULTS

Characteristics of the Sample

In total, 911 patients were recruited at baseline, 792 (87%) completed the first follow-up assessment during early convalescence (2–4 months post-event) and 723 (79%) completed the second follow-up assessment during late convalescence (6–12 months post-event). The flow of patients through the study is shown in **Figure 1**.

Sociodemographic and clinical information for the sample of 911 patients is shown in **Table 1**. As shown, two thirds of the patients were male, and almost three quarters were over 55 years of age. Almost four out of five lived with other(s), and around two thirds were partnered. Over half were or had been in non-manual occupations. While almost two thirds had no health insurance, fewer than one in four were classified as being of low SES and just under 10% were experiencing extreme or considerable financial strain. Most patients were admitted following AMI or to undergo CABGS. Almost one in five were smokers at the time of admission, almost one in four had diabetes, one in three was obese, and over one in four had a history of depression. Just over one in ten rated their health as poor.

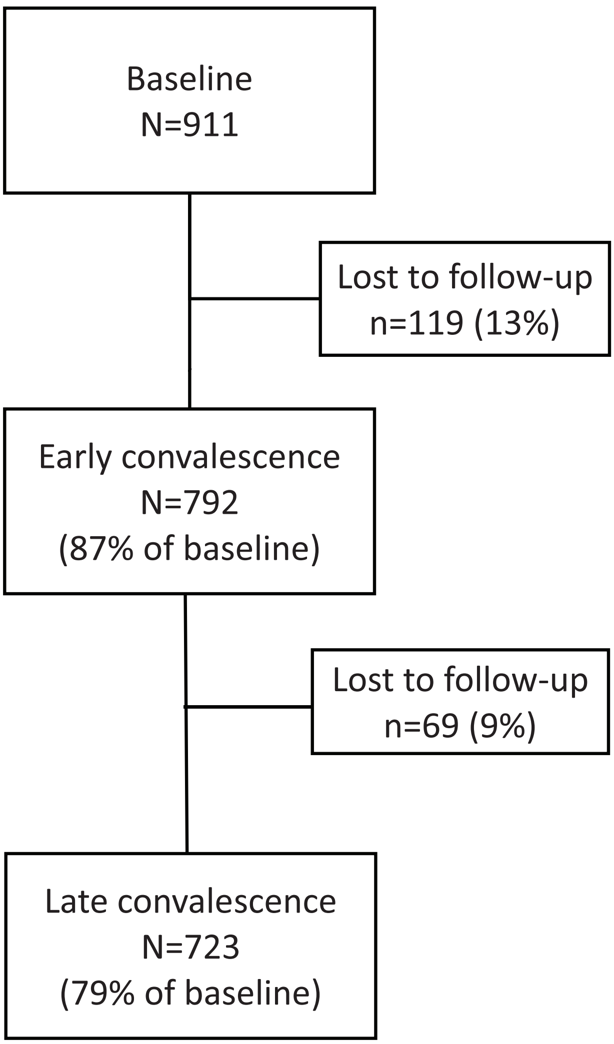

FIGURE 1 | Flow of patients through the study from baseline to late convalescence.

Prevalence of Anxiety and Depression at Baseline, Early, and Late Convalescence

The number and proportion of patients classified as anxious and/or depressed at each of the three timepoints are also shown in **Table 1**. More than two in five patients were anxious at the time of the event and more than one in four were anxious during early and late convalescence. Rates were slightly lower for depression: over one in five patients were depressed at the time of their event, with under one in five depressed during early and late convalescence. When totaled, almost half the patients were *either* anxious or depressed at the time of the event, with rates of 32% for early and 31% for late convalescence.

In terms of comorbidity, almost one in five patients were *both* anxious and depressed at the time of the event, with rates of 13 and 11% for early and late convalescence, respectively. Indeed, there was a significant overlap between anxiety and depression at both early ($\chi 2 = 186.11$, df = 1, $p < 0.001$) and late ($\chi 2 = 154.53$, df = 1, $p < 0.001$) convalescence. At early convalescence, 46% of patients who were anxious were also depressed, while 76% of those who were depressed were also anxious. At late convalescence, these overlap rates were 42 and 77% respectively.

Predictors of Anxiety in Early and Late Convalescence

The factors significantly associated with anxiety in early and late convalescence are shown in **Table 2**. For each factor, the table shows the proportion of patients classified as anxious, together with the odds ratios, 95% confidence intervals, chi-square value and *p*-value.

As shown in **Table 2**, the rate of anxiety in early and late convalescence was significantly increased for patients with a history of depression, those aged under 55, those reporting moderate or severe financial strain, those with poor self-rated health, smokers, those classified as low SES, and those classified as obese. Having a depression history conferred a 3 to 3.5-fold increased risk of early and late anxiety, while financial strain conferred an almost 3-fold increased risk of early anxiety and an almost 6-fold increased risk of late anxiety. Being aged under 55 and having poor self-rated health each conferred a 2-fold or greater increased risk of early and late anxiety. Smoking conferred a 60% increased risk of early anxiety and doubled the risk of later anxiety. Low SES and obesity each conferred at least a 30% increased risk of anxiety in early and

TABLE 1 | Characteristics of the sample.

		N	n	%
Sociodemographic characteristics				
Sex	Male	911	605	66.4
	Female		306	33.6
Aged under 55		911	247	27.1
Lives alone		909	195	21.5
Unpartnered		896	291	32.5
Manual occupation		711	287	40.4
Low socioeconomic status		635	149	23.5
No private health insurance		552	334	60.5
Extreme or considerable financial strain		547	49	9.0
Clinical characteristics				
Event type	Coronary artery bypass graft surgery	911	491	35.2
	Acute myocardial infarction		317	54.5
	Acute coronary syndrome/unstable angina		93	10.3
Current smoker		910	172	18.9
Diabetes mellitus		900	206	22.9
Poor self-rated health		835	97	11.6
Obese		639	205	32.1
History of depression		491	140	28.5
Anxiety and depression rates				
Anxious or depressed	Baseline	910	440	48.4
	Early convalescence	791	257	32.5
	Late convalescence	723	222	30.7
Anxious	Baseline	911	394	43.2
	Early convalescence	792	225	28.4
	Late convalescence	723	197	27.2
Depressed	Baseline	910	205	22.5
	Early convalescence	791	136	17.2
	Late convalescence	723	107	14.8
Anxious and depressed	Baseline	911	159	17.5
	Early convalescence	792	104	13.1
	Late convalescence	723	82	11.3

N = 911 at baseline; missing data on some variables due to variations in baseline questionnaires used at different hospitals. Low socioeconomic status based on being in manual occupation and having no private health insurance. Anxious = HADS-A ≥ 8; Depression = HADS-D ≥ 8; Early convalescence = 2–4 months post-event; Late convalescence = 6–12 months post-event.

late convalescence. Being unpartnered also marginally increased the risk of early anxiety. Sex, event type, living arrangements, and diabetes were not predictive of anxiety at either timepoint during convalescence.

Predictors of Depression in Early and Late Convalescence

The factors significantly associated with depression in early and late convalescence are shown in **Table 3**. Financial strain conferred a 4 to 5-fold increased risk of early and late depression, while poor self-rated health conferred over a 3-fold increased risk. Having a history of depression conferred a 2.5-fold and 3.4-fold increased risk of early and late depression, respectively. Low SES, age under 55 and smoking each conferred around a 2-fold increased risk at both timepoints. Being unpartnered and living alone both significantly increased the risk of late but not early depression. Obesity and diabetes increased the risk of early or late depression, respectively, although their effects were less statistically significant than other factors. Neither sex nor event type were predictive of depression at either timepoint.

Predictors of Comorbid Anxiety and Depression in Early and Convalescence

The factors significantly associated with being both anxious and depressed in early and late convalescence are shown in **Table 4**. For both early and late comorbid anxiety and depression, there were again six common risk factors: financial strain, history of depression, poor self-rated health, being aged under 55, low SES and smoking. Financial strain conferred a 3.8 increased risk of comorbid anxiety and depression in early convalescence and an almost 5-fold risk in later convalescence. Depression history conferred an almost 4-fold increased risk at both timepoints, while poor self-rated health carried around a 3-fold increased

TABLE 2 | Factors associated with *anxiety* in early and late convalescence.

	N	Proportion anxious (%)	Odds ratio Exp(B)	95% CIs	Chi-square	df	*p*
Early convalescence							
Overall	792	28					
Depression history	434	45	2.96	1.89–4.64	23.43	1	<0.001
Financial strain	486	56	2.77	1.39–5.50	9.02	1	0.003
Aged under 55	792	40	2.05	1.45–2.88	17.04	1	<0.001
Poor self-rated health	691	42	2.00	1.25–3.22	8.46	1	0.003
Low SES	522	36	1.68	1.09–2.60	5.53	1	0.019
Smoker	790	37	1.62	1.10–2.37	6.19	1	0.013
Obese	565	30	1.54	1.03–2.29	4.45	1	0.035
Unpartnered	778	32	1.35	0.98–1.87	3.30	1	0.069
Late convalescence							
Overall	723	27					
Financial strain	440	71	5.94	2.55–13.86	20.98	1	<0.001
Depression history	415	48	3.54	2.24–5.59	31.07	1	<0.001
Aged under 55	723	43	2.60	1.80–3.76	26.84	1	<0.001
Poor self-rated health	629	44	2.35	1.41–3.93	11.13	1	0.001
Smoker	721	40	2.00	1.34–3.00	11.75	1	0.001
Low SES	480	38	1.84	1.16–2.93	6.85	1	0.009
Obese	524	30	1.62	1.06–2.47	4.96	1	0.026

Anxious = HADS-A $\geq$ 8; Early convalescence = 2–4 months post-event; Late convalescence = 6–12 months post-event. CI, confidence intervals; SES, socioeconomic status. Statistical test, chi-square. Significance level set at $p < 0.1$. All predictors are presented in descending order in terms of odds ratios. For early convalescence associations with living alone, diabetes, sex, and event type were $p \geq 0.1$. For late convalescence associations with living alone, partner status, diabetes, sex and event type were $p \geq 0.1$.

TABLE 3 | Factors associated with *depression* in early and late convalescence.

	N	Proportion depressed (%)	Odds ratio Exp(B)	95% CIs	Chi-square	df	*p*
Early convalescence							
Overall	791	17					
Financial strain	485	42	3.93	1.93–8.00	16.09	1	<0.001
Poor self-rated health	690	35	3.37	2.03–5.59	23.96	1	<0.001
Depression history	434	26	2.57	1.51–4.37	12.64	1	<0.001
Low SES	522	26	2.21	1.34–3.65	10.07	1	0.002
Aged under 55	791	24	1.78	1.19–2.66	8.15	1	0.004
Smoker	789	24	1.75	1.13–2.71	6.43	1	0.011
Obese	564	19	1.57	0.97–2.55	3.39	1	0.066
Unpartnered	777	20	1.38	0.94–2.04	2.75	1	0.097
Late convalescence							
Overall	723	15					
Financial strain	440	39	4.91	2.17–11.09	17.25	1	<0.001
Depression history	415	26	3.42	1.95–6.03	19.64	1	<0.001
Poor self-rated health	629	29	2.81	1.58–5.00	13.20	1	<0.001
Aged under 55	723	24	2.30	1.48–3.57	14.23	1	<0.001
Low SES	480	24	2.11	1.22–3.66	7.39	1	0.007
Smoker	721	22	1.87	1.15–3.02	6.58	1	0.010
Unpartnered	711	20	1.71	1.10–2.68	6.26	1	0.012
Lives alone	720	20	1.65	1.04–2.61	4.66	1	0.031
Diabetes	718	19	1.50	0.95–2.38	3.03	1	0.082

Depressed = HADS-D $\geq$ 8; Early convalescence = 2–4 months post-event; Late convalescence = 6–12 months post-event; CI, confidence intervals; SES, socioeconomic status. Statistical test, chi-square. Significance level set at $p < 0.1$. All predictors are presented in descending order in terms of odds ratios. For early convalescence associations with living alone, diabetes, sex and event type were $p \geq 0.1$. For late convalescence associations with obesity, sex, and event type were $p \geq 0.1$.

risk. Being under 55 and smoking each carried an increased risk of around 2–2.5. Being unpartnered, living alone, being obese and having diabetes each contributed to the risk of comorbid anxiety and depression at some point during the convalescent period, although the strength of these factors was relatively less statistically significant. Neither sex nor event type were

TABLE 4 | Factors associated with *comorbid anxiety and depression* in early and late convalescence.

	N	Proportion comorbid A and D (%)	Odds ratio Exp(B)	95% CIs	Chi-square	df	*p*
Early convalescence							
Overall	792	13					
Financial strain	486	36	3.82	1.83–7.96	14.41	1	<0.001
Depression history	434	25	3.50	1.96–6.09	19.87	1	<0.001
Poor self-rated health	691	27	2.97	1.71–5.14	16.13	1	<0.001
Low SES	522	22	2.52	1.47–4.31	11.99	1	0.001
Aged under 55	792	21	2.20	1.43–3.40	13.18	1	<0.001
Smoker	790	20	1.95	1.21–3.13	7.83	1	0.005
Obese	565	14	1.72	0.99–2.99	3.76	1	0.052
Unpartnered	778	16	1.44	0.94–2.21	2.80	1	0.095
Late convalescence							
Overall	723	11					
Financial strain	440	36	4.90	2.12–11.30	16.39	1	<0.001
Depression history	415	23	3.71	2.01–6.83	19.42	1	<0.001
Poor self-rated health	629	23	2.95	1.57–5.52	12.31	1	<0.001
Aged under 55	723	20	2.52	1.55–4.08	14.69	1	<0.001
Low SES	480	21	2.46	1.37–4.44	9.40	1	0.002
Smoker	721	19	2.18	1.29–3.67	8.92	1	0.003
Unpartnered	711	15	1.76	1.10–2.83	5.67	1	0.017
Lives alone	720	16	1.68	1.01–2.80	4.10	1	0.043
Diabetes mellitus	718	15	1.48	0.90–2.47	2.28	1	0.088

Comorbid anxiety and depression = HADS-A $\geq$ 8 and HADS-D $\geq$ 8; Early convalescence = 2–4 months post-event; Late convalescence = 6–12 months post-event; CI, confidence intervals; SES, socioeconomic status. Statistical test, chi-square. Significance level set at $p < 0.1$. All predictors are presented in descending order in terms of odds ratios. For early convalescence associations with living alone, diabetes, sex, and event type were $p \geq 0.1$. For late convalescence associations with obesity, sex, and event type were $p \geq 0.1$.

predictive of comorbid anxiety and depression at either timepoint during convalescence.

Cumulative Impact of Predictors of Anxiety and Depression

Using decision tree analysis, the cumulative impact of multiple risk factors was demonstrated. The single most critical factor (initial node) determining presence of *either* anxiety or depression in late convalescence was age: 47% of patients under 55 were anxious or depressed, compared with only 26% of patients aged 55 or more. Amongst those aged under 55, the most important contributor to anxiety/depression risk was history of depression: 66% of those with a depression history were anxious or depressed in late convalescence, compared to only 39% with no depression history or an unknown history. The next most important contributor was partner status: amongst those aged under 55, with a depression history and no partner, 85% were anxious or depressed, compared to 53% of their partnered counterparts. Amongst those age 55 or more, again history of depression was the most important contributor to risk: 41% of those with a depression history were anxious or depressed in late convalescence, compared with only 19% of those without a history. The classification tree analysis accurately predicted patients' anxiety or depression status (71.5% correct). The cross-validation estimate for risk of misclassification (0.30) approximated that of the full model (0.28). Findings of the decision tree analysis are shown in **Figures 2**, **3**.

DISCUSSION

In this large sample of cardiac patients, the rates of anxiety were 28 and 27% in early and late convalescence, while the rates of depression were 17 and 15% respectively. Not surprisingly, these rates are substantially higher than seen in the Australian population where 12-month prevalence rates are 14% for anxiety disorders and 6% for depressive disorders (Australian Bureau of Statistics, 2008). These figures suggest that in the 12 months after an acute event, the prevalence rates increase 2-fold for anxiety and 2.5-fold for depression. Moreover, these rates of anxiety and depression are largely consistent with those seen after other traumatic events such as stroke (Broomfield et al., 2014) and cancer diagnosis (Linden et al., 2012).

Notably 13% of patients had *comorbid* anxiety and depression in early convalescence and 11% in late convalescence. This is significant as the overlap of anxiety and depression complicates both diagnosis and treatment (Coplan et al., 2015). Comorbid anxiety with depression predicts poorer outcomes than either disorder occurring alone, with a higher rate of treatment resistance (Coplan et al., 2015). The complexity of treatment underscores the importance of identifying patients at risk of mental health comorbidity in the year after a cardiac event.

At the time of the event, almost half the patients reported *either* anxiety or depression. However, symptoms resolved for many patients, with most resolution occurring during early convalescence from hospital discharge to the 2 to 4-month mark. This is consistent with other studies that have demonstrated a

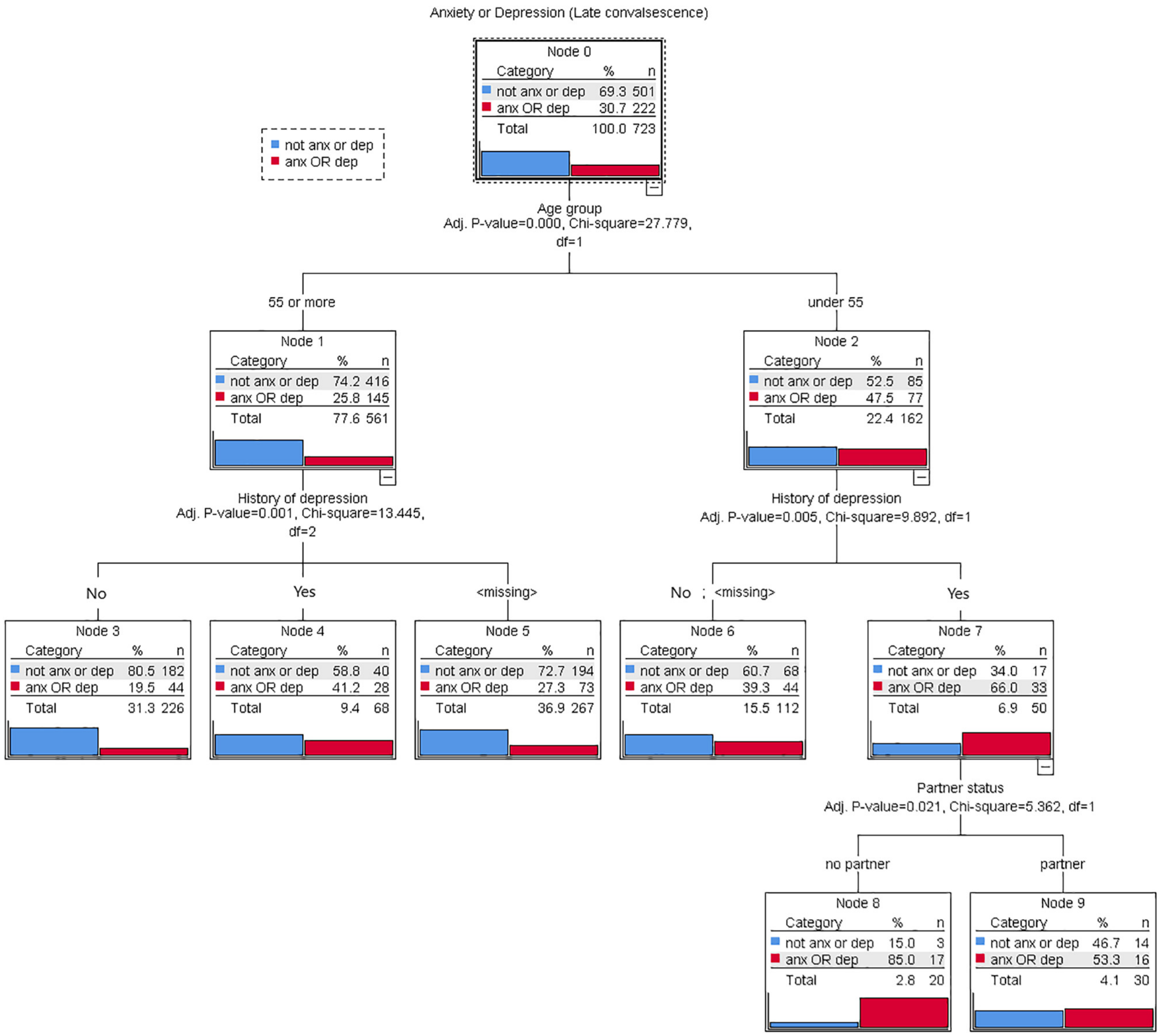

FIGURE 2 | Decision tree (using the CHAID algorithm) for predicting presence of anxiety or depression in late convalescence among 723 patients admitted to hospital for acute myocardial infarction (AMI), coronary artery bypass graft surgery (CABGS), acute coronary syndrome (ACS), percutaneous coronary syndrome (PCI), or angina. At each node the best predictor for anxiety or depression was selected from the six key potential predictors identified in bivariate analyses, and the optimal forecasting values were determined.

resolution of symptoms for many patients during the early post-event period (Murphy et al., 2008a, 2013, 2016). Nonetheless, almost a third of patients had symptoms at the 6 to 12-month mark.

The present study has successfully identified some key risk factors for anxiety and depression in early and late post-event convalescence. Factors consistently associated with increased risk included having been depressed prior to the event, experiencing financial strain, rating one's health poorly, being of low SES, being younger, and smoking. A patient's mental health history has previously been identified as a key risk factor for anxiety and depression (Martens et al., 2008), as have younger age (Cheok et al., 2003), low SES and financial difficulties (Cheok et al., 2003; Freeman et al., 2016), poorer health status (Cheok et al., 2003), and smoking (Perez et al., 2008; Tjora et al., 2014; Sever et al., 2019). One recent study identified financial strain as a predictor of recurrent cardiac events in CHD patients, highlighting its negative prognostic impact (Georgiades et al., 2009). Another linked financial hardship to job loss, also highlighting its negative impacts on both physical and mental health outcomes (Warraich et al., 2018).

Indeed, financial strain was identified as an important and strong predictor, and screening for it could easily be implemented in clinical practice. The present study used a simple 5-point scale

	Risk factor ticked as present	Risk of anxiety or depression in late convalescence
All patients		31%
If aged under 55	☐	47%
Plus history of depression	☐	66%
Plus unpartnered	☐	85%

FIGURE 3 | Cumulative risk of anxiety or depression for three key risk factors.

(from not at all to extreme financial strain) and demonstrated that those self-reporting as experiencing either considerable or extreme financial strain were at substantially increased risk of poor mental health outcomes post cardiac event. Indeed, screening for all the factors identified here would serve as a useful approach to identifying patients at risk. All the factors included in the present study could be easily assessed in hospital or at discharge.

There was also evidence of increased risk for socially isolated patients, indicated by significant associations between both living alone and being unpartnered with depression at late convalescence, as well as through the decision tree analysis. Again this is consistent with earlier research that has demonstrated that social isolation is associated with poor mental health including depression and suicide (Cheok et al., 2003; Iliffe et al., 2007; Manemann et al., 2018). Similarly, lack of marital support has been shown to significant predict adverse outcomes (Compare et al., 2013). Social isolation has also been shown to be an important contributor to hospital readmission in both heart disease (Murphy et al., 2008b) and heart failure patients (Saito et al., 2018). Moreover, the general health risk associated with social isolation is comparable to that associated with smoking (Iliffe et al., 2007). Notably, it is possible that the decision tree analysis was more effective in identifying partner status as a predictor than was the bivariate analyses, given its multivariate nature and ability to identify predictors of unique variance.

Obesity and diabetes were also identified as important albeit less significant risk factors. Again, both these factors have been identified previously as risk factors for depression in particular (Frasure-Smith et al., 2000). For people with diabetes, having a comorbid condition such as CHD can have a profound effect, complicating the treatment regime, undermining medication adherence and compromising diabetes self-care (Piette and Kerr, 2006). When comorbid illnesses need to be comanaged, vulnerability to mental health problems can increase. Likewise, the relationship between obesity and depression is well established (Luppino et al., 2010). Indeed, meta-analyses have confirmed a reciprocal relationship between the two conditions, whereby obesity increases the risk of depression and, conversely, depression is predictive of developing obesity (Luppino et al., 2010).

The results of the decision tree analysis highlight the cumulative effect of two or more risk factors in increasing risks of post-event anxiety and depression, demonstrating that having multiple risk factors can substantially elevate one's mental health risk. Being under 55 was identified as the single most important risk factor for *either* anxiety or depression in late convalescence, with history of depression and being unpartnered further contributing to the risk for these younger patients. Almost all (85%) patients with all three risk factors – aged under 55, having a depression history and being unpartnered – were either anxious or depressed in late convalescence. **Figure 3** shows how the factors could be combined and used as a simple screening tool in clinical practice.

It is notable that neither sex nor event type were predictive of anxiety or depression at any timepoint. Some studies have reported higher rates of post-event depression in women (Cheok et al., 2003), possibly due to higher rates of help-seeking and reporting amongst women compared to men. On the other hand, other studies report higher depression in men (Sever et al., 2019). Further, there is some evidence that AMI patients experience more anxiety and depression than CABGS patients in early convalescence (Westin et al., 1997), although there is no evidence that this difference is sustained (Westin et al., 1997; Moser et al., 2010). Importantly, the possibility of overlap between the diagnostic categories, the degree of which was not recorded in the present study, might in part explain the null findings for this variable.

Limitations

There are some study limitations that should be noted. First, there was substantial attrition of participants over time, from 911 at baseline to 723 (79%) by the late convalescent follow-up. This is typical of longitudinal studies of this type, particularly where mailed questionnaires are used. Efforts were made to contact patients and next of kin to optimize participation of survivors over the study period. Second, there was also considerable missing data for several independent variables, most notably history of depression, financial strain, SES, and obesity. Unfortunately, these data were not collected from all participants, with different baseline questionnaires being used at the different participating hospitals. Nonetheless, the sample for each of these variables is still relatively large and therefore the results can be regarded as valid. Moreover, the missing data was not due to skipped items or other systematic bias. Third, we did not record patients' treatment, if any, for anxiety or depression, including the use of anti-depressive or anti-anxiolytic medication, CBT or other treatments. We were therefore unable to control for these factors in the analysis. Similarly, we did not systematically collect data on patients' illness severity, although their self-reported health rating provides a good indication of this and, not surprisingly, strongly predicted both anxiety and depression. Finally, we did not collect information on patients' dietary habits or physical activity levels, both of which are important factors in mental health and wellbeing (Sever et al., 2019).

Two of the key predictors – patients' history of depression and financial strain – were established using subjective self-report measures rather than objective indicators. Whilst this could be considered a limitation, we believe that the identification of these subjective reports as predictors has important and positive clinical implications. For a clinician assessing a patient's risk of anxiety and/or depression in the 12 months after their cardiac event, it is useful to be able to ask the patient simple questions such as these, to identify these risk factors or "red flags" for future mental health problems. A cardiac nurse on the ward, or an allied health professional working in the cardiac rehabilitation setting, will not always have reliable clinical information regarding a previous diagnosis of depression available to them: this information is not systematically included in a medical record. By using a simple question such as "have you been depressed in the past, prior to your cardiac event?", a clinician is able to easily identify an important red flag to suggest that the patient may be at risk of mental health problems during recovery. Likewise, the use of a simple question to identify financial strain, as used in the present study, could be considered somewhat less intrusive than asking a patient to report their income or their objective financial demands.

Finally, we dichotomized patients' HADS scores rather than using continuous scale scores to measure anxiety and depression. While the latter could be considered a more statistically powerful approach, it was necessary to dichotomize patients' HADS scores in order to identify prevalence rates of anxiety and depression over the study period.

Implications

The present study has identified several risk factors for the development or persistence of anxiety and depression after a cardiac event. By identifying patients early, during hospitalization or at discharge, those at risk can be assisted, potentially mitigating or even preventing future mental health problems. This may in turn reduce the use of health services, therefore reducing costs (Pouwer and Nefs, 2019). Moreover, early identification and treatment has the potential to improve patients' overall wellbeing and quality of life.

DATA AVAILABILITY STATEMENT

The datasets generated for this study are available on request to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Melbourne Health Ethics Committee, Bendigo Health Ethics Committee, and the St John of God Ethics Committee. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

BM drafted the manuscript. ML, MA, MW, and AJ contributed to the final version. MW and BM designed the study and led the data collection. ML and BM undertook the data analyses. All authors contributed to the interpretation of results and approved the final version of the manuscript.

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Relationship Between Psychological Distress and Cognitive Function Differs as a Function of Obesity Status in Inpatient Heart Failure

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Heart failure (HF) is a chronic medical condition rapidly growing in prevalence. Evidence links HF to cognitive decline, obesity, and psychological distress. The current study examined the association between cognitive function and ejection fraction (EF%), anxiety, depression, and obesity in inpatient HF. Patients completed the Generalized Anxiety Disorder 7-Item Scale (GAD-7), Patient Health Questionnaire 9-Item Scale (PHQ-9), and Mini-Cog while hospitalized for HF. Additional demographic and medical information was gathered via chart review. All models controlled for age. Of 117 patients assessed (49% male), 55% (n = 64) were obese. ANCOVA analyses were conducted comparing those with obesity and without on cognitive function: model A included EF%, model B included depression, and model C included anxiety. All three models were significantly related to cognitive function. There was a significant interaction effect of EF% and obesity and of anxiety and obesity to predict Mini-Cog scores. *Post hoc* partial correlational analyses revealed that anxiety was negatively associated with Mini-Cog scores among only patients without obesity. Depression was not significantly related to cognitive function in either group. However, patients with obesity demonstrated higher depression and anxiety than patients without. Results suggest that at lower EF%, and with higher anxiety, patients without obesity may be at greater risk of cognitive dysfunction than those with obesity. Cognitive dysfunction among HF patients with obesity may be independent of psychological distress. These findings may reflect the "obesity paradox" observed among HF patients, in that patients with obesity may have a different biopsychosocial presentation, which may lead to unexpected clinical outcomes. Further research is necessary to articulate the relationship of obesity and cognitive function in HF.

Keywords: heart failure, obesity, cognition, depression, anxiety

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INTRODUCTION

Heart failure (HF) is rapidly growing in prevalence, affecting over 5 million U.S. adults, with several hundred thousand more diagnosed each year (Mozaffarian et al., 2016; Ziaeian and Fonarow, 2016). HF accounts for 5% of all hospitalizations, with up to a quarter of those patients readmitted within 30 days (Krumholz et al., 2009; Bergethon et al., 2016). These hospitalizations result in significant economic and public health burden (Ziaeian and Fonarow, 2016).

Given the chronicity of HF, it is critically important to identify risk factors for repeated hospitalizations.

Growing evidence links HF with a disease-specific (Leto and Feola, 2014), progressive decline in cognitive function (Van Den Hurk et al., 2011; Almeida et al., 2012; Hjelm et al., 2012), with nearly 3/4 of HF patients showing signs of possible cognitive impairment (Hoth et al., 2008). Increased severity of HF is associated with greater cognitive dysfunction (Hoth et al., 2008; Pressler et al., 2010), although there is some evidence to the contrary (Feola, 2013). Cognitive dysfunction has been associated with poor self-care (Leto and Feola, 2014) and low adherence to medication and treatment recommendations (Alosco et al., 2012b; Hawkins et al., 2012; Agarwal et al., 2016; Huynh et al., 2016; Dolansky et al., 2017), potentially contributing to increased HF morbidity, hospitalization, and death (Agarwal et al., 2016; Huynh et al., 2016). Given the established impact of cognitive dysfunction on medical outcomes in HF, it is of particular interest to examine factors that interact to predict cognitive dysfunction in this population to better understand variables that increase risk for frequent hospitalization.

Elevated body mass index (BMI, weight in kg/height in m^2) is independently related to reduced performance on measures of learning, memory, executive function, and global cognition in otherwise healthy individuals (Stanek et al., 2011; Dye et al., 2017). More than 40% of HF patients are obese (Kapoor and Heidenreich, 2010) and obesity may exacerbate cognitive deficits in the HF population (Alosco et al., 2012a, 2014c). However, the way in which elevated BMI interacts with HF severity to promote cognitive dysfunction is unclear.

In healthy individuals, anxiety and depression are also independently associated with poorer cognitive function (McDermott and Ebmeier, 2009; Rock et al., 2014; Snyder et al., 2015; Shields et al., 2016). Psychological distress is quite prevalent in HF, with depression affecting up to 60% of patients (Yohannes et al., 2010) and up to 55% of patients demonstrating elevated anxiety (Easton et al., 2016). Both depression and anxiety in HF are risk factors for reduced quality of life, poor self-care, and higher rates of hospitalization and mortality (Yohannes et al., 2010; Sherwood et al., 2011; Kato et al., 2012; Ketterer et al., 2014; Suzuki et al., 2014; Alhurani et al., 2015; Tovar et al., 2016). While a growing literature demonstrates a relationship between depression and cognitive dysfunction in cardiovascular disease in general (Armstrong et al., 2018), and HF in particular (Foster et al., 2011; Garcia et al., 2011; Alosco et al., 2014a; Hawkins et al., 2015a), it is unknown how anxiety impacts cognitive function in HF. A better understanding of mechanisms through which depression and anxiety may interact with HF severity to exacerbate cognitive dysfunction is an important step toward improving self-care and outcomes for this patient population.

It is essential to identify risk factors for poor self-care and repeated hospitalizations among HF patients. By investigating relationships among obesity, depression, anxiety, EF%, and cognitive function in HF, we can identify potential targets for cognitive and behavioral health treatment and contribute to improved quality of life for this population. While evidence suggests that obesity, psychological distress, and HF severity are independently related to cognitive dysfunction in HF, the current study aimed to address gaps in the literature by examining the interactive relationship between these variables. It was hypothesized that obesity and psychological distress would be related to reduced cognitive function, potentially interacting with HF severity.

MATERIALS AND METHODS

Participants

Assessment was completed as a part of a quality improvement project at Christiana Hospital in Newark, DE, United States. Participants were current inpatients who were identified as being at high risk for 30 day re-admission to the hospital using model-driven machine learning technology described in greater detail in the **Supplementary Material**. Upon identification, they were assessed for criteria that would limit their ability to attend outpatient appointments with the Advanced Heart Failure service at Christiana, and for medical comorbidities that would take precedent at that hospital visit, such as end-stage renal failure or severe lung disease. They were then referred for assessment by the Heart Failure Task Force multidisciplinary team. As part of this pilot program to incorporate cognitive and behavioral health screening into inpatient HF treatment, 117 patients were assessed as a part of routine clinical care. Of those patients, 49% were male, and the mean age was 72.6 years (SD = 11.46). Patients with obesity (BMI $\geq$ 30 kg/m^2) made up 55% (n = 64) of the sample. Patients had both preserved and reduced ejection fraction (EF%), a measure of the amount of blood pumped from the left ventricle with each heartbeat and one indicator of HF severity and risk (Cikes and Solomon, 2016). Analyses were conducted upon completion of 6 months of the quality improvement project.

These *post hoc* analyses were determined to be exempt from 45 CFR 46 Research Regulations by the Institutional Review Board of Christiana Care. A Waiver of HIPAA Authorization was granted, given the study involved no more than minimal risk to the privacy of individuals and as such consent was not required.

Inclusion Criteria

To be included in analyses, patients must (1) have had a current diagnosis of HF or cardiomyopathy as determined by inpatient cardiologists trained in advanced HF diagnosis and treatment, (2) be between the ages of 18 and 100 years old, (3) be proficient in written and spoken English, (4) be willing and able to write, and (5) have at least an 8th grade education.

Exclusion Criteria

Patients were excluded from analyses if they (1) had a diagnosis of neurological or seizure disorder, (2) met diagnosis of alcohol or drug dependence in the 3 months prior to assessment, (3) had a diagnosis of a severe major affective or anxiety disorder or presence of other psychopathology that might interfere with ability to participate in the study (e.g., requiring inpatient hospitalization), (4) were diagnosed with organic brain syndromes, dementia, psychotic disorders or severe intellectual disability, (5) demonstrated delirium or altered mental status on assessment days.

Measures

Mini-Cog (Borson et al., 2000)

The Mini-Cog consists of a three-item memory/recall test and a clock-drawing test to measure cognition. The Mini-Cog is scored on a 5-point scale, with lower scores indicating greater cognitive dysfunction. A cut point of <4 may indicate cognitive impairment and need for further evaluation of cognitive status. It is a reliable, valid measure for assessing clinically significant cognitive impairment (Borson et al., 2003, 2005; Patel et al., 2015), though Cronbach's alpha has been found to be low (0.278) (Costa et al., 2012), likely due to it comprising only two questions. The Mini-Cog has been used in prior studies of HF and has been shown to predict posthospitalization readmission risk (Patel et al., 2015; Agarwal et al., 2016).

Patient Health Questionnaire (PHQ-9; Kroenke et al., 2001)

Depressive symptoms were measured with this 9-item, self-report measure reflecting the diagnostic criteria for major depressive disorder. Patients were asked to rate how often each symptom has bothered them during the past 2 weeks on a rating scale from 0 (not at all) to 3 (nearly every day). Total scores range from 0 to 27, with higher scores indicating a greater severity of depression. It is a reliable, valid measure of depressive symptoms in patients with HF (Cronbach's $\alpha = 0.85$) (Hammash et al., 2013).

Generalized Anxiety Disorder 7-Item Scale (GAD-7; Spitzer et al., 2006)

Anxiety symptoms were measured with this 7-item self-report measure reflecting the diagnostic criteria for generalized anxiety disorder. Patients were asked to rate how often they have been bothered by the described symptoms over the last 2 weeks using a 4-point rating scale from 0 (not at all) to 3 (every day). Total scores range from 0 to 21, with higher scores reflecting higher severity levels of generalized anxiety disorder symptomology. It has good reliability (Cronbach's $\alpha = 0.89$), as well as criterion, construct, factorial, and procedural validity (Löwe et al., 2008).

Procedure

Assessors were masters- and doctoral-level members of the cardiovascular behavioral health (CVBH) clinical team trained in administering measures. CVBH assessors administered the Mini-Cog, PHQ-9, and GAD-7 with patients during their inpatient hospitalization in their hospital room. Following assessment, CVBH provided feedback, psychoeducation, and referrals if necessary to all patients. Assessments were completed within a week of admission to the Advanced HF service. Patients were typically discharged within 5 days following assessment. Further data regarding demographic and medical information, including BMI and EF%, was collected via chart review following initial evaluation. All patients were scheduled to attend outpatient appointments in the HF clinic following hospital discharge for continuity of care.

Statistical Analyses

All statistical analyses were performed using IBM SPSS Statistics for Windows, Version 24.0. In order to characterize the relationship of cognitive function with EF%, psychological distress, and obesity status, three ANCOVA analyses were conducted, adjusting for age and sex. Two *post hoc* partial correlational analyses were conducted within each group (those with and without obesity) to determine if the relationships between cognitive function and other variables differed based on obesity status. *Post hoc* power analysis using G*Power (Faul et al., 2007) determined the sample size of 118 was adequately powered ($1-\beta = 0.82$) with the achieved effect size of the corrected ANCOVA models ($f2 = 0.33$; $\alpha = 0.05$). Power analysis suggests the sample size is too small to adequately power an interaction effect, and as such these results should be interpreted with caution.

RESULTS

Descriptive Data (Table 1)

Male and female participants did not significantly differ on age, nor on cognitive function, depression, anxiety, or BMI with or without controlling for age. Men ($m = 35.26$, $SD = 15.77$) had a significantly lower EF% ($F = 6.05$, $p = 0.015$) than women ($m = 42.98$, $SD = 17.7$). Participant BMI ranged from 19.8–59.8 kg/m^2. Patients with obesity were significantly younger than those without (both with and without controlling for sex), and had significantly lower EF% when controlling for age and sex. Patients with obesity did not differ significantly on Mini-Cog scores but did report significantly greater depression ($p = 0.01$) and anxiety ($p = 0.019$) compared to those without, adjusting for age and sex.

Obesity and Ejection Fraction (Table 2A)

Controlling for age and sex, the model of obesity, EF%, and their interaction was significantly associated with Mini-Cog score ($F = 3.38$, $p = 0.017$, $\eta 2 = 0.12$). There was a significant interaction effect of EF% and obesity ($F = 4.06$, $p = 0.046$, $\eta 2 = 0.04$) such that lower EF% was related to worse performance in patients without obesity, but better performance in those with obesity. The main effect of obesity was related to Mini-Cog score at a trend level, while the main effect of EF% was non-significant.

Obesity and Depression (Table 2B)

Controlling for age and sex, the model of obesity, PHQ-9 score, and their interaction was significantly associated with Mini-Cog score ($F = 2.59$, $p = 0.03$, $\eta 2 = 0.12$). The interaction of depression and obesity was not significantly related to cognitive function

TABLE 1 | Descriptive data for the full sample.

	N	Mean	*SD*	Minimum	Maximum
Age (years)	117	72.6	11.5	38	94
BMI (kg/m^2)	117	32.8	8.7	19.8	59.8
EF (%)	114	39.5	17.2	10	75
Mini-Cog	116	3.1	1.5	0	5
PHQ9	116	6.4	4.6	0	21
GAD7	116	4.3	5.0	0	20

TABLE 2A | Relationship between obesity, ejection fraction (EF%) and cognitive function as measured by Mini-Cog score, controlling for age.

	df	Mean square	*F*	*p*	η2
Corrected Model	5	6.03	2.9	0.017	0.12
Intercept	1	74.9	35.8	<0.001	0.25
Age	1	17.8	8.5	0.004	0.07
Sex	1	1.5	0.7	0.398	0.01
Obesity	1	6.7	3.2	0.077	0.03
EF%	1	1.7	0.8	0.364	0.01
Obesity ∗ EF%	1	8.5	4.1	0.046	0.04

R Squared = 0.119 (Adjusted R Squared = 0.078)

TABLE 2B | Relationship between obesity, depression (as measured by the Patient Health Questionnaire, PHQ-9) and cognitive function (as measured by Mini-Cog score), controlling for age and ejection fraction (EF%).

	df	Mean square	*F*	*p*	η2
Corrected Model	6	4.8	2.3	0.044	0.11
Intercept	1	78.3	36.6	<0.001	0.26
Age	1	16.6	7.8	0.006	0.07
Sex	1	1.7	0.8	0.382	0.01
EF	1	1.0	0.5	0.495	0.00
Obesity	1	0.4	0.2	0.664	0.00
PHQ9	1	6.4	3.0	0.086	0.03
Obesity ∗ PHQ9	1	1.3	0.6	0.435	0.01

R Squared = 0.114 (Adjusted R Squared = 0.063)

(F = 0.28, p = 0.6). The main effect of depression was related to Mini-Cog score (F = 4.12, p = 0.045, η2 = 0.036), with higher depression linked to lower cognitive function, while the main effect of obesity was non-significant. Adding EF% as a covariate did not substantially change the strength of the model (F = 2.25, p = 0.044, η2 = 0.11).

Obesity and Anxiety (Table 2C)

Controlling for age and sex, the model of obesity, GAD-7 score, and their interaction was significantly associated with Mini-Cog score (F = 3.41, p = 0.007, η2 = 0.14). The interaction of obesity with anxiety was significantly linked to Mini-Cog score (F = 4.03, p = 0.047, η2 = 0.036). The main effect of anxiety was related to Mini-Cog score (F = 7.49, p = 0.007, η2 = 0.064), with higher anxiety linked to lower cognitive function, while the main effect of obesity was non-significant. Adding EF% as a covariate did not substantially change the strength of the model (F = 3.15, p = 0.007, η2 = 0.15).

Correlations

Among patients with obesity, EF%, depression, and anxiety were not significantly related to cognitive function when controlling for sex and age. However, GAD-7 scores were negatively associated with Mini-Cog scores (r = −0.33, p = 0.018) among patients without obesity (**Figure 1**). Depression and EF% were not significantly related to cognitive function in patients without obesity. Notably, among those with obesity, anxiety was significantly correlated with EF% when controlling for sex and age (r = 0.31, p = 0.021). This effect was not evident in patients without obesity. Anxiety and depression were correlated significantly among both groups ($p < 0.001$).

TABLE 2C | Relationship between obesity, anxiety (as measured by the Generalized Anxiety Disorder 7-item scale, GAD-7)and cognitive function (as measured by Mini-Cog score), controlling for age and ejection fraction (EF%).

	df	Mean square	F	p	η2
Corrected Model	6	6.3	3.1	0.007	0.15
Intercept	1	78.4	39.0	<0.001	0.27
Age	1	17.3	8.6	0.004	0.08
Sex	1	1.5	0.7	0.397	0.01
EF	1	1.8	0.9	0.348	0.01
Obesity	1	1.2	0.6	0.437	0.01
GAD7	1	15.4	7.6	0.007	0.07
Obesity ∗ GAD7	1	7.4	3.7	0.057	0.03

R Squared = 0.152 (Adjusted R Squared = 0.104)

DISCUSSION

We aimed to determine if interactive relationships between obesity, psychological distress, and HF severity would contribute to cognitive function, given the importance of these variables for quality of life for this population. Obesity status appears to interact with HF severity, depression, and anxiety to predict cognitive dysfunction, particularly among patients without obesity. In contrast, cognitive function in those with obesity may not vary to the same extent as a function of HF severity or psychological distress. Patients without obesity demonstrate an association between cognitive function and both EF% and anxiety, such that lower EF% and higher anxiety in this population may confer greater risk of cognitive dysfunction. These relationships are not evident in patients with obesity. However, HF patients with obesity do report higher levels of depression and anxiety than those without, and anxiety was higher among those with higher EF%. These results suggest that obesity status is linked with differing profiles of psychological distress and cognitive function, emphasizing the utility of behavioral health intervention with the inpatient HF population.

Greater psychological distress among patients with obesity is consistent with prior studies showing that BMI in general, and obesity in particular, are related to elevated rates of depression in HF (Hawkins et al., 2015b). Depressive symptoms appear to interact with obesity to impact quality of life in HF patients (Evangelista and Miller, 2006) and in cardiovascular disease more broadly (Oreopoulos et al., 2010). There is less consistent research demonstrating a relationship between anxiety and obesity in cardiovascular disease (Labad et al., 2010), but among non-clinical samples there is moderate evidence of a link between anxiety and obesity (Gariepy et al., 2010). Obesity may be associated with psychological distress in a number of ways. Weight-based discrimination and stigma can contribute to depression and anxiety (Papadopoulos and Brennan, 2015) through reduced quality of life and the awareness of others' judgment and biases, and this distress can be compounded when

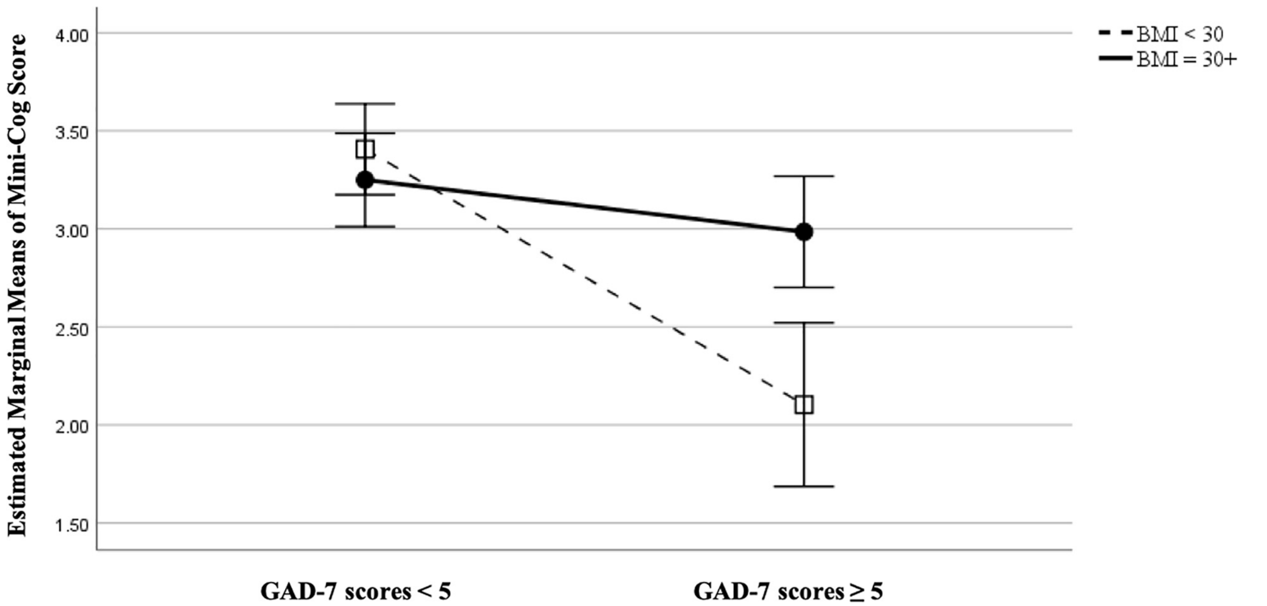

FIGURE 1 | Comparing patients with obesity (BMI ≥ 30 m/kg^2) versus those without (BMI < 30 m/kg^2) on relationship between anxiety (as measured by the Generalized Anxiety Disorder 7-item scale, GAD-7) and cognitive function (as measured by Mini-Cog score), controlling for age at 72.6 years, EF at 39.3%, and sex.

experiencing chronic medical conditions. Reduced social and physical activity in obesity has been linked to higher depression and anxiety in non-clinical samples (De Wit et al., 2010), as well as in those at risk for cardiovascular disease (Bonnet et al., 2005). Furthermore, individuals with obesity demonstrate elevated HF symptoms (Clark et al., 2014), which can promote distress, and compound the physical and mobility limitations that may accompany more severe obesity.

We had predicted that obesity would predict cognitive dysfunction given prior research showing an inverse association between BMI and cognition (i.e., worsening performance at higher weights). Our results do not demonstrate this relationship. There are several possibilities that may explain this discrepancy. Alosco et al. (2012a) demonstrated a relationship between BMI and cognitive function in a more comprehensive battery of neuropsychological tests, which may have allowed for greater sensitivity than the brief Mini-Cog (Borson et al., 2000) screen. Further, we assessed patients during hospitalization, which may introduce additional variables that could influence cognitive function such as sleep (Blackwell et al., 2006), medication changes, or the mere fact that the patient's illness is particularly exacerbated (Kindermann et al., 2012). Decompensation may have a greater impact on cognition than obesity itself, but may interact with depression and anxiety.

Patients without obesity demonstrate an association of cognitive dysfunction with higher anxiety. While anxiety has been shown to interfere with cognitive function in healthy individuals (Snyder et al., 2015; Shields et al., 2016), it is also true that cognitive dysfunction is significantly anxiety-provoking, with elevated rates of anxiety reported in treatment-seeking patients with mild cognitive impairment (Chen et al., 2018). While anxiety does not appear to predict progression to dementia (Gulpers et al., 2016), the relationship of anxiety to morbidity and mortality is somewhat unclear (Celano et al., 2018). Anxiety symptoms do not appear to be related to mortality in the HF population (Pelle et al., 2010), but in other cardiovascular populations it is associated with adverse medical outcomes (Roest et al., 2010, 2012; Celano et al., 2015). Anxiety may also independently increase risk of incident HF in patients free of cardiovascular disease (Garfield et al., 2014). Notably, this relationship was not evident in those with obesity. Given the finding that higher EF% is related to higher anxiety in these patients, and research suggesting that HF patients with obesity tend to be younger (including in this sample) (Lavie et al., 2016), hospitalization among those with better left ventricle function may be more unexpected and thus more anxiety provoking. Alternatively, patients with obesity who have a diagnosis of HF with preserved ejection fraction (HFpEF) may be more at risk for anxiety than their lean counterparts or those with reduced EF% diagnoses. More research is necessary to elucidate the relationship between EF%, anxiety, and obesity in the HF population.

The interactive relationship between psychological distress and cognitive function is also in line with findings in the biological literature. There are a number of pathways through which this association may develop (Sohani and Samaan, 2012). HF is a cardiac condition in which the heart functions below metabolic requirements (Brunwald, 2005) and as such, reductions in cognitive function may potentially be attributable to cerebral hypoperfusion and ischemia (Alosco et al., 2012a, 2013, 2015b). Both depressive symptoms and anxiety have been shown to interact with cerebral hypoperfusion to predict cognitive dysfunction in HF as well (Alosco et al., 2013, 2015a, 2014b). It is possible that HF- induced reductions in blood flow to the brain may potentiate psychological distress and cognitive dysfunction, which may in kind worsen neurobiological function. However, obesity is also linked with reduced cerebral blood flow and vascular abnormalities (Volkow et al., 2009; Willeumier et al., 2011), and while our findings do suggest elevations in depression and anxiety, these variables do not appear to predict cognitive function in patients with obesity.

Other brain-based changes in HF may play a role in this unexpected result. HF, cognitive impairment, and depression are all associated with elevated levels of proinflammatory cytokines (Pasic et al., 2003). Elevated cytokines are related to decreased levels of serotonin, which may result in depression and cognitive dysfunction (Sohani and Samaan, 2012). While it appears anxiety is related to an elevated inflammatory response in healthy individuals, there is less evidence of cytokines playing a role (Costello et al., 2019). However, higher anxiety is associated with inflammatory markers in patients with diabetes (Brennan et al., 2009), and inflammation during acute coronary syndrome has been shown to predict anxiety and cognitive symptoms of depression (Steptoe et al., 2013). Pasic et al. (2003) have argued that the increased mortality seen with depression in HF is potentially due to elevations in inflammatory markers, causing left-ventricular dysfunction. While obesity has also been shown to be associated with elevations in inflammatory biomarkers (Choi et al., 2013), patients with obesity also demonstrate higher levels of antiinflammatory adipokines, which may be protective of poor clinical outcomes (Clark et al., 2014). Elevations in adipokines are linked to depression and anxiety (Brennan et al., 2009; Bove et al., 2013; Carvalho et al., 2014), but also to higher performance on cognitive assessments (Diano et al., 2006; Lee, 2011), though there is some conflicting research (Spitznagel et al., 2010). This raises the possibility that inflammation due to obesity may contribute to psychological disturbance, but be protective of the effects of that disturbance on cognitive performance. Unfortunately we are unable to test this hypothesis with the current sample, but future research would be vital to identify the neurobiological mediators of the relationship between obesity, psychological distress, and cognitive function.

Our findings demonstrate a link between anxiety and cognition in patients without obesity, but this relationship was not evident in patients with obesity. Distress and cognitive function may be somewhat independent of each other in this obese HF sample. Previous research suggests that patients with obesity may demonstrate different clinical outcomes as compared to their counterparts without obesity. Research suggests that HF patients with obesity have lower rates of hospitalization and mortality than do those with normal or low weights (e.g., Sharma et al., 2015), typically described as the "obesity paradox" (Clark et al., 2014; Lavie et al., 2016), though this may be in contention (Eckel et al., 2018; Khan et al., 2018). There are a number of neural, biological, and behavioral reasons why patients with obesity do not show expected clinical outcomes. Patients with obesity tend to be younger and demonstrate symptoms earlier (Clark et al., 2014; Lavie et al., 2016); it is possible that anxiety in these patients is attributable to factors outside of cognitive function, such as symptom severity.

Limitations

There are several limitations that should be addressed. While the assessed sample size was sufficiently powered for our statistical models, it was too small to adequately power interaction effects and as such these results should be interpreted with caution. Our sample was at high risk for readmission, and as such we do not know whether these results would generalize to the wider HF population. Unfortunately, due to limits on patient record access or inconsistent charting procedures, we were unable to assess variables such as socioeconomic status, antidepressant use, natriuretic peptide levels, or functional class, that may have impacted the relationships described herein. We do not know the cognitive function of these patients prior to hospitalization, and thus cannot control for this variable. In addition, the timing of assessment during the course of patient's hospitalization was not controlled, thus patients had variable lengths of stay prior to and following assessment administration that we were not able to control for. Despite limited control of variables when assessing patients while hospitalized, gathering information during hospitalization is critical, as factors that lead to readmission may not otherwise become apparent until the incidence of that readmission, and it may offer an opportunity to intervene clinically before the patient is discharged. Lastly, we did not have access to a control sample of patients without HF, or with a different form of cardiovascular disease. Future research would benefit from between-group comparisons to determine if these relationships are unique to HF, or if this phenomenon is transdiagnostic.

CONCLUSION AND CLINICAL IMPLICATIONS

Cognitive dysfunction and psychological distress have been shown to be closely related in the general population, with a growing literature demonstrating this in HF (Foster et al., 2011; Garcia et al., 2011; Alosco et al., 2014a; Hawkins et al., 2015a). Interestingly, treatment of depression may support cognitive function. Antidepressants may help to slightly improve cognitive function (Gallassi et al., 2006), and behavioral activation has been shown to not only improve depressive symptoms, but also help prevent cognitive and functional decline in a community sample (Rovner et al., 2018). Additional inquiry is necessary to determine if treatments for depression can improve cognition in HF, or if treatment outcomes differ by obesity status. Unfortunately, it less well-known how anxiety impacts cognitive function in HF, and whether treatments for anxiety similarly would help to improve cognitive function. This study is the first we are aware of linking anxiety to cognitive function in HF, particularly in patients without obesity. Research suggests that cognitive function can improve in the HF population (Stanek et al., 2009, 2011; Alosco et al., 2014a), and that self-care can improve despite cognitive dysfunction (Cameron et al., 2017). Given the relationship with morbidity, hospitalization, and mortality in HF (Yohannes et al., 2010; Sherwood et al., 2011; Kato et al., 2012; Ketterer et al., 2014; Agarwal et al., 2016; Huynh et al., 2016; Tovar et al., 2016), cognitive assessment in HF is of critical importance, particularly in those patients at high risk for readmission. This research highlights cognitive dysfunction, depression, and anxiety as critical targets in HF treatment, and further emphasizes the need to identify populations at elevated risk.

DATA AVAILABILITY STATEMENT

The datasets generated for this study are available on request to the corresponding author.

ETHICS STATEMENT

This study was determined to be exempt from 45 CFR 46 Research Regulations by the Institutional Review Board of Christiana Care. A Waiver of HIPAA Authorization was granted, given the study involved no more than minimal risk to the privacy of individuals and as such written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

AE, CA, MB, and EW conducted assessments with patients. AE conceived of the research question and analyzed the data. DB assisted with chart review and analysis. AE, CA, DB, and EW were involved in writing the manuscript and had final approval of the submitted and published versions.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyg.2020.00162/full#supplementary-material

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Exploratory Analyses of Cerebral Gray Matter Volumes After Out-of-Hospital Cardiac Arrest in Good Outcome Survivors

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Background: Survival rates of cardiac arrest have increased over recent years, however, survivors may still be left with significant morbidity and functional impairment. A primary concern in cardiac arrest survivors is the effect of prolonged hypoxia/ischemia on the brain. The objectives of the present study were threefold: (1) to explore the effect of cardiac arrest on brain gray matter volumes (GMV) in "good outcome" survivors of out-of-hospital cardiac arrest (OHCA), (2) to examine the relationship between GMV, cognitive functioning and arrest factors, and (3) to explore whether OHCA patients differ from a group of patients with myocardial infarction (MI) uncomplicated by cardiac arrest and a group of healthy controls in terms of GMV.

Methods: Medically stable OHCA survivors with preserved neurological function and who were eligible for magnetic resonance imaging scanning (MRI; $n = 9$), were compared to: (1) patients who had experienced a MI ($n = 19$) and (2) healthy controls ($n = 12$). Participants underwent brain MRI on a 3T Siemens Trio MRI scanner and GMV was measured by voxel-based morphometry. A comprehensive neuropsychological assessment was also conducted. Global GMV was compared in the three samples using analyses of variance. The relationships between cognition and GMV were examined within group using correlations.

Results: The OHCA and MI groups showed a similar pattern of differences compared to the healthy control group. Both groups had decreased GMV in the anterior cingulate cortex, bilateral hippocampus, right dorsolateral prefrontal cortex, right putamen, and bilateral cerebellum. There were no significant differences in global or regional GMV between the OHCA and MI groups. Cognitive functioning was correlated with global GMV in the OHCA group; no such correlation was observed in the MI group.

Conclusion: Regional atrophy was observed in OHCA and MI survivors, compared to a healthy control group, suggesting a common mechanism, presumably preexisting cardiovascular disease. Although similar regional volume differences were observed between the MI and OHCA groups, the relationship between GMV and cognition was only observed in OHCA survivors. We suggest the acute hypoxia/ischemia ensuing from the arrest may interact with diminished neural reserve in select brain areas to expose occult cognitive dysfunction.

Keywords: out-of-hospital cardiac arrest, gray matter volume, cognition, myocardial infarction, magnetic resonance imaging

INTRODUCTION

Survival rates from cardiac arrest are improving (Benjamin et al., 2017) but survivors, even those who have made a seemingly good neurological recovery, are at risk for cognitive impairments that can negatively impact quality of life (Green et al., 2015). During a cardiac arrest, the heart stops beating and blood flow throughout the body and brain ceases until it is restored by either cardiopulmonary resuscitation (CPR) or defibrillation. Without adequate blood flow, the cells of the body and brain are deprived of oxygen and nutrients, and neurons are among the most sensitive cells to this hypoxic/ischemic state. Neuronal death can occur within minutes of a cardiac arrest (Busl and Greer, 2010), and even after successful resuscitation, reintroduction of oxygen to the abnormal biochemical cascades initiated by an arrest can result in reperfusion injuries (Weisfeldt and Becker, 2002). Those most at risk are individuals who experience an out-of-hospital cardiac arrest (OHCA) compared to those who arrest in hospital, as OHCA patients often do not receive immediate medical attention, putting them at particular risk for brain injury or death (Benjamin et al., 2017).

Magnetic resonance imaging (MRI) is often utilized to predict survival in comatose OHCA survivors given its high spatial resolution and ability to detect brain injury *in vivo* (Rossetti et al., 2016; Keijzer et al., 2018). According to the selective vulnerability hypothesis, not all neurons are uniformly affected by hypoxia. Regions of the brain with higher metabolic demands and rich in glutamate receptors are at the greatest risk for brain injury (Busl and Greer, 2010; Björklund et al., 2014). These more vulnerable regions include CA1 cells in the hippocampus, cortical gray matter, and deep gray matter, such as the thalamus and striatum (Busl and Greer, 2010; Gutierrez et al., 2010). Although no definitive prognosticators have been identified, signal abnormalities reflecting cytotoxic edema in regions like the occipital and medial-temporal cortices and the putamen (Wijdicks et al., 2006; Rossetti et al., 2016; Keijzer et al., 2018) are common among those who do not make good neurological recovery. Not only do certain neurons have higher metabolic requirements, some neurons may be at preferential risk due to their location relative to cerebral vascular supply (Torvik, 1984). Cortical and subcortical regions distal to major cerebral arteries are known to be affected in stroke, and also are at increased risk for cell death due to hypoperfusion (Caine and Watson, 2000).

As the majority of neuroimaging research on cardiac arrest survivors to date has focused on prognostication of survival in comatose individuals (Booth et al., 2004; Madl and Holzer, 2004), whether there are similar changes among "good outcome" survivors is still relatively unknown. This is understandable, given that approximately 80% of individuals resuscitated from cardiac arrest do not regain consciousness immediately (Booth et al., 2004). Cognitive deficits, however, are present in 34–50% of cardiac arrest survivors (Moulaert et al., 2009; Green et al., 2015), including those with "good neurological outcome" (Raina et al., 2008; Cronberg et al., 2009; Torgersen et al., 2010; Byron-Alhassan et al., unpublished). Memory dysfunction is the most common area of deficit (Green et al., 2015), though deficits in attention and executive functions are also observed (Harve et al., 2007; Hofgren et al., 2008; Lim et al., 2014; Ørbo et al., 2014). The neurophysiological correlates of these cognitive deficits may be understood using the selective-vulnerability hypothesis. For example, memory dysfunction has been found to correlate with hippocampal reductions in this population (Stamenova et al., 2018; Ørbo et al., 2019). However, a general pattern of widespread volumetric reduction across cortical (Horstmann et al., 2010; Ørbo et al., 2019) and subcortical structures (Horstmann et al., 2010) are commonly observed. As such, a more generalized impact of hypoxic injury across the brain may be the cause of cognitive sequelae, highlighting the importance of examining both regional and whole-brain reductions.

A better understanding of the underlying neuropathological mechanisms may allow better prognostication of which survivors are at greatest risk for persistent cognitive deficit, but few studies have examined neurophysiological sequelae in those who have survived and appear to be doing well neurologically. For example, to our knowledge, only one known study has examined the relationships between cortical thickness, cognitive dysfunction, and two key clinical variables, the duration between arrest and spontaneous circulation (i.e., downtime) and duration of coma after arrest (Ørbo et al., 2019). They found only duration of coma was correlated with cognitive function; subcortical gray matter (GM) regions that, according to the selective vulnerability hypothesis, may also be susceptible to hypoxia were not explored (Busl and Greer, 2010).

Most studies of cognitive dysfunction after cardiac arrest have focused on hypoxic/ischemic mechanism, while the contribution of cardiovascular disease to cognitive dysfunction has been relatively overlooked in OHCA survivors (Cronberg and Lilja, 2015). Cardiovascular disease, a risk factor for cardiac arrest, is well known to be associated with cognitive function (Irani et al., 2009; Jefferson et al., 2011; Cronberg and Lilja, 2015), however, few studies have included a cardiovascular control group when examining the neurophysiological and cognitive outcomes in cardiac arrest survivors (Grubb et al., 2000; Stamenova et al., 2018). In the largest known study of cognitive outcomes after cardiac arrest (Lilja et al., 2015), decreased memory performance was observed not only in the cardiac arrest group but also in the myocardial infarction (MI) group that had not experienced an arrest.

Very few MRI studies have focused specifically on OHCA survivors with relatively good neurological outcome (Grubb et al., 2000; Horstmann et al., 2010; Ørbo et al., 2018, 2019; Stamenova et al., 2018) even though these individuals are known to experience cognitive deficits. To date, research has understandably focused on survivorship, but with novel medical interventions leading to increased survival rates (Chan et al., 2014), a gap has appeared in our understanding of the residual impacts on the brain caused by cardiac arrest. The MRI studies that exist in this area have been limited in scope, perhaps because of the inherent logistic difficulty of sampling patients during such a vulnerable period as following an arrest. Some studies, for example, have included patients who have experienced an arrest due to non-cardiac causes such as electrocution (Horstmann et al., 2010). Others have not included a cardiac control group (Ørbo et al., 2018), or have focused solely on memory functioning when evidence suggests that other cognitive domains are likely to be implicated (Ørbo et al., 2018). To our knowledge, no studies have evaluated individual arrest characteristics in relation to cortical and subcortical brain volumes.

The primary objectives of the present study were: (1) to explore the effect of cardiac arrest on brain gray matter volumes (GMV) in survivors within 3 months of the OHCA; (2) to compare the GMV of OHCA patients to both a group of patients who had experienced an MI uncomplicated by cardiac arrest, and a group of healthy controls; (3) to examine the relationship between GMV and cognitive functioning as measured by a neuropsychological assessment among patients in the OHCA and MI groups; and, (4) to examine the relationships between GMV, cognitive functioning, downtime and duration of coma among OHCA survivors.

MATERIALS AND METHODS

Participants

Participants in the OHCA group were drawn from a larger study of cognitive function in patients with relatively preserved neurological function (Byron-Alhassan et al., unpublished). Participants had to score 1 or 2 on the Cerebral Performance Categories (CPC; Jennett and Bond, 1975), indicating normal, mild or moderate impairments in cerebral functioning but independence in activities of daily living. In an effort to distinguish cognitive dysfunction caused by cardiac arrest from any pre-existing cognitive disturbance related to underlying cardiovascular or cerebrovascular disease, patients who had been hospitalized for MI without cardiac arrest were enrolled to serve as a control group. MI participants were recruited either while in hospital post-MI or at an outpatient follow-up appointment. Healthy control (HC) participants were recruited by word of mouth at the hospital and university, or nomination by patients or study team members.

Exclusion criteria for all groups included pre-existing conditions that could influence performance on neuropsychological testing such as current substance abuse disorder, history of traumatic brain injury with loss of consciousness $>$30 min, and serious pre-existing neurological or psychiatric illnesses (e.g., stroke or schizophrenia). Participants were also excluded if they were non-MRI compatible (e.g., had an implanted cardioverter defibrillator), claustrophobic, or if they had any physical or mental health problems that precluded them from lying in relative stillness for the duration of the scans. Participants were also excluded if they were not fluent in English or younger than 18 years of age. Participants received a $25 gift card for participating in the study. This study was approved by the Ottawa Health Science Network Research Ethics Board. Informed, written consent was obtained from all participants.

Procedures

Participants were either scanned while still in hospital or shortly after hospital discharge by a medical radiation technologist. A clinical neuroradiologist (SC) reviewed all MRI scans for any clinically significant abnormalities. Any patients with acute or gross structural abnormalities (i.e., infarcts, tumors) that would influence group-level comparisons were excluded from final analyses.

Measures

Demographic Information and Arrest Factors

Participants reported their age, sex, ethnicity, education level, employment status, and smoking history in an interview with research personnel. Where possible, this information was verified by chart review. Downtime and length of coma (i.e., time in days from arrest to successful extubation, when coma persisted after initial return-of-spontaneous circulation) were obtained from patient's medical charts and emergency medical services records.

Cognitive Assessment

Cognitive functioning was measured using the Neuropsychological Assessment Battery (NAB), a paper-pencil neuropsychological assessment. comprised of five modules measuring memory, attention, language, spatial, and executive functions, respectively. A score is generated for each module and these are summed to obtain the global NAB index, a global measure of cognitive performance (Stern and White, 2003). The global NAB index reflects individual performance compared to the standardization sample in standard scores (e.g., mean value = 100, standard deviation = 15), where higher values equate to better performance. The NAB provides normative data stratified by age, education, and sex from a large standardization sample comprised of neurologically healthy individuals. Given the extensive normative data that exists for this battery, cognitive functioning was not assessed in the HC group. Psychometric properties of the NAB, including reliability and validity, have been well established and it has been shown to be sensitive to cognitive impairment in a variety of clinical populations (Stern and White, 2003).

Magnetic Resonance Imaging

Imaging data were collected on a 3.0 Tesla Siemens TRIO MR scanner. Participants lay flat on an automated bed fitted with a 32-channel head coil. They were in two-way communication at all times with the medical radiation technologist performing the scanning. A 3D FLASH (TR/TE 11.2/21 ms, flip angle 60°, field of view (FOV) 26 × 26 cm^2, 256 × 256 matrix, slice thickness 1.5 mm) anatomic image was acquired for structural analyses.

Data Analyses

Sample Characteristics

Patient demographics (i.e., age, sex, and medical comorbidities), cognitive performance (i.e., mean NAB scores), and time since event (i.e., time to cognitive testing and time to scanning) were compared between groups using analysis of variance (ANOVA) and t-tests for continuous variables, and chi-squared tests for categorical variables.

Voxel-Based Morphometry

Structural images were analyzed using the SPM12 toolbox with the DARTEL algorithm[1]. Before analyses, all images were reoriented to be aligned with the AC-PC line. We followed the step-by-step processing sequence suggested by the DARTEL toolbox for the voxel-based morphometry (VBM) analysis: (1) The MR images were first field bias-corrected to correct non-uniform fields. (2) Next, using the tissue probability maps based on the International Consortium of Brain Mapping (ICBM), the images were segmented to GM, white matter (WM), and cerebrospinal fluid (CSF). (3) The average study-specific GM and WM templates were subsequently computed and created. (4) After an initial affine registration of the GM DARTEL templates to the tissue probability maps in Montreal Neurological Institute (MNI), non-linear warping of individual GM images was performed to the DARTEL GM template and an individual flow field for each participant was created. (5) The individual GM images were normalized into the MNI space with a 1.5 mm × 1.5 mm × 1.5 mm voxel size with the normalized images modulated to ensure the relative volumes of GM were preserved following the spatial normalization procedure. (6) The modulated, normalized GM images were then smoothed with an 8 mm FWHM Gaussian kernel. (7) Finally, the tissue volumes utility of SPM12 was used to extract the average global (whole-brain) value of GM (GMV) for each participant based on the segmentation files, which was applied in the further analyses.

Group-Level Analyses

GMV Between-Group Differences

The smoothed, normalized individual GM images were applied in the second-level group analyses using SPM12. The voxel-wise ANOVA analyses and *post hoc* two-sample *t*-tests were conducted to examine the GMV differences among three groups (i.e., HC vs. OHCA, HC vs. MI, OHCA vs. MI). Individual age and global GMV were included in the SPM group-level GLM model and controlled for as covariates of no interests in all imaging analyses. The global GMV was included as a nuisance variable to control the effect of individual differences in the global GMV. Reported regions were derived at the threshold of uncorrected $p < 0.001$, cluster size >30 voxels at the whole-brain level. Multiple comparison corrections were then applied to all regions at the cluster level to verify the results. Both family-wise-error (FWE) and small volume corrections (SVC) were performed (Poldrack et al., 2008). For SVC correction, anatomical independent regions of interests (ROIs) were defined as masks using the WFU pickatlas AAL template[2], then the SVC function in SPM for the correction was applied. All regions were reported regardless of the significance after multiple comparison corrections.

Correlation Between GMV and Cognitive Functioning

Next, ROI analyses were performed to explore the relationship between cognitive functioning and the regional GMV, as well as the global GMV. Regional GMV that differed significantly for the patient groups compared with the HC group were extracted using marsbar[3] based on the voxel-wise analyses results. Partial correlation analyses were then conducted between the cognitive performance scores and the regional GMV with global GMV and age as covariates of no interests. Also, the partial correlation analysis was performed between the cognitive functioning and global GMV, with age as a covariate of no interest using IBM SPSS 25.0.

Cardiac Arrest Clinical Variables and GMV Regression Analyses

To further explore the relationship between downtime and duration of coma with GMV among the OHCA sample, whole-brain spatial regression analysis was conducted in SPM12. Clinical values (i.e., downtime, days of coma) were entered in the model as covariates to examine which regional GMVs were correlated with clinical values. Threshold applied was uncorrected $p < 0.005$, cluster size >30 voxels at the whole-brain level.

RESULTS

Sample Characteristics

A description of the sample and clinical variables can be found in **Table 1**. Participants across the three groups ranged in age from 30 to 84 years (M_{age} = 59.65, SD_{age} = 11.61). There were no group differences in age [$F(2,37) = 1.699$, $p = 0.197$] or sex [$n_{female\_OHCA} = 2$, $n_{female\_MI} = 2$, $n_{female\_HC} = 3$, χ^2 (2, $N = 40$) = 1.502, $p = 0.560$]. Patients in the MI group generally had higher rates of cardiovascular risk factors (e.g., diabetes, dyslipidemia, and hypertension) however differences were not statistically significant (see **Table 1**). Participants in the OHCA group completed cognitive assessment and MRI scanning closer to the date of their cardiac event than the MI group. However, time to test and time to scan were not significant covariates in the between-group analyses of cognitive functioning [$F(1,24) = 3.972$, $p = 0.058$], or global GMV [$F(1,24) = 0.064$, $p = 0.802$], suggesting that they did not contribute to group differences in cognitive functioning or global GMV.

Cerebral GMV

Group mean values for global GMV, did not differ significantly between the three groups. Although this study focused on

[1] https://www.fil.ion.ucl.ac.uk/spm/

[2] https://www.nitrc.org/projects/wfu_pickatlas/

[3] http://marsbar.sourceforge.net/

TABLE 1 | Demographics, cognitive performance, and clinical variables.

	OHCA	MI	HC	*p*-Value
N	9	19	12	
Mean age in years (SD)	59.89 (14.63)	62.58 (9.69)	54.83 (11.32)	0.197
Sex (% male)	77.8	89.5	75	0.560
Hypertension (%)	3 (33.33)	12 (63.16)	n/a	0.228
History of MI (%)	2 (22.22)	3 (15.79)	n/a	1.000
Dyslipidemia (%)	2 (22.22)	12 (63.16)	n/a	0.103
Diabetes (%)	1 (11.11)	4 (21.06)	n/a	0.645
Mean NAB Index (SD)	101.33 (17.68)	108.42 (11.30)	n/a	0.294
Mean downtime (minutes; SD)	10.78 (7.03)	n/a	n/a	n/a
Mean duration of coma (days; SD)	3.11 (4.51)	n/a	n/a	n/a
Mean time to test (SD)	13.78 (13.04)	40.52 (21.96)	n/a	0.001
Mean time to scan (SD)	26.67 (16.21)	62.84 (28.63)	n/a	0.001

NAB, Neuropsychological Assessment Battery; time to test refers to time in days from index event to date of cognitive testing; time to scan refers to time in days from index event to date of magnetic resonance imaging scans; OHCA, out-of-hospital cardiac arrest; MI, myocardial infarction; HC, healthy controls; SD, standard deviation; n/a, not applicable.

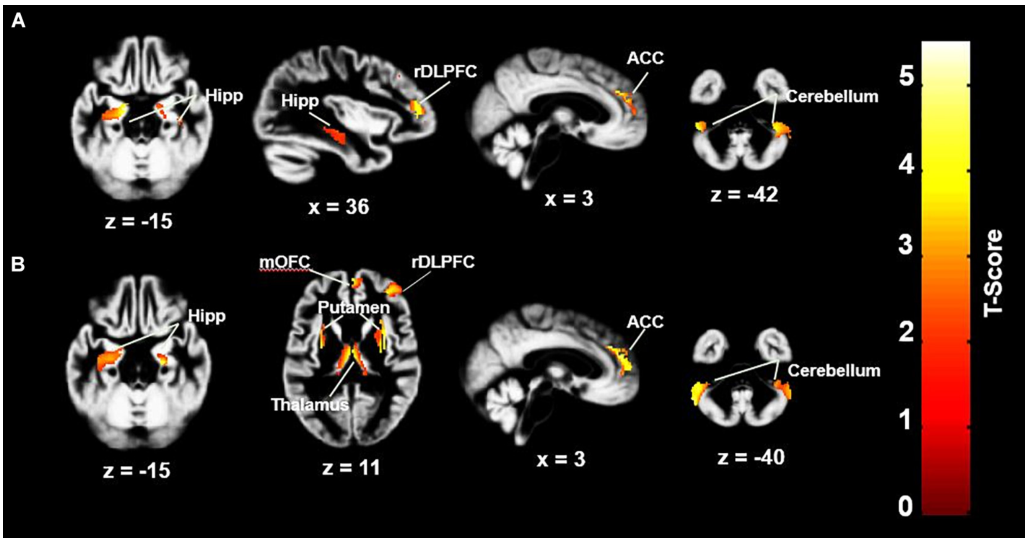

FIGURE 1 | GMV differences between HC group and MI and OHCA group. **(A)** HC > OHCA; **(B)** HC > MI. ACC, anterior cingulate cortex; rDLPFC, right dorsolateral prefrontal cortex; Hipp, hippocampus; mOFC, medial orbitofrontal cortex. Statistical inferences were performed at a threshold of uncorrected $p < 0.001$ at the whole-brain level and $p < 0.05$, family wise error or small volume corrected at the cluster level. There were no significant differences in GMV between the OHCA and MI groups at the whole-brain level.

GMVs, global WM volumes were also compared, and did not differ significantly between the three groups (**Table 1**), [$F(6,68) = 1.818$, $p = 0.109$, partial $\eta^2 = 0.138$]. In whole-brain analyses controlling for age and global GMV, between-group comparisons revealed regional GMV decreases in the both the OHCA and MI groups in comparison to the HC group; the OHCA group had decreased GMV in the anterior cingulate cortex (ACC), right dorsolateral prefrontal cortex (rDLPFC), bilateral hippocampus, right putamen, and bilateral cerebellum areas; the MI group had decreased GMV in the ACC, medial orbitofrontal cortex (OFC), rDLPFC, bilateral hippocampus, thalamus, bilateral putamen, and bilateral cerebellum areas. Most of these regions remain significant after the SVC correction at the cluster level ($p < 0.05$) (see **Figure 1** and **Table 2**) or were approaching significance. There were no significant differences in GMV between the OHCA and MI groups at the whole-brain level even before correction. Further exploratory analyses conducted without defining the cluster size limitation revealed an additional small cluster (six voxels) of reduced GM in the lDLPFC for the MI group compared to the HC group. These results are presented in **Table 2**.

Cerebral GMV and Cognitive Functioning

Mean cognitive performance in both groups was within the average range as compared to the normative data and did not differ between the cardiac groups in this sample [$t(26) = -1.101$, $p = 0.294$; for an in-depth analysis of cognitive performance between OHCA and MI groups, refer to Byron-Alhassan et al.,

TABLE 2 | GMV differences between HC and MI, OHCA.

Brain regions	MNI coordinates			Peak	Cluster-level correction (*p*-value)	
	x	*y*	*z*	*t*-score	FWE	SVC
HC > OHCA						
ACC	2	36	29	4.16	0.967	0.090
rDLPFC	36	42	14	4.07	0.641	0.048
rHipp	15	−9	−12	4.17	0.870	0.019
lHipp	−14	−9	−11	4.96	0.552	0.016
rPutamen	32	−2	12	3.68	0.937	0.062
rCerebellum_Crus2	44	−38	−47	4.80	0.414	0.051
lCerebellum_7b	−47	−44	−50	3.97	0.294	0.020
HC > MI						
ACC	2	45	20	4.79	0.151	0.016
mOFC	9	42	−14	4.74	0.020	0.004
rDLPFC	38	45	5	4.55	0.339	0.022
lDLPFC	−38	33	12	3.55	0.929	0.253
rHipp	17	−9	−12	3.61	0.796	0.011
lHipp	−14	−9	−11	3.98	0.777	0.022
Thalamus	−2	−18	12	4.51	0.384	0.024
rPutamen	29	−6	12	3.92	0.019	0.006
lPutamen	−29	−9	12	4.19	0.648	0.050
rCerebellum_Crus2	44	−38	−47	5.38	0.135	0.028
lCerebellum_Crus1	−56	−62	−36	4.59	0.006	0.002

Table presents three-dimensional Montreal Neurological Institute (MNI) coordinates for significant brain regions with peak cluster t-score value and corrected significance values. r, right side; l, left side; ACC, anterior cingulate cortex; mOFC: medial orbitofrontal cortex; DLPFC: dorsolateral prefrontal cortex; Hipp, Hippocampus; FWE, family-wise error correction; SVC, small volume correction; OHCA, out-of-hospital cardiac arrest; MI, myocardial infarction; HC, healthy controls.

unpublished). Regional volumes that differed significantly for the patient groups compared with the HC group were extracted (i.e., ACC, OFC, DLPFC, hippocampus, thalamus, putamen, and cerebellum) and correlated with cognitive functioning in each cardiac group. Although no regional volumes were correlated with cognitive performance in the MI or OHCA group when controlling for age and global GMV, global GMV alone was correlated with cognitive performance in the OHCA group but not the MI group (see **Table 3**). A strong positive correlation between GMV and cognitive performance was observed. However, a z-test comparing the correlation between GMV and total NAB scores in the OHCA group to the MI group only approached statistical significance ($z = -1.62$, $p_{one-tailed} = 0.053$).

TABLE 3 | Correlations between GMV and cognitive performance on the global NAB Index.

Brain regions	MI	OHCA
Total GMV	0.308	0.798*
ACC	0.279	0.396
mOFC	−0.050	0.348
rDLPFC	0.339	0.044
bHipp	0.045	0.574
Thalamus	0.33	0.663
bPutamen	−0.302	0.326
bCerebellum	0.233	−0.403

*Cognitive function is measured with the Neuropsychological Assessment Battery, scores are standardized to a normative sample for age, gender, and education. Correlations are controlled for age and total GMV. r, right side; l, left side; b, bilateral; ACC, anterior cingulate cortex; mOFC, medial orbitofrontal cortex; DLPFC: dorsolateral prefrontal cortex; Hipp, Hippocampus; OHCA, out-of-hospital cardiac arrest; MI, myocardial infarction. *p < 0.05.*

Cerebral GMV and Clinical Variables

Downtime ranged from 1 to 21 min in the OHCA group ($M = 10.78$, SD = 7.03). When controlling for age, global GMV did not correlate significantly with downtime ($R^2 = -0.568$, $p = 0.142$). However, when controlling for age and global GMV, downtime was negatively correlated with GMV in the left putamen (−30, 5, 3, $p < 0.005$) and right putamen (32, 3, 6, $p < 0.005$) although, only the correlation with right putamen retained significance after SVC (see **Figure 2**).

Days of coma ranged from 0 to 14 ($M = 3.11$, SD = 4.51) with four patients not having experienced any coma. When controlling for age, global GMV did not correlate significantly with days of coma ($R^2 = -437$, $p = 0.292$). At the whole-brain level, when controlling for age and global GMV, no regional GMVs correlated significantly with days of coma.

DISCUSSION

The purpose of this study was to evaluate GMV in a sample of OHCA survivors, who had made seemingly good neurological

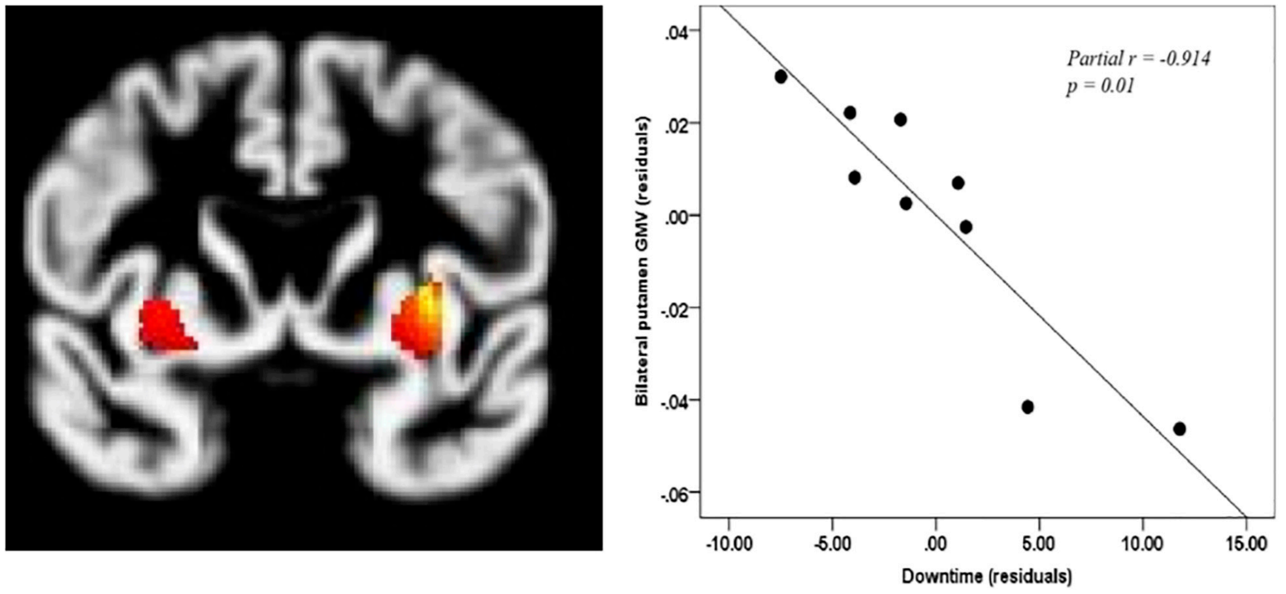

FIGURE 2 | Correlation between downtime and putamen. Coordinates of bilateral putamen: left: –30, 5, 3; right: 32, 3, 6, $p_{corr} < 0.005$. Only right putamen remains significant after small volume correction $p < 0.05$.

recovery, as compared to MI and HC groups. These participants were drawn from a comprehensive study of cognitive functioning after OHCA, which allowed us to explore the association between cognitive functioning and GMV. This study is novel in its inclusion of both an MI control group and a healthy control group. Their inclusion allowed us to further address the issue of the etiology of cognitive dysfunction after cardiac arrest, particularly the relative contributions of pre-existing cardiovascular disease and acute hypoxia/ischemia.

The findings of this study revealed cortical and subcortical volumetric reductions in select brain regions of OHCA survivors. These regions included the ACC, rDLPFC, bilateral hippocampus, right putamen, and bilateral cerebellum. Reductions in hippocampal volumes were expected in this population given reports that memory impairment is the predominant cognitive sequela of OHCA (Green et al., 2015; Moulaert et al., 2009) and the known vulnerability of the hippocampus to hypoxia (Busl and Greer, 2010; Björklund et al., 2014). The ACC and right dorsolateral prefrontal cortex are both key structures in executive functioning (Cummings, 1993), another commonly observed domain of cognitive impairment for survivors of OHCA (Green et al., 2015). Though volumetric reductions in these regions fit the cognitive profile for OHCA survivors, we also observed similar reductions in the MI group. These results suggest that pathology in these regions may result from risk factors common to both cardiac groups. Some of the regions with decreased volume observed in this study have been linked with cardiovascular risk factors (O'Donnell et al., 2016). For example, decreased prefrontal cortex volumes have been observed in patients with hypertension (Raz et al., 2003) and activations in the anterior cingulate, which purportedly play a role in the autonomic nervous system, has been found to correlate with behavioral stress (Gianaros et al., 2005). Reduced cerebellar volumes have been observed in heart failure patients and may relate to decreased perfusion (Alosco and Hayes, 2015). Our findings suggest an increased need for studies of the pathophysiologic relationships between cardiac functioning and the brain.

In this study, we did not observe any differences between the OHCA group and either control group in terms of global GMV. Ørbo et al. (2018) found decreased global GMV compared to healthy controls among individuals who were comatose upon arrival in hospital after OHCA, but not among those who were conscious upon arrival. This may be pertinent to our results, given that approximately half (n = 4) of our sample were non-comatose hospital admissions. While we suspect that GMV is likely reduced in the OHCA population, our analyses were likely underpowered to observe such differences. The fact that our participants were scanned closer to the index event than in other studies may further account for some differences in findings.

Only the OHCA group had significant correlations between cognitive functioning and volumetric data; lower global GMV volume was correlated with worse cognitive performance. This correlation was not observed in the MI group, although the strength of the two correlations did not differ significantly. We would expect, with a larger sample, that the MI group would show a correlation between GMV and cognition, as has been observed in the literature (Kanai and Rees, 2011). However, we observed a strong correlation within our small sample of OHCA survivors, suggesting that volume loss among OHCA patients may be related to increased risk for cognitive impairment. Such correlations between brain volumes and cognitive function have been observed in other MRI studies of cardiac arrest survivors. Grubb et al. (2000) similarly found that, although volumes were reduced in some regions, only total brain volumes were significantly correlated with cognitive performance and Stamenova et al. (2018) likewise found that correlations between cognitive functioning and hippocampal volumes were only apparent in their OHCA group, and not within the MI group. One possible explanation could be that pre-existing cerebrovascular disease burden diminishes neural reserve rendering an individual more vulnerable to the effects of cerebral hypoxia.

The OHCA group performed worse on cognitive testing in all domains than the MI group and, although these differences were not statistically significantly different in this sample. The lack of difference between the OHCA group and MI group may be a result of a small sample size, or due to sampling bias in the OHCA given that individuals who are eligible for MRI cannot have an implanted cardioverter defibrillator, a commonly used preventative measure after OHCA. To investigate this possibility, we compared participants in the present study to the larger sample of OHCA who underwent cognitive assessment from which they were drawn (n_{OHCA} = 77). Results showed that those who participated in the imaging sub-study performed significantly better on cognitive testing than those who did not (M_{MRI} = 101.33 SD = 17.68, M_{COG_ONLY} = 83.48, SD = 14.42, U = 471.50, p = 0.009), although this was not the case for the MI group (M_{MRI} = 108.42, SD = 11.30, M_{COG_ONLY} = 104.16, SD = 12.93, U = 560.50, p = 0.194). These results indicate that individuals who participated in our MRI study performed significantly better on cognitive testing than those who participated in a study involving cognitive assessment alone. Despite this, we found reduced GMV in this group of OHCA survivors who were doing relatively well from a cognitive standpoint, which may suggest a large effect in the greater population. With increasing survival rates and the advent of MRI-compatible defibrillators, future studies may see larger sample sizes to further understand this interesting population.

Downtime was correlated with volumetric data in order to understand the potential relationship between the duration of hypoxia and cerebral GMV. Unlike other studies which have focused primarily on the hippocampus as a region that is primarily susceptible to hypoxia (Ørbo et al., 2018; Stamenova et al., 2018), our results revealed a strong, negative correlation between the putamen and downtime (partial $r = -0.914$, p = 0.01). The putamen has been identified as a region that is susceptible to cytotoxic edema in individuals who do not have a favorable outcome from coma after cardiac arrest (Rossetti et al., 2016; Keijzer et al., 2018). The putamen is a key region in motor control and it also contributes to cognitive processes such as working memory (Arsalidou et al., 2013). Days of coma was not correlated with any regional volumes at the whole-brain level. Although another study identified significant correlations between days of coma, cortical thickness, and some aspects of cognition (Ørbo et al., 2019), the sample differed from the one in this study in that it included only patients comatose upon hospital arrival and therefore likely experienced more severe neurological impairment.

This study has some limitations. Survival rates of cardiac arrest are low, and many patients are treated with implanted cardioverter-defibrillators, which are not MRI-compatible; thus, the individuals included in MRI studies may not be representative of typical cardiac arrest survivors. As previously mentioned, compared to our larger study of cognitive functioning, those who participated in this neuroimaging sub-study demonstrated better cognitive performance. Eligibility restrictions also contributed to a small sample size; this is a common limitation of imaging studies of cardiac arrest survivors (n = 9–13; Horstmann et al., 2010; Stamenova et al., 2018; Ørbo et al., 2019). Uneven sample sizes were also a limitation given that OHCA survivors were more difficult to recruit than the control groups. We wished to evaluate patients prior to hospital discharge at the point in time when rehabilitation planning typically occurs; however, medical complications prevented many patients from participating within this time frame which may have further detracted from the representativeness of the sample. We have found in our larger study that the MI patients perform somewhat better on the NAB than the American standardization sample, suggesting that the test norms may not be ideal for a Canadian sample. As a result, inferences about cognitive functioning in both groups as compared to the healthy control group, and its relation to volumetric data, may be distorted. Finally, hypoxic-ischemic brain injury and reperfusion injuries are dynamic processes that change over time (Busl and Greer, 2010). The current data were obtained at a time when neurological recovery was still ongoing. Identifying neural patterns in the acute phase which may predict long-term functioning are important next steps for future research.

CONCLUSION

Our results highlight the importance of considering baseline neurophysiology when evaluating the neural impact of OHCA. Findings suggest that there may be an interplay of acute and chronic neural changes, such that acute hypoxia/ischemia from the arrest may give rise to subtle deficits in cognitive functions subserved by regions with diminished neural reserve due to pre-existing cerebrovascular disease. Future imaging studies that include a functional component will be important in understanding the functional implication of volumetric reductions observed in this population.

DATA AVAILABILITY STATEMENT

The datasets presented in this article are not readily available because all requests for data must be reviewed by our institution and/or ethical review board. Requests to access the datasets should be directed to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ottawa Health Science Network Research Ethics

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

AUTHOR CONTRIBUTIONS

HT, AS, BC, BQ, SC, ML, and LD conceived of the study and designed the analyses. AB-A collected the data with the support of BQ, SC, ML, LD, and AS. AB-A and ZF contributed to and performed data analysis. AB-A wrote the manuscript with the support of HT, BC, ZF, and AS. AB-A, HT, BC, BQ, ZF, SC, ML, LD, and AS critically reviewed and accepted the contents of the manuscript.

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SYSTEMATIC REVIEW
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What Do We Know About Young Adult Cardiac Patients' Experience? A Systematic Review

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Background: Studies interested in patients coping with a cardiac illness usually focus on children, teenagers, and adults above the age of 55. Apart from the field of congenital heart diseases, there is a general lack of literature regarding young adult cardiac patients (18–55 years old) who seem to cope with psychosocial issues. Therefore, the objective of this paper was to gather all the research carried out concerning the psychological experiences of young adult cardiac patients.

Methods and Results: A comprehensive, systematic review was conducted on quantitative, qualitative, and mixed-method studies in PsycINFO, PubMed, ScienceDirect, and Cochrane Library databases. Out of the 10,747 articles found, 32 were included. While we aimed to include many cardiac diseases, coronary patients dominated the data. Five main themes emerged: emotional states (depression, anxiety, emotional distress, and stress), quality of life (health-related quality of life, physical functioning, and sexuality), adjusting to the medical environment (coping with the disease, health behavior change, financial barriers, and interactions with medical professionals), social life (social support and work), and identity (parenthood, new challenges, and new meanings). The results highlighted that their levels of depression, anxiety, stress, and quality of life were sometimes worse than in the general population and than in older and younger patients coping with a cardiac illness. Social isolation, identity changes, work, and parenthood were the specific challenges that this population had to face. Furthermore, young adult cardiac patients showed worse health behavior profiles than the general population and felt that they lacked information from professionals, especially regarding sexuality. Compared to men, women had worse psychosocial outcomes, especially regarding depression, stress, emotional distress, and quality of life.

Conclusions: Young adult cardiac patients are to be considered with their own identity and challenges. They may be in need of specific interventions, some dedicated to women, and better communication is necessary with their families and professional caregivers so as to improve the patient's mental health, quality of life, coping skills, and adherence.

Keywords: young, adults, cardiac, experience, review

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INTRODUCTION

Cardiac illnesses, such as myocardial infarctions (MI), coronary diseases, and cardiac arrests are most common among adults over 55 years old, yet since congenital heart defects can be discovered as early as during childhood, young people might also find themselves coping with a cardiac illness (HAS, 2016; Al-Dury et al., 2017; Inserm, 2019).

Young adult patients represent 10–23% of all men and women with a coronary illness (Rosengren et al., 2006; Bangalore et al., 2012; Izadnegahdar et al., 2014). In cardiac settings, adults are classified as young when they are between 18 and 40 years old (McDonough, 2009). However, the age limit of young men with coronary illness is often considered by cardiologists to be 45 and, for women, who are protected by their hormones, it could rise up to 55 as their symptoms and peak illness incidence happen 10 years later (Rosengren, 2001; Estève et al., 2008; Vazquez et al., 2008; Schiele and Chopard, 2014).

Being younger is associated with more adverse psychological outcomes in cardiac settings: young adult patients tend to have more difficulties in adjusting to their disease, present unique challenges and coping behaviors, and experience more depression, anxiety, post-traumatic stress symptoms, and decreased quality of life (QoL) compared to older patients (Sears et al., 1999, 2009; Friedmann et al., 2006; Mallik et al., 2006; Vazquez et al., 2008; McDonough, 2009; Larimer et al., 2016; Andonian et al., 2018; Richardson et al., 2018). Additionally, there is growing evidence suggesting that young cardiac women are a subgroup especially at risk for mortality and psychological difficulties (Mallik et al., 2006; Vazquez et al., 2008; Sears et al., 2009; Pelletier et al., 2016b; Sabbag et al., 2017; Vaccarino et al., 2019).

However, most studies include samples whose mean age is above 55 years old and rarely focus on younger adult patients (Whalley et al., 2014; Protogerou et al., 2015; Easton et al., 2016; Ooi et al., 2016; Craner et al., 2017). Studies that include young adults coping with a cardiac illness are scarce (McDonough, 2009; Wong et al., 2017). Systematic reviews interested in the psychosocial aspects of individuals coping with a cardiac illness do not specifically deal with young adults (Fredericks et al., 2012; Foxwell et al., 2013; Herr et al., 2014; Doyle et al., 2015; Li et al., 2015; Tully et al., 2015; Ooi et al., 2016; Le et al., 2018), and studies that do usually focus on patients coping with congenital heart diseases (Van Rijen et al., 2004, 2005a,b; Fredriksen et al., 2009; Asp et al., 2015; Uzark et al., 2015, 2016; Jackson et al., 2017; Abda et al., 2018; Andonian et al., 2018; Grady et al., 2018; Monti et al., 2018).

Therefore, the aim of this systematic review is to identify and gather all the data available on young adult cardiac (YAC) patients (between 18 and 55 years old), coping with all types of cardiac conditions and treatments (coronary, heart failure, arrhythmias, heart transplants, etc.) apart from congenital diseases, regarding their experience and their relationship to their environment, whether social, familial, or medical.

METHODOLOGY

In order to conduct this systematic review, the Preferred Reporting Items for Systematic Reviews and Meta-Analysis guidelines as well as narrative recommendations (Baumeister and Leary, 1997) were followed.

Search Strategy and Eligibility

We conducted our search on PsycINFO, PubMed, ScienceDirect, and Cochrane library databases, the most relevant ones regarding our topic. Several searches were run on these databases before coming up with the appropriate keywords. The keywords retained related to three categories (both in French and in English): (1) cardiac diseases, (2) young adults, and (3) psychology and patients' experience. The final list was discussed with a cardiologist in order to make sure that no important condition was missing. As we wanted to focus only on cardiac diseases, it was decided not to include the following words (also entered in French): stroke, brain, and cerebral. Our search had to be adapted to the specific constraints of each database. For example, on PsycINFO and PubMed, the search was limited to "human research" (this filter was not available otherwise). On ScienceDirect, the search was limited to titles, abstracts, and keywords among research, review, and data articles. The search terms and equations are available in the **Supplementary Material**.

Articles published in English or French up to March 1, 2019 were included. We included (1) quantitative, (2) qualitative, and (3) mixed-method articles, which are (4) available online and (5) focusing on the psychological issues (6) of young patients coping with a cardiac illness. Research dealing with patients on a wider age range than 18–55 years old was included only if part of the data concerned our target age range. When necessary, the authors were contacted to request the full texts or to receive more information (mainly regarding the exact age of the participants). Those that were excluded were classified as: (1) non-cardiac-related articles, (2) theses, (3) dissertations, (4) purely medical studies, (5) risk factor studies, (6) congenital heart disease studies, and (7) studies mixing their data with children, (8) adolescents, and (9) adults over 55 years old.

Data Extraction

First, only titles were screened by the main researcher (JJ) to make sure that the data extracted dealt with our inclusion criteria. If there was any doubt, the articles remained in the selection. Then, abstracts were read in order to proceed to a more precise selection. At that stage, a second researcher (CV) screened the articles independently. The eligibility of articles was then discussed by CV and JJ until a consensus was reached. Eventually, full texts were screened to meet the previously stated criteria. JJ took part in each step of the process and Zotero reference manager was used. The flow diagram illustrating the full process described above is presented in **Figure 1**.

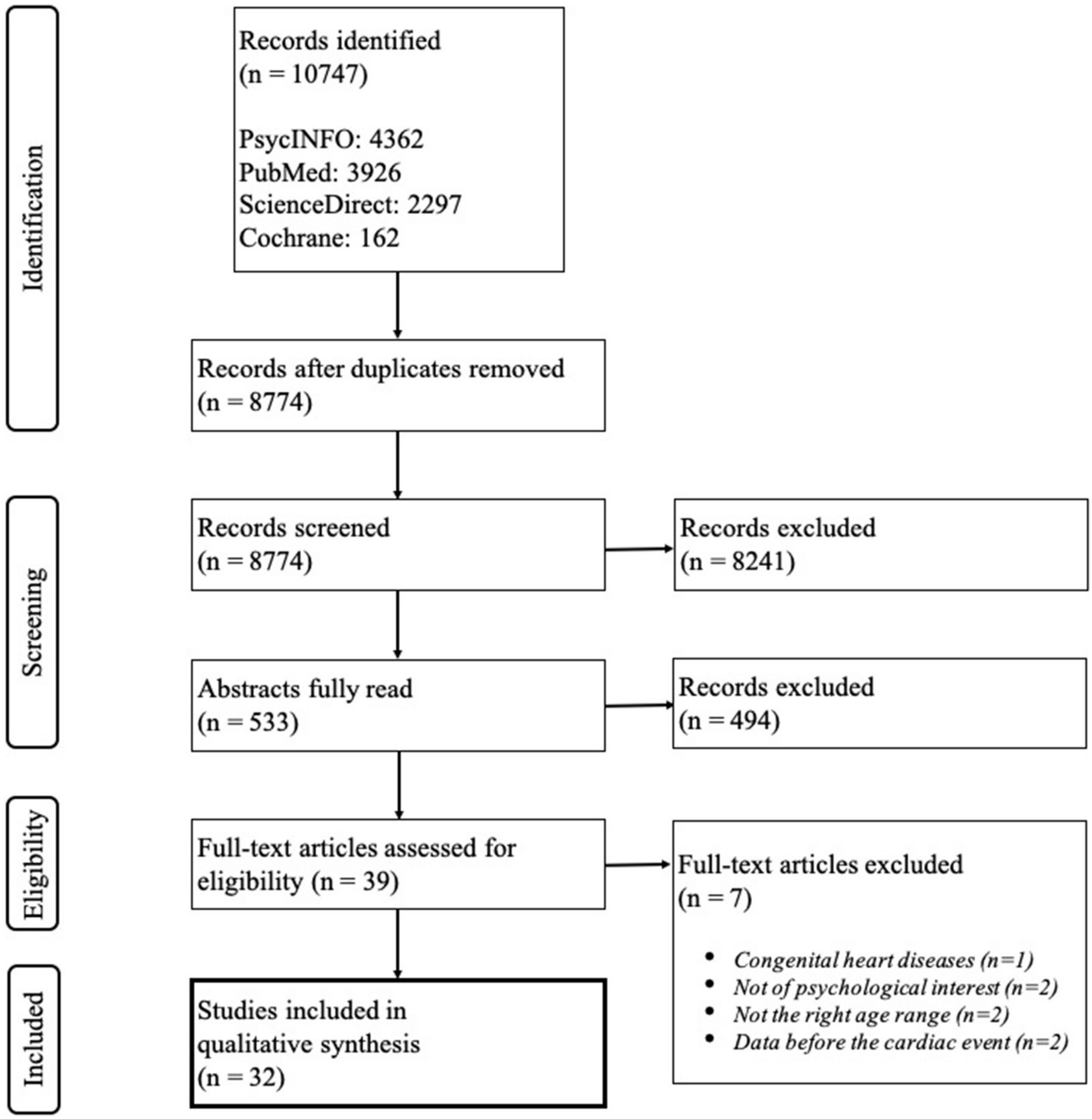

FIGURE 1 | Flow diagram of the study selection.

Quality Assessment

The Crowe Critical Appraisal Tool (CCAT) was used for quality assessment (Crowe and Sheppard, 2011; Crowe et al., 2011, 2012). It is one of the few tools that assess the quality of quantitative, qualitative, and mixed-method studies. The CCAT is composed of eight categories: preliminaries, introduction, design, sampling, data collection, ethical matters, results, and discussion. Each category is rated on five points. The tool provides a grade reaching up to 40, which is then transformed into a quality percentage.

All articles had their quality assessed individually by two authors (JJ + AJ or JJ + CE). They discussed it until a consensus was reached.

RESULTS

General Characteristics and Quality Assessment of the Included Studies

Thirty-two studies were included in this review, with a majority of quantitative articles (23) involving between 30 and 3,572 patients. Research was conducted internationally (12 articles) in Europe (nine articles), North America (eight articles), Australia (two articles), and in the Middle East (one article) between 1996 and 2018 (**Table 1** and **Figure 2**). Many articles were published since 2012 because important cohort studies (VIRGO and GENESIS-PRAXY) gave way to numerous publications.

All the included participants were patients with a cardiac issue, whether the study focused on their disease (MI and coronary artery disease), their cardiac event (cardiac arrest), or their treatment (catheterization and heart transplant).

The YAC patients represented 66% of the patients from the included studies. The studies mainly focused on individuals after a MI, and most of these patients were coronary patients. Their mean or median age was between 35 and 50 years old. Measures were taken from the time of hospitalization until up to 24 years later.

According to the CCAT's criteria, the overall quality was medium to good (mean 75%), with excellent researchers' inter-rater reliability (0.88). An overview of the articles and their main information, results, and quality data are available in **Tables 1**, **2**.

TABLE 1 | Characteristics of the included studies.

	N
STUDY DESIGN	
Quantitative	23
Qualitative	5
Quantitative and qualitative	2
Quantitative and visual*	2
COUNTRY	
International (multi-country)	12
United States	7
Australia	2
Finland	2
Germany	2
United Kingdom	3
Czech Republic	1
Estonia	1
Israel	1
Sweden	1
POPULATION	
Myocardial infarction/acute coronary syndrome	19
Coronary heart/artery disease	7
Cardiac catheterization	2
Cardiac arrest	1
Heart failure	1
Heart transplant	1
Peripartum cardiomyopathy	1

**Myocardial perfusion imaging.*

Themes

Each article was thoroughly analyzed and its data of interest was extracted. Data were gathered in themes and then clustered into superordinate themes.

Five main subjects of interest were revealed: (1) emotional states, (2) quality of life, (3) adjusting to the medical environment, (4) social life, and (5) identity. Each theme included different subthemes that are presented below.

The questionnaires used in each quantitative study are presented in **Table 3**. The themes explored in each qualitative study are presented in **Table 4**.

Emotional States

Regarding emotions and mood, the researchers investigated depression, anxiety, emotional distress, and stress.

Depression

Even though depression was investigated in 75% of the included studies (see **Table 3**), it was usually considered as part of sociodemographic data rather than as a topic of focus in itself. Moreover, almost all studies which included depression rates

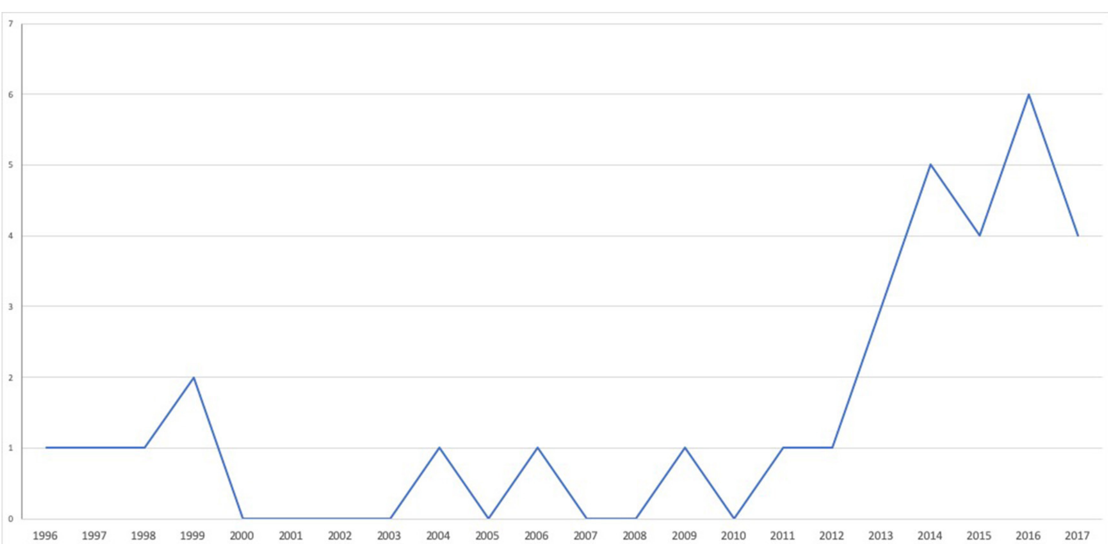

FIGURE 2 | Time distribution of the included published articles on young adult cardiac patients' experience.

TABLE 2 | Detailed information on the included studies.

References	Range age population at baseline	*N*	Mean or median age	Pathology/ treatment	Time of measures	Country	Study design	Quality assessment (researcher 1)	Quality assessment (researcher 2)
Andersson et al. (2013)	23–53	17	45	MI	During the 1st year following their MI	Sweden	Qualitative (interpretative phenomenological analysis, IPA)	85	83
Beckman et al. (2016)	18–55	3,437	47	MI	Within 24 h after MI + 1 month + 12 months	USA and Spain	Quantitative	85	83
Brummett et al. (2004)	<55	No data	No data	CAD (cardiac catheterization)	Hospitalization + 1 month post-catheterization + 3-month intervals over 2 years	USA	Quantitative	63	73
Bucholz et al. (2014)	18–55	3,432	48	MI	Initial hospitalization + 1 month + 12 months	USA and Spain	Quantitative	88	83
Deasy et al. (2012)	29–41	56	35	Cardiac arrest	5 years after the event (range 2.7/8.6 years)	Australia	Quantitative	75	80
Dostálová et al. (2017)	<45	76	No data	MI	< 5 years after the event	Czech Republic	Quantitative	60	58
Dreyer et al. (2015)	18–55	3,501	47	MI	Hospitalization, 1 and 12 months post-AMI	USA and Spain	Quantitative	83	88
Dreyer et al. (2016)	18–55	436	No data	CAD (pre-MI)	Hospitalization	USA and Spain	Quantitative	83	85
Hinz et al. (2011)	30–39/40–49	652	No data	MI (or bypass)	At the beginning of their rehabilitation	Germany	Quantitative	70	75
Joubert et al. (2013)	<55	30	47.7	MI	Hospitalization, 3 and 6 months	Australia	Quantitative and qualitative	63	65
Koutrolou-Sotiropoulou et al. (2016)	>18	116	36	Peripartum cardiomyopathy (HF)	0.2 to 24 years after the event	USA	Quantitative and qualitative	65	68
Lacharity (1999)	31–47	11	40	CAD	4 months to 10 years after the event	USA	Qualitative (ethnographic)	70	65
Lavie and Milani (2006)	22–54	104	48	CAD	Baseline 2–6 weeks after CAD event + 1 week later	USA	Quantitative	60	75
Leung Yinko et al. (2014)	18–55	1,123	49	ACS	Baseline (48 h after admission) + 1 month + 6 months + 12 months	Canada, USA, and Switzerland	Quantitative	73	80
Leung Yinko et al. (2015)	18–55	740	50	ACS	48 h after admission + 1 year later	Canada, USA, and Switzerland	Quantitative	73	73
Lindau et al. (2014)	18–55	3,498	48	MI	Hospitalization + 1 month post-MI	USA and Spain	Quantitative	83	83
Lindau et al. (2016)	18–55	2,802	48	MI	Hospitalization + 1 month post-MI + 1 year	USA and Spain	Quantitative	80	83
Lukkarinen and Hentinen (1997)	35–54	No data	No data	CHD	1 or 2 years after medication prescribed for group 1; right before the surgery in the other groups	Finland	Quantitative	65	65
Lukkarinen and Hentinen (1998)	35–54	80	No data	CAD	1 or 2 years after medication prescribed for group 1; right before the surgery in the other groups	Finland	Quantitative	70	70

(Continued)

TABLE 2 | Continued

References	Range age population at baseline	*N*	Mean or median age	Pathology/ treatment	Time of measures	Country	Study design	Quality assessment (researcher 1)	Quality assessment (researcher 2)
McAnirn et al. (2015)	35–47	7	42	MI	6–8 weeks after the event	UK	Qualitative (Heideggerian phenomenological)	75	78
Merritt et al. (2017)	29–44	10	40.1	MI	116 mean days since MI	UK	Qualitative (IPA)	90	88
Pelletier et al. (2016a)	42–54	909	48	ACS	Hospitalization (within 24 h of admission) + 12 months	Canada, USA, and Switzerland	Quantitative	70	75
Schweikert et al. (2009)	45–54	No data	No data	MI	7.4 median years since first MI	Germany	Quantitative	80	85
Shah et al. (2014)	<55	851	No data	CAD (angina, MI, and HF)	The day of or before cardiac catheterization	USA	Quantitative	78	83
Uusküla (1996)	30–44	64	37.3, 38.6	MI	Between 4 and 7 days after infarction	Estonia	Quantitative	55	50
Vaccarino et al. (2014)	38–50	49	No data	MI	Within 6 months (5 months median time) after the event	USA	Quantitative and visual	73	78
Vaccarino et al. (2016)	34–50	68	No data	CHD	At least 1 week after the event	USA	Quantitative and visual	80	78
Waldron et al. (2017)	19–29	9	No data	HT (dilated cardiomyopathy, restrictive cardiomyopathy, and previous medical treatments)	7 months to 9.5 years (mean 3.6 years) after the event	UK	Qualitative (IPA)	88	90
Wong et al. (2013)	20–39/40–49	658	No data	HF (ICM, valvular, and ischemic HD)	At least 4 weeks after the event	USA and Canada	Quantitative	68	65
Xu et al. (2015)	18–55	3,572		MI	Baseline + 1 month	USA, Spain, and Australia	Quantitative	75	85
Xu et al. (2017)	18–55	3,509	47	MI	Screening at baseline 3 days after admission + 1 month + 12 months	USA, Spain, and Australia	Quantitative	85	90
Zipori-Beckenstein et al. (1999)	18–55	57	No data	Cardiac catheterization	Right before catheterization and 6 weeks later	Israel	Quantitative	63	63

MI, myocardial infarction; CHD, coronary heart disease; CAD, coronary artery disease; ACS, acute coronary syndrome; HF, heart failure; ICM, idiopathic cardiomyopathy; HT, heart transplant; HD, heart disease.

TABLE 3 | Questionnaires used in each quantitative study.

References	Depression	Anxiety	Stress	Emotional distress	Health-related quality of life	Physical functioning	Sexuality	Interactions with medical professionals	Health behavior change	Money	Social support	Work
Beckman et al. (2016)	PHQ-9		PSS-14		SF-12 and SAQ	SF-12			SD	QC	ESSI	
Brummett et al. (2004)			PSS-10									
Bucholz et al. (2014)	PHQ-9				SF-12 and SAQ	SF-12					ESSI	
Deasy et al. (2012)	EQ-5D	EQ-5D			EQ-5D and SF-12	EQ-5D and SF-12					GOS-E and SF-12	SF-12 and SD
Dostálová et al. (2017)							IIEF-5	SAQ	Biological measures of statins, beta blockers, ACEi/ARBs, and antiplatelet therapy			
Dreyer et al. (2015)	EQ-5D	Item in sex questionnaire			SF-12, SAQ, and EQ-5D	EQ-5D and SF-12		SAQ				SD
Dreyer et al. (2016)	EQ-5D	Item in sex questionnaire			SF-12, SAQ, and EQ-5D	EQ-5D and SF-12		SAQ				SD
Hinz et al. (2011)	HADS	HADS										
Joubert et al. (2013)	CDS				SF-12	SF-12					SF-12 and CPIEAS	
Koutrolou-Sotiropoulou et al. (2016)	QC			QC	QC							
Lavie and Milani (2006)	SF-36	SF-36		KSQ and SF-36	SF-36							
Leung Yinko et al. (2014)	HADS	HADS	Unclear		SF-12 and SAQ	SF-12					ESSI	SD
Leung Yinko et al. (2015)	HADS	HADS							FFQ, GSLPAQ, smoking characteristics, and alcohol consumption habits			
Lindau et al. (2014)	PHQ-9		PSS		SF-12	SF-12	Items adapted from prior large-scale interviewer-administered studies of adult sexuality	QC				
Lindau et al. (2016)	PHQ-9		PSS				Items adapted from prior large-scale interviewer-administered studies of adult sexuality	QC				

(Continued)

TABLE 3 | Continued

References	Depression	Anxiety	Stress	Emotional distress	Health-related quality of life	Physical functioning	Sexuality	Interactions with medical professionals	Health behavior change	Money	Social support	Work
Lukkarinen and Hentinen (1997)	NHP			NHP	NHP						NHP	SD
Lukkarinen and Hentinen (1998)	NHP			NHP	NHP						NHP	SD
Pelletier et al. (2016a)	HADS	HADS	QC			Unclear						QC
Schweikert et al. (2009)	EQ-5D	EQ-5D	Unclear		EQ-5D and EQ-VAS	EQ-5D						
Shah et al. (2014)	PHQ-9											
Uusküla (1996)		PARQ		Type A Finnish scale								
Vaccarino et al. (2014)	BDI-II and SCI	STAI-T/S and visual analog ratings of anxiety	SUDS, PSS, blood pressure, and heart rate								ESSI	
Vaccarino et al. (2016)	BDI-II and SCI	STAI-T/S	SUDS, PSS, blood pressure, and heart rate									
Wong et al. (2013)					MLHFQ				Number of pills taken as prescribed			
Xu et al. (2015)	EQ-5D		PSS-14, PSS-10, ISLES	SF-12	SF-12, SAQ, and EQ-5D	EQ-5D and SF-12				QC	ESSI	QC
Xu et al. (2017)	EQ-5D		PSS-14, and ISLES		SAQ						ESSI	QC
Zipori-Beckenstein et al. (1999)		Teichman's questionnaire of trait and state anxiety and QC	QC			QC		QC				

SCI, Structured Clinical Interview for DSM IV; CDS, Cardiac Depression Scale; NHP, Nottingham Health Profile; SUDS, Subjective Units of Distress Scale; PSS, Cohen's Perceived Stress Scale; ISLES, INTERHEART Stressful Life Events Scale; KSQ, Kellner Symptom Questionnaire; SAQ, Seattle Angina Questionnaire; GOS-E, Glasgow Outcome Scale Extended; SF-12, Medical Outcomes Study Short-Form General Health Survey; HADS, Hospital Anxiety and Depression Scale; EQ-5D, EuroQoL 5 Dimensions; BDI-II, Beck Depression Inventory; IIEF-5, International Index of Erectile Function; FFQ, Food Frequency Questionnaire; GSLPAQ, Godin–Shephard Leisure-Time Physical Activity Questionnaire; CPIEAS, Computerized PIE Assessment Schedule; MLHFQ, Minnesota Living HF Questionnaire; QC, questionnaire created for the study; SD, sociodemographic questionnaire.

TABLE 4 | Themes explored in each qualitative study.

References	Depression	Anxiety	Stress	Emotional distress	Physical functioning	Sexuality	Coping	Interactions with medical professionals	Health behavior change	Money	Social support	Parenthood	Work	Identity
Andersson et al. (2013)		×	×	×	×	×	×		×	×	×	×	×	×
Joubert et al. (2013)			×	×			×	×					×	
Koutrolou-Sotiropoulou et al. (2016)				×				×					×	
Lacharity (1999)	×		×	×		×	×	×	×		×	×	×	×
McAnirn et al. (2015)			×	×			×		×		×	×		×
Merritt et al. (2017)	×	×	×	×					×		×	×	×	×
Waldron et al. (2017)							×		×		×	×	×	×

x, theme explored in this study.

were quantitative, and many studies used QoL questionnaires to investigate this subject.

Depression rates were inconsistent across studies, ranging from 3 to 90% depending on the sample and the measures used (Lavie and Milani, 2006; Schweikert et al., 2009; Hinz et al., 2011; Deasy et al., 2012; Joubert et al., 2013; Bucholz et al., 2014; Leung Yinko et al., 2014, 2015; Lindau et al., 2014, 2016; Shah et al., 2014; Vaccarino et al., 2014, 2016; Dreyer et al., 2015, 2016; Xu et al., 2015, 2017; Koutrolou-Sotiropoulou et al., 2016; Pelletier et al., 2016a). In the VIRGO studies, which had the most important samples and the highest quality methodology despite the use of different tools, depression rates ranged from 21 to 48%. This wide range was often accounted for by gender, with women being more depressed than men. Several studies compared the depression rates among young patients and among older patients without finding significant differences (Lavie and Milani, 2006; Schweikert et al., 2009; Shah et al., 2014). A year after a cardiac event, the levels of depression decreased (Joubert et al., 2013; Bucholz et al., 2014; Beckman et al., 2016).

Young women were more at risk of being depressed (27%) than older women (12%) (Shah et al., 2014). Women appeared to have higher rates of depression than men after a MI or a coronary disease (Lindau et al., 2014; Vaccarino et al., 2014; Leung Yinko et al., 2015; Xu et al., 2015). This difference between men and women seemed to persist 1 year after the cardiac event (Lindau et al., 2016). However, Pelletier et al. (2016a) made a distinction between feminine *gender* (as a social and cultural condition) and physiologically being a woman. According to them, feminine gender is characterized by specific roles, identity, relationships, and tasks traditionally ascribed to women but which can also be embodied by men. These cultural roles and tasks could predict higher depression rates than biologically being a woman.

In summary, age specificities were observed in women for depression, with younger women being more depressed than older women. Women tended to develop more depressive symptoms than men both during hospitalization and 1 year later.

Anxiety

Although anxiety was investigated in 47% of the included studies, it was rarely defined. Some defined it as trait or state.

After a MI, the patients' anxiety was higher than that of the general population both during rehabilitation (Hinz et al., 2011) and 7 years later (Schweikert et al., 2009). Five years after a cardiac arrest, more than half of the individuals included in the study by Deasy et al. (2012) had presented with moderate to severe anxiety. However, apart from the study of Hinz et al. (2011), these samples were too small to allow for generalization.

Depending on the disease and its treatment, the levels of anxiety differed. Right before their cardiac catheterization, state anxiety was lower in the young patients included in the study of Zipori-Beckenstein et al. (1999) than in the older patients ($\geq$55). Within 6 months after a MI, perceived anxiety did not differ between the age groups studied by Vaccarino et al. (2014) ($\leq$50 and >50). However, young coronary patients appeared to score higher on anxiety scales than the other age groups ($\geq$70 and $\geq$55), whether weeks after a cardiac event (Lavie and Milani,

2006) or years later (Schweikert et al., 2009). Here again the samples were too small to allow for generalization.

After an acute coronary syndrome, the studies showed varying results regarding anxiety levels. According to some authors (Vaccarino et al., 2014), the anxiety levels did not differ between men and women after an acute coronary syndrome, yet another study found that, years later, men had higher levels of anxiety (Schweikert et al., 2009). However, studies on bigger samples suggested that women were more likely to develop anxiety symptoms than men (with 51.7 *vs*. 33.6%, $p < 0.01$) (Leung Yinko et al., 2015). Overall, individuals with feminine-gender characteristics seemed to develop more anxiety than individuals with masculine-gender characteristics, whether they were men or women (Pelletier et al., 2016a).

Therefore, according to the information available, cardiac diseases or their treatment may trigger anxiety that tends to remain over time, but evidence regarding age and sex was inconsistent.

Emotional distress

A focus on emotional distress was found in 34% of the included studies. Anger and irritability were often evoked by patients and seemed to be part of their emotional state from their hospitalization until at least a year later, both in quantitative and qualitative studies (Uusküla, 1996; Lacharity, 1999; Lavie and Milani, 2006; Andersson et al., 2013; McAnirn et al., 2015). According to Lavie and Milani (2006), hostility was higher among younger patients (<55) compared to older patients (≥70).

In qualitative studies, a "heightened sense of mortality" was described by the participants throughout the first year after diagnosis (Lacharity, 1999; Andersson et al., 2013; Joubert et al., 2013), although it was described less often by men for whom it was difficult to accept death as a nearby possibility (Merritt et al., 2017). Emotional distress and the heightened sense of mortality were found in several expressions of fear: of dying in their sleep, of dealing with another MI (Andersson et al., 2013), of pain (Joubert et al., 2013), or of other injuries provoked by the disease (Lacharity, 1999; Koutrolou-Sotiropoulou et al., 2016). Worry was part of the young patients' emotional states 1 week after hospitalization in a quantitative study (Uusküla, 1996), and up to 6 months later in a qualitative study (Merritt et al., 2017). The patients also felt guilt and responsibility with regards to their family and to past bad lifestyle choices (McAnirn et al., 2015). These feelings seemed to last up to a year later, according to some high-quality studies (Andersson et al., 2013; Merritt et al., 2017).

Few of these studies compared men and women. Among the quantitative studies, Uusküla (1996) found that women were more subject to irritation, inability to relax, and impatience. Lukkarinen and Hentinen (1997, 1998) found that women had more frequent emotional reactions than men, and in the study by Xu et al. (2015), women tended to develop more severe mental health issues than men during hospitalization. However, several qualitative articles included men only (Merritt et al., 2017) or women only (Lacharity, 1999; Andersson et al., 2013; Koutrolou-Sotiropoulou et al., 2016). Koutrolou-Sotiropoulou et al. (2016) found that few women felt that they had recovered emotionally during the 6 months following their first symptoms and more than half of them never returned to their normal previous emotional level. According to the quantitative study of good quality of Xu et al. (2015), mental functioning was worse among young adult MI patients a year after their hospitalization compared to during their hospitalization.

To conclude, YAC patients expressed emotional distress, with feelings such as hostility and a sharpened fear of death. Women may have a stronger risk of not recovering emotionally from their disease.

Stress

Stress was rarely properly defined, even though it was accounted for in 53% of our selection. Most of the articles referred to stress as a risk factor and in relation to work, children, finances, and lifestyle. Informative data were mainly found in quantitative articles. Out of the 17 articles with a focus on stress, "perceived stress" was only investigated in six articles. Stressful life events were separately assessed in two studies. Two studies assessed stress in experimental conditions (Vaccarino et al., 2014, 2016): they used blood pressure and heart rate measures as they intentionally induced mental stress with a standardized public speaking task. Surprisingly, post-traumatic stress was never explored in these studies.

After significant stress during hospitalization for a cardiac event, stress decreased over time, both 1 month later and 2 years later (Brummett et al., 2004; Beckman et al., 2016; Xu et al., 2017). Ischemia due to stress was three times higher among young women than among men (Vaccarino et al., 2014, 2016). Furthermore, perceived stress scores were higher among coronary women compared to the scores of coronary men both during their hospitalization and over a 2-years period (Brummett et al., 2004; Lindau et al., 2014, 2016; Xu et al., 2015, 2017). However, these data are to be taken lightly as the number of YAC patients in these studies was either small or undisclosed.

When young patients were compared to older patients regarding stress, no difference was found during hospitalization or 6 months later (Vaccarino et al., 2014), but the youngest tended to score higher over a 2-years period (Brummett et al., 2004).

From these studies, it appeared that the levels of stress decreased over time, that YAC patients may develop more stress than older patients years after a cardiac event, and that women were often found to be more stressed than men.

Quality of Life

Quality of life was explored in 62% of our included articles. These studies examined either health-related QoL or more specific aspects, such as physical functioning or sexuality.

Health-related quality of life

Half of the articles corresponding to our inclusion criteria investigated QoL, and they were all quantitative. Out of these 16 articles, quality of life was only properly defined three times: it was defined as the way patients felt, perceived, and defined their health in relation to physical, psychological, and social aspects (Lukkarinen and Hentinen, 1997; Deasy et al., 2012; Leung Yinko et al., 2014). Most of the time, QoL was explained through the tools used and was used as a way to measure the effectiveness of medical interventions.

From the moment of their hospitalization to 7 years later, young adult MI patients presented lower QoL scores than the general population (Schweikert et al., 2009; Leung Yinko et al., 2014). Some patients improved after a year (Bucholz et al., 2014; Beckman et al., 2016), and a small sample improved 5 years after their cardiac arrest (Deasy et al., 2012). Several authors found that being a woman was a risk factor for worse QoL from hospitalization to months and years after (Lukkarinen and Hentinen, 1997; Schweikert et al., 2009; Dreyer et al., 2015, 2016), but according to Leung Yinko et al. (2014), this difference could be attributed to a more feminine gender role, low social support, and high housework responsibilities.

From 1 month to a year after hospitalization, two studies of poor quality found that younger adults had lower QoL scores than older patients (Wong et al., 2013), even though their medical state was not objectively considered as worse (Lukkarinen and Hentinen, 1997).

Moreover, high QoL scores have been shown to be linked to lower depression, anxiety, and stress scores, both when patients were hospitalized and a month later (Leung Yinko et al., 2014; Xu et al., 2015).

Therefore, being a woman and being young may represent a higher risk for low QoL among individuals with a cardiac illness. High levels of QoL seemed to be associated with better mental health. Over time, QoL appeared to improve.

Physical functioning

Physical functioning was part of the QoL tools used by the researchers and thus represented an important aspect of QoL and the experience of individuals with a cardiac illness. It was explored in 40% of the studies.

Being young was associated with better health and better chances of recovering from a cardiac intervention, such as cardiac catheterization (Zipori-Beckenstein et al., 1999).

Years after a cardiac arrest, the vast majority of the patients of the study of Deasy et al. (2012) had good mobility, personal care, usual activities, and no pain or discomfort, yet 11% had a severe disability. After a MI, it was found that physical functioning in daily activities improved during the following 3–6 months, offering renewed independence in work-related and daily occupations (Joubert et al., 2013). From a qualitative point of view, during the first year after a MI, the patients described recurrent moments of "overwhelming fatigue," preventing them from doing anything (Andersson et al., 2013).

Cardiac events and interventions were shown to have physical impacts on young patients, but they tended to disappear. However, studies were too scarce, and too few participants were included to conclude on this aspect.

Sexuality

A focus on sexuality was found in 15% of the articles reviewed. The studies of Lindau et al. (2014, 2016) made a substantial contribution to this theme with their important samples and good-quality quantitative methodology.

There was a higher rate of declared sexual problems among patients after a MI than in healthy people of the same age (Lindau et al., 2016). A month after a MI, sexual activity was found to have declined compared to before the infarction but almost completely resumed during the following year (Lindau et al., 2014, 2016). However, one in 10 women and one in 20 men never resumed a sexual activity. The following factors associated with being a "late resumer" were identified: being a woman and in a relationship, of American nationality (as opposed to Spanish), coping with stress, having lost general physical functioning, not communicating with a physician about these issues, and being in the older range of a cohort of individuals 18–55 years old. In this cohort, the incidence of sexual problems was much higher than the incidence of depression (Lindau et al., 2016).

Some discrepancies between countries, regarding the way these issues were addressed by professionals, emerged. Women and Americans were less likely to bring up the subject with their physician, and the discussion was initiated more often by the professional in Spain than in the USA (Lindau et al., 2016). Men did not often dare talk about their erectile dysfunctions, and there was a lack of screening and treatment for this issue (Lindau et al., 2014; Dostálová et al., 2017). The physicians' recommendations were inconsistent: they tended to suggest limiting sexual activity even though it was not related to the patients' state of health (Lindau et al., 2016). Qualitatively, the lack of counseling and advice was a source of dissatisfaction for the patients (Lacharity, 1999).

To sum up, young individuals coping with a cardiac illness encountered diverse sexual problems that were not necessarily addressed by their doctor.

Adjusting to the Medical Environment

In addition to focusing on the impact that cardiac diseases may have on YAC patients, some articles were also interested in the way the patients adjusted to the medical environment. They presented the patients' coping strategies, the way the patients changed their health behaviors, the financial barriers that they had to face and their relations with medical professionals.

Coping with the disease

Coping strategies were addressed by the patients interviewed in more than half of the qualitative studies. They were only explored in 15% of the overall included studies. The main strategies evoked were:

- *Living in the present*: Even though some patients were struggling, this strategy may be a way of remaining positive about the future (Andersson et al., 2013) and of limiting the impact of the disease on their identities (Waldron et al., 2017).
- *Avoidance*: Some patients tried to avoid thoughts about their own mortality (Waldron et al., 2017), avoided expressing their emotions for fear of the impact on their personal and working relationships, and avoided expressing their sexual needs to their partner (Andersson et al., 2013).
- *Change*: Some patients changed their behaviors to focus on what matters in life and in order to modify the risk factors (Lacharity, 1999). The participants tended to believe that those

changes were important and under their control (McAnirn et al., 2015). On the other hand, the patients sometimes felt the urge to go back to their previous lifestyle regarding work, leisure, and relationships to effectively manage their emotions and difficulties (Joubert et al., 2013).

- *Acceptance* of the disease and its inherent physical limitations (Lacharity, 1999).
- *Social support*: Even though the participants looked for social support (emotional and material) and wanted to stay close to their relatives at all times, they sometimes found it difficult to accept help from their friends and family (Lacharity, 1999; Andersson et al., 2013).
- *To take refuge in spirituality* was also seen as a way to gain strength for some patients (Lacharity, 1999).

Health behavior change

We define health behavior change as therapeutic adherence and following recommendations regarding medication, diet, physical activity, smoking, alcohol, and drug consumption. This issue was explored in 28% of the included studies, which were of rather good quality and mostly comprised of large samples.

Generally, right after a MI, young patients had a worse health behavior profile than the general population (Leung Yinko et al., 2015). However, for the first 4 months, they were motivated to change (McAnirn et al., 2015) and felt good about implementing a healthier lifestyle (Merritt et al., 2017). These qualitative data matched the quantitative information: some patients thus improved their lifestyle regarding physical activity, alcohol consumption, and dietary changes and were more compliant to medication (Leung Yinko et al., 2015; Dostálová et al., 2017). Others maintained the healthiest possible lifestyle but with "planned exceptions" in order to cope with their frustration (Lacharity, 1999). On the other hand, adopting a healthy behavior regarding diet and physical activity was qualified as a constant struggle that could be improved with professional help (Andersson et al., 2013). Medication was also associated with negative feelings, such as the loss of independence (Merritt et al., 2017). To that extent, in quantitative studies, the youngest heart failure patients were less likely to adhere to medication and dietary changes (Wong et al., 2013). It also appeared that women had more barriers to medication, smoking cessation, and dietary changes than men (Leung Yinko et al., 2015; Beckman et al., 2016).

After a cardiac event, contrasted health behavior profiles arose: they were negatively invested by some individuals who see medical recommendations as constraints, whereas some transformed these obligations into a renewed, healthier, and rewarding lifestyle.

Financial barriers

Financial barriers were only mentioned in 9% of the included articles. These studies were all of good quality and had good methodology, with large samples.

After a MI, one third of the young patients had trouble accessing healthcare services (follow-up visits and rehabilitation) because of financial barriers and 20% were not able to get access to medication. These rates were higher than in older MI patients. These financial barriers led to lower QoL, more depressive symptoms, and higher perceived stress (Beckman et al., 2016).

Even though not having enough money was linked to more stress for men (Xu et al., 2015), women were more at risk of having financial problems. They considered their medical costs a moderate or severe burden, especially when living with children at home (Xu et al., 2015; Beckman et al., 2016). In a qualitative study, some young patients described having to face such important financial problems that they borrowed money from their relatives or sold their personal possessions (Andersson et al., 2013).

All in all, the specific situation of younger patients (with children and without jobs) led to financial difficulties which could prevent them from being compliant to their treatment. However, we must bear in mind that this issue is strongly dependent on the healthcare system unique to each country and therefore cannot be generalized.

Interactions with medical professionals

Regarding interactions with the medical world, communication between patients and physicians and the delivery of sufficient and adequate medical information were the two main topics that emerged. This theme appeared in 31% of articles. Only 26% of the women interviewed by Koutrolou-Sotiropoulou et al. (2016) were satisfied with the counseling that they received from their physician. One third reported not receiving adequate counseling. Not receiving information on their disease, its causes, consequences, and prevention of recurrence brought large amounts of fear (Andersson et al., 2013; Joubert et al., 2013). Quantitatively, Zipori-Beckenstein et al. (1999) also found that low levels of anxiety were correlated with high positive expectations that produced better treatment satisfaction.

The patients sometimes found it difficult to gain access to medical support (Joubert et al., 2013) and when they did, for instance in rehabilitation, they sometimes felt a lack of attention to their actual needs (Andersson et al., 2013). Dissatisfaction was also expressed when healthcare professionals were too demanding, resulting in a feeling of stress.

In quantitative studies, women showed less treatment satisfaction than men (Dreyer et al., 2015, 2016). They felt less counseled than men 1 month after their hospitalization, even though they would have considered it appropriate for their physician to do so (Lindau et al., 2014). A year after hospitalization, both men and women had received more sexual counseling than a month after hospitalization, even if it remained scarce (Lindau et al., 2016). For men, communication about erectile dysfunctions did not happen often and was deemed insufficient (Dostálová et al., 2017).

Even though the quality and the samples of the studies varied, they agreed on the fact that many patients were dissatisfied with the communication received from healthcare professionals, specifically regarding information given by physicians.

Social Life

Some studies took into account the patients' personal environment and addressed the social aspects of young individuals' lives when coping with a cardiac illness, such as perceived social support and work.

Social support

The studies investigated different social aspects: activities, support, isolation, dependence, and the social impact of the disease. These were investigated through dedicated questionnaires or through QoL subscales (see **Table 3**) and were a topic for almost half (47%) of the included studies.

Lack of social activities (such as visiting friends or relatives) was associated with difficulties, such as emotional and physical health problems (Joubert et al., 2013). Lack of social support was correlated to lower QoL, lower mental functioning, and more depressive symptomatology (Bucholz et al., 2014; Leung Yinko et al., 2014). Even though these problems generally did not last a year after the cardiac event, in one study with a small sample (Joubert et al., 2013), QoL was impacted throughout the year following a MI. In another better-quality study with a bigger sample, this result was more significant among women because of low social support (Leung Yinko et al., 2014).

Patients coped with limitations in their social activities (Joubert et al., 2013) and had to carefully plan their outings to save energy (Andersson et al., 2013). They also coped with isolation, which was more prevalent among younger patients (Lukkarinen and Hentinen, 1997), but these data have to be confirmed.

In qualitative studies, friends and family were seen as one of the most important sources of support, and their support was preferred to rehabilitation (Lacharity, 1999; Joubert et al., 2013; McAnirn et al., 2015). However, it was difficult for many patients to accept the change in their close relationships arising from their increased dependence (Lacharity, 1999; Andersson et al., 2013; Joubert et al., 2013). They sometimes felt their relatives were overprotecting them and prevented them from participating in physical activities that patients knew (from professionals) they were allowed to perform. This resulted in anxiety, avoidance, and conflicts (Merritt et al., 2017; Waldron et al., 2017). The patients sometimes also felt misunderstood by people with whom they used to partake in unhealthy behaviors (such as smoking and drinking) and expressed the need to meet other young patients (Merritt et al., 2017).

Low social support was therefore associated with psychosocial difficulties (regarding health, mental functioning, depression, anxiety, and conflicts). Over time, only the association between low social support and QoL remained. Young patients coped with isolation and found it difficult to accept the switch toward dependent relationships despite social support being very important to them.

Work

Work status or thoughts about work were assessed in almost half (47%) of the articles through sociodemographic data, questionnaires, and qualitative interviews. However, even though the nature of work was indicated, it was not often explored in detail after the disease onset. More often, it was investigated as a risk factor before the disease onset.

While heart-transplanted patients all went back to work years after their surgery (Waldron et al., 2017), coronary patients did not (Lacharity, 1999). Only 68% of adults having coped with a cardiac arrest were working 5 years later (Deasy et al., 2012) and 28% of the women coping with peripartum cardiomyopathy discontinued their job (Koutrolou-Sotiropoulou et al., 2016). The main motivations to go back to work were financial and a will to return to "normality" (Lacharity, 1999).

Qualitative studies showed that work became worrisome for patients after a MI: they expressed fear of not being efficient, of losing or not getting their job back, of financial difficulties, and of stress (Andersson et al., 2013; Joubert et al., 2013). Some saw this crisis as an opportunity to rethink their priorities by finding employment more suitable to their new situation, mainly looking for more meaning and less stress (Merritt et al., 2017).

The YAC patients showed no pattern regarding going back to work. The issue of work was a source of stress and anxiety for many. For some, the disease acted like a wake-up call, leading them to orient toward more meaningful work. However, the lack of large samples and quantitative data pleads for more research in this area.

Identity

After a cardiac event, one's identity is challenged: "you're just not the same" (Lacharity, 1999). Individuals become patients, with new challenges to face and a new equilibrium to find (Waldron et al., 2017). Through this experience, some of them reflected on their status as parents (Lacharity, 1999; Andersson et al., 2013; Merritt et al., 2017; Waldron et al., 2017).

These topics were a subject of interest in 16% of the included studies and were only explored in qualitative articles.

Parenthood

On the one hand, the disease or its treatment was sometimes the starting point for the desire to have children. It was described as a new motivation to start a family and was occasionally discussed with professional caregivers (Merritt et al., 2017; Waldron et al., 2017). On the other hand, other patients feared parenthood as they became aware of their disease and worried about leaving their children behind (Andersson et al., 2013; Merritt et al., 2017). They also worried about the impact of the illness on their children: they feared not being able to meet their offspring's expectations, not being able to fulfill their duty as parents, and seeing them cope with the same disease (Lacharity, 1999; Andersson et al., 2013).

New challenges

Faced with a cardiac disease, the participants started feeling different from their former selves (Lacharity, 1999): a body described as unfamiliar and weak resulted in decreased self-confidence in front of such a life-threatening situation (Andersson et al., 2013; McAnirn et al., 2015).

Among coronary and heart-transplanted patients, some referred to this search for new equilibrium as a "fight" (Andersson et al., 2013; Waldron et al., 2017). Men felt less masculine, strong, and independent (Merritt et al., 2017; Waldron et al., 2017) and women found it hard to see their physical attractiveness lessen, partly due to the weight gain caused by their treatments (Waldron et al., 2017).

The heart-transplanted patients described a "paradoxical position": they wanted to move away from the disease while still having to undergo medical routines (Waldron et al., 2017). However, an old study, which was mediocre in quality, reported that coronary women tended to accept their illness and understand their limits (Lacharity, 1999). Additionally, both coronary and heart-transplanted patients felt different from older cardiac individuals: they felt like they should not be here precisely because they were too young to experience this (Waldron et al., 2017) or because they may have had different needs (Andersson et al., 2013).

New meanings

New meanings were evoked in two studies of good quality (Andersson et al., 2013; Waldron et al., 2017). In these studies, individuals coping with a cardiac illness viewed their new situation as a "second chance" or a "gift of life." For transplanted individuals specifically, there was a feeling of debt to donor families and they had high expectations to become even "better than normal." According to the authors, the patients had difficulty grasping the idea that this feeling of normality was more a process than an instant state resulting from the surgery.

For some patients, these experiences resulted in the search for a new meaning of life, with material possessions, work, and risk taking becoming less valued than quality time with family members. Aspirations in these areas were challenged. Although this was scary for some individuals even years after, others found some sort of stability after a year.

The identities of YAC patients were characterized by a struggle with their previous concept of normality, a new look upon their body, and the sense of being different from older patients. Moreover, parenthood was not taken lightly. Those who already had children started worrying about the impact of the disease on their offspring, while many of those who were not yet parents built a parental project in spite of their fears.

DISCUSSION

This systematic review showed that YAC patients are a specific group with specific needs. Compared to older patients coping with a cardiac illness, YAC patients sometimes had higher levels of depression, anxiety, and stress. They had lower QoL and coped with social isolation and financial barriers. Other issues, such as work and parenthood, were specific to this age range. Furthermore, these individuals felt different from older patients with a cardiac illness: they felt too young to experience these issues and had different needs compared to the older patients. Women represented a special sub-group more at risk of developing depression symptoms, stress, emotional distress, and lower QoL.

The results from this systematic review established that the levels of depression are sometimes high among YAC patients (Joubert et al., 2013) but, similarly to previous studies with wider age ranges, age comparisons led to unconvincing results (Lavie and Milani, 2006; Schweikert et al., 2009; Shah et al., 2014).

Our results highlighted the link between QoL, depression, anxiety, and stress (Leung Yinko et al., 2014; Xu et al., 2015). In the literature, depression was found to be the strongest predictor of young adult coronary patients' QoL (Lane et al., 2001, as cited by Vaccarino et al., 2019). The QoL of YAC patients seemed low and lower than that of the healthy population (Schweikert et al., 2009; Wong et al., 2013; Leung Yinko et al., 2014). A recent systematic review and meta-analysis showed that this was also true for older adult patients (mean age = 61 years old) with coronary heart disease (Le et al., 2018). This may not be the case for younger congenital heart disease patients (7–17 years old) who had QoL levels identical to those of healthy controls (Reiner et al., 2019). However, in the context of implantable cardioverter defibrillators (ICD), younger patients were found to cope with a lower QoL than older patients (Friedmann et al., 2006). This could be explained by a feeling of lost independence in the young, whereas the older patients saw this treatment as a way to extend their life (Arteaga and Windle, 1995, as cited by McDonough, 2009). It could also be argued that, in cardiac settings, the young are struck in a moment of their life perceived as disease-free, while older patients may accept the disease and its treatments as the growing burden of age and impairment. This could explain the differences between young and old patients with a cardiac illness regarding QoL.

Our findings demonstrated the importance of social support for YAC patients, especially from close relatives (Lacharity, 1999; Joubert et al., 2013; Bucholz et al., 2014; Leung Yinko et al., 2014; McAnirn et al., 2015). For YAC patients, a lack of social support was associated with health, emotional, mental, and depressive issues and lower QoL (Joubert et al., 2013; Bucholz et al., 2014; Leung Yinko et al., 2014). These results are consistent with the literature in older patients for whom the presence of friends, family, and partners seems crucial after the appearance of a cardiac disease (Kristofferzon et al., 2008; Bertoni et al., 2015; Ooi et al., 2016). According to the findings, young patients (≤40 years old) may be more at risk of isolation after the implant of an ICD (Dubin et al., 1996; Sears et al., 2009; Larimer et al., 2016). This leads us to underline the importance of developing research among patients and their relatives, especially couples, to improve their emotional and physical outcomes (Sher et al., 2014; Varela Montero and Barrón López de Roda, 2016; Lyons et al., 2017; Trump and Mendenhall, 2017).

Our data underlined issues already expressed in previous studies. It was found that even though YAC patients needed support from their friends and family, it was sometimes difficult for them to accept their assistance (Lacharity, 1999; Andersson et al., 2013; Joubert et al., 2013). Similarly, while many patients (47–90 years old) received support from their network, they found it difficult to communicate with them after a MI (Kristofferzon et al., 2007). We also found that many patients were unhappy about the support received from professionals (Andersson et al., 2013; Joubert et al., 2013; Koutrolou-Sotiropoulou et al., 2016; Ooi et al., 2016), especially regarding sexual issues (Lacharity, 1999; Lindau et al., 2014, 2016; Dostálová et al., 2017). Indeed the patients expressed the need for sexual counseling after cardiac issues and wanted professional health caregivers to provide for it (Byrne et al., 2013; Mc Sharry et al., 2016; Ooi et al., 2016). This finding is not specific to cardiac settings: it is common that professionals do not feel eligible to address these issues and instead feel uncomfortable (Mellor et al., 2013).

Regarding these topics, we can conclude on two aspects: Firstly, training healthcare providers in efficient communication with patients could improve patient satisfaction. To that extent, more information regarding the key issues expressed by the patients is needed. Secondly, in order to increase social support, it could be argued that systemic patient and relative care would be beneficial as well (Liljeroos et al., 2017; Smith and Baucom, 2017).

Studies highlighted the way in which YAC patients' identities were challenged because of their new perception of their bodies (Lacharity, 1999; Andersson et al., 2013; McAnirn et al., 2015; Merritt et al., 2017), their desire to return to normality while having to change habits (Waldron et al., 2017), and their feeling of difference from older patients with a cardiac illness (Andersson et al., 2013; Waldron et al., 2017). The new perception of themselves also challenged their equilibrium and status, such as parenthood (Lacharity, 1999; Andersson et al., 2013; Merritt et al., 2017; Waldron et al., 2017). While our findings highlighted the way the participants attribute new meaning to life after a cardiac issue, other studies went further by reporting a form of resilience or personal growth after a MI (Kristofferzon et al., 2008), among teenagers with a congenital disease (Apers et al., 2016) or people living with an ICD (Ooi et al., 2016). As in our review, most other results focused on the physical difficulties and especially perceptions of the injured body. These provoked impairment and feelings of dependence and uselessness, with social limitations as a result (Vazquez et al., 2008; Allison and Campbell, 2009; McDonough, 2009; Ooi et al., 2016; Jackson et al., 2017; Chong et al., 2018). Weakness was especially incompatible with the vision men had of themselves (Allison and Campbell, 2009). Additionally, young patients with a cardiac illness felt different from older populations, having to deal with specific issues related to their age, such as childbearing and financial concerns (Allison and Campbell, 2009; McDonough, 2009; Ooi et al., 2016).

These concerns might explain, to some extent, the non-adherence found among young patients with a cardiac illness in our included studies. Indeed young patients tend to have a less stable professional life, with college to attend or children to raise. Moreover, the literature highlights associations between non-adherence and younger age (Tumin et al., 2017). To our knowledge, while the rate of non-adherence among YAC patients has not been studied, meta-analyses show that 20 to 30% of older coronary patients do not take their medication (Crawshaw et al., 2016, 2017). Whatever their age, the common difficulty lies in time: even when coronary patients are compliant right after the event, as years go by their adherence seems to decrease (Baldacchino, 2011; Andersson et al., 2013; Leung Yinko et al., 2015). Studies also highlight that non-adherence is linked to depression (Crawshaw et al., 2016, 2017; Vaccarino et al., 2019). Therefore, interventions need to target health behavior changes right after a cardiac event, with regular reminders to increase or maintain adherence.

Finally, women emerged as a specific sub-group in this systematic review. Women seem more at risk of developing depression (Lindau et al., 2014, 2016; Vaccarino et al., 2014; Leung Yinko et al., 2015; Xu et al., 2015), poor QoL (Lukkarinen and Hentinen, 1997; Schweikert et al., 2009; Dreyer et al., 2015, 2016), and poor psychological and physical outcomes (Uusküla, 1996; Lukkarinen and Hentinen, 1997, 1998; Brummett et al., 2004; Lindau et al., 2014; Vaccarino et al., 2014; Leung Yinko et al., 2015; Xu et al., 2015, 2017; Pelletier et al., 2016a). This is consistent with the literature in other age ranges (Mallik et al., 2006; Vazquez et al., 2008; Sears et al., 2009; Ingles et al., 2013; Doyle et al., 2015; Pelletier et al., 2016b; Sabbag et al., 2017; Benderly et al., 2019; Vaccarino et al., 2019). Some studies suggest that mental health issues could partly be explained by the impact on body image that seems to be more difficult for women (Vazquez et al., 2008; Starrenburg et al., 2014; Ooi et al., 2016) and by the multiple social roles women have to handle, such as parenting and housekeeping, as well as developing their career (Vazquez et al., 2008).

Although this systematic review highlighted several specificities of YAC patients, it also brought to light the difficulties encountered to aggregate data on this subject. Indeed different methods (quantitative, qualitative, mixed) and also different tools (specific validated questionnaires, more general ones with only some items of interest, or questionnaires created for the study) were used to assess the psychosocial variables. Furthermore, different populations (MI, coronary artery disease, cardiac arrest, catheterization, and heart transplant) and different times of measures (during hospitalization or years later) were studied. Therefore, it was difficult to compare the data. It appears that research on patients with a cardiac illness is dominated by quantitative studies, with significant focus on MI (see **Table 2**). This was partly due to a major group of research, the VIRGO studies, that accounted for a quarter of these articles (Bucholz et al., 2014; Lindau et al., 2014, 2016; Dreyer et al., 2015, 2016; Xu et al., 2015, 2017; Beckman et al., 2016). Furthermore, studies on YAC patients seem to be more about "young adults" and middle-aged adults, who are probably easier to include because they are more numerous in cardiac settings than "emerging adults" (Arnett, 2000).

To our knowledge, this is the first systematic review summarizing the psychological experiences of YAC patients. It shows their specific needs and identity compared to older cardiac individuals. However, there are several limitations to this review. Firstly, a majority of the studies reviewed concerned patients with coronary diseases. Our results might then be a more accurate description of coronary patients rather than of all individuals with a cardiac illness. However, our aim was to develop an overview of multiple cardiac diseases, and while the distinction between heart diseases is essential for professionals, it may not be for patients. Moreover, apart from heart-transplanted patients, few differences were found between patients with different cardiac issues. Therefore, regrouping patients according to their age, not their disease, may be more relevant.

Secondly, we were not able to include specific information regarding patients living with ICD or valvular prostheses as the relevant studies identified always focused on participants with

BOX 1 | **Practice and research implications**

Implications for practice

- Consider young patients coping with a cardiac illness as a specific population, different from teenagers and older adults.
- Explore adherence and present it as a way to a healthier and a more meaningful way of life.
- Help young adult cardiac (YAC) patients get in touch with other young patients and promote communication with their families and professional caregivers.
- Accompany YAC patients in their new identity and help them find effective ways of coping.
- Provide sexual counseling.

Implications for research

- Consider YAC patients as a specific population.
- Study other cardiac diseases than coronary/myocardial infarction.
- Pay attention to the specificities of women.
- Identify the most efficient coping strategies to enhance mental health issues and quality of life.
- Test interventions (psychoeducation and psychotherapies) to help these patients cope with their difficulties.

congenital heart diseases. However, almost all the references of our included articles were checked for this subject matter. Therefore, it is highly probable that all the relevant research studies were included.

Lastly, the data selection was conducted by the main researcher only. However, the risk of selection bias was reduced thanks to two independent authors performing the study selection, and frequent discussions took place on the data, themes, and interpretation within the author's team. Moreover, the quality of each study was assessed by two researchers. Eventually, the results seemed to represent the healthcare system of each country where recruitment took place well since we found, for instance, financial barriers in the USA where patients spend a lot for their medical expenses.

CONCLUSION

YAC patients seem to constitute a specific population among individuals with a cardiac illness. This systematic review presented the psychosocial experience expressed by these patients who cope with symptoms of depression, stress, anxiety, low QoL, and social isolation. Several of these outcomes may be more difficult to endure for YAC patients than for other age groups due to their life context with careers to develop, children to raise, and financial responsibilities while coping with the disease. In spite of the specific threats inherent to each cardiac disease, YAC patients are to be considered with their own identity and challenges. Moreover, young women are a particularly fragile group among patients with a cardiac illness. Therefore, psychosocial interventions targeting YAC patients to improve their mental health and adherence should be trialed. Practice and research implications are available in **Box 1**. Interventions could focus on the exploration of emotions, beliefs, and the feeling of self-efficacy (Riegel et al., 2006; Riegel and Dickson, 2016). It would also be interesting to test whether or not interventions specific to their age group would be beneficial to YAC patients in terms of mental health and quality-of-life improvements, with a special focus on women. Future studies should also include a focus on post-traumatic stress disorder as, despite the vast literature pointing out its prevalence among cardiac patients (Vilchinsky et al., 2017), it was not addressed in the included studies. Research could also include caregivers as they were found to be impacted by the disease (Trump and Mendenhall, 2017); thus, they may influence both the well-being and the adherence of patients (Sher et al., 2014; Varela Montero and Barrón López de Roda, 2016; Lyons et al., 2017).

AUTHOR CONTRIBUTIONS

JJ and AU contributed to the conception and the design of the study. Data were screened by JJ and CV. JJ, AJ, and CE assessed the material. JJ extracted the data. JJ, CV, and AU analyzed the data. JJ wrote the manuscript. CV rewrote some sections of the manuscript. All authors contributed to manuscript revision and read and approved the submitted version.

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SUPPLEMENTARY MATERIAL

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Psychosocial Cardiological Schedule-Revised (PCS-R) in a Cardiac Rehabilitation Unit: Reflections Upon Data Collection (2010–2017) and New Challenges

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Introduction: The Psychosocial Cardiological Schedule (PCS) was developed as a screening tool for patients undergoing cardiac rehabilitation (CR) to detect clinically relevant psychosocial/cognitive problems requiring psychological assessment/intervention. Filled out by a trained nurse, it classifies patients according to their need or not for a psychological interview and intervention provided by the psychologist (PCS-Yes vs. PCS-No).

Aims: The main aim was to compare PCS data collected, respectively, in 2010 and 2017, regarding patients' socio-demographic characteristics, clinical variables, and the inclusion criteria for psychological counseling. Subsequently, the original Italian PCS was revised and an English version of the schedule was provided [PCS-Revised (PCS-R)].

Results: 28 patients (aged 53.5 + 12.6 years, M = 20) of the 87 recruited in 2010 vs. 35 (aged 64.9 + 12.7 years, M = 28) of the 83 recruited in 2017 met the criteria for PCS-Yes: age < 55 years, social problems (living alone, no social support), manifest psychological/behavioral problems, suspected neuropsychological disorders, low prescription adherence, inadequate disease awareness. Comparing the two samples (2010 vs. 2017), clinical variables were similar, and the need for a psychological interview did not differ substantially (32.2 vs. 42.2%), but age increased significantly (PCS-Yes: 53.5 ± 12.6 vs. 64.9 ± 12.7 years, p = 0.001; PCS-No: 68.3 ± 8.0 vs. 75.0 ± 7.7 years, p = 0.0001). A significant increase was observed in the recommendation for neuropsychological assessment (3.6 vs. 25.7%, p = 0.02) to confirm eventual cognitive deficits. These results, the clinical experience, and the recent evidences from literature led to the PCS-R, incorporating a psychosocial screening, a psychological/neuropsychological deeper assessment, and a recommendation for a specific intervention to be carried out either during rehabilitation or in outpatient services.

Conclusion: The data comparison highlight changes in the cardiac population, which is aging and more frequently requires neuropsychological assessment. The PCS-R could be considered in clinical practice as a useful screening tool to implement a timely coordinated interdisciplinary intervention, comprehensive of specific and tailored psychotherapeutic techniques.

Keywords: psychosocial screening, psychological interview, cardiac rehabilitation, nursing, interdisciplinary intervention, rehabilitation medicine

INTRODUCTION

Cardiac rehabilitation (CR) is a comprehensive multidisciplinary program individually tailored to the needs of patients with cardiovascular (CV) disease (Smith et al., 2006; Balady et al., 2007). The objectives in the medium and long term are to reduce the risk of subsequent CV events (morbidity and mortality) and delay the progression of atherosclerosis, of the underlying cardiopathy and clinical deterioration (Piepoli et al., 2016; Fattirolli et al., 2018). The overall focus is on improving daily function and reducing CV risk factors. CR includes interventions to lower blood pressure and improve lipid and diabetes mellitus control, tobacco cessation, behavioral counseling, and graded physical activity (Anderson and Taylor, 2014; Pogosova et al., 2015; Piepoli et al., 2016; Servey and Stephens, 2016; Albus et al., 2019a; Long et al., 2019). Many CR guidelines and position statements recommend screening for psychosocial risk factors, although there is wide variation in the recommended factors and recommended screening tools (Jackson et al., 2017; Sommaruga et al., 2018; Albus et al., 2019b). National and European CV prevention and rehabilitation guidelines (Pogosova et al., 2015; Griffo et al., 2016; Fattirolli et al., 2018) recommend multidisciplinary interventions involving nurses, physiotherapists, dieticians, and psychologists in collaboration with cardiologists. The core tasks to be performed by each single team member have been detailed in recent position papers (Piepoli et al., 2016; Fattirolli et al., 2018).

The increased participation in CR of complex, elderly comorbid patients with psychological and neuropsychological problems raises the need to refine the screening models used to identify patients requiring psychological support (Gellis and Kang-Yi, 2012; Forman and Wenger, 2013; Cameron et al., 2017). This is matched by a growing interest on the part of nurses to improve their own skills in identifying and managing patient psychosocial difficulties, within the time limits of their workload in a CR setting (Turner et al., 2017; Winder et al., 2017). The synergy between these two professional figures—nurse and psychologist—can be seen as a valid reflection of the multidisciplinary nature of CR today. The CR short-term goals are clinical stability, limitation of the physiological and psychological consequences of CV disease, and overall improvement of the patient's functional capacity and degree of autonomy, independence, and quality of life. In CR, the psychologist's specific contribution is to help identify and implement, through health and clinical psychology, adequate diagnostic-therapeutic pathways (Pogosova et al., 2015; Richards et al., 2018; Sommaruga et al., 2018; Albus et al., 2019b; Pedersen and Doyle, 2019).

The starting point of an appropriate psychological intervention in CR is to early identify problems or needs that may indicate the necessity for specific psychological support according to the latest cardiac guidelines (Giannuzzi, 2016; Piepoli et al., 2016; Jbilou et al., 2019; McPhillips et al., 2019).

In this process, the dialog between the psychologist and the other healthcare professionals allows a useful and timely collection of information and observations that are registered and codified. To this end, the Psychology Unit in collaboration with the Cardiac Rehabilitation Department of ICS Maugeri – Montescano (PV) developed a Psychosocial Cardiological Schedule (PCS) aimed to detect indicators of psychological, behavioral, social, and cognitive problems/needs. The psychologists, who have been working at the Cardiac Rehabilitation Department for many years, previously trained the nursing staff to detect patients' psychosocial manifestations/needs, cardiac behavioral risk factors, and problems in dealing with illness management. A trained nurse fills in the PCS, providing screening information and a written clinical report for care pathways management according to the need or not for a psychological interview and intervention (Pierobon et al., 2012). The screening process considers data from nursing and medical records, observational data related to the patient's behavior in the hospital ward, information about the patient given by the caregiver, and any other clinical data available.

The first version of the PCS (Pierobon et al., 2012) was in the Italian language. The sections required the compilation of demographic, anamnestic, clinical-psychosocial data, and information related to both the knowledge and the management of the disease. It is a screening schedule, structured as a checklist, which indicated the selection criteria for a deeper psychological interview. These criteria, outlined in gray in the PCS, are described below in Section "Procedure." More precisely, any psychological/psychiatric problems and risk factors detected in the medical history constitute a specific indication for psychological assessment only when they have a clinically relevant impact on the patient's current health status (Graham et al., 2007; Piepoli et al., 2016). The age criterion (arbitrarily set at $\leq$ 55 years) responded to the clinical need to evaluate the impact of the disease in a phase of the life cycle that is still fully active from a personal, family, and work status point of view and therefore involves a process of complex psychological adaptation (Olano-Lizarraga et al., 2016; Helgeson and Zajdel, 2017). The other selection criteria were decided based on scientific evidence from the literature (Sommaruga et al., 2003; Lichtman et al., 2008; Albus et al., 2019a).

The main aim of the present study was to compare the PCS data collected in January–February 2010 with those collected in January–February 2017, focusing on the differences between patients' socio-demographic characteristics, clinical variables, and the inclusion criteria for psychological interview. Subsequently, a second aim was to update the Italian version of the PCS in light of the reflections made upon PCS data comparison, as well as the most recent CR guidelines and position papers. Besides, an English translation of the revised PCS was provided [PCS-Revised (PCS-R)].

MATERIALS AND METHODS

Procedure

The data analysis of this retrospective comparative study was performed considering all cardiac patients consecutively admitted for inpatient rehabilitation to the Cardiac Rehabilitation Department of ICS Maugeri – Montescano (Pavia), Italy in 2 months: January–February 2010 and January–February 2017. All patients underwent a screening evaluation with the original version of PCS (Pierobon et al., 2012) filled in by a trained nurse, within 2 days of admission. Patients were divided into two groups based on whether they met the selection criteria for a deeper psychological interview (PCS-Yes) or not (PCS-No). The selection criteria for PCS-Yes were: age (≤55 years), absence or lack of social and/or family support, current smoking, current manifestation of at least one psychological/psychiatric symptom, inadequate illness awareness, presence of a neuropsychological disorder, and poor adherence to clinical prescriptions. Patients who met one of the aforementioned criteria underwent a planned psychological interview (and/or test evaluation) and the related psychological intervention. All patients were enrolled in the CR program following an acute cardiac event (acute myocardial infarction, myocardial revascularization, cardiac surgery, and acute pulmonary edema) or an instability of a chronic condition, in accordance with the CR guidelines (Piepoli et al., 2016; Fattirolli et al., 2018). Patients signed an informed consent for all procedures and explanations at the admittance. The study was approved by our Institutional Review Board and Central Ethics Committee of the ICS Maugeri SpA SB (CEC) (approval number: CEC N.927, 27/06/2013).

After data collection and analysis, the original Italian version of the PCS (Pierobon et al., 2012) was modified and integrated (**Supplementary Data Sheet S1**) based on the results of the PCS data comparison, the evidence from the psychosocial literature about CV diseases (Pogosova et al., 2015; Sommaruga et al., 2018; Albus et al., 2019b), the scientific evidence about screening tools in CR (Jackson et al., 2017), and the most recent CR guidelines (Piepoli et al., 2016; Fattirolli et al., 2018). Besides, an English version of the revised PCS was prepared (**Supplementary Data Sheet S2**).

Statistical Analysis

Descriptive statistics are reported as mean ± standard deviation (SD) for continuous variables and as number (percentage) for discrete variables. Comparisons between groups (2010–2017) for continuous variables were assessed by Student's t-test for independent samples, while categorical variables were assessed by chi-square test. The analysis focused on differences between patients' socio-demographic characteristics, clinical variables, and the inclusion criteria for a psychological interview. All statistical tests were two-tailed and statistical significance was set at $p < 0.05$. All analyses were carried out using the SAS/STAT statistical package, release 9.2 (SAS Institute Inc., Cary, NC, United States).

RESULTS

Table 1 reports the PCS data on socio-demographic and clinical characteristics of the two study samples (2010–2017). We found a significantly lower mean age in 2010 compared to 2017 (PCS-Yes, 53.5 ± 12.6 vs. 64.9 ± 12.7, $p < 0.001$; PCS-No, 68.3 ± 8.0 vs. 75.0 ± 7.7, $p < 0.0001$). Furthermore, the number of male patients increased significantly from 2010 to 2017 (71.4 vs. 80%, $\chi^2 = 8.43$, $p = 0.0037$). As to patients' current and past clinical cardiac characteristics, social status, and risk factors, no significant differences were found between the two samples. **Table 2** shows the frequency distribution of the selection criteria for in-depth psychological interview (PCS-Yes) in the two samples. 28 patients of the 87 recruited in 2010 and 35 of the 83 recruited in 2017 met the criteria for PCS-Yes. The indication for psychological interviews based on anxiety symptoms was significantly higher in 2010 (32.1%) than in 2017 (11.4%). Instead, the indication for neuropsychological assessment due to cognitive disorders was significantly lower in 2010 (3.6%) than in 2017 (14.3%).

After PCS data comparison, several changes, integrations, and additions were made to the original schedule, to provide a revised version (**Supplementary Data Sheets S1, S2**) available in two languages. The PCS-R is divided into the following three sections:

- PCS-R (I)—Clinical and socio-demographic information, filled in by a trained nurse. A dedicated space is also provided for any notes or observations/clarifications concerning the patient's clinical status (Pierobon et al., 2012).
- PCS-R (II)—Psychosocial checklist, filled in by a nurse previously trained by a psychologist. It has six sub-sections: psychological comorbidity manifestations, general/specific psychological and neuropsychological problems, disease management, social issues, caregiver needs, and positive affectivity. At the end of PCS-R (I-II), there is a sub-section where the interdisciplinary team (nurse, cardiologist, and psychologist) could indicate the need for further psychological/neuropsychological interview and/or testing (Pierobon et al., 2012; Sommaruga et al., 2018).
- PCS-R (III)—Psychological intervention, filled in by the psychologist after the psychological interview. It indicates

TABLE 1 | Socio-demographic and clinical results of the two samples.

	2010 (*n* = 87)		2017 (*n* = 83)	
	PCS-YES (*n* = 28) M(SD)	**PCS-NO (*n* = 59) M(SD)**	**PCS-YES (*n* = 35) M(SD)**	**PCS-NO (*n* = 48) M(SD)**
Age	53.5 ± 12.6^a	66.6 ± 8.0^c	64.9 ± 12.7^b	75.0 ± 7.7^d
Duration of cardiac illness (years)	7.7 ± 5.5	9.0 ± 7.9	4.9 ± 7.4	10.0 ± 9.3
BMI	27.4 ± 6.9	26.7 ± 3.7	26.5 ± 5.9	25.7 ± 4.4
	***n* (%)**	***n* (%)**	***n* (%)**	***n* (%)**
Gender (male)	20 (71.4)	24 (40.7)	28 (80.0)	32 (66.7)
Family status (married)	15 (53.6)	48 (81.4)	19 (54.3)	28 (58.3)
Current occupation (yes)	12 (42.8)	4 (6.8)	9 (25.8)	3 (6.3)
Dwelling status (living alone)	9 (32.1)	7(11.9)	5 (14.3)	7 (14.6)
Social problems (yes)	3 (10.7)	1 (1.7)	–	–
Current smoking habit	8 (28.6)	12 (20.3)	9 (25.7)	7 (14.6)
Anamnesis risk factors				
Smoking	18 (64.3)	30 (50.8)	16 (45.7)	11 (22.9)
Dyslipidemia	12 (42.9)	35 (59.3)	13 (37.1)	19 (39.6)
Hypertension	17 (60.7)	34 (57.6)	19 (54.3)	33 (68.8)
Diabetes	10 (35.7)	11 (18.6)	10 (28.6)	20 (41.7)
Overweight	10 (35.7)	16 (27.1)	10 (28.6)	13 (27.1)
Familiarity	11 (39.3)	18 (30.5)	13 (37.1)	16 (33.3)
Cardiological clinical history and/or index event				
Recent or previous AMI	12 (42.9)	26 (44.1)	18 (51.4)	14 (29.2)
Angioplasty	13 (46.4)	19 (32.2)	7 (20.0)	5 (10.4)
Revascularization	1 (3.6)	15 (25.4)	–	1 (2.1)
Valvulopathy (valve replacement)	1 (3.6)	12 (20.3)	2 (5.7)	5 (10.4)
Chronic obstructive arteriopathy	–	2 (3.4)	1 (2.9)	–
Heart transplantation	9 (32.1)	9 (15.3)	1 (2.9)	–
Chronic heart failure	8 (28.6)	14 (23.7)	2 (5.7)	6 (12.5)

BMI, body mass index; AMI, acute myocardial infarction; $Age^a < Age^b$, $p < 0.001$; $Age^c < Age^d$, $p < 0.0001$.

the recognition of specific risk and protective psychosocial factors in the sensory, emotional, behavioral, cognitive, as well as interpersonal, social, and family areas. This section also specifies the technique(s) adopted during the psychological intervention (Bettinardi et al., 2014).

DISCUSSION

This retrospective comparison of PCS data collected in 2010 with data collected in 2017 provided an interesting overview of the evolution in the profile of cardiac patients attending CR, particularly concerning differences in socio-demographic characteristics, clinical variables, and the specific motivations for psychological counseling. In addition, it led to PCS-R adding more specific classifications regarding heart diseases and broadening the psychosocial investigation and intervention in a rehabilitative setting.

The results of the retrospective analysis of the PCS data highlighted the progressive aging of the cardiac patient population participating in CR, although the framework of social and cardiac clinical history characteristics remained quite similar. In fact, we found a significant difference in the mean age of the two samples and this is in line with the well-known aging population phenomenon (United Nations, 2017). Moreover, we found an increase in the number of male patients in 2017. This finding, however, does not fully reflect the latest epidemiological trends, which show that the prevalence of males in CV disease is declining while CV problems are increasing in females, above all in the older population (Pectoris, 2013; Townsend et al., 2016).

As concerns the patients' current and past clinical cardiac characteristics and risk factors, there was no significant difference between the two samples. We found a modest increment (non-significant) in the number of PCS-Yes in 2017 with respect to 2010 (32.2 vs. 42.2%). This data might outline an increased attention of healthcare professionals on the issues presented in the latest cardiac (Forman and Wenger, 2013; Piepoli et al., 2016; Jackson et al., 2017) and psychosocial guidelines and position papers (Pogosova et al., 2015; Sommaruga et al., 2018; Albus et al., 2019b).

Concerning the criteria for an in-depth psychological interview, two significant differences were found. First, a significant decrease in reported signs of anxiety was unveiled. The detection of these anxiety signs may disappear behind the stronger influence of depression on self-care (Muller-Tasch et al., 2018) or other behavioral manifestations

TABLE 2 | Frequencies of selection criteria for in-depth psychological evaluation (PCS-Yes).

	2010 *n* (%)	2017 *n* (%)	χ^2 *p*-Value
PCS-Yes	28 (32.2)	35 (42.2)	0.1778
Selection criteria			
Age (≤55 years)	10 (35.7)	11 (31.4)	0.7199
Anxiety	9 (32.1)	4 (11.4)	0.0435*
Depression	7 (25.0)	6 (17.1)	0.4438
Behavioral/psychiatric problems	2 (7.1)	–	0.1081
Cognitive disorders	1 (3.6)	5 (14.3)	0.0169*
Inadequate illness awareness	6 (21.4)	2 (5.7)	0.0627
Treatment non-adherence	8 (28.6)	7 (20.0)	0.4274
Current smoking	7 (25.0)	11 (31.4)	0.5746
Addiction	2 (7.1)	1 (2.9)	0.4274
Severe sleep disorders	–	–	–
Other (e.g., apathy, ambivalent behavior, extreme fear)	1 (3.6)	3 (8.7)	0.4187

*$p < 0.05$.

such as apathy, ambivalent behavior, or extreme fear that represented 8.7% of the selection criteria for in-depth psychological evaluation in 2017. Second, there was a significant increase in reported cognitive disorders. This is in line with the growing number of elderly patients (United Nations, 2017) who may require a specific neuropsychological assessment. These data could also be linked to the well-known associations between cardiac disease and cognitive issues (Pressler et al., 2010; Cameron et al., 2017). Even though the PCS is based simply upon observations by trained nurses, the data collected on the incidence of psychological manifestations (anxiety, depression), behavioral issues (smoking and addiction), and disease management (disease awareness and adherence to treatment) are in line with the most recent research and position papers (Pogosova et al., 2015; Sommaruga et al., 2018; Albus et al., 2019b).

Furthermore, in accordance with the recent CR guidelines and position papers, these results led to the revision of the schedule. As to PCS-R (I), data from literature offered the opportunity to provide a more specific and updated classification of heart diseases. As to PCS-R (II), the growing number of older adults and the reported necessity of a cognitive evaluation are often associated with an increasing need to provide a dedicated socio-familiar care pathway (Carmeli, 2014; Jaul and Barron, 2017; Grant and Graven, 2018). To this regard, the present data strengthened the paramount importance of evaluating the caregivers' needs that were not specifically addressed in the original version of the PCS. Moreover, the reported patients' psychological problems led to a rearrangement of the psychosocial checklist by adding more specific and updated issues (**Supplementary Data Sheets S1, S2**).

A psychological assessment/intervention creates a specific setting in which patients could report some additional and useful information that might be fundamental to enhance their treatment adherence and could help the interdisciplinary team to better tailor their rehabilitative program (Pogosova et al., 2015; Pedersen et al., 2017; Pedersen and Doyle, 2019). The early recognition of patient's psychosocial problems and the subsequent psychological intervention can reduce, in turn, the burden of care for both nurses and cardiologists (Feo et al., 2018). It is clear that nurses would require a training program in which the psychologist teaches them how to accurately identify and collect all the necessary information for the schedule compilation. This could be quite tough if nurses are not motivated or perceive the screening as simply a further, perhaps useless, addition to their workload (Turner et al., 2017). In this regard, trained nurses could do the first screening along with their other standard data collection. Therefore, it would not increase their amount of work. Instead, it would save time for psychologists in screening patients and allow them to dedicate their time to interventions on the selected patients. The resulting decrease in the extra working hours of psychologists might lower hospital administrative costs. At the same time, the early recognition of not clinically relevant psychosocial problems could reduce the patient-related costs, by avoiding unnecessary time and money spent on interventions (Shields et al., 2018). Hence, the PCS-R might constitute an important asset for reducing healthcare costs.

Moreover, the PCS-R (III) highlights the patients' challenging and protective factors, according to the biopsychosocial model applied in rehabilitation (Engel, 1977, 1980). Specifically, it suggests useful information about the psycho-educational intervention implemented, the strategies for preserving and/or stimulating cognitive capacities, and the eventual referral to psychiatric counseling and/or social services (Fattirolli et al., 2018; Sommaruga et al., 2018).

The PCS-R format is designed for easy digitalization. Hence, an accurate PCS-R data collection and subsequent digitalization, besides enhancing clinical practice, would be of use both in writing the psychological report and in providing information for clinical research (Giardini et al., 2018). The report could refer also to the patient and caregiver's psychosocial evaluation and it could suggest relevant indications to improve disease awareness, management skills, and treatment adherence. Therefore, the PCS-R could be a handy tool to strengthen the communication and cooperation between the different professional figures of the interdisciplinary rehabilitation team. Moreover, it could allow an early classification of patients and caregivers' needs and issues that is crucial in patient-centered interventions in both acute and chronic diseases (Korner et al., 2016; Fattirolli et al., 2018; Poitras et al., 2018; La Rosa et al., 2020).

This study has to be read in the light of its strengths and limitations. Concerning the PCS-R, several limitations could be highlighted: its complexity, the need for a real sharing of rehabilitative outcomes among the team, the necessity of specific training to detect psychosocial issues, and the professional's high motivation to fill in the schedule. Another important limitation is the lack of updated PCS-R data, in particular those regarding the new sections on psychosocial needs, challenges, and psychotherapeutic intervention. Nevertheless, some points of strength are present too. First, the PCS-R allows the early recognition of patients' psychosocial problems that may suggest tailored subsequent psychological interventions. Second, the report of the different psychological techniques adopted could also consent to better focus on patients' needs, helping to reduce the burden of care for the interdisciplinary team. Finally, since the PCS-R is a screening checklist and not a diagnostic test, a validation process is not mandatory. Nevertheless, future studies, which are already in progress, could be useful to evaluate its feasibility and reliability in the hospital ward's routine.

Conclusively, this study presents interesting screening data on the evolution of CR patients over time. Moreover, these data, in accordance with recent literature, led to a revision process of a well-established screening tool finalized to collect data that could be representative of the actual population attending CR. Indeed, the PCS-R might represent an ideal screening tool for the interdisciplinary team's detection of psychosocial problems in patients undergoing CR that could help to tailor the psychological intervention according to the patient's emotional, cognitive, and social needs.

DATA AVAILABILITY STATEMENT

The datasets generated for this study are available on request to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Review Board and Central Ethics Committee of the ICS Maugeri SpA SB (CEC). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

AP, VT, and MF did the data collection of the first PCS version. NG, EN, and MV managed the database and did the statistical analysis. AP, VT, MF, MS, EA, CR, and AC contributed to the conception of the new Italian and English version of the schedule (PCS-R). NG and AP wrote the manuscript. All authors contributed to the manuscript review and read 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/fpsyg.2020.01720/full#supplementary-material

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Psychosocial Functioning, BMI, and Nutritional Behaviors in Women at Cardiovascular Risk

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Psychosocial factors such as depression, anxiety, and stress are associated with increased cardiovascular risk. Health behaviors may play a role in this relationship, as individuals experiencing elevated levels of anxiety, stress, and/or depression may be less likely to engage in risk-reducing behaviors such as diet and exercise. Some evidence suggests that this relationship is particularly relevant for women. This study explored the relationship between levels of anxiety, depression, stress, and specific nutritional behaviors in a sample of 187 women at cardiovascular risk. BMI was explored as a possible moderator of these relationships. Higher levels of depression in patients with high BMI was associated with increased fruit consumption, whereas this was not seen in highly depressed patients with normal BMI. The reverse pattern was seen for consumption of sweet drinks. Anxiety was found to have a complex relationship with consumption of sweetened drinks and white bread, with higher consumption at moderately elevated levels of anxiety and reduced consumption at the highest levels. Possible interpretations of these findings, as well as their implications for lifestyle interventions with this population are discussed. These findings suggest a number of questions for further research.

Keywords: cardiovascular risk, health behaviors, anxiety, depression, stress, emotional eating, physical activity

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INTRODUCTION

Psychosocial factors such as depression, stress, and anxiety are associated with increased cardiovascular risk (Fan et al., 2008). People who suffer depression are at greater risk for cardiovascular disease, and patients with comorbid cardiovascular disease and depression have a higher mortality rate. The risk increases for those with more severe depression (Hare et al., 2014). Psychological stress is also described in the 2016 European clinical guidelines for the prevention of cardiovascular disease as a factor that may contribute to both the development and progression of cardiovascular disease (Piepoli et al., 2016). Although the evidence for the impact of depression and stress is more consistent, multiple studies suggest that chronic anxiety may also have a deleterious effect on cardiovascular health (Cohen et al., 2015). According to one meta-analysis (Roest et al., 2010), anxiety is associated with a 26% increase in risk of incident coronary heart disease as well as a 48% increase in risk of cardiac death.

The mechanisms by which psychological factors influence cardiovascular illness are not fully understood, but health behaviors may play a role (Cohen et al., 2015). Some researchers have suggested that individuals at cardiovascular risk with comorbid psychiatric disorders may adopt behaviors that run counter to risk reduction (Szlejf et al., 2019). The relationship between psychological distress and negative health behaviors is well-supported. For example, one study found an association between general emotional distress and poorer exercise behaviors, i.e., greater sedentariness and reduced physical activity (St.-Pierre et al., 2019). Psychological distress has also been found to predict greater consumption of palatable, non-nutritious foods (e.g., Groesz et al., 2012). Psychological factors may augment the challenges faced by individuals at cardiovascular risk who seek to adopt positive health behaviors (Rippe and Angelopoulos, 2014). Addressing these factors, therefore, could significantly impact the effectiveness of lifestyle interventions.

The relationship between emotional factors and health behaviors for individuals at cardiovascular risk is particularly relevant for women. Rates of stress and depression are higher in women (Vaccarino and Bremner, 2017), and both the presence and severity of anxiety disorders are higher in women than in men (Serpytis et al., 2018). Compared with men, women have been found to be more disturbed by psychosocial stress (Beutel et al., 2018). Additionally, the effects of anxiety on cardiovascular health vary by gender. For example, the presence of an anxiety disorder was found to be associated with higher odds of compromised cardiovascular health among women, but not in men (Szlejf et al., 2019).

Psychological functioning appears to have a differential effect on health behaviors for men and for women. One study of cardiac patients found that women with cardiovascular disease and comorbid depression were less likely to engage in physical activity compared with their male counterparts (Allabadi et al., 2019). In one particularly striking study, higher levels of anxiety for women were associated with a significant decrease in a score measuring healthy lifestyle (i.e., physical activity, diet, BMI, and alcohol and tobacco consumption) over 20 years. This effect was independent of measured healthy lifestyle at the onset of the study; women with high anxiety had reduced odds of maintaining a healthy lifestyle over 20 years even if their lifestyle had been healthy initially (Trudel-Fitzgerald et al., 2016).

This study, focusing on a sample of women at high risk for cardiovascular disease, explored the relationship between psychological functioning and health behaviors. Our goal was to understand the particular impact of depression, anxiety, and stress on specific nutrition behaviors in this population. We were also interested in whether this relationship would vary for patients with high BMI as opposed to normal BMI. Emotional eating has been found to be associated with high BMI (Lazarevich et al., 2016); as such, we speculated that the relationship between psychosocial factors and unhealthy eating choices would be stronger for those with a high BMI than for those with a low BMI. This study builds on previous studies which examined psychological stress as a global construct (e.g., St.-Pierre et al., 2019) or evaluated healthy lifestyle as a whole (e.g., Trudel-Fitzgerald et al., 2016), taking a closer look at the relationship between individual emotional factors and specific eating behaviors.

MATERIALS AND METHODS

Study Sample

This sample included 187 consecutive patients seen at the Linda Joy Pollin Cardiovascular Wellness Center for Women (LJPCWW) at Hadassah University Medical Center between January 2014 and August 2019. LJPCWW is a prevention clinic aimed at reducing cardiovascular mortality in women. Patients may be referred by their doctor or self-referred. Patients were included in this study if they had undergone a cardiovascular event (myocardial infarction, percutaneous coronary intervention, or stroke), had an active cardiac symptom (e.g., chest pain or arrhythmia), or had three or more active risk factors (i.e., diabetes, hypertension, hyperlipidemia, peripheral artery disease, current smoker, family history of premature coronary disease, gestational diabetes, pregnancy-induced hypertension/pre-eclampsia, or obesity). Patients were excluded if they were pregnant, had type 1 diabetes, a psychiatric diagnosis that precluded participation, dementia, or if they were under the care of another multi-disciplinary clinic.

Data Collection

Data was collected using self-report questionnaires completed by the patients at their initial clinic evaluation.

Measures

Demographic data included age, education, and monthly income. Patients' weight and height were measured by the nurse, and their BMIs were calculated using the standard BMI equation (weight divided by height-squared).

Depression, anxiety and stress were measured utilizing a validated translation of the DASS-21 (Depression, Anxiety, and Stress Scale) (Lovibond and Lovibond, 1995/2019). The DASS-21 is a valid and reliable self-report scale assessing depression, anxiety and stress, which has been widely used in clinical and non-clinical populations. The DASS-21 is a set of three subscales of seven items each: depression, anxiety, and stress. Subjects are asked to use four-point severity/frequency scales to rate the extent to which they have experienced each state "over the past week." Scores for Depression, Anxiety and Stress are calculated by summing the scores for the relevant items; higher scores are consistent with more severe symptomatology. Normal, mild, moderate, and severe depression, anxiety, and stress were determined based on the scoring system published for the scale.

Nutrition behaviors were measured using questions from a culturally adapted translation of the Healthy Heart Score (Chiuve et al., 2014) which is based on questions from the food frequency questionnaire of the Nurses Health Study (2019) (available at https://www.nurseshealthstudy.org/participants/questionnaires; accessed 27-11-19). Self-reported data was collected from patients with regard to consumption of fruits and vegetables, whole grains, white flour, sugar-sweetened beverages, and red and processed meats. For each food item, participants were asked how often, on average, a specified portion was consumed during the past week. In accordance with the Healthy Heart Score, consumption of fruits, vegetables, and whole grains were considered health-promoting nutrition behaviors. Consumption of white flour, sugar-sweetened beverages, and red and processed meats were considered non-health promoting nutrition behaviors.

Statistical Analysis

Demographic and other quantitative data were analyzed with SPSS version 25 (IBM SPSS Statistics, Armonk, NY, United States).

These data were collected from community participants as part of an existing research program; as such, the number of respondents was fixed. As such, sample power was calculated a posteriori for a multiple-regression analysis with four independent variables and effect size = 0.05 (Faul et al., 2009). This *post hoc* power analysis (N = 180; significance level = 0.05; effect size = 0.05; $k_{measurement}$ = 4) yielded a power (1-β) of 0.85.

Descriptive statistics and regression analyses were used. Linear and curvilinear regressions were used to assess the effects of the psychological predictors (i.e., anxiety, depression, and stress) together with BMI as a physiological predictor. All dependent variables were continuous, although some were measured on an ordinal (Likert) scale or count. In each linear model engagement in positive and negative nutrition behaviors (i.e., consumption of health-promoting foods or non-health-promoting foods) were measured as a function of the two predictors, psychological and physiological.

To test for potential confounding effects, we correlated three possible confounders with the measures of depression, anxiety, and stress. We also correlated these factors with BMI, which we expected to affect the daily consumption of various food products. None of the background variables were shown to have potential confounding effects. Since these variables did not show any correlation with the independent measures, any potential confounding effect would be insignificant notwithstanding their association with the daily consumption of various food products.

Two additional tests were added to this model: (1) A curvilinear association between the measured psychological variables and eating habits; and (2) An interaction effect between BMI and the psychological predictors. The first test was meant to assess the possibility of a non-linear association between psychological factors and eating behaviors, i.e., that the association between psychological factors and eating behaviors would change direction after a certain point. The second was a

TABLE 1 | Demographic data.

Characteristic	Percentage
Age	
<40	5.0
41–50	14.4
51–60	26.5
61–70	41.4
71–80	11.0
>81	1.7
Marital status	
Married	75.8
Separated/divorced	10.2
Widowed	9.7
Single	4.3
Level of education	
Elementary School	3.3
High School Equivalency	16.5
High School Diploma	17.6
Professional Certificate	3.8
Bachelor's Degree	37.4
Graduate Degree	21.4
Monthly income	
Up to 4000 NIS	12.9
4001–7500 NIS	33.1
7001–15000 NIS	47.2
Over 15000 NIS	6.7

TABLE 2 | Descriptive statistics.

Variable	Categories	Count	Percent	Means	*SD*
Age		181		59.93	11.12
BMI		179		29.20	5.71
	Normal	43	23		
	Overweight	64	36.9		
	Obese	72	40.2		
Depression				3.81	3.92
	Normal	100	70.4		
	Mild-moderate	29	20.4		
	Severe-extremely severe	13	9.2		
	Total	142	100		
Anxiety				3.83	3.73
	Normal	83	57.2		
	Mild-moderate	38	26.2		
	Severe-extremely severe	24	16.6		
	Total	145	100		
Stress				6.20	4.47
	Normal	93	65.0		
	Mild-moderate	34	23.8		
	Severe-extremely severe	16	11.2		
	Total	143	100		
Hyperlipidemia	Yes	100	54.6		
Hypertension	Yes	55	30.1		
Systolic		180		130.41	18.71
Diastolic		178		70.78	9.88
Diabetes	Yes	29	16.1		

TABLE 3 | Regression analyses for depression, BMI, and food consumption, standardized coefficients.

	Fruit per day	Vegetable per day	Whole grains	Sweet drinks per day	White bread per day	Red meat per day
Step 1						
BMI	0.08	−0.02	−0.02	0.19*	0.20*	−0.15
Dep.	0.16	−0.01	0.11	0.03	0.17	−0.05
R^2	0.03	0.01	0.01	0.03	0.06*	0.03
Step 2a						
Dep.	−0.10	−0.44*	0.15	0.13	0.31	0.18
Dep.^{2}	0.30	0.39*	−0.05	−0.12	−0.16	−0.26
ΔR^2	0.02	0.04*	0.00	0.00	0.01	0.02
R^2	0.05	0.05	0.01	0.04	0.07*	0.04
Step 2b						
BMI X Dep.	0.19*	0.02	0.18	−0.19*	−0.03	−0.06
ΔR^2	0.03*	0.00	0.03	0.03*	0.001	0.004
R^2	0.06*	0.01	0.05	0.07*	0.06	0.03

$p < 0.05$; Step 1, linear; Step 2a, curvilinear; Step 2b, interaction; Dep, depression.

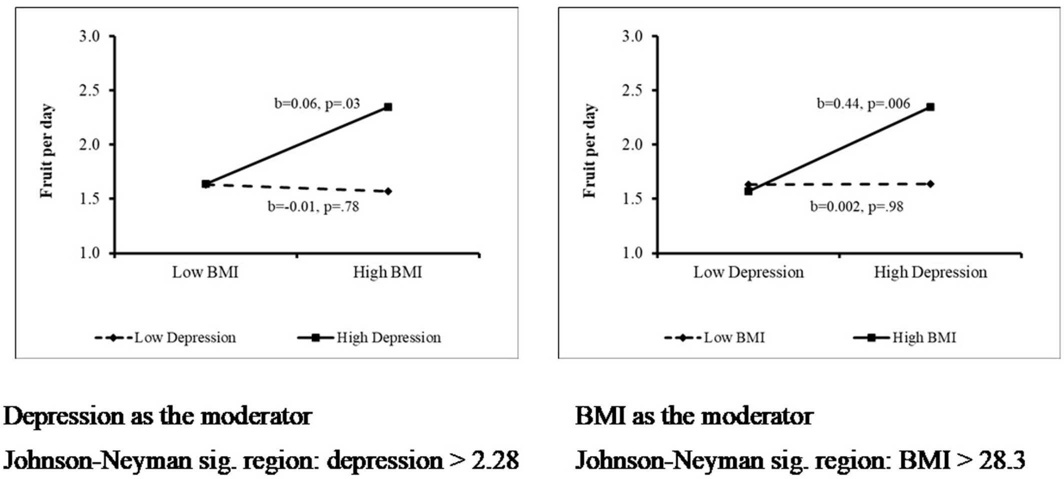

FIGURE 1 | Interaction effect of BMI and depression on daily fruit consumption.

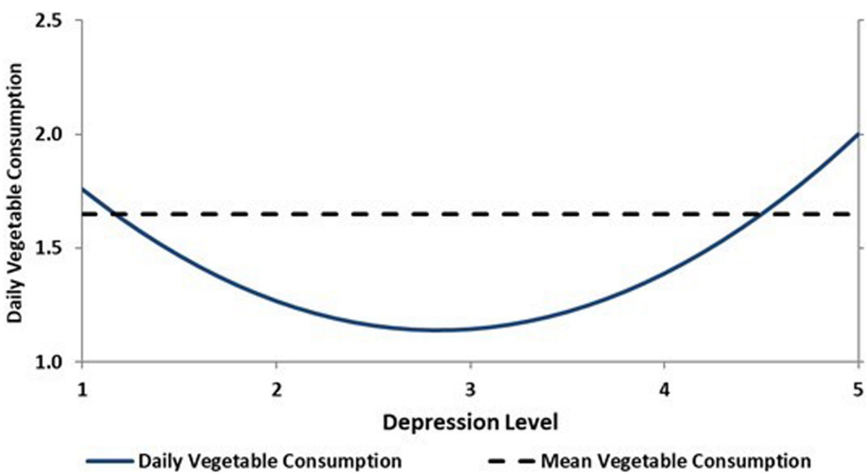

FIGURE 2 | Curvilinear prediction of daily vegetable consumption by depression.

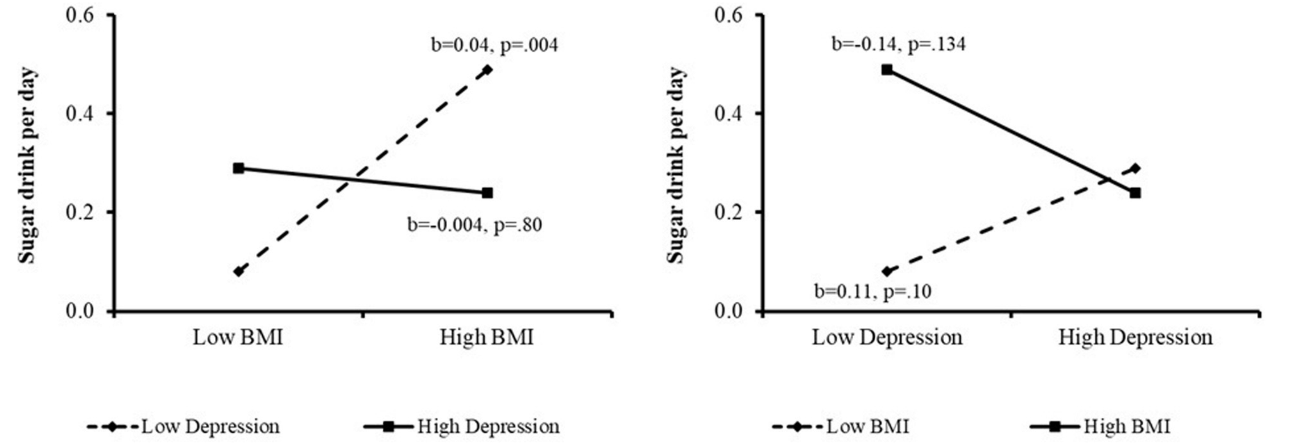

FIGURE 3 | Interaction effect of BMI and depression on daily sugar drink consumption.

TABLE 4 | Regression results for anxiety, BMI, and food consumption, standardized coefficients.

	Fruit per day	Vegetable per day	Whole grain	Sweet drinks per day	White bread per day	Red meat per day
Step 1						
BMI	0.06	0.03	−0.02	0.15	0.13	−0.14
Anx.	0.05	−0.04	−0.02	0.16	0.21*	−0.02
R^2	0.01	0.00	0.00	0.06*	0.07*	0.02
Step 2a						
Anx.	0.08	0.00	−0.09	0.65*	0.53*	0.23
Anx.^{2}	−0.04	−0.05	−0.08	−0.61*	−0.40*	−0.31*
ΔR^2	0.00	0.00	0.00	0.13*	0.06*	0.03*
R^2	0.01	0.00	0.00	0.19*	0.13*	0.05
Step 2b						
BMI X Anx.	−0.05	−0.07	−0.02	0.03	−0.02	0.01
ΔR^2	0.002	0.01	0.001	0.001	0.00	0.00
R^2	0.01	0.01	0.001	0.06	0.07*	0.02

$*p < 0.05$; Step 1, linear; Step 2a, curvilinear; Step 2b, interaction; Anx, anxiety.

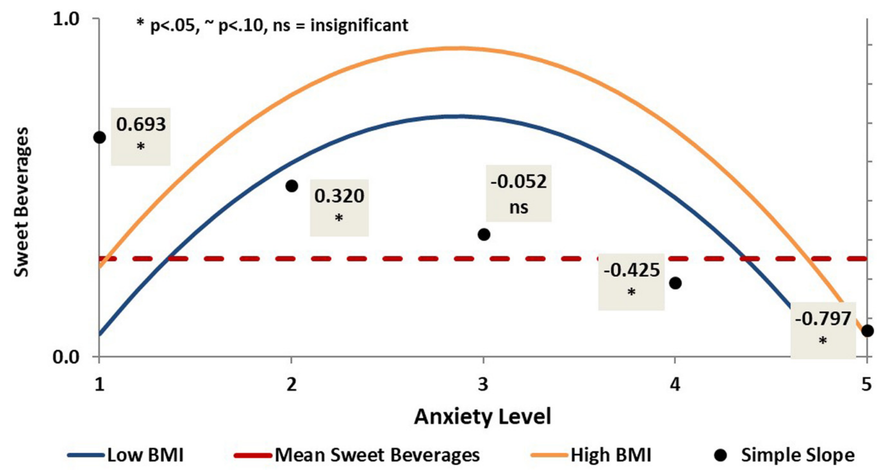

FIGURE 4 | Curvilinear prediction of daily sweetened drink consumption by anxiety.

test of non-independency between the two indicators, i.e., for varying BMI levels, the association between the psychological indicators and eating behaviors would change, and vice versa. We presented interaction results in the high-low approach (Aiken and West, 1991) and the point estimation approach (Johnson and Neyman, 1936). Results are presented in tables and relevant charts.

Ethical Considerations

Human subject approval was obtained from the Hadassah Medical Organization Institutional Review Board, and the study conformed to the principles outlined in the Declaration of Helsinki (Study # HMO- 0419-17).

RESULTS

Demographic data describing the participants are presented in **Table 1**, and descriptive statistics in **Table 2**. The average age of patient participants was 59.3 ($SD = 11.12$), with a range of 25–95. 37% of the participants were overweight (BMI = 25–29.9), and 40% were obese (BMI > 29.9). Mean depression (3.81), anxiety (3.83), and stress (6.20) levels were higher than would be expected in the general population. No differences were seen in the prevalence of depression, anxiety or stress in diabetic, hypertensive or hyperlipidemic patients ($F = 0.247$–2.11; $p = 0.147$–0.619). No differences in the prevalence of depression, anxiety, or stress were found for any of the demographic variables.

Depression, BMI, and Nutrition Behaviors

Regression analyses of the relationship between depression and BMI and eating behaviors are presented in **Table 3**.

When the effects of depression and BMI on daily fruit consumption were analyzed using linear regression, results were not significant. However, assessment of interaction effects revealed that for individuals with higher levels of depression, BMI showed a positive association with fruit consumption ($b = 0.06$, $p = 0.03$). For individuals with lower levels of depression, BMI was not significantly associated with fruit consumption (cutoff point: depression greater than 2.28, $p < 0.05$). Additionally, for individuals with high BMI, depression was positively associated with daily fruit consumption ($b = 0.44$; $p = 0.006$). For individuals with lower BMI, this association was not significant (see **Figure 1**).

Daily vegetable consumption did not have a significant linear association with psychological variables or with BMI. However, when we tested for curvilinear effects, the association between depression and daily vegetable consumption was found to have a parabolic shape ($\beta_{linear} = -0.44$, $p < 0.05$; $\beta_{quadratic} = 0.39$, $p < 0.05$). That is, depression and daily vegetable consumption were negatively associated when depression scores were low, from normal to mild. When depression scores were higher than 1.18 (i.e., ranging from mild to extremely severe; maximum = 14+), increasing levels of depression were associated with increased vegetable consumption (see **Figure 2**). Note that this relationship was significant with respect to the curvilinear model. However, this model did not explain a significant percentage of the overall variance.

With regard to sweet drink consumption, higher BMI was associated with increased consumption of sweet drinks ($\beta = 0.19$, $p < 0.05$). Depression had no direct linear effects on sweet drink consumption, but the additional interaction term (model 2b) indicated differing effects of depression on sweet drink consumption in high vs. low BMI study participants. When depression was low, a positive association between BMI and sweet drink consumption was maintained ($b = 0.04$, $p = 0.004$). However, this relationship did not hold at higher levels of depression.

When we further explored this relationship, we found that in low BMI participants, consumption of sweet drinks increased as levels of depression increased. In high BMI participants, in contrast, sweet drink consumption decreased as depression increased. Both of these associations were insignificant, however, other than at the extremes of the sample. [The Johnson-Neyman analysis (see **Figure 3**) showed that for those whose BMI fell below 20.15, slightly below the sample mean, the association between depression and sweet drink consumption was positive, while this association was negative for those whose BMI exceeded 49, two standard deviations above the sample mean].

In addition, we found a linear positive association between BMI and daily consumption of white bread ($\beta = 0.20$, $p < 0.05$). Consumption of whole grains or red and processed meats was not affected by depression or by BMI, neither alone nor in interaction.

Anxiety, BMI, and Nutrition Behaviors

We examined the effects of anxiety and BMI on nutrition (see **Table 4**). Anxiety was not found to significantly affect daily consumption of fruit or daily consumption of vegetables, alone or in interaction with BMI. No linear relationship was found between anxiety and consumption of sweet drinks, alone or in interaction with BMI.

However, anxiety did have a significant curvilinear relationship ($\beta_{linear} = -0.65$, $p < 0.05$; $\beta_{quadratic} = -0.61$, $p < 0.05$) with consumption of sweetened drinks (see **Figure 4**). Specifically, at low and mild levels of anxiety, as anxiety increased, consumption of sweet drinks increased. The direction of this relationship reversed for patients with severe and extremely severe levels of anxiety, such that as anxiety increased, daily consumption of sweet drinks decreased. The direction of this relationship was not affected by BMI.

Anxiety was also found to have a curvilinear relationship ($\beta_{linear} = 0.23$, ns; $\beta_{quadratic} = -0.31$, $p < 0.05$) with consumption of red and processed meats (see **Figure 5**), although this relationship was only significant at severe and extremely severe levels of anxiety. Specifically, red and processed meat consumption showed a slight (non-significant) increase as anxiety increased for patients with normal and mild levels of anxiety. After anxiety reached a moderate level, consumption of red and processed meat decreased as anxiety increased to severe and extremely severe levels.

Finally, anxiety displayed a significant curvilinear relationship ($\beta_{linear} = 0.53$, $p < 0.05$; $\beta_{quadratic} = 0.40$, $p < 0.05$) with

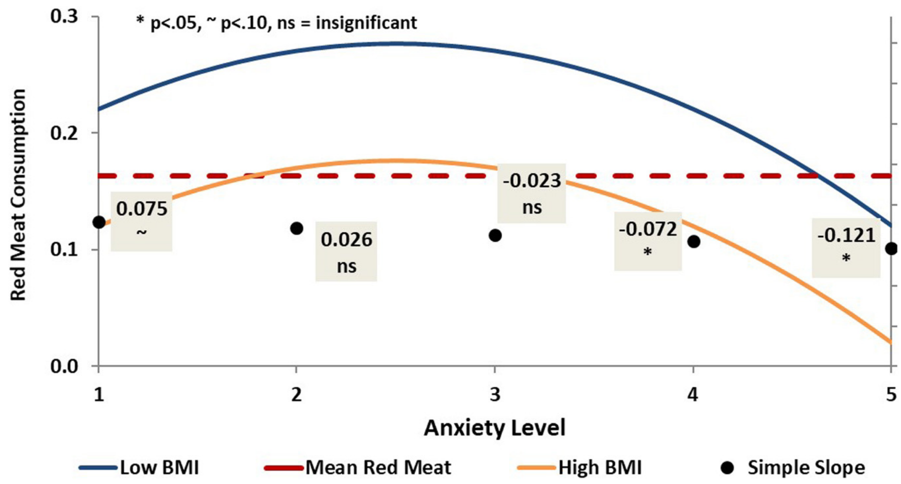

FIGURE 5 | Curvilinear prediction of red and processed meat consumption by anxiety.

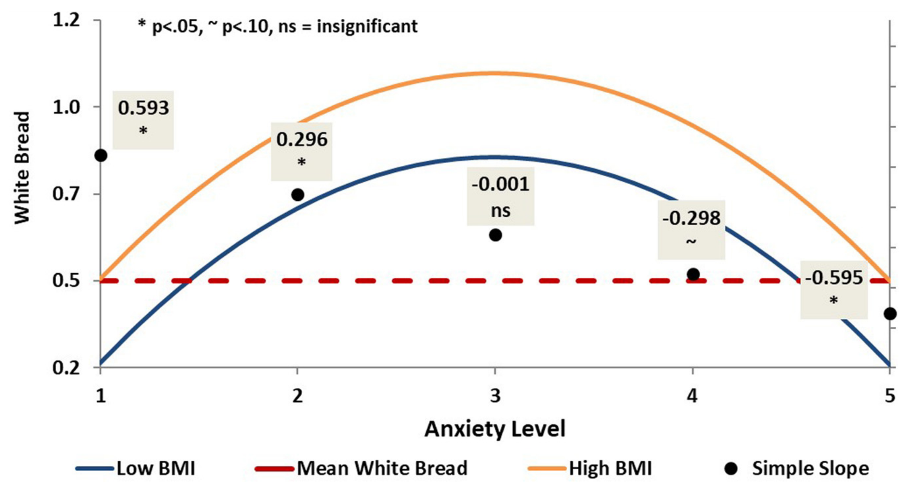

FIGURE 6 | Curvilinear prediction of white bread consumption by anxiety.

consumption of white bread (see **Figure 6**). For patients with normal and mild levels of anxiety, increased anxiety led to increased consumption of white bread ($p < 0.05$). For patients with moderate and severe levels of anxiety, this relationship appeared to reverse its direction with increased anxiety correlating with decreased consumption of white bread, although the relationship was no longer significant at these levels. As anxiety increased to extremely severe levels, the effects of anxiety on white bread consumption reached significance but were now negative, with increased anxiety leading to decreased white bread consumption. Anxiety did not have a significant effect on consumption of whole grains, neither alone nor in interaction with BMI.

Stress, BMI, and Nutritional Behaviors

We finally examined the effects of stress and BMI on eating behaviors (see **Table 5**). Although BMI was consistently found to predict daily sweetened drink consumption and daily white bread consumption, this relationship was not affected by changes in stress levels. Level of stress was not found to affect any of the nutrition behaviors studied. No significant linear, curvilinear, or interaction effects were found for stress and fruit and vegetable consumption, stress and sweet drink consumption, stress and red and processed meat consumption, stress and white bread consumption, or stress and whole grain consumption.

DISCUSSION

This research examined the relationship between reported levels anxiety, depression, and stress and nutrition behaviors, i.e., specific food consumption practices in a sample of women at cardiovascular risk. It also examined whether having a high BMI would affect these relationships. We focused specifically on health-promoting consumption (i.e.,

TABLE 5 | Regression results for stress, BMI, daily activity and diet consumption, standardized coefficients.

	Fruit per day	Vegetable per day	Whole grain	Sweet drinks per day	White bread per day	Red meat per day
Step 1						
BMI	0.06	−0.01	−0.03	0.19*	0.19*	−0.14
Stress	0.02	−0.03	0.11	0.09	0.12	0.13
R^2	0.00	0.00	0.01	0.04	0.05	0.04
Step 2a						
Stress	0.33	−0.12	0.19	0.37	0.39	0.35
Stress^2	−0.33	0.10	−0.09	−0.30	−0.29	−0.23
ΔR^2	0.01	0.00	0.00	0.01	0.01	0.01
R^2	0.02	0.00	0.01	0.05	0.06	0.05
Step 2b						
BMI X Stress	0.02	−0.13	0.12	−0.18	−0.02	−0.16
ΔR^2	0.00	0.01	0.01	0.02	0.00	0.01
R^2	0.004	0.01	0.02	0.06	0.05	0.05

**p* < 0.05; *Step 1, linear; Step 2a, curvilinear; Step 2b, interaction.*

fruit, vegetable, and whole grain consumption) and non-health promoting consumption (i.e., sweetened drink, white bread, and red and processed meat consumption). With regard to health-promoting food consumption, we found that depression was related to consumption of fruits and vegetables. With regard to non-health promoting food consumption, we found that anxiety was related to consumption of sweetened drinks, white bread, and red and processed meats.

Depression and Consumption of Health-Promoting Foods

With regard to health-promoting food consumption, we examined the relationship between BMI, psychological factors, and fruit and vegetable intake. Our study found no relationship between fruit and vegetable consumption and level of anxiety or stress, regardless of BMI level, but did find an association between depression and fruit and vegetable consumption, moderated by BMI in the case of fruit consumption. For high-BMI individuals, increased depression was associated with greater intake of fruits. The relationship between depression and fruit consumption was not significant for low-BMI individuals. One meta-analysis found that increased fruit and vegetable consumption were associated with a lower risk of depression (Liu et al., 2016) although the relationship between depression and fruit and vegetable consumption has not been consistently supported (e.g., Whitaker et al., 2014; Wu et al., 2018). Other studies have found that increased fruit and vegetable consumption predicted were associated with reduced depression and also reduced anxiety (e.g., McMartin et al., 2013).

This result is somewhat surprising in light of previous findings that fruit consumption was negatively associated with obesity (e.g., Porter Starr et al., 2014) as well as with depression (Liu et al., 2016). It is worth noting that it was difficult to find studies exploring the interaction of BMI and depression with regard to fruit consumption. Our findings may suggest that, notwithstanding the fact that high-BMI individuals may be generally less likely to eat fruit, high-BMI individuals with depression may actually consume more fruit. Conversely, although depressed individuals may generally consume less fruit, depressed individuals with high BMI may consume more fruit. More research is needed to understand the particular combined impact of BMI and depression with regard to fruit consumption.

The relationship between depression and vegetable consumption in our study was also multifaceted although in this case, BMI did not influence this relationship. As depression increased from normal to mild levels, vegetable consumption decreased. This tendency then reversed itself, with vegetable consumption increasing as depression increased from mild to severe and extremely severe levels.

In light of other studies that found that increased depression was generally associated with lower consumption of vegetables (e.g., Payne et al., 2012), our finding that this was only the case for patients with normal-to-mild levels of depression is quite surprising. It was even more surprising to find that the reverse was true for patients with more severe depression. Although the overall model for this analysis was not significant and the implications of this finding are therefore more tentative, it is worth exploring whether the relationship between depression and vegetable consumption might change for a subgroup of highly depressed patients. Obtaining a further understanding of the complex relationship between depression and fruit and vegetable consumption is especially important since fruit and vegetable consumption may partially mediate the relationship between depression and progression of heart disease (Rutledge et al., 2014).

Our research found no association between whole grains and BMI, depression, anxiety, or stress. This contrasts with previous research suggesting that whole grain consumption is associated with decreased anxiety (Sadeghi et al., 2017) as well as lower depressive symptoms (Rius-Ottenheim et al., 2017). On the other hand, other studies found no association for depression and whole grain consumption (e.g., Grases et al., 2019) or for whole grain consumption and reduced distress (e.g., Soltani et al., 2018). If there is a relationship between psychological functioning and consumption of whole grains, these conflicting results suggest that other factors may need to be examined for their impact on this relationship.

Depression, Anxiety, and Non-health Promoting Food Consumption

In exploring the relationship between psychological factors, BMI, and consumption of non-health promoting food items, we examined daily consumption of red and processed meats as well as simple carbohydrates, i.e., sweetened drinks and white bread. With regard to red and processed meats, in our sample consumption demonstrated a curvilinear relationship with anxiety was albeit only significant at severe and extremely severe levels of anxiety. At severe and extremely severe levels of anxiety, red and processed meat consumption were seen to decline as anxiety increased. In contrast, other research has found a positive association between anxiety and a diet high in both sugars and saturated fat (e.g., Masana et al., 2019) or specifically high in saturated fat from meat and processed foods in particular (e.g., Yannakoulia et al., 2008; see Dutheil et al., 2016). Our finding may be a function of our unique population, an older group of Israeli women. While red and processed meat has become more popular in Israel, this is a relatively recent change (Endevelt et al., 2017). It is possible that our sample of older Israeli women may eat less red and processed meat in general, and that the relationship between anxiety and consumption of red and processed meat for these women may not be generalizable to the broader population.

With regard to consumption of simple carbohydrates, it was not surprising to find that high BMI was associated with both greater consumption of sweetened drinks and greater consumption of white bread. This is consistent with research indicating that consumption of sugar-sweetened beverages is correlated with obesity risk (for a recent review, see Luger et al., 2017), as is white bread consumption (e.g., de la Fuente-Arrillaga et al., 2014). In our population, however, the relationship between BMI and daily sweetened drink consumption was moderated by level of depression.

Specifically, for patients at low levels of depression, daily sweet drink consumption increased as BMI increased. For patients with more severe depression, sweetened drink consumption did not increase with increased BMI. Our findings may suggest that, notwithstanding the fact that in general high-BMI individuals may be more likely to consume sweetened drinks, this may not be the case for high-BMI individuals who also have depression.

This is consistent with the fact that our research also found no direct relationship between depression and sweet drink consumption. This contrasts with previous research which identified an association between depression and sweetened beverages (e.g., Knüppel et al., 2017; Huang et al., 2019). Some of these findings on this relationship were a bit more ambiguous on closer examination, though. For example, in one study this association was more relevant for diet drinks (Guo et al., 2014) and did not seem to be related to the drink's sugar content *per se*. Another study suggesting a preference for sweetened foods among women with depressive symptoms reported small effect sizes (Jeffery et al., 2009). Clearly, the association of increased depression with increased sweetened drink consumption is not unequivocal.

Our findings reflect the possibility that elevated levels of depression include anhedonia and reduced motivation to seek sensory pleasure. The relevance of this to sweetened drinks in particular is illustrated by one study of rats bred to be highly susceptible to developing learned helplessness (a precursor to depression). These rats were found to be less motivated to press levers in order to drink a sugar solution (Vollmayr et al., 2004). Increased depression, then, might not lead to a desire for sweets and increased sweet drink consumption.

Anxiety, on the other hand, was found to have a complex relationship with daily sweetened drink consumption. We found that, irrespective of BMI level, at normal and mild levels of anxiety, increased anxiety predicted a higher number of sweetened drinks consumed per week. In contrast, more severe levels of anxiety predicted fewer sweetened drinks consumed per week. This tendency was similar with regard to consuming white bread. At lower levels of anxiety, irrespective of BMI, increased anxiety predicted an increase in servings of white bread consumed per week, whereas more severe levels of anxiety predicted fewer servings of white bread consumed per week.

That this study found a significant relationship between sweet drink consumption and anxiety is not surprising. Research demonstrates that many individuals tend to eat tasty, non-nutritious foods in response to distress (Groesz et al., 2012). Concerning sweetened foods, both the metabolic and pleasurable properties of sugar are believed to reduce the intensity of the stress response, suggesting that some people may overindulge in sugary foods as a means of relieving stress (Ulrich-Lai, 2016). With regard to sweet drinks in particular, an earlier study found that consumption of a sugar-sweetened drink, in contrast to a drink that was artificially sweetened, increased calmness for participants who had experienced an acute stressor (Samant et al., 2016).

While a tendency to consume sweet drinks may be a form of self-medication for individuals with anxiety, the relationship between sugar consumption and anxiety might be bidirectional. The Western diet, based on a high consumption of added sugar as well as other high calorie low nutrient foods (Casas et al., 2018), is associated with anxiety (Jacka et al., 2011). One study of rats found that a diet high in refined carbohydrates increased vulnerability to stress (Santos et al., 2018). These findings could suggest a vicious cycle whereby increased anxiety and increased consumption of sweet drinks are mutually self-perpetuating.

The relationship between anxiety and white bread consumption may be similarly bidirectional. According to some research, long-term consumption of sugar results in reduced basal dopamine levels, which may trigger the desire to overindulge in carbohydrate-rich foods in order to return dopamine to homeostatic levels (Jacques et al., 2019). As with sweet drinks, if consuming foods high in refined flour is an attempt to self-medicate, it may be misguided. Although some authors have suggested an association between carbohydrate-rich foods and improved mood (e.g., Christensen and Pettijohn, 2001), more recent research counters this (Matantzis et al., 2019). It is possible that a craving for carbohydrate-rich foods and negative mood are mutually reinforcing, perpetuating a cycle of anxiety and unhealthy eating.

Anxiety and Consumption of Simple Carbohydrates: Proposed Physiological Explanations

As noted earlier, a physiological mechanism may underlie the relationship between anxiety and difficulty resisting food cravings. Much research on anxiety has suggested that increased anxiety is associated with autonomic nervous system dysfunction, particularly reduced parasympathetic nervous system activity and reduced heart rate variability (see Sperry et al., 2018 for a brief review), although these findings are not uniform. While some research has resulted in similar findings for depression, these findings have been more heterogeneous and might be more accurately attributed to comorbid anxiety rather than to the specific impact of depression (Rottenberg, 2007).

Adaptive levels of heart rate variability, a measure of autonomic nervous system functionality, are associated with flexible emotional responding to the environment and self-regulation (Thayer et al., 2009). Self-regulation includes the ability to modulate one's response to food cravings. Not surprisingly, heart rate variability is positively associated with the ability to regulate one's eating behavior (Meule et al., 2012a,b). In fact, higher levels of sympathetic activation, as measured by decreased heart rate variability, may be associated with increased levels of craving and decreased self-regulation (Quintana et al., 2013; Moretta and Buodo, 2018). Taken together, this suggests that as anxiety increases and heart rate variability decreases, one would expect to see a corresponding decrease in self-regulation and in the ability to resist unhealthy food cravings. Since the relationship between depression and heart rate variability has been proposed to be a function of comorbid anxiety (Rottenberg, 2007), it makes sense that giving in to unhealthy food cravings would be more predictable for patients with anxiety than for patients with depression.

These findings, though, would likely predict a direct linear relationship between increased anxiety and simple carbohydrate consumption. As such, the curvilinear relationship between anxiety and simple carbohydrate consumption found in this study is surprising. Our findings show that while respondents who reported lower levels of anxiety were most prone to consuming simple carbohydrates as anxiety increased, respondents who reported severe anxiety were far less likely to indulge. This would suggest that simple carbohydrate consumption increases together with greater anxiety up to a particular threshold, and then decreases.

Polyvagal theory may lie at the root of our curvilinear findings. According to polyvagal theory (Porges, 2009), the autonomic nervous system has evolved over time while retaining vestiges of older systems. The newest and most sophisticated responses to stress involve a range of behavior and physiological states. The fight-or-flight response is an earlier, more primitive reaction to an environmental challenge. And the earliest and most primitive reaction to a threat is passive avoidance, or immobilization.

Perhaps the curvilinear relationship we found between anxiety and non-health promoting eating behaviors mirrors neurophysiological regression to increasingly primitive systems. As anxiety increases from normal to mild and moderate levels, the physiological response may revert from more adaptive responses to more primitive fight-or-flight responses, involving an increase in cortisol (see Porges, 2009) which has been implicated in increased sweet food consumption (Epel et al., 2001). But as anxiety increases from moderate to severe levels, the body's response may switch from the increased cravings associated with cortisol and fight-or-flight, to the more primitive passive avoidance or immobilization response. The latter response may predict a withdrawal from comfort eating and other means of self-soothing.

The direction of our curvilinear findings is surprising, though, if we take a closer look at the relationship between anxiety, autonomic functioning, and self-regulation. As noted above, increased anxiety appears to be associated with decreased heart rate variability and deficits in self-regulation. For example, anxiety has been conceptualized as a compromised ability to respond flexibly to the environment, particularly with regard to continuing to feel threatened despite the absence of a verified threat (Thayer and Lane, 2000). This self-regulatory ability has been proposed to be directly associated with cardiac vagal tone, i.e., the vagus nerve's ability to regulate the heart rate (as measured through heart rate variability) (Kogan et al., 2013).

Interestingly, the relationship between cardiac vagal tone and well-being has also been suggested to be curvilinear. Patients with low-to-moderate cardiac vagal tone were found to have a positive linear link between cardiac vagal tone and well-being. That is, as cardiac vagal tone increased, well-being showed a corresponding increase. However, for patients in the moderate-to-high range of cardiac vagal tone, increased cardiac vagal tone was found to have no relationship, or even a negative relationship, with well-being (Kogan et al., 2013).

If cardiac vagal tone is a direct index of anxiety and self-regulation, than individuals with lower vagal tone should have higher anxiety and poorer self-regulation. For these high-anxiety individuals, as vagal tone improves and anxiety decreases, there should be a corresponding improvement in self-management, including the ability to regulate one's eating. Yet we found that at higher levels of anxiety, reduced anxiety was actually associated with increased consumption of refined carbohydrates. In our study, the tendency to succumb to unhealthy food cravings appeared to be greater for those with moderate anxiety than for those with high anxiety.

One possible explanation for this finding is that the physiological response underlying anxiety may not be as well-understood as is commonly believed. In fact, some researchers have suggested that although anxiety is frequently assumed to have a predictable underlying physiological response based on self-reported physical symptoms (e.g., rapid heartbeat, sweating, and hyperventilation), when physiological indicators of anxiety are measured objectively, their presence and intensity are not always consistent with patient self-report. In fact, some findings have suggested that patients with higher, more chronic anxiety have reduced, rather than intensified, physiological responses in contrast to their perceived experience (see Lang and McTeague, 2009).

Notwithstanding the widely accepted view that anxiety is uniformly associated with autonomic reactivity and reduced heart rate variability, several researchers suggest that anxiety disorders are physiologically heterogeneous. Autonomic responses to psychological stresses have actually been found to vary from individual to individual (Berntson and Cacioppo, 2004) as well as from anxiety disorder to anxiety disorder. For example, in contrast to patients with more situationally triggered anxiety (e.g., simple phobias), patients with more diffuse chronic anxiety have been found in some studies to actually to have lower levels of measured physiological responsiveness. Defensive physiological responses may be blunted for individuals with high, chronic anxiety (Lang and McTeague, 2009). Additional research has supported the conclusion that the more enduring, wide-ranging, and intense the negative affect across a variety of anxiety disorders, the greater the reduction in physiological reactivity (McTeague and Lang, 2012). Respondents whose DASS-21 anxiety scores fell at the severe end likely fall into this category. This may offer a physiological explanation for our findings that at high levels of anxiety, emotional eating appeared to decrease rather than continuing to increase in the expected direction.

Anxiety and Consumption of Simple Carbohydrates: Proposed Psychological Explanations

From a psychological perspective, it is possible that while the temptation to overindulge in sweet drinks may increase together with anxiety for those who are less anxious, those experiencing more extreme levels of anxiety may feel too overwhelmed to attempt to reduce their tension through this particular means of self-regulation. As with sweet drink consumption, the curvilinear relationship between anxiety and white bread consumption, which starts out positive and then becomes negative as anxiety increases to severe levels, may be a function of learned helplessness and an inability to self-soothe through emotional eating at extreme levels of anxiety. It is possible that as individuals become more than moderately emotional dysregulated, other coping mechanisms – more dangerous ones, perhaps – take the place of emotional eating.

Comfort eating as an attempt to self-soothe may be most relevant for those whose anxiety has reached a moderate level, whereby they are feeling sufficiently taxed so as to engage in negative health behaviors as a means of self-soothing and not too paralyzed to do so. This is actually a reversal of the Yerkes–Dodson inverted U-shaped performance law (Yerkes and Dodson, 1908), which suggests that performance is enhanced by an optimal amount of arousal and compromised at lower and higher amounts.

An application of the Yerkes-Dodson Law to the relationship between psychosocial functioning and health behaviors might predict that individuals at cardiovascular risk reporting moderate levels of anxiety would be most likely to engage in health-promoting behaviors while individuals who report normal or severe levels would be less committed to adhering to health behaviors. Yet, findings of this study displayed the opposite pattern.

Of note, in rodent models, acute and chronic distress have been associated with decreased food intake and weight loss, and increased caloric efficiency (Rabasa and Dickson, 2016). Human studies have demonstrated that distress is associated with increased preference for palatable food and central weight gain (Wardle et al., 2000). It is possible that animal stress models represent a high stress situation, compared to more moderate stressors in the human study.

With regard to anxiety in particular, another possibility might be that individuals with high anxiety are more prone to social desirability bias and, as a result, likely to be less accurate when reporting their health behaviors. Studies suggest that individuals asked to report on their risky behaviors may not always be consistent or accurate in their reporting (e.g., Palen et al., 2008). People with high social desirability bias may be uncomfortable providing accurate information on their health behaviors when these behaviors are contrary to common medical and public health advice (Latkin et al., 2017).

In relation to self-reported nutrition behaviors, several studies have found that social desirability bias can influence underreporting of calorie intake, particularly in women (for a review, see Maurer et al., 2006). In fact, one study of 450 post-menopausal women, a population resembling that of the current study, found that participants who scored high in social desirability were more likely to underreport their calorie intake (Mossavar-Rahmani et al., 2013). Some research suggests a possible connection between elevations in traits such as neuroticism or social anxiety and inauthentic self-presentation (e.g., Twomey and O' Reilly, 2017). Taken together, it is plausible that as anxiety increased in this sample, a tendency to underreport negative health behaviors may have increased as well, resulting in a decrease in reported soft drink consumption for respondents with severe or very severe anxiety.

Lack of Findings for Stress

It is interesting to note that, in this study, we found no relationship between stress as measured by the DASS-21 and level of physical activity, positive eating habits, or negative eating habits. This might be a function of the DASS-21 scoring system, where thresholds for increased stress scores are higher than those for mild and moderate depression and anxiety scores, requiring a greater frequency and degree of endorsed stress-related items to earn a higher score. Additionally, studies suggest that while the DASS-21 showed high correlations with established measures with regard to depression and anxiety, stress as measured by the DASS-21 has more heterogeneous associations with psychological distress (Alfonsson et al., 2017). As such, measurement fluctuations may have contributed to this result.

A physiological explanation is also possible. Some researchers have suggested that whereas anxiety may be associated with high levels of autonomic activation, stress may be associated with reduced cardiovascular activation (Borkovec and Hu, 1990). Others have argued that no single pattern of autonomic activity and heart rate variability will manifest uniformly across a variety of stresses, given that the concept of stress is vague and poorly defined in the literature. Studies of the autonomic response to psychological stress found a great deal of variability between individuals (Berntson and Cacioppo, 2004). While our findings suggest that the physiological reaction to anxiety may be more heterogeneous and complex than the literature would suggest, the available research indicates that the physiological reaction to stress might be even less predictable and consistent than the physiological response to anxiety.

Limitations and Strengths

This study is limited by a moderate rather than large sample size, which may lead to lowered sensitivity to subtle behavioral differences. The *post hoc* power analysis, however, suggested that the sample size was sufficient for the performance of these analyses.

Another limitation of this study was its use of self-report with regard to diet, which calls accuracy into question. Social desirability bias, unreliable memory, and other factors could affect precise reporting of eating habits. In particular, anxiety and depression may affect recall (Hertel and Brozovich, 2010) which may have ramifications for the nutrition behaviors reported by participants with greater anxiety and depression. The differences found between high BMI and low BMI participants with depression, however, suggests that depression itself did not account for the differences in reported behaviors. Similarly, the curvilinear responses to anxiety suggests that this is not a linear response to anxiety.

With regard to psychological functioning, depression, anxiety, and stress were measured with a brief questionnaire which could not fully assess all of the psychological symptoms a respondent may have been experiencing at the time of the study. We chose this measure because it has been extensively used to identify psychological factors in cardiovascular patients and individuals at risk for CVD (e.g., Nekouei et al., 2014; Kang et al., 2019) and has been validated in Hebrew. The measure does not, however, provide a complete picture of psychological functioning.

Finally, this study only examined women at risk of heart disease who voluntarily presented at a preventive health clinic. The results may not be generalizable to men. Additionally, these women's choosing to seek out preventive heart care suggests a level of motivation and attention to their health which may not be characteristic of a more general population. The characteristics of our population may be unique in other ways as well. Almost 60% of our respondents had completed college, with more than one-third of this subgroup having completed graduate degrees. This study may also reflect cultural factors associated with the local population, including the high prevalence of adherence to the Mediterranean diet. Results from this population may not be generalizable to populations with more heterogeneity with regard to education or nutrition culture.

This study also had a number of strengths. Participants' weight and height were assessed objectively, as opposed to using self-report for all measures. Additionally, data collection was conducted at patients' initial evaluation, before an intervention might have impacted on participants' nutritional habits. Finally, the inclusion of a broad spectrum of highly anxious and depressed individuals as well as a broad range of BMIs in our study contributed to the robustness of our conclusions.

Implications and Future Research

Our findings showed that, for this population of women at cardiovascular risk, increasing anxiety at lower levels of anxiety are related to increased consumption of sugars and refined grains, while this relationship changed direction at more severe levels of anxiety. Severe anxiety was also correlated with a decrease in processed meat consumption. These findings were consistent for both normal BMI and high BMI patients. These curvilinear relationships between psychosocial functioning and nutrition behaviors may suggest that unhealthy eating behaviors are most affected from mild to moderate levels of psychopathology. For depressed patients, BMI was associated with different nutrition behaviors at lower and higher levels of depression.

Anxiety is often assumed to have a predictable association with autonomic nervous system activity, which has also been implicated in the physiology of food cravings and self-regulation of eating behavior. Our findings suggest that the physiological reaction to anxiety, in general and as it relates to food cravings and self-regulation, may be more multifaceted than is often supposed. The physiology behind anxiety and food cravings is an important area of study, especially for researchers interested in cardiovascular health. Heart rate variability and vagal tone, which are implicated in anxiety, self-regulation, and eating behavior, have significant implications for cardiac wellness. A better understanding of this complex relationship could lead to multi-level interventions that could simultaneously address anxiety, nutrition, and cardiovascular health.

Future research could examine the relationship between particular levels of anxiety and particular ways of self-soothing in a population at cardiovascular risk. In particular, qualitative research using clinical interviews might focus on eliciting specific ways that individuals in this population attempt to regulate their emotions at varying levels of psychosocial functioning.

These findings have implications for those designing lifestyle interventions to decrease cardiovascular risk. In attempting to help individuals at cardiovascular risk, it is clearly important not only to screen for anxiety, but to assess the level at which these qualities may be present. Emotional eating may be most relevant, or most helpful to address, for those with mild to moderate levels of anxiety. Different levels of anxiety may have different effects on health behaviors and other means of coping. These are questions which future studies should explore.

Lifestyle interventions aimed at decreasing cardiovascular risk often focus on improving diet and exercise. However, weight loss with these interventions is often not maintained (Wu et al., 2009). Even interventions specifically focused on maintaining weight loss show modest and heterogeneous effects (Dombrowski et al., 2014). Our study points to the importance of evaluating and treating psychological functioning as well as individual eating behaviors as part of a lifestyle intervention.

To address the needs of women at cardiovascular risk who present with mild-to-moderate levels of anxiety, interventions specifically targeting emotional eating behaviors should address the underlying mechanisms contributing to maintaining weight loss after dieting. Specifically, mindfulness-based interventions appear to be a promising approach (O'Reilly et al., 2014). Mindfulness practices, particularly those which emphasize the impermanence of experiences, have been found to reduce impulsive and high-calorie eating as well as perceived cravings (Keesman et al., 2017). Mindfulness-based approaches could have the dual benefit of addressing eating behavior and reducing depression, anxiety, and stress (see Janssen et al., 2018).

Our findings support the need to identify and treat mental health issues in women at cardiovascular risk when implementing lifestyle interventions. Our findings also suggest that the level at which these issues are present is particularly relevant. In particular, moderate levels of anxiety appear to be most predictive of engaging in unhealthy comfort eating behaviors. Women at cardiovascular risk presenting with these levels of anxiety would likely benefit most from interventions providing alternatives to emotional eating and teaching positive coping skills, whereas women with higher levels of anxiety may benefit from treatment of anxiety prior to initiation of lifestyle interventions. Women with higher levels of depression and with high BMI may benefit from a tailored approach that differs from depressed women with low BMI.

DATA AVAILABILITY STATEMENT

The datasets generated for this study are available on request to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Hadassah Medical Organization Institutional Review Board. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

KE contributed to analysis or interpretation of data for the work, drafting the manuscript, and critical revision for important intellectual content. EL and DZ contributed to the conception and design of the work, the acquisition, analysis or interpretation of data, drafting the manuscript, and critical revision for important intellectual content. RM contributed to analysis and interpretation of data for the work, drafting the manuscript, and critical revision for important intellectual content. TR assisted with acquisition of data. All authors approved the publication of this content and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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The Monitoring of Psychosocial Factors During Hospitalization Before and After Cardiac Surgery Until Discharge From Cardiac Rehabilitation: A Research Protocol

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Introduction: There is considerable evidence that psychosocial factors contribute to the etiology and prognosis of cardiac illness. Currently, in Italy, psychologists are only obligatory in the cardiac rehabilitation setting, although there are indications that patients could be experiencing distress also during other moments of hospitalization, such as on admission for cardiac surgery.

Objective and Methods: The objective of this protocol is to gain more information about cardiac patients, specifically during the various moments of hospitalization for cardiac surgery, by collecting data at admission before cardiac surgery (t0), at admission to cardiac rehabilitation (t1), and at discharge (t2) at the Istituto di Ricovero e Cura a Carattere Scientifico (IRCCS) Policlinico San Donato hospital. A psychosocial questionnaire was constructed after consulting the relevant national and international guidelines. Patients admitted for cardiac surgery and attending a rehabilitation program will be evaluated by acquiring data about their civil status, religiosity, education and work capacity, social condition (including the presence and quality of intimate relationships and support received), previous psychological and psychiatric histories, psychological status, lifestyle (including questions on nutrition, smoking, alcohol, and substance abuse), adherence to therapy, quality of life (QoL), health perception, anxiety, and depression at t0. Health perception, anxiety, and depression are also measured at t1 and t2.

Discussion and Conclusion: This study is an attempt to identify the recommended psychosocial variables which need to be monitored during cardiac patients' hospitalization for cardiac surgery, through to the completion of cardiac rehabilitation. After implementing this study at the IRCCS Policlinico San Donato, attempts will be made to create studies on a national and international level to generate more evidence regarding these variables, in order to create tailor-made interventions for these patients during these specific and delicate moments.

Keywords: cardiac surgery, cardiac rehabilitation, psychosocial, psychocardiology, psychosocial risk factors, clinical psychology, heart disease

INTRODUCTION

The leading cause of deaths in the latest National Vital Statistics Report to date in 2017 was "Diseases of the heart" (Murphy et al., 2018). Anxiety, depression, and stress are among the most important psychological risk factors related to heart disease and are predictive of mortality and/or of a worsening of the quality of life (QoL) (Hare et al., 2013).

The most recent 2016 European Guidelines for Cardiovascular Diseases reported that a series of psychosocial factors, including low socio-economic status, lack of social support, stress at work and in family life, hostility, depression, anxiety, and other mental disorders are associated with the risk of developing cardiovascular disease (CVD). In addition, when these factors are absent there is a lower risk of developing CVD and a better prognosis of CVD. Psychosocial risk factors are also linked to treatment adherence, type of lifestyle, and the promotion of health in patients and populations. For this reason, it is recommended that assessment of psychosocial risk factors with the use of clinical interview or standardized questionnaires is carried out (Piepoli et al., 2016).

The biopsychosocial model (Engel, 1977) was further elaborated in the field of cardiac illness with the development of psychocardiology, which can be defined as an effort to see how psychology can contribute in the prevention, treatment, and rehabilitation of patients with cardiac disease (Molinari et al., 2006). The relevance of the multidisciplinary team (Tramarin et al., 2007; Griffo et al., 2008) and also economic benefits of psychological intervention in hospitals have been highlighted, with effective teams providing increased patient safety and better information sharing about the patients (Bettinardi et al., 2014; Gilardi et al., 2014).

In the paper "Best practice in psychological activities in cardiovascular prevention and rehabilitation: Position Paper" (Sommaruga et al., 2018), psychologists of the Italian Association for Cardiovascular Prevention, Rehabilitation and Epidemiology (GICR-IACPR) reviewed the key components of psychological activities in cardiovascular prevention and rehabilitation (CPR). The existence of an association between depression, anxiety, social factors, stress, personality and illness onset/outcome, and coronary heart disease (CHD) was confirmed. When it comes to interventions, cognitive-behavior therapy, interpersonal therapy, and short-term psycho-dynamic therapy are the main ones proposed, together with psychoeducational initiatives. An interesting factor, which is highlighted, is the analysis of the family/caregivers and their need for psychological support. Today, many examples in the literature show the positive effects of good family and social support on the outcome of CVD in terms of better adherence and a decrease in new hospital admissions (Sommaruga et al., 2018).

Following a review of the national and international guidelines and operational instructions in force from 2018 in various national and international jurisdictions, the "Minimal Care" requirements for clinical practice have been identified for individual professionals constituting a cardiological rehabilitation team (Fattirolli et al., 2018). In these requirements, it was specified that when it comes to psychological care, during the assessment phase, both a clinical interview and standardized tests can be utilized covering the areas of psychological functioning, perceived social and family support, disease awareness, and motivation for treatment. When it comes to possible interventions, the clinical interview, relaxation techniques, inclusion of the caregiver, involvement of community welfare services in the case of social issues, psychoeducation, and collaboration with the multidisciplinary team are suggested.

In the German heart society clinical commission (DGK) position paper, it is recommended that in clinical practice for patients with acute and chronic CHDs, there is a need for psychotherapeutic and psychological support for these patients since affective disorders [e.g., depression, anxiety, and post-traumatic stress disorder (PTSD)] are often noticed in patients with cardiac problems (Ladwig et al., 2014).

In a 2018 update, based on the results of a systematic review of evidence-based guidelines and clinical experiences, it was found that psychosocial variables such as low socio-economic status, acute and chronic stress, depression, anxiety, and poor social support are associated with an unfavorable prognosis. According to these data, it is advisable to systematically evaluate both the psychosocial aspects and the cognitive function of all patients as a part of routine clinical assessment. In all cases where critical values emerge from the evaluation, continuing psychosocial and psychotherapeutic interventions and/or psychopharmacological interventions should be carried out since the clinical evidence has shown that such interventions are positive for the prognosis of patients suffering from CHD, chronic heart failure, arterial hypertension, and some arrhythmias (Albus et al., 2019).

There has been a lot of attention paid to psychosocial aspects in cardiac rehabilitation guidelines, and on hospitalized patients (Piepoli et al., 2016; Fattirolli et al., 2018; Sommaruga et al., 2018). In the next paragraphs, we report studies in which psychosocial factors were investigated in the pre-operative phase, and other studies in which longitudinal research was carried out, in order to further consolidate the basis of this psychosocial research protocol and questionnaire.

CARDIAC PATIENTS PSYCHOLOGICAL AND PSYCHOSOCIAL VARIABLES

When it comes to cardiac diseases, we need to take into consideration the behaviors that are linked to health outcomes, such as physical inactivity, smoking, poor dietary habits, and stressful behaviors, which are difficult to change. Most social-cognitive theories assume that an individual's intention to change is the best direct predictor of actual change. A discrepancy between intention and behavior is normally seen in these patients, however. The health action process approach (HAPA) suggests a distinction between the pre-intentional motivation processes that lead to a behavioral intention and post-intentional volition processes that lead to the actual health behavior (Schwarzer, 2008). For this reason, the psychosocial questionnaire will be utilized in order to make an initial assessment and increase the awareness of the patients on these variables in order to facilitate the adoption and maintenance of health behaviors in the post-hospitalization phase.

The pre-surgery phase is considered a very delicate one since patients are at particular risk for psychological vulnerability. Patients who undergo cardiac surgery, in fact, are prone to emotional imbalance, distress, and fear that in many cases may result in anxiety and depression (Gomes et al., 2019).

This phase also represents a possibility of cure, but at the same time also of failure. The fear of the unknown, coupled with the likelihood of failure, could worsen the patient's state of anguish. Often this is associated with the risks, uncertainties, limitations, and pain that come with it. Initially, the intervention is seen and perceived by patients as something "magical" that could free them from pain and suffering, while during the hospitalization, they experience states of anxiety, depression, stress, and other negative feelings (Gomes et al., 2019).

Anxiety and Depression

When it comes to anxiety and depression, surgery can represent a real trauma and is often associated with a high level of anxiety. Pre-operative anxiety is defined as a state of discomfort or malaise secondary to the pathology and the hospitalization. A high pre-operative level of anxiety increases the risks associated with surgery, including morbidity, mortality, and the recovery process (Frazier et al., 2003).

In recent decades, there has been a high level of recognition of the significant relationship between depression and CVD with 20–25% (Andrew et al., 2000; Tully and Baker, 2012; Murphy et al., 2016) of patients undergoing heart surgery reporting high rates of severe depression. While depression resolves for many patients, pre-operative depression states have been shown to persist even after surgery, increasing the risk of cardiac morbidity or mortality (van Melle et al., 2004; Murphy et al., 2013; Patron et al., 2014). One possible reason for the association between depression and cardiac morbidity is that patients with depression are less likely to adhere to medical care and participate in cardiological rehabilitation programs (Borowicz et al., 2002). In addition, physiological mechanisms involved in the associations between mental illness and CHD have been well-documented in several reviews published in recent years (Jackson et al., 2018). Some examples of these are: (a) hypothalamic pituitary adrenal axis dysregulation, (b) platelet activation, and (c) inflammation (Brydon et al., 2006; Smith and Blumenthal, 2011; Goldstein et al., 2015). Patients with depression have higher levels of biomarkers that promote atherosclerosis; in anxiety and depression, we see reduced heart rate variability, suggesting decreased parasympathetic activity, altered serotonergic pathways, altered platelet aggregability, and increased C-reactive protein, an indicator of increased inflammatory response.

A study by Gardner (Gardner and Worwood, 1997) detected high levels of anxiety and depression in patients undergoing heart surgery, both in the pre-operative and post-operative phases. The study showed that a psychological assessment and intervention can be useful and contribute to a better prognosis. It has been observed that the same pre-operative mood could persist after surgery, and for this reason, the mood tone is often used as a predictive indicator of anxiety-depressive symptoms in the post-operative phase (Magni et al., 1987).

In a study by Gallagher and McKinley (2007), 172 patients admitted for coronary artery bypass surgery were interviewed in order to determine their major concerns and anxiety level at three different times: before surgery, before discharge, and 10 days after discharge. The hospital anxiety and depression scale (HADS) and the stressor scale were used. The results showed that the Cardiac Surgery Unit represents a very stressful environment for patients waiting to undergo cardiac surgery, as well as for their families. Major concerns reported by the patients were related to the surgery and its possible consequences, such as fear of death, being away from home or work and experiencing pain. It is noticeable that being away from home caused feelings similar to those related to physical pain.

In this study, many patients had traveled extensively to reach the hospital to undergo this surgery. The distance variable had consequences not only for the patient who perceived it as a moment of discontinuity, but also for the families who had to quickly adapt to this new condition. Concerns about the economic and the general family management spheres were identified as some of the causes of depressive and anxious symptoms in these patients (Gallagher and McKinley, 2007), as has been reported more recently (Murphy et al., 2019). A high level of pre-operative anxiety has been shown to be correlated with the presence of persistent post-operative pain (Choinière et al., 2014) while a study by Andrew et al. (2000) found that the degree of pre-operative and post-operative depression and anxiety is related to post-operative neuropsychological dysfunction. High levels of anxiety and depression at both pre-operative and post-operative assessments are predictive of attention and verbal memory impairment, which are the cognitive domains known to be affected by mood tone.

Another study showed that patients with a history of depression are exposed to a higher risk of developing post-operative infections (Theodore et al., 2019). These results confirm findings of Scheier et al. (1999) evaluating re-hospitalization rates due to sternal wound infections in association with depression and risk of re-intervention. In conclusion, we can say that depression and anxiety are predictive and detectable factors with standard and objective assessments, which can negatively affect post-operative recovery. The identification and the treatment of these factors in the pre-operative phase could represent an enhancement to improve care, decrease patient hospitalization, and improve overall patient well-being.

Quality of Life and Health Perception

Heart surgery is an important stressful event that can have a negative effect on patients' QoL and can cause post-traumatic reactions from acute stress and cumulative long-term stress. The concept of health-related quality of life (HRQoL) is a multidimensional concept linked to the self-perception of physical, emotional, mental, and social well-being. It indicates both the functional impact of the disease and at the same time, the overall satisfaction of the patient undergoing the intervention (Gražulytė et al., 2019).

The correlation between HRQoL, marital status, and various comorbidities has been assessed in a sample of men and women undergoing heart surgery. Results showed that women have a slower recovery and lower HRQoL results compared to men after heart surgery. This suggests the importance of considering both gender and the presence of social support as factors that can affect the recovery of patients from heart surgery. The study showed the need for follow-up and support especially for women who live alone (Bjørnnes et al., 2017).

Social Support, Loneliness and Intimate Relationships

It has been noted that being married or having a partner is associated with a lower risk of developing heart disease. Living alone, on the other hand, could be an indicator of a particularly stressful psychosocial situation in terms of isolation or lack of social support (Murphy et al., 2008; Hagström et al., 2018).

Therefore, it would be appropriate to investigate the social situation and the quality of social support of patients undergoing heart surgery. It has been noted that poor and ineffective social support increases the risk of post-operative depression in patients over the age of 55 (Oxman et al., 1994; Jackson and Murphy, 2019).

Loneliness has been associated with significantly poorer patient-reported outcomes across various cardiac diagnoses, and in addition has been shown to predict all-cause mortality 1 year after the cardiac event in both men and women (Christensen et al., 2020). The importance of the perception of the quality of support in this population is also linked to patient-reported outcomes on mood and health behaviors (Vilchinsky et al., 2011).

Pharmacological Adherence

Poor adherence to medications can cause recurrent problems, high morbidity, and higher mortality rates. Many factors contribute to poor adherence, including low self-efficacy and depression. The use of technology may be considered as an effective tool to promote good adherence, as it promotes self-monitoring strategies, education, and greater knowledge (Park et al., 2015).

Smoking

Smoking is linked to high mortality along with alcohol abuse, low physical activity, and poor diet. Cigarette smoking contributes to the development of coronary artery disease and myocardial infarction. Furthermore, persistent smoking after cardiac surgery is considered a predictor of the possibility of increased mortality. Studies on elderly populations admitted to cardiac surgery have indicated smoking as a significant risk factor (Jones et al., 2011).

A meta-analysis showed that smoking leads to an increased level of mortality while a decrease in smoking in the post-operative phase improves duration of life expectancy. The period prior to cardiac surgery is a favorable period for educating patients about smoking damage, especially because the relationship between smoking and CVD is not evident for many patients (Bayfield et al., 2018).

Substance Abuse

The use of drugs is associated with significant cardiovascular complications, including cardiomyopathies (Awtry and Philippides, 2010). The current guidelines of the American college of cardiology for the management of acute coronary syndromes (ACSs) recommend a toxicological screening of urine when substance abuse is suspected. It is known that cannabinoid receptors are present in myocardial muscle cells, and it has been shown that the use of marijuana is associated with adverse cardiovascular outcomes, including stroke, coronary artery dissection, ACSs, and cardiomyopathies (DeFilippis et al., 2018). Ischemia and acute myocardial infarction are the most frequently described diseases seen in cocaine abuse while several studies describe the link between abuse of methamphetamine and cardiomyopathies (Segawa et al., 2019; Tiako et al., 2019; Wang et al., 2019). It has been found that the use of cocaine causes a series of pro-thrombotic alterations and as well as myocardial infarction with intravenous users more likely to develop episodes of endocarditis and myocarditis (Badarienė et al., 2019).

Alcohol Consumption

Moderate alcohol consumption is associated with a lower risk of CHD, and an association between moderate and low morbidity and mortality among patients with recent myocardial infarction has also been found (Maclure, 1993). A study of 1,919 patients undergoing aorto-coronary bypass assessed the association between alcohol consumption and mortality, showing that heavy drinkers showed an increased risk of mortality (Grabas et al., 2016).

Level of Education

In a study of modifiable risk factors, CVD, and mortality in a large sample, behavioral risk factors contributed most to deaths although the single largest risk factor was a low education level. The level of education is strongly associated with a high risk of mortality due to the its association with health literacy and patient activation (Yusuf et al., 2019).

Recently, some studies have shown that post-operative delirium is associated with increased cognitive impairment and a higher incidence of dementia up to 15 months after surgery (Sprung et al., 2017).

Quality of Sleep

Sleep represents another predictive factor of rapid recovery from surgery. A study published in 2013 highlighted that the presence of sleep disorders prior to aorto-coronary bypass surgery may partly explain why some patients fail to have adequate and comprehensive physical recovery (Poole et al., 2013).

There is a high prevalence of obstructive sleep apnea (OSA) in ACS patients that persists within the first 6 weeks following hospital admission (Garcia-Rio et al., 2013; Nakashima et al., 2015). Studies have shown that close to two-thirds of ACS patients exhibit mild to moderate OSA. Even mild levels of OSA with minimal daytime symptoms are associated with adverse effects on endothelial function and hypertension (Kohler et al., 2008; Li et al., 2017). In the Nakashima (2015) study, close to half of all patients were diagnosed with moderate to severe OSA, a level that has been independently associated with 2.3 times the risk of recurrent ACS events after adjusting for covariates, such as age, sex, body mass index (BMI), smoking, and diabetes.

Religiosity

Religiousness refers to subjective attributes, such as religious doctrine and behaviors, including praying and participating in religious initiatives. In a prospective study, the influence of religiosity, as another psychosocial factor, was assessed to measure the impact on patients undergoing surgery (Contrada et al., 2004).

Fear of death associated with heart surgery can increase spiritual beliefs. Such beliefs can offer patients feelings of comfort and provide them with a means to address these fears and concerns related to surgery. Ai et al. (2002) found evidence that praying during the period before surgery was associated with a high level of optimism the day before the procedure.

Stronger religious beliefs are associated with lower surgical complications and shorter hospitalization (Contrada et al., 2004).

Working and Socio-Economic Status

Changes in the working environment can be a cause of stress causing psychological repercussions and potentially having an impact on the post-operative recovery of patients. It would therefore be appropriate to investigate in the pre-operative phases: the type of work of the patient, the level of work stress, the required physical and mental efforts, and job satisfaction. These are considered to be important elements (Hanson et al., 2019) as low socio-economic status has an effect comparable to that of the main risk factors for the development of CVD and post-operative recovery (Stringhini et al., 2017).

Nutrition

The role of nutritional behaviors and dietary intake in the prevention of CVDs or in its progression has been extensively studied. Numerous studies have highlighted the importance of healthy dietary choices and improved lifestyle with a higher level of physical activity and increased intake of healthy food choices, including fruits and vegetables and food antioxidants for the prevention and treatment of cardiovascular events (Farhangi and Najafi, 2018).

Older patients undergoing cardiac surgery show greater prevalence of comorbidity with malnutrition being a determining factor for the dysfunction of many organs.

Adequate nutritional therapy has been suggested to improve patient outcomes through maintenance of energy metabolism, intestinal integrity, microbial diversity, and better wound healing. Pre-operative nutritional status and post-operative nutritional management can be important factors for clinical outcomes in patients undergoing cardiac surgery who are at high nutritional risk.

Malnutrition has been reported to increase morbidity and mortality after cardiac interventions. Several researchers have reported a correlation between a poor diet and an increase in complications and negative results following a heart surgery. Many studies (Engelman et al., 1999; van Venrooij et al., 2008, 2012; van Straten et al., 2010) suggest that nutritional status should be a factor to be evaluated, even in the pre-operative phase, to determine whether patients are selectable for surgery. Although obesity may be associated with a high risk in cardiac surgery, a study by Loop et al. (1983) suggested that paradoxically, lean patients might actually have a higher risk after coronary operations than obese patients (Sanchez et al., 2011).

Physical Activity

Many studies have shown that adequate physical activity and exercise-based cardiac rehabilitation have a positive effect on the recovery of CHD patients. This activity improves cardio-respiratory function and reduces cardiac mortality as well as shortening length of hospital stay (Warburton et al., 2006).

In a 2017 study, it was noted that a reduction in physical activity represents a negative predictive factor for post-cardiac intervention outcomes for patients over the age of 65 (van Laar et al., 2017). In an Australian study, physiotherapists monitored the physical activity of the patients from pre-hospitalization up to the day before heart surgery. It was shown that the activity monitored and followed by a physiotherapist promotes the improvement of post-operative functional and physiological capacities, reducing the length of hospitalization (Mungovan et al., 2017).

It can be seen that the assessment and treatment of psychosocial risk factors improve the QoL and provide an ethical obligation to provide comprehensive and effective psychosocial care (Gallagher et al., 2015).

IRCCS POLICLINICO SAN DONATO: AN ITALIAN EXAMPLE

In 2007, in Italy, the Italian SurveY on carDiac rEhabilitation-2008 (ISYDE-2008; Tramarin et al., 2007) showed an imbalance between the request and the offer of cardiac rehabilitative intervention, encouraging the development of organizational models suitable for ensuring for all patients in the stage of chronicity, a unique process of preventive and rehabilitative cardiology. This led to the drafting of a second survey that provided a complete overview of the available activities in cardiac rehabilitation (Griffo et al., 2016). In this multicenter survey, it was reported that there was an incremental trend of cardiac rehabilitation provision in Italy.

Since 2013, at the IRCCS Policlinico San Donato, the units of cardiac surgery, cardiac rehabilitation, and the Clinical Psychology Service were structured based also on these services. It is unusual to have both cardiac surgical and cardiac rehabilitation of a considerable size in the same hospital structure, and this provides a good opportunity to identify the psychosocial characteristics of acquired cardiac patients from the pre-surgery phase up to the stage of discharge from cardiac rehabilitation in the case of patients who continue their rehabilitation process in the same institute.

Another interesting consideration is that in Italy, the psychologist is legally obligatory only in the cardiac rehabilitation setting and not in the cardiac surgery and other settings. In order to effectively implement the guidelines, 0.5 psychologists are suggested for every 12 patients in institutes, which treat 275 patients a year (Griffo et al., 2008).

Along with the national recommendations, there are also regional recommendations. When it comes to psychological activity in cardiac rehabilitation, the inclusion of a psychologist in the multidisciplinary team is calculated on the basis of the total number of minutes which each patient must complete with the multidisciplinary team. It is not specified that the patient must do a certain number of minutes per week only with the psychologist, but that each patient must do a total of at least 500 min per week with the following professional figures: physiotherapist, occupational therapist, speech therapist, neuro-psychomotor therapist, educator, psychologist, and dietician (Jayasinghe et al., 2009).

From a clinical point of view, the psychosocial evaluation requested in the cardiac rehabilitation multidisciplinary setting should now be provided in the cardiac surgery setting. The patients would be seen for an initial evaluation and at least for another two sessions (t0, t1, and t2). During the first evaluation, it is established if more sessions will be required.

In order to construct and update the psychosocial questionnaire administered during admission, the pertinent national and international medical and psychosocial guidelines were consulted (Griffo et al., 2008; Piepoli et al., 2016; Fattirolli et al., 2018; Pedretti et al., 2018; Sommaruga et al., 2018). In addition, the pertinent literature addressing the areas indicated by the guidelines were further explored.

STUDY RESEARCH PROTOCOL

The Clinical Psychology Service of the IRCCS Policlinico San Donato created in August 2016 has developed the following study protocol, which has been approved by the Ethics Committee of the San Raffaele Hospital in Milan on the 16th of September 2020 (registration number 159/int/2020), which will be conducted according to the principles expressed in the Declaration of Helsinki, the institutional regulation and Italian laws and guidelines. Written informed consent will be obtained from the patients.

This study is partially supported by Università degli Studi di Milano through the Open Article Process Charges (APC) Project and the Ricerca Corrente funding from the Italian Ministry of Health to IRCCS Policlinico San Donato. The authors have no competing interests to declare.

The study is a longitudinal observational prospective study aimed at detecting the psychosocial variables of patients admitted to the IRCCS Policlinico San Donato, which includes the units of cardiac surgery, cardiac rehabilitation, and the Service of Clinical Psychology. This organizational set-up is almost unique in Italy, allowing psychologists of the Clinical Psychology Service to contact all cardiac patients before heart surgery and follow them until their discharge from hospital.

This unique organizational condition enables the identification of the psychosocial characteristics of acquired heart patients, from the moment they are admitted for heart surgery to their discharge from cardiac rehabilitation in our institute.

Objective of the Study

Primary Outcome

The main objective of the study is to measure health perception (EuroQoL VAS 0-100), anxiety (GAD-7), and depression (PHQ-9) before cardiac surgery (t0) and at discharge from cardiac rehabilitation (t2) and to identify the medical and psychosocial variables which influence these scores.

Secondary Outcomes

Health perception, anxiety, and depression will be assessed also at discharge from cardiac surgery or admittance to cardiac rehabilitation (t1) to explore possible trends.

In addition, the evaluation of possible correlations between all other psychosocial factors, cardiac diagnosis, ejection fraction (EF), duration of hospitalization, and the performance of the 6 min walking test (6MWT), which is done twice by the physiotherapists during the admission in cardiac rehabilitation and just before discharge (t1 and t2) and the New York heart ability index (NYHA) administered during all times (t0, t1, and t2) will be carried out.

Study Design

This is a longitudinal observational prospective study.

Patient Selection

Target Population

Patients with acquired heart disease admitted to heart surgery, who will undergo heart surgery, either through a sternotomy or with minimally invasive surgery, who will also be admitted to the cardiac rehabilitation operative unit in the same institution, after surgery will be included in this study. Most patients hospitalized in our center undergo elective surgery for heart valve repair or replacement followed by those who undergo coronary artery bypass surgery. Heart surgery patients undertake a 20-day cardiac rehabilitation program (CRP) either at IRCCS Policlinico San Donato or in another CRP, sometimes closer to the residence of the patients. Only in the case of minithoracotomy or transcatheter aortic valve implantation (TAVI), or transcatheter aortic valve replacement (TAVR) in most of the cases, no CRP is needed.

The number of psychological sessions given and their classification according to the taxonomy of behavior change techniques (Abraham and Michie, 2008) will be taken into consideration in the analysis. For example, for patients who report high anxiety and depression, the following interventions could be indicated: prompt self-monitoring of behavior, agreement on behavioral contract, and stress and time management. In the case of a lack of adherence and the presence of behaviors linked to risk factors, such as smoking, motivational interviewing, and prompt behavioral goals could be recommended. Finally, in the cases of social isolation, provision for opportunities for social comparison and the planning of social support or social change could be enacted by facilitating the referral of the patients to an adequate center, where they are resident once they are discharged.

Inclusion Criteria:

1. The patients' age is ≥18 years.
2. The patient is being treated at the Cardiac Surgery Unit of the IRCCS Policlinico San Donato.
3. The patient will undergo cardiac surgery.
4. The patient is able to understand the condition of the study.

Exclusion Criteria:

Patients with:

1. Cognitive impairment.
2. Diagnosis of a severe psychopathology with impaired reality data.
3. Genetic syndrome.
4. Language barriers.

Study Procedure

The questionnaire is given to the patient by the staff of the Clinical Psychology Service, and they are instructed to complete it on their own. It is specified to the patients that if they encounter any difficulties the clinical psychology staff will help them to complete it, and that there will be an initial session in which it will be discussed, in order to decide what kind of support is required.

The Clinical Psychology Service team will be informed about admitted and discharged patients and their medical conditions by participating in the daily medical morning briefings and by consulting the internal patient management system (Galileo e-Health Solutions).

All patients being admitted to the Cardiac Surgery Unit will be eligible for inclusion in the study if they meet the inclusion criteria.

Times of Administration of the Psychosocial Questionnaire:

1. At time zero (T0), pre-operative phase, the administration of the full questionnaire and validated tests.
2. At time one (T1), after a minimum 7 days from T0 (post-operative phase or admission to cardiological rehabilitation), administration of the following tests: PHQ-9, GAD-7, and EuroQoL-VAS.
3. At time two (T2), cardiac rehabilitation discharge administration only of the following tests: PHQ-9, GAD-7, and EuroQoL-VAS.

At the time of admission to the Cardiac Surgery Unit, it is not possible to foresee if the patient will perform their rehabilitation program at IRCCS Policlinico San Donato; however, all patients will still be enrolled in the study so that the psychosocial assessment will be useful to support the patients throughout the course of hospitalization especially if critical areas should emerge. In addition, the data that will be collected at T0 and T1 will be useful to define a psychosocial profile of patients undergoing cardiac surgery.

Study Variables

The following medical and functional variables will be considered: cardiac diagnosis, ejection fraction (EF), duration of hospitalization, and the performance of the 6MWT.

The variables taken into consideration from the guidelines and the other pertinent literature can be summarized in the following **Table 1**. Each variable will be described in detail in the following paragraphs.

Assessment Tools

General patient history-in the initial part of the questionnaire, the following demographic and social variables are explored: marital status, presence/absence of children, culture of origin, education level, occupation situation, and religion.

Patients are also asked if they are recieving social support and if they feel it is adequate, if they feel lonely, if they have a partner and to specify the quality of this relationship. Although numerous scales have been developed to assess social support in this population, no standard scale has gained widespread acceptance in clinical practice, and it was indicated that enquiring about who the patients turn for social support is sufficient in clinical practice (Rozanski, 2016).

Furthermore, they are asked information about physical activity, alcohol and drug use, and other addictions. Active smokers are asked to complete the Fagerström questionnaire in order to identify the degree of nicotine dependence. *The Fagerström test* (Heatherton et al., 1991) is a self-administered test that evaluates the current dependence on nicotine. The original 1978 questionnaire was simplified and further developed. It consists of six items, the different answers of which allow a classification of nicotine addiction. Total score ranges from 0 to 10, 10 being the highest level of addiction and 0 indicating the lowest level of nicotine dependency. The test was copyrighted in 1991, but can be used without permission. This instrument has also been utilized to measure nicotine addiction in the CHD population (Papazisis et al., 2019).

Morisky, Green, and Levine Adherence Scale

This is the most widely used questionnaire on adherence to drug therapy (Morisky et al., 1986). It is a one-dimensional questionnaire that contains four items, and the 1986 version does not require a license for usage. The total score ranges from 0 to 4, and a score lower than 3 indicates a bad adherence

TABLE 1 | Variables and measurement tools.

Variables	Measurement tools	# items
Age and gender	Determination of age and gender from medical records	2
Citizenship	Indication if citizenship is Italian or Foreign (with specification of citizenship)	1
Religion	Indication of religion and level of religiosity	2
Civil status	Indication of civil status (single, married, widowed, legally separated, or divorced)	1
Education level	Indication of the level of education obtained and the total number of years of studying	2
	Items on type of occupation [part time or full time, unemployed, looking for a job, housewife, disability and percentage of disability, student, retired, or other condition (with specification)]	
Occupation and retirement	Indication on type of work (mental or physical). satisfaction with work, level of stress perceived, and capacity to work	8
	In case of retirement, satisfaction regarding the previous working years and enquiry whether the patients have found a satisfactory way of employing their time	
	Marital status or presence of intimate relationship	
Social condition, presence and quality of a close relationship, and perceived support	Evaluation of the quality of the relationship	
	Number of children	5
	Enquiry about cohabitation status and with whom the patients live	
	Enquiry about perception of receiving adequate support specifically during the moment of enquiry	
Psychological and/or psychiatric history	Previous psychological and psychiatric visits and reasons for them. Past psychological and psychotherapeutic treatment and utilization of psychotropic drugs	5
Nutrition	Items regarding whether appetite is normal and about eating habits	2
Quality of sleep	One item regarding sleep quantity and quality	1
Physical activity	One item regarding the amount of physical exercise outside of work	1
Smoking addiction	Fagerström test	8
Alcohol consumption	One item exploring alcohol consumption	1
Substance abuse	Items on current and past drug use and in case of a positive answer, an enquiry about the intention of stopping	3
Gambling	One item on the presence and frequency of gambling	1
Therapy adherence	Morisky, Green, and Levine (MGL) adherence scale	4
Life satisfaction scale	Satisfaction with life scale (SWLS)	5
Psychological functioning (Anxiety and depression)	Patient health questionnaire-9 (PHQ-9) General anxiety disorder-7 (GAD-7)	16
Perceived health	Visual analog scale (EuroQoL-VAS)	1
Quality of life	Visual analog scale quality of life (QoL-VAS)	1
Health questionnaire	The short form (12) health survey	12
∑ items		82

to drug therapy. This version of the test was utilized to assess the adherence to cardiovascular medicines (Santra, 2015).

Satisfaction With Life Scale

This is a short tool, which takes only 1 min to complete; it consists of five items that measure the overall cognitive assessment of life satisfaction experienced by the patient (Broadbent et al., 2006). Patients are asked about their level of agreement/disagreement with each of the five options, indicating for each statement the corresponding number on a seven-point Likert scale ranging from 7, very much in agreement to 1, strongly disagree. The total score ranges from 0 to 35, 0 indicating the least satisfaction with life and 35 indicating the highest satisfaction with life. The scale shows good convergent validity with other scales that evaluate subjective well-being. Life satisfaction, as assessed by the satisfaction with life scale (SWLS) test, shows some stability over time and has shown sufficient sensitivity in the detection of change and life satisfaction during a clinical intervention. Since the scale evaluates the patient's conscious and subjective judgment on his life, it is advisable to use this tool in a complementary way to other tests focused on psychopathology and emotional well-being to capture more unconscious and latent aspects. This tool has been copyrighted since 1985 but the authors, Ed Diener, Robert A. Emmons, Randy J. Larsen, and Sharon Griffin, have allowed its use without a request for authorization and without charge (Diener et al., 1985). This test has been previously utilized in the cardiac population (Gao et al., 2019).

Patient Health Questionnaire-9

This is a short psychological screening tool designed to measure symptoms of depression in primary care facilities (Kroenke et al., 2001). The patient health questionnaire-9 (PHQ-9) test is completely free for healthcare professionals. Pfizer Inc., the legal copyright holder, explicitly states that "no authorization is required to reproduce, translate, view, or distribute the PHQ-9." It contains nine questions that help identify patients with clinically significant symptoms of depression. Patient responses are rated 0–3 with 0 representing "not at all" and 3 indicating "almost every day;" the PHQ-9 contains a total score range of 0–27, with a higher score meaning a higher level of depression. In addition, it has been utilized for the screening of depression in the cardiac population (Berge et al., 2019).

Generalized Anxiety Disorder

This is a valuable screening tool for generalized anxiety disorder in clinical practice and research (Kroenke et al., 2007).

In addition, it provides a measure of severity and is linked to the criteria of the diagnostic and statistical manual of mental disorders (DSM-IV). The general anxiety disorder-7 (GAD-7) can be particularly useful in assessing the severity of symptoms and monitoring changes over time, although its responsiveness to changes remains to be tested in treatment studies (Spitzer et al., 2006). GAD-7 has been evaluated as a reliable tool for detecting the most common anxiety disorders. There was a specificity of 82% for GAD. It is moderately effective in panic disorder (PD) screening (sensitivity-74% and specificity-81%), social anxiety disorder (sensitivity-72% and specificity-80%), and PTSD (sensitivity-66% and specificity-81%). Total score ranges from 0 to 21, with a higher score indicating a higher level of anxiety and the presence of severe anxiety when scores are equal to or higher than 15. Permission for use, replay, and deployment is not required. The GAD-7 has been utilized for the screening of anxiety in cardiac patients (Berge et al., 2019).

EuroQoL-VAS

This is the second part of the EuroQoL-5D questionnaire, a standardized tool that measures the health of respondents and their QoL on the basis of which it is possible to assess their health care, a technique, and a technology (EuroQol Group, 1990). It consists of a visual analog scale (VAS) of 20 cm, graphically represented as a graduated thermometer, on which the patient indicates the best (score-0) or worst (score-100) possible state of health. In addition, its psychometric properties were considered adequate for hospitalized and rehabilitation cardiac patients (Schweikert et al., 2006; Quanjel et al., 2019).

QoL-VAS

The term QoL generally refers to the well-being (emotional and social) of an individual and the patient's ability to fulfill the tasks of daily life satisfactorily (Moons et al., 2006). It consists of a VAS of 20 cm, graphically represented as a graduated thermometer, on which the patient indicates the best (score-100) or the worst (score-0) about the perception of own QoL. A VAS is the recommended method to evaluate overall QoL. This type of scale has been utilized to assess QoL in patients with congenital heart disease (Apers et al., 2015).

The Short Form (12) Health Survey

The short form-12 (SF-12) questionnaire is the abbreviated version of the "Short Form 36 items Health Survey" (SF36) and serves as a generic indicator of QoS and assesses the individual's subjective perception of the concept of health (Apolone et al., 1997). Through the 12 questions proposed in the test, SF-12 investigates eight aspects of health: physical activity, limitations due to physical health, emotional state, physical pain, perception of general health status, vitality, social activities, and mental health. The synthesis of total scores allows you to build two synthetic indices, a physical health index-12 (PCS-12) and a mental health index-12 (MCS-12). The lower the score of the two indices (indicatively below 20 points), the higher the level of disability. The SF-12 is a valid questionnaire (Apolone et al., 1997), which is reliable and suitable for self-administration, even in the case of geriatric users and has been used in cardiac populations (Quanjel et al., 2019) and in a 2009 study of a sample of heart patients before and after 3 months of surgery (Juergens et al., 2010).

Statistics

Categorical variables will be shown as count and percentage, normal variables as mean ± SD, non-normal variables as median and interquartile range. Normality assumption will be tested in continuous variable by visual inspection of qq-plot. Correlations between continuous variables will be evaluated according to Pearson's R or Spearman's Rho, depending on the distribution. *t*-test or Wilcoxon rank sum test will be used to compare unpaired means in normally or non-normally distributed variable, respectively. Fisher's exact test will be used to compare categorical data between groups. Change at discharge from cardiac rehabilitation (t2) from before cardiac surgery (t0) will be analyzed to assess the treatment effect on measure health perception (EuroQoL VAS 0-100), anxiety (GAD-7), depression (PHQ-9), and the identification of medical and psychosocial variables, which influence these scores using ANCOVA analysis.

Based on previous clinical experience, the minimal expected intra-subject difference before/after rehabilitation should be in depression with a score = 1.5 with a standard deviation of 5.0. Therefore, a sample size of 155 patients would be required, using a two-sided paired Wilcoxon signed-rank test, $\alpha = 0.01$ and a power of 0.90. We decide to extend the sample size to 310 patients considering the possibility of a 50% dropout, which would be comprised of the patients who will be hospitalized in other institutions for cardiac rehabilitation, most often due to logistical reasons (they would be closer to home in these institutes).

DISCUSSION

In recent years, psychology has strengthened the link between psychological factors and organic pathologies, giving rise to new disciplines, such as psychocardiology or cardiac psychology as it is also known, which brings to light the importance of a multidisciplinary and biopsychosocial approach when dealing with cardiovascular patients and their problems (Griffo et al., 2008; Greco et al., 2014).

According to this new integrated vision, the role of the psychologist in the medical field is becoming increasingly necessary and advisable to grant to the patients a full and complete recovery, after critical cardiac pathologies.

The European Guidelines of 2016 support the importance of the evaluation and the treatment of psychosocial factors, in order to improve the QoL of patients and their prognosis (Piepoli et al., 2016).

In support of this new perspective, recent studies have shown how psychosocial factors, such as anxiety, depression, QoL, relationships and social status, adherence to drugs, smoking, drugs, alcohol, education, sleep, religiosity, work, nutrition, and physical activity can affect the recovery of patients after a cardiac surgery (Fattirolli et al., 2018).

In addition to the crucial cardiac rehabilitation phase for the full psycho-physical recovery of patients, the pre-operative phase is considered an equally delicate phase, during which patients are particularly vulnerable from a psychological point of view. The pre-operative period represents a possibility of cure, but at the same time also of failure. Fear of the unknown, together with this probability of failure, can aggravate the state of anxiety in which the patient finds themselves, causing further complications (Gomes et al., 2019).

An assessment and treatment of psychosocial risk factors both in the pre-operative phase in preventive terms and in the rehabilitation phase in terms of treatment can therefore improve the QoL of patients, and for this reason, it would be an ethical obligation to provide a complete and effective psychosocial treatment (Pogosova et al., 2015).

LIMITATIONS

A limitation of our study concerns the fact that not all patients undergoing cardiac surgery are admitted for cardiac rehabilitation at IRCCS Policlinico San Donato; hence, the three time-period assessment will not always be possible for all patients. Data will be initially included from a single center, specifically investigating the hospitalization phase, but we hope that our protocol will be extended both on national and international levels.

CONCLUSION

In Italy, the IRCCS Policlinico San Donato for its particular organizational structure, from 2013 allows psychologists to come into contact with patients before cardiac surgery. This organization makes it possible to identify the psychosocial characteristics of acquired cardiac patients from the pre-operative phase up to the discharge phase from rehabilitative cardiology, in the case of those patients who continue their rehabilitation process in the same institute. From what has been said so far, the close link between cardiovascular pathologies and psychological and psychosocial factors is evident. The use of a biopsychosocial and multidimensional approach is recommended to optimize and make cardiac care more effective. Based on the study results, the research protocol could be extended to a multi-centric level and to a European/Worldwide level.

DATA AVAILABILITY STATEMENT

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

AUTHOR CONTRIBUTIONS

EC proposed the study design and the idea, analyzed the literature and its development, and gave the final approval of the manuscript. SP and VF analyzed the literature, contributed to the study protocol, and prepared the manuscript. EGB contributed to the shaping of the manuscript and the psychodiagnostic tools selection. SB contributed to the statistical analyses. ACJ, CV, SC, MV, and LM have revised and approved the final manuscript. All authors contributed to the article and approved the submitted version.

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Challenges for Adolescents With Congenital Heart Defects/Chronic Rheumatic Heart Disease and What They Need: Perspectives From Patients, Parents and Health Care Providers at the Institut Jantung Negara (National Heart Institute), Malaysia

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Objectives: This study aimed to describe the experiences and challenges faced by adolescents with moderate and severe congenital heart defects (CHD) or Chronic Rheumatic Heart Disease (CRHD) and to determine their needs in order to develop an Adolescent Transition Psychoeducational Program.

Methods: The study involved seven adolescents with moderate to severe CHD/CRHD, six parents, and four health care providers in Institute Jantung Negara (National Heart Institute). Participants were invited for a semi-structured interview. Qualitative data were analyzed through the Atlas.ti 7 program using triangulation methods.

Results/conclusions: We identified five themes concerning the experience and challenges of adolescents relating to: (1) emotional/psychological issues; (2) the progress of the illness; (3) relationship issues; (4) future preparation; and, (5) school and community. These themes were identified together with eleven subcategories. The staff expressed support for the development of the Adolescent Transition Psychoeducational Program and adolescents with CHD/CRHD and their parents were willing to participate in the program if their schedule allowed. Their suggestions to improve the program were classified into six categories, with two main themes, (1) the self-management of illness in life and the future; and, (2) social support. In conclusion, the findings from the situation analysis act as a basis for a conceptual framework that will contribute to the development of an Adolescent Transition Psychoeducational Program that aims to empower adolescents with CHD/CRHD, enabling them to manage challenges during the transition phase between childhood and adulthood.

Keywords: adolescents, congenital heart defects, chronic rheumatic heart disease, challenges, transition

INTRODUCTION

The advancement of technology and research in congenital heart surgery has had positive effects on the survival rates of children with CHD, leading into adolescence and adulthood (Marelli et al., 2007; Stoutz and Leventhal, 2009). Living with CHD adds additional burdens to the life of an adolescent, particularly concerning medical symptoms and lifestyle (Brickner et al., 2000), mental and emotional challenges (Johnson, 2014; Wang et al., 2014), relationships (Dellafiore et al., 2016; Tye et al., 2017), employment (Pahl and Grady, 2012), and healthcare (Sable et al., 2011).

A number of patients with moderate to severe congenital heart defects usually require palliative or corrective surgery at an early age and require ongoing medical care (Marino et al., 2001). They face various complications and challenges, such as frequent readmission, neurocognitive deficits, restrictions in exercise, issues with pregnancy, and often need to take medication long-term to survive (Brummett et al., 1998; Schultz and Wernovsky, 2005).

Emotionally, if adolescents with these conditions fail to adapt to the changes resulting from an illness, it can cause anxiety, fear, and even increase their risk of depression (Brummett et al., 1998). Constant experiences of continuous negative feelings, especially hopelessness, during the lives of young people may jeopardize the risk of mortality in patients with cardiovascular diseases (Stern et al., 2001). Even though patients with CHD have a high risk of developing mood and anxiety disorders, their emotional health is often under-treated or ignored (Kovacs et al., 2009).

Socially, the illness might affect a patients' relationship with their family, peers, and romantic partners. For instance, Pahl and Grady (2012) found that adolescents or young adults have difficulties in developing and maintaining significant relationships. Where interaction with peers is concerned, they often find themselves hindered by illness as they are unable to participate in social activities that require physical exertion such as hiking and camping, and subsequently feel left out and excluded by peers (Kendall et al., 2003).

Some patients experience overprotective and controlling behavior from their parents, which carried forward from childhood and persists into adolescence or even adulthood. This can cause a great barrier for adolescents in achieving their needs and developing autonomy as adults (Bertoletti et al., 2013). The impact of parental overprotection/control could be severe, as the risk of internalization behavior (anxiety and depression) and suicidal thinking can be high if the mother is overprotective, while the risk of externalizing behavior (aggression and rules breaking behavior) can increase if the father is over-controlling (Csomortani, 2011).

Similar to the normal population, adolescents or adults with CHD also desire an education or career (Pahl and Grady, 2012). The employment statistic of patients with disabilities and chronic illness conditions in Malaysia do not currently exist, but a study from the United States indicated that only 44% of respondents were employed and that 67% of those who were unemployed wished to work (Blomquist, 2006).

From the perspective of healthcare, adolescents with CHD are in a transition moment, when the services they receive shift from pediatric to adult management. This transition is often described as random and non-organized, which can cause non-adherence and difficult behavior. Moreover, if the transfer is sudden and unprepared, the adolescents might interpret the transition as a punishment and a sign of rejection (Viner, 2001). Adolescents with CHD are also expected to manage their health care, including taking medication and organizing appointments. Unfortunately, if these adolescents are not equipped with good analytical and decision-making skills and because emotion management skills are involved with risk-taking behaviors, they are more likely to adhere poorly to medical care, which may eventually lead to poor health outcomes (Pahl and Grady, 2012).

Patients with CRHD face challenges in relation to sociological and disease-specific factors as well as in terms of the health services they require. In the sociological domain, they can have life experiences of disease, poverty, powerlessness, and racism. The disease-specific domain comes from the fact that these patients have insufficient access to primary healthcare and lack information about their condition. Finally, patients with rheumatic heart disease often experience a lack of health communication and a positive experience is emphasized in the challenges of the health service domain (Haynes et al., 2020).

To address and resolve the issues above, particularly health care and lifestyle issues, various studies have suggested the need to have the services of formal Adolescent Transition to Adulthood programs to prevent discontinuity of care, financial or psychology related issues, to meet vocational, educational and other social needs and to promote future health (Hergenroeder, 2002; Moons et al., 2009; Sable et al., 2011; Kovacsa et al., 2012; Hays, 2015; Moceri et al., 2015; Said et al., 2015). However, Adolescent Transition Programs for CHD are not widely available (McPheeters et al., 2014). Even in the United States, only five percent of state mental health administrators have reported the existence of transition services or programs (Hunt and Sharma, 2013).

There is currently limited literature on the experiences and challenges faced by adolescents with CHD/CRHD in Malaysia. The challenges faced by adolescents in the Malaysian cultural context and the psychosocial programs needed to support them are still unclear. Based on the World Bank, Malaysia is categorized as an upper-middle-income economy (The World Bank, 2020). Compared with developed countries, patients in Malaysia face several challenges. First, only Kuala Lumpur, the capital of Malaysia, has a Congenital Heart Centre. Second, awareness of CHD and CRHD from the public is generally still low. Furthermore, to date, there is no proper transition program designed for CHD/CRHD in Malaysia. Our hospital planned to conduct this study to understand the challenges faced by adolescents with CHD/CRHD from the perspective of patients, parents, and healthcare providers, before designing a comprehensive transition program that includes education and psychosocial supports.

The purpose of this study is, (1) to describe the experiences and challenges faced by adolescents with moderate and severe CHD and CRHD, and (2), to explore what the precise needs of those patients are in our development of an Adolescent Transition Psychoeducational Program.

MATERIALS AND METHODS

This is a qualitative study that uses phenomenology to describe and analyze the common features participants have as they experience a phenomenon (Creswell, 2007). As the aim of the study was to identify the common themes/phenomena relating to the challenges faced by adolescents with CHD/CRHD, thus this research design was selected. Semi-structured interviews were conducted according to interview protocols, which were validated in a pilot study. The IJN Research Ethics Committee provided ethical approval for the research.

Respondents

To align with the research objectives and design, purposive sampling was used to identify respondents who would provide information relevant to CHD/CRHD (Palinkas et al., 2013). The current study interviewed 17 respondents, seven adolescents with CHD/CRHD, six parents, and four health care providers. Data saturation and variability were achieved when no new themes were observed in patient's challenges and needs from the program. Despite case numbers being low, the analysis was detailed and of quality.

The reason the researchers interviewed three groups of participants (patients, parents, and healthcare providers) was to ensure data trustworthiness by using the triangulation method of multiple respondents. This method ensured that fundamental biases arising from a single group are overcome to ensure the credibility of research findings. To ensure that the finding is valid, the researchers need to compare findings from different groups to determine whether they point to similar results (Creswell and Miller, 2000).

Adolescents with CHD/CRHD between the age of 16–19 years old at the date of recruitment and diagnosed with moderate or severe CHD or CRHD were included in the study. Patients with acquired heart diseases, genetic or mental disorders were excluded from the study. Patients who were home or bed-bound and unable to join the interviews were also excluded. The demographics of the participants are shown in **Table 1**. The interview sessions were conducted in the clinic and ward of the Institute Jantung Negara (National Heart Institute), Malaysia.

Measures and Pilot Study

To ensure that the data collected are valid, the interview protocols were formed based on objectives and Creswell's guidelines, including title and demographic, instructions, multiple similar questions for one theme, guidance for further elaboration, and verbal appreciation (Creswell, 2007).

First, three types of interview protocols were designed in English. Each set of interview questions had seven questions tailored to the perspectives and understanding of the three types of respondents. Example: "What has it been like living with your medical condition (Congenital Heart Defects)?"

TABLE 1 | Demographic of participants.

Participants	Variable	Categories	Number	Percentage
Patient	Gender	Male	4	57.14%
		Female	3	42.86%
	Ethnicity	Malay	5	71.42%
		Chinese	1	14.29%
		Indian	1	14.29%
	Diagnosis	Moderate	3	42.86%
		Complex	4	57.14%
Parents	Gender	Male	2	33.33%
		Female	4	66.67%
	Ethnicity	Malay	4	66.67%
		Indian	2	33.33%
Healthcare provider	Gender	Female	4	100%
	Ethnicity	Malay	3	75%
		Indian	1	25%

The interview protocols were then sent to four translators for translation and back translation in Malay and Mandarin versions. Then, these interview protocols were sent to three experts for review to ensure that these questions were suitable for qualitative inquiry, participants' educational and cultural context, achieving objectives, and fulfilling ethical and legal standards.

Finally, a pilot study was conducted on three adolescents with CHD/CRHD, three parents, and two health care providers to ensure their understanding of the interview protocols. The pilot study was recruited in the clinic. The findings from the pilot study showed that the participants were able to understand the interview protocols with some amendment in wording. No further questions were added or removed.

Data Analysis

Moustakas's (1994) phenomenological data analysis was adopted using the Atlas.ti version 8. First, the recorded interviews were transcribed and translated, followed by the identification of significant statements in the transcript. These statements would later be categorized into clusters to ensure they were sufficient to form a valid theme. To form a valid theme, we used the triangulation method of dividing multiple respondents into three groups (patients, family, and healthcare providers), in which they described similar shared concerns and overall experiences (Moustakas, 1994; Creswell, 2007).

RESULTS

The Experience and Challenges Faced by Adolescents With CHD and CRHD

Initially, 41 categories of challenges were coded. Following the triangulation analysis for the three types of participants, only eleven categories were found valid, which was further classified into five themes as shown in **Table 2**. Ideally, all perspectives from the three different groups are shown in one category, based on the triangulation of multiple respondents. Due to word limits, only selected interview responses are presented below.

TABLE 2 | Findings on the experiences and challenges of adolescents with CHD.

Themes	Categories
Challenges related to emotional/psychological issues	Feeling sad and afraid Feeling angry and denial
Challenges related to progress of illness	Experience physical symptoms Experience physical limitation/restriction Experience of lifestyles changes
Challenges related to relationship issues	Family interaction issue Friendship and social life issue
Challenges related to future preparation	Concern about their future/employment issues
Challenges related to school and community	Issue in schools Lack of support groups and community supports

Challenges Related to Emotional/Psychological Issue

Feeling sad and afraid

Emotional/psychological issues are one of the most common themes cited in interviews. Most adolescents reported a degree of sadness due to their illness. In some cases, they compared themselves with a healthy population. Others were worried about the progression of their illness. They were afraid that they may lose the capacity to do what they were able to do before. They became stressed because they were unable to manage their emotions

> I scare about how long could I walk, the distance how long could I walk, I scare of it, I get stress then I can't breath properly because of that.
>
> (Patient, CRHD)

> (Really difficult, if we feel he is sad. . . When he feels sad, isolated, and he wants to talk about it, he can't, like isolating himself.)
> *Memang susah, jika kita rasa dia sedih, mungkin dia rasa sedih, dipinggirkan, tapi dia nak luah, tak boleh, macam mengasing dirinya.*
>
> (Parents, CHD)

Feeling angry and in denial

The experience of being a patient triggered feelings of anger and frustration in some patients. If these adolescents are unable to control their emotions, it affects their relationships, as well as their medical condition:

> (Ya, because when the emotion is not stable and meet up others, I might release anger on them.)
> *Aha, sebab nanti kalau macam emosi sedang tidak stabil dan bila jumpa orang nanti, saya akan termarah mereka.*
>
> (Patient, CHD)

> So that's why we have a lot of compliance problem among the teenagers, because most of them they feel. . . I'm well, I don't need to take medication, a lot of denial, a lot of anger, they always angry, angry with their family.
>
> (Healthcare provider)

Challenges Related to Progress

Experience physical symptoms

Common physical symptoms experienced by adolescents with complex heart disease were tiredness and shortness of breath. Some complained of pain and dizziness. Due to the progression of their illness, some patients would need medication to control their symptoms. Some patients had significant symptoms like fainting, causing them to be fearful of recurrence and being a burden to others.

> (Like. . .. Afraid I may suddenly faint. This will cause trouble to others, like calling an ambulance to this hospital. This condition will frighten other people)
> *Macam. Takut tiba-tiba saya pengsan, akan menyusahkan orang, macam panggil ambulan ke hospital ini. Menakutkan orang la macam keadaan ini.*
>
> (Patient, CHD)

> (Sometimes when I looked at her difficult in breathing, I do not allow her to go to school.)
> *Kadangkala dia macam susah nak bernafas, kadangkala fikir juga. Ah. . . Tengok dia kadangkala tak bagi dia pergi sekolah.*
>
> (Parents, CHD)

Experience physical limitation

The majority of adolescents experience challenges due to physical limitations. Compared to the other categories, physical limitations ranked highest. Physical limitations could be caused by the progression of the illness, or due to unwarranted restriction by people around them. This physical limitation has a bigger impact on those who previously had normal functional capacity. These patients experience more grief, frustrations, and have difficulty dealing with their worsening functional capacity:

> For example, my front gate in my school to behind gate is so long, must walk. . . so I stand and rest in three places and breath deeply, then only I can walk.
>
> (Patient, CRHD)

> (Ok, the other challenges I feel is from the perspective of sporting activities . . . Starting from the age of 13, I purposely limits her activities. Thankfully until 12 years of age, she manage to be active in sports. However, I feel this current restriction should not be a problem as there are still a lot of light activities she can join.)
> *Ok, cabaran-cabaran lain itu saya berasa dalam segi active sukan itu memang dia. Bermula daripada 13 tahun memang dia. . . Saya memang had-kan dia punya activiti. So. . . dari kecil sampai 12 tahun, Alhamdulilah dia sempat bersukan, jadi saya berasa tak ada masalah kot, ada banyak lagi sukan yang ringan-ringan yang dia boleh join.*
>
> (Parents, CHD)

Experience of lifestyles changes

As the illness progresses, adolescents with complex heart disease need to adapt and manage lifestyle changes, particularly those with mechanical valves. These types of patients need to take anti-coagulants throughout their life to prevent mechanical valve dysfunction. They need regular blood reviews, adjustments to their diet, and lifestyles. Furthermore, female patients of childbearing age have an increased risk of morbidity and mortality.

> My medication. It was large different before 2 years and now.
>
> (Patient, CRHD)

> (I just need to prepare my child and myself. . . When using a mechanical valve, there are few things she is forced to comply with. First is the diet. Second. . . it might cause bleeding if she doesn't follow her diet precautions. And third. . . the most

challenging, because she is a girl, she is not encouraged to get pregnant.)
Cuma saya perlu persiapkan saya dan anak saya... Apabila menggunakan injap mechanical, ada beberapa perkara yang dia paksa patuhi. Pertama permakanan. Kedua... boleh berlaku pendarahan bila-bila masa jika permakanan tadi dia tidak patuhi. Dan yang ketiga. agak. paling mencabar, because dia adalah perempuan, dia tidak digalakkan untuk pregnant.

(Parent, CRHD)

Challenges Related to Relationship Issues

Family interaction issue

There were controversial responses from the interviewees with regards to family interactions. Four patients did not have any family issues. Others reported issues like overprotectiveness, pampering, and a lack of independence. This could be partly due to a family's fear of losing the child. Some interviewees felt that this reliance on parents was undesirable as it could limit an adolescent person's capacity to care for themselves, especially in the absence of the parents.

> And the another thing is . . . ya. . . my family doesn't like me to go out more than my other siblings. So it's like they kept me in house, doesn't let me to get social.
>
> (Patient, CRHD)

> (Sometimes I am afraid of even letting her take the bus alone. I am frighten. Usually I will drive her wherever she wants to go. However, I am aware that at some point, I have to let go as she cannot stay with me forever right? She will need to make friends and go dating. I have thought a lot about that, and I worry about what I should do.)
> *Kadangkala nak lepas dia naik bus pun takut! Takut kan? Selalu saya drive kereta, mana dia nak pergi pun saya bawa. Bila satu tahap tak kan saya nak bagi dia duduk dengan saya sahaja kan? Dia akan berkawan, dia mesti nak dating pada masa akan datang. Banyak terfikir, masa itu la saya risau apa nak buat.*
>
> (Parents, CHD)

Friendship and social life issue

Despite sufficient data for this category to form a valid code, the majority of the participants alleged that they did not have any issues in forming friendships. Some adolescents did, however, need to frequently explain their illness to their friends to prevent misconceptions and unintentional injuries. Those unable to manage their emotions were at times treated with hostility and isolated by peers and some were subjected to bullying.

> So far my life with this disease is quite difficult, quite challenging. There is a lot of things I need to manage, there is a lot of things I need to adjust, there is a lot of things I need to explain. And that happened everywhere, high school, university and within my friends.
>
> (Patient, CRHD)

> Because once they feel frustrated, they will become. . . err. . . either they will isolate themselves and start doing their own things since they cannot join their peers. This may cause some grief among the family. . . the parents and their children or it can cause lots of animosity against the teachers or friends. Sometimes they are subjected to bullies in the school.
>
> (Health care provider)

Challenges Related to Future Preparation

Concern about their future/employment issues

Three adolescents and one parent discussed that they did not think about the future. Another parent remained positive about the future. However, the majority of respondents were concerned about the future, especially employment. Patients with complex heart disease may be physically restricted, leading to stereotypes and discrimination that they are unable to perform tasks.

> Because industrial company will want healthy and fit employees right? So I think it will be a challenges for me to get a job.
>
> (Patient, CRHD)

> First of all is employment. They will have problem in employment. Of course some of the adolescents dropped of their school because their illness. Financial they are going to have financial issue, they need financial support. If they are capable enough to work and providing, sometimes if the disease itself progress, they might not able to work. Sometimes when these adolescents, when they proceed into adulthood, they might need to support their parents. So I foresee a lot of financial issue.
>
> (Health care provider)

Challenges Related to School and Community

Issue in schools

The issues faced in schools range from minor to major. Four out of the seventeen participants claimed that they coped well in school, but some had issues related to acceptance by teachers and peers, a lack of understanding of their disease, high absenteeism, and poor school performance.

> (The teacher and my peers have difficulty accommodating me, I am less favored because I seldom go to school due to chest pain and this is unavoidable. I am unable to achieve the target given by my teacher as I did not go to school. So, it is difficult. . .)
> *Penerimaan orang terhadap diri kita agak susah, sebab sekarang di alam persekolahan pun dah macam, orang tak suka sangat sebab saya jarang datang sekolah, sebab sakit dada dan tak boleh dielakkan, so macam cikgu bagi target tak tercapai sebab kita tak datang ke sekolah. So susahlah.*
>
> (Patient)

> Sometimes even when they are undergone surgery and considered sort of cured from the disease, they are also a lot of hesitancy in the part of teachers/school to allow them to take part in physical activities or take part in any activities in school, this makes them feel alienated and frustrated.
>
> (Health care provider)

Lack of support groups and community supports

The health care providers acknowledged that providing medical care and education alone was not sufficient to help this group of patients. Unfortunately, there is a lack of adequate support groups and community support for adolescents with heart disease.

> (Difficult, because we Kelantanese don't have any association. Before have heart foundation, but now when we find it, it doesn't exist.)
> Susah, sebab kita Kelate tak ada apa-apa kesatuan. Dulu ada Yayasan jantung, tapi kita cari-cari tak ada.
>
> (Parents, CHD)

Even Down Syndrome they have Kiwanis. Argh... Congenital Heart Defects, they don't. Even the cancer, the children with cancer, they have their own supports, err... what else do I know? Cancer especially is very strong, but congenital heart defects. We don't.

(Health care provider)

The Needs of the Program Development

To explore what the patients might need from a new support program, the researchers first reviewed the staff perception of an Adolescent Transition Psycho Educational Program and the willingness of adolescents with CHD and their parents to participate in such a program. Second, important elements of the program were suggested by the respondents.

All of the health care providers who participated in the interview felt that the Adolescent Transition Psycho Educational Program would be helpful and were happy to support the program. Both the adolescents with CHD and their parents showed a positive attitude toward the program. All adolescent respondents were keen to join the program, but two of them said they would need to review their schedules before committing to it. Some parents also had encouraging responses, pending 50% (n = 3) need to review their schedules.

Atlas.ti version 8 was used to review the elements of the program and recognized 19 categories. After triangulation of the three types of respondents, four valid categories were identified, which have been classified into two themes, as indicated in **Table 3**.

Self-Management of Illness and Life

Coping with illness and emotions

Some adolescents felt they had difficulties in handling their illness and hoped the program would help them cope with the challenges associated with the illness. Parents and health care providers hoped the program would help the adolescents self-manage health issues and become more independent.

(I don't know what specifically hospital can offer, but give anything that can help us cope with the illness.)
Saya tak tahu specific apa hospital boleh bagi, tapi bagilah apa yang boleh bantu saya menangani penyakit ini la.

(Patient, CHD)

(What is suitable, what is not suitable. But when she grow up, I felt I need to give her a chance to take care of herself.)
Apa yang sesuai, apa yang tak sesuai. Tapi bila dah dewasa nanti, saya rasa saya kena bagi peluang untuk dia menguruskan diri sendiri.

(Parents, CHD)

TABLE 3 | Findings on the elements to be included to the program.

Themes	Categories
Coping with illness and future	Self-management on illness and emotions Preparation for future
Social support	Support group Psychosocial support

Preparation for future

Some respondents were uncertain about the future of these adolescents, especially with regards to the progression of illness and employment issues. They outlined that they would like the program to provide adolescents with guidance for preparing and dealing with potential issues in the future:

(Like if my situation deteriorate at the future, what I should do? Do I need to do operation again?)
Macam jika situasi saya teruk pada masa depan, bagaimana saya perlu buat? Perlu saya buat pembedahan lagi ke?

(Patient, CRHD)

(I ... what the best is... I also don't have information from hospital la. What my child can do to... Move forward and pursue her career.)
Saya... apa yang terbaik adalah... saya pun tak tahu daripada hospital la. Apa yang anak saya boleh buat untuk... maju jaya dan mengejar kerjaya nya.

(Parents, CHD)

Social Supports

Support groups

A number of respondents suggested that having a patient support group might be helpful. They outlined that it would reassure them that they are not alone and that others share similar concerns. It would also enable them to learn constructive coping strategies from one another.

Maybe for the feelings, maybe we can have the support group or regular meetings with the counselors.

(Patient, CRHD)

Support group I think is very important because they can link, they can do activities together, they don't feel they are alone. So they can have their own organization. like a group, so that they know. someone from the world, they have the same situation. condition with them.

(Healthcare provider)

Support from psychologists/counselors

The respondents outlined that they wanted support from psychologists and counselors, who could assist them in managing the challenges they face, as discussed by ACHD9 and HCP4:

(Probably the hospital can set up a counseling department, then for those who don't know what to do, the counselors could tell them how to manage.)
*可能医院可以设立一个counselor的部门,这样*就给那些不知道怎样做的人,去告诉他们怎样做。

(Patient, CHD)

Yes, psychological program, how to cope with the disease. I am not sure whether we can put some elements into their program.

(Healthcare provider)

DISCUSSION

The findings of the current research concurred with past literature on the topic. It has been reported that adolescents with CHD experience more emotional issues than those without chronic disease (Johnson, 2014). There is a higher prevalence of anxiety and depression (Wang et al., 2014), and a higher risk of internalizing and externalizing problems (Karsdorp et al., 2007) in adolescents with a chronic disease. Physical limitations and restrictions were the most common issues reported in the present study. This increased the risk for lower quality of life (Dahan-Oliel et al., 2011; Riaz et al., 2018) and worsened psychosocial issues (Johnson, 2014).

Moreover, data in the current study showed that the respondents hoped that a program would help guide adolescents with CHD/CRHD, enabling them to self-manage their illness, and preparing them for facing possible challenges in the future. These findings are validated by Chen et al. (2016), whose study observed that it was crucial to assist adolescents with CHD and help them to learn health self-management and how to cultivate a positive attitude when handling disease (Chen et al., 2016, 2019).

With better knowledge and understanding of their cardiac condition adolescents with CHD are expected to have a better health-related quality of life (Wang et al., 2014). Even though some adolescents were aware that they needed to take active responsibility for their health, they did not know where to begin. Moreover, they were not certain about their lifespan due to the progress of the illness and were unsure of how to manage it. In the Malaysian cultural context, adolescents outlined that medical staff tended to communicate only with caregivers and expected the caregivers to deliver the message to the patients, instead of directly communicating with the patients. Thus, adolescents with CHD/CRHD were not sure of the progress of their illness, and only followed the instructions of the parents and medical staff in taking care of themselves.

Chen et al. (2016) have suggested that a transitional health passport and clinical interventions to smoothen the transition process from adolescence to adulthood should be developed. Lee et al. (2014) also suggest that a comprehensive educational program and support group that enhances the task-oriented coping-mechanisms of adolescents will further increase their resiliency toward illness. Transitional health-related issues, such as medical-related issues, employability, and sexuality, should be targeted in such a program to prepare adolescents for their future (Canobbio, 2001).

Psychosocial supports and support groups are another theme or element that could be included in a support program. Psychosocial support from counselors could provide psychological interventions. Support groups provide a place where patients who have similar conditions can gather and meet, enabling them to understand, learn, and support one another.

The patients included in this study expressed emotional challenges. These findings are supported by another recent study by Sheikh et al. (2019), stating that most patients with CRHD suffer from moderate levels of anxiety and depression, which are associated with physical pain, social functioning, and general health. In comparison to the general population, patients with CHD showed a higher prevalence of depression, anxiety, and posttraumatic stress disorder, which lead to a greater risk for cardiovascular morbidity and mortality. On top of that, only a small number of people receive psychosocial treatment (Andonian et al., 2018).

Another contributing factor could be avoidance or disengagement coping strategies, such as maladaptive coping, as it is correlated with high levels of anxiety, depression, and somatic complaints (Compas et al., 2006). Even though avoidance coping could contribute to resiliency in managing stressful events, findings have shown that task-oriented and emotion-oriented coping could cultivate better resiliency for adolescents with CHD (Lee et al., 2014). Unfortunately, a worrying tendency seen in CHD patients, is that these patients tend to use avoidance strategies, such as denial or distract themselves with something unrelated, more often compared with a normal population (Iwaszczuk et al., 2014).

Support groups for patients with CHD are still underdeveloped in Malaysia. NGOs have provided support for patients with terminal diseases like cancer, but patients with CHD still lack support groups and some can only attend support groups overseas through internet access. However, the use of online support is not yet a common practice.

Patients in Malaysia have similar needs to those in other countries. They would like to receive an education and improve their self-management of their condition through knowledge and by receiving psychosocial support. Additional challenges faced by patients in Malaysia compared with developed countries include the lack of congenital heart centers (so far only one is available in Kuala Lumpur), a lack of awareness of CHD/CRHD, and the absence of an Adolescent Transition Program for patients who require complex congenital heart surgery in government hospitals, particularly in Sabah and Sarawak, where they need to join a waiting list to transfer to Kuala Lumpur for surgery.

Strengths and Limitations

A key strength of this study is its triangulation of multiple respondents (patients, parents, and health-care providers) to ensure reliable data. It compared multiple sources to determine whether they point to similar results and to avoid fundamental biases from a single group.

Even though the saturation of data was achieved, the study is limited by its small sample size. There is also a potential selection bias as we used purposive sampling to recruit respondents in the study. In Malaysia, the majority population has Malay, Chinese, and/or Indian heritage, and there is a lack of representation from other minorities, such as Kadazan and Ibans. Moreover, there is an absence of representatives from states, such as Sabah and Sarawak. Furthermore, patients with comorbid conditions (genetic disorders and mental disorders) were excluded from the study. The present study highlighted the needs of patients, but there was a lack of comprehensive comparison with international data like the research of APPROACH-IS.

CONCLUSION

The present study suggests that an Adolescent Transition Psycho educational Program should be developed to assist adolescents with moderate to severe heart disease. This program would assist them to develop tools for self-managing emotional and psychological issues, the lifestyle impact of the disease progression, and prepare them for the future. Support groups and psychosocial support should also be incorporated into the program.

DATA AVAILABILITY STATEMENT

The datasets generated for this study are not publicly available. Requests to access the datasets should be directed to windofheart2000@msn.com.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by IJN Research Ethics Committee. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin. Written informed consent was obtained from the individual(s), and minor(s)' legal guardian/next of kin, for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

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