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Psychological Aspects of Cardiac Care and Rehabilitation: Time to Wake Up to Sleep?

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Abstract:

Psychological and psychosocial factors have long been linked to cardiovascular disease. These psychosocial factors, including low socioeconomic status, social support/isolation, stress and distress, personality and sleep disturbance increase risk of cardiovascular events and negatively impact on quality of life. These factors may have direct effects on cardiovascular disease via immune or neuroendocrine pathways, or more indirect effects, by for example limiting adherence to recommended therapies and cardiac rehabilitation. Most psychosocial risk factors can be assessed relatively easily using standardised tools. Sleep disturbance, in particular, is gaining evidence for its importance, and may be crucial to address. While the management of certain psychosocial risk factors is an ethical requirement for care and improves quality of life, unfortunately there is little evidence that such strategies impact on 'hard' endpoints such as recurrent myocardial infarction. A comprehensive biopsychosocial approach to management of these psychosocial factors is required to maximise the benefits patients derive from cardiac care.

Introduction

A growing evidence base suggests that a range of psychosocial risk factors (PSRFs) are linked to the pathogenesis of cardiovascular disease (CVD). Factors such as anxiety, depression and low socioeconomic status have been reliably linked with both the development of cardiovascular disease and poorer prognosis post-onset [1, 2]. In addition, the ubiquitous term 'stress' is now an established feature of modern parlance and may be an increasingly important determinant of cardiovascular health. In the face of improvement in traditional risk factors for CVD, PSRFs such as chronic stress show no sign of abating. For example, the INTERHEART study of 11119 patients with myocardial infarction (MI) from 52 countries demonstrated that perceived stress and depression accounted for 32.5% of the population attributable risk for CVD, suggesting that combined they were as important as smoking, and more important than hypertension (17.9%) and diabetes (9.9%) [3]. Furthermore, greater than 90% of the causes of CVD identified by this landmark study were attributable to modifiable risk factors, largely influenced by health behaviours, which are in turn impacted by PSRFs. In fact, PSRFs play such a prominent role in a multifactorial condition such as CVD that they have been incorporated into the guidelines of medical associations [2], in order to maximise the effectiveness of treatment of this population and deliver truly biopsychosocial care.

The aims of the current review are to (a) summarize the extant literature regarding the links between PSRFs and cardiovascular disease; (b) provide an overview of the management of psychological aspects of CVD, with a particular focus on cardiac rehabilitation, and make recommendations as appropriate; and (c) to highlight emerging areas of interest and identify potentially novel targets for cardiovascular disease reduction (*e.g.* insomnia). Although this paper will primarily refer to psychological aspects of care targeted in the setting of cardiac rehabilitation, the experiences of patients with heart failure or those living with an ICD will also be addressed to some extent. Functional heart complaints (*e.g.* non-cardiac chest pain) are beyond the scope of the current review, but with regard to emerging areas of interest, particular attention will be given to the role of sleep disturbance.

PSRFs and CVD outcomes

Social factors and CVD

Low Socioeconomic Status (SES): Various systematic reviews have documented an association between low SES (defined as low education level, low income, holding a manual job, or residing in a disadvantaged area) and an increased risk of cardiac and all-cause mortality risk [4-6]. Patients recovering from an MI with both low income and low educational attainment have a significantly increased risk of mortality [7]. Furthermore, patients of low SES with CHD are less adherent to secondary preventive medications [8], have poorer behavioural control of cardiac risk factors [9], and may even benefit less from CR [10] . Unfortunately, there is also consistent evidence that those of lower SES are less likely to attend/complete cardiac rehabilitation (CR) [11, 12].While CR programmes primarily attempt to mitigate the SES-CVD link by addressing the cardiac risk factors known to account for much of this relationship [13], selected interventions have been shown to increase the uptake of CR programmes in patients of low SES [14] , although the evidence to support interventions that improve adherence is weak [15]. Financial incentives have also been explored for their potential to improve CR participation rates in patients from disadvantaged communities [16]. However, while these interventions are promising [17], further studies are needed to determine costs and generalizability of findings. Although it is important to identify and target patients with low SES, efforts should also be taken by CR staff to accommodate patients with associated literacy difficulties by avoiding the use of medical jargon and communicating with patients using language familiar to them.

Social isolation and poor social support:

Social isolation refers to the circumstances in which one lives (*i.e.* alone or with others) whereas social support relates to the availability of practical or emotional support enjoyed by an individual. The evidence that social isolation and low social support respectively increase the risk of incident CVD in healthy people is much less convincing than prognostic studies of their effect in patients with established CVD and/or MI [18, 19]. A recent meta-analysis established that a smaller social network was less important than low functional support (*e.g.* tangible and perceived emotional support) in predicting increased cardiac and all-cause mortality, even after controlling for other somatic factors [19]. While it was initially thought that high levels of social support may moderate the effect of depression on mortality in post-MI patients [20], the ENRICHD trial, which targeted and improved perceived social support, had no impact on cardiac endpoints [21]. Although there is currently insufficient data to inform clear recommendations regarding targeting social support in patients with CHD, attempts to enhance social support and reduce social isolation should definitely be encouraged, however these efforts are more likely to improve quality of life than cardiac outcomes.[22].Social support may be addressed both directly and indirectly in CR, via individual psychological support, a therapeutic group dynamic, family interventions (*e.g.* spousal anxiety/ caregiver burden), onward referral to specialised community supports (*e.g.* ICD support groups), and the enlisting peer support to facilitate adherence to lifestyle changes post CR (*e.g.* phase IV exercise maintenance programmes) [2][23]. With regard to identifying at-risk patients the ENRICHD Social Support Instrument (ESSI) is recommended as a screening measure for low perceived social support in CR and has been shown to be predictive of cardiac endpoints [24, 2].

Personality Characteristics and CVD:

Type A Behaviour Pattern (TABP): TABP refers to a combination of highly competitive goal-oriented behaviour, impatience, time urgency, cynical hostility and frequent expressions of anger. This behavioural pattern was the first psychosocial risk factor in CHD to be studied scientifically [25], and was considered the most likely candidate for a ‘coronary prone personality’ until the late 1980s, when anger and hostility were identified as the “toxic” components of TABP [26]. Subsequent research has

since focused on these two constructs to the detriment of TAPB, and a meta-analysis concluded that 'Type A personality' was not a valid indicator of cardiac prognosis [26]. Some observers have suggested that TABP may have suffered a premature demise given recent evidence showing that interventions targeting TABP have led to improved depression [27], and even improved cardiac endpoints for female CHD patients in particular [28, 29]. Aspects of TAPB are also implicitly addressed in interventions such as transcendental meditation (TM) and mindfulness based stress reduction (MBSR) which are sometimes available to patients attending CR [30].

Anger and Hostility:

Anger is a transient emotional state associated with feeling threatened or frustrated, whereas *hostility* is more of a persistent attitude of opposition and anger towards others [31]. Hostile beliefs and attitudes (*e.g.* cynicism and mistrust of others' motives), are considered to lower the anger provocation threshold, and anger-proneness as a trait is the tendency to experience more frequent, pronounced and prolonged episodes of anger and resentment [31]. In a recent meta-analysis, the presence of anger and hostility were shown to both precede the development of CHD and worsen its course [32]. Few studies have investigated the effects of anger-specific interventions on recurrent cardiac events or survival. In comprehensive CR, treatments typically address anger/hostility only as one component of stress management., and address, for example, the popular misconception that "holding anger in" is hazardous to one's health and should therefore be expressed regularly [33], an assumption not supported by empirical findings on the cardiovascular effects of anger [34]. Cognitive behavioural stress management (CBSM) has been shown to significantly reduce anger/hostility in ICD recipients, but not arrhythmias or other cardiovascular outcomes [35], and exercise-based CR has also been shown to reduce anger and hostility in patients with CHD [36]. Although a reduction in hostility may contribute to reduced mortality risk in patients with CHD [37], this finding needs to be replicated in more rigorously designed studies. While identifying clinically significant anger/hostility is recommended in patients attending CR [2], targeting anger in isolation is unlikely to be as impactful as taking a more comprehensive approach as may be achieved in the setting of CR. Expanded psychosocial interventions that encompass anger management in addition to other modes of treatment (*e.g.* exercise, pharmacotherapy) may be more likely to improve cardiovascular outcomes in these patients [38].

Type D personality: The emergence of Type D or 'distressed' personality [39] brought renewed interest in the role of personality traits as vulnerability factors for adverse health outcomes in cardiac patients, but recent literature in this area has been critical. Similar to hostility, Type D individuals are characterised by a general propensity to psychological distress (negative affectivity), but unlike their hostile counterparts, they have a tendency to consciously inhibit self-expression in social interactions to avoid disapproval of others (social inhibition)[39]. These traits are thought to operate synergistically [39], and Type D cardiac patients have been found to be less adherent to cardioprotective medications, to view their heart condition more negatively, experience higher levels of depressive symptoms over time, and gain fewer benefits from CR [40-44]. While a number of meta-analyses have also shown Type D personality to predict worsened prognosis in persons with CHD [45, 46], recent studies have failed to replicate these results [47-50], which has generated considerable critique. Critics of Type D highlight that the majority of these studies included small samples, were conducted by a single investigator group, and statistically analysed Type D personality as a dichotomized variable instead of an interaction term, thereby increasing the risk of spurious results [50-52]. Although Type D patients have been shown to improve in health status following CR, they do not experience the same health gains as non-Type D patients [53], and firm empirical

evidence that interventions targeting this population result in improved outcomes is lacking. Potential interventional strategies in the context of Type D personality have been identified to focus on mood (*e.g.* CBT, relaxation training, mindfulness based stress reduction); health behaviours (*e.g.* smoking cessation, exercise therapy); and interpersonal functioning (*e.g.* Interpersonal therapy (IPT), assertiveness training) [54]. Irrespective of the controversy surrounding Type D, there is a clinical rationale to formally screen for distressed cardiac patients who, by definition, are likely to conceal their suffering, and who may be at risk for non-adherence to recommended therapies such as CR.

Stress and CVD

Work stress: The majority of studies examining the link between stress and cardiovascular disease have focused on situational stressors, with chronic work stress being the most widely investigated. Individuals who report excessive work demands coupled with low decisional latitude are deemed to be experiencing "job strain" [55]. However a recent meta-analysis found only a small increase in incident CHD associated with job strain (HR 1·23; 95% CI 1·10-1·37) [56]. Similarly, the perception of an imbalance between the effort of work (*e.g.* demands, challenges, sacrifices) and its associated rewards (e.g. financial, self-esteem, advancement opportunities) is understood as the effort-reward imbalance (ERI) model of work stress [57] and has also been investigated with respect to its ability to predict CHD. A meta-analysis examining this relationship did not find a significant effect [58]. There is a distinct lack of intervention studies evaluating the effect of reducing work stressors on CHD risk, although there is some evidence that the effects of job strain can be mitigated by attending CR [59]. Return to work is an explicit goal of CR, and vocational counselling is a feature of many CR programmes [60]. Psychological interventions specifically targeting work stress primarily comprise of tailored individual stress management and may focus on (a) increasing social support at work; (b) reduction of job demands (*e.g.* avoiding overtime, assertiveness training, pacing, delegating, modifying work practices); and (c) targeting 'overcommitment' to work (*e.g.* re-establishing work-life balance, challenging perfectionistic thinking)[61]. Acute stressors and stressful life events: Acute mental stressors may serve as 'triggers' to cardiac events including ACS [62], Takotsubo ('stress-induced') cardiomyopathy [63] or ventricular arrthymias [64], with these events particularly seen in patients with established CHD. Intense episodes of anger have been shown to trigger cardiac events within 2 hours [65], and other acute stressors such as natural disasters, major sporting events, bereavements and military/terrorist attacks have been shown to transiently increase cardiac events, *e.g.*[66, 67]. Although stress management interventions with cardiac patients have successfully targeted potential triggers such as anger [28], overall there is currently no strong evidence for specific modes of prevention for acute stressors in individuals. In light of this, efforts to buffer the cardiovascular impact of acute stressors via health behaviours (*e.g*. exercise, diet) should also be encouraged. Equally, while cardiac patients should be helped to acquire stress management skills in CR, it is also important to convey to patients that successfully coping with a hectic lifestyle is not harmful to their cardiac health, and staff should be vigilant to signs of excessively cautious behaviour borne of such misconceptions which may inadvertently impede patients' physical and/or psychological recovery (*e.g.* avoidance of exercise, excitement, sexual activity) [68]. Stress management in cardiac care:

Stress management interventions in CR typically target chronic stress, and it has been suggested that they provide an incremental impact to exercise-based CR [69]. However, while a recent Cochrane review of psychological interventions for patients with CHD demonstrated small to moderate improvements in depression and anxiety with such interventions, there was no strong evidence that they reduced cardiac morbidity or mortality [70].Similarly, although encouraging results have been reported for interventions such as mindfulness-based stress reduction, TM, and yoga, overall these

studies have been of low quality and thus no firm recommendations can be made for their ancillary use with cardiac populations [30; 71]. Stress management programmes most likely to be effective with cardiac populations should be multimodal, intensive, initiated only after the acute phase of illness has passed, delivered by appropriately trained clinicians and possibly should involve booster sessions after the intervention has been completed [72, 28, 73].

Emotional Distress and CVD

Depression:

Approximately 20% of patients with CHD meet DSM criteria for major depression, with up to a further 31% evidencing sub-clinical levels of depressive symptoms [74,75]. Rates of depression in women with CHD are double those of men, and it is possible that depressive symptoms may have a different aetiology between sexes [74]. While mild depression may remit spontaneously for some, depressive symptoms typically persist in about half of affected patients [76, 40, 77], and can negatively affect the course of their recovery [77]. In patients living with an ICD major depression ranges from 11% to 28% [78], and has been shown to predict both the incidence of shock therapy and mortality [79, 80]. The prevalence of depression in patients with chronic heart failure is even greater and tends to increase with the clinical severity of heart failure [81]. Both major depression and elevated depressive symptoms have been associated with both an increased risk of developing CVD, and an increased risk of death in patients with existing CVD in several meta-analyses [74, 75, 82, 81]. Accordingly, a recent AHA scientific statement recommended that depression should be elevated to the status of independent risk factor for poor prognosis in patients Acute Coronary Syndrome (ACS) [83].

Patients with CHD and co-morbid depression are more likely to experience physical limitations and poorer quality of life, often independent of objective measures of cardiac function [2]. Depression is also associated with other behavioural risk factors for heart disease, such as smoking and medication non-adherence [84, 85, 2, 86] and reduced participation in cardiac rehabilitation [87, 88]. Although studies suggesting links between particular subtypes of depression (*e.g.* somatic or anhedonic depression) have tended to be inconsistent [89, 90], recent meta-analytic findings suggest that somatic/affective (*e.g.* insomnia, fatigue) rather than cognitive/affective (*e.g.* guilt, pessimism) symptoms of depression may predict increased risk of mortality seen in CHD patients [91]. Such somatic symptoms are suspected to be a physiological consequence of CVD processes, and some authors hypothesise that depression should be seen as a variable risk marker, rather than risk factor, for CVD [92].

Although a number of psychotherapeutic and pharmacological options exist to treat depression, treatments that improve both depression and reduce the risk of cardiovascular events have not yet been identified. For example, cognitive behavioural therapy (CBT), Interpersonal psychotherapy (IPT), and problem-solving therapy (PST) have all been shown to be beneficial for depression in cardiac patients but did not affect cardiac endpoints [21, 93, 96]. Currently, collaborative care, or stepped care, is considered to be optimal in treating cardiac patients with depressed mood [94, 95]. The COPES trial employed a stepped-care treatment approach in patients with ACS and persistent depression, involving an initial patient choice of PST and/or pharmacotherapy [96]. This intervention resulted in significantly less depression after 6 months compared to usual care and although most patients chose to commence PST initially, half were treated with medication by the end of the trial due to persistent depression. Exercise has also been evaluated as a treatment for depression, with the UPBEAT trial demonstrating that for patients with CHD and concurrent depressed mood, 4 months of

aerobic exercise training 3 times weekly was as effective as antidepressant medication for improving depressed mood [97]. Similarly, the HF-ACTION randomised trial of 2322 patients with heart failure (28% of whom were depressed), demonstrated that exercise not only reduced mortality and hospitalization, but significantly reduced depression with this effect remaining after 1 year [98].

Although antidepressant medications (typically SSRIs), have been shown to improve depression in patients with CHD, particularly in patients with relapsing or severe depression [21], a stable finding across trials appears to be that there is little, if any, evidence that pharmacotherapy improves cardiac endpoints in depressed patients with CHD [99, 21], and in patients with heart failure antidepressant medication has not been demonstrated to increase survival *or* significantly reduce depression [100].

Cardiac patients may be reticent to disclose depressed mood [101], and depression in patients with heart failure frequently goes unnoticed as symptoms such as tiredness, sleep disturbance, and impaired concentration are typical of the cardiac disease itself. However a large proportion of CR programmes do not routinely screen for depression [102], and screening itself does not necessarily translate into improved clinical outcomes for cardiac patients unless followed by comprehensive care [94, 102]. It is recommended that clinically significant levels of depression be systematically identified via clinical interview and/or use of a brief, reliable screening measure validated in cardiac populations (*e.g.* PHQ-9) [103]. Screening should ideally take place before hospital discharge, at CR programme entry (*i.e.* within 2-3 months), and again at CR completion. Staff should be aware of the appropriate referral process, and patients screening positive for depressed mood should be followed up for diagnostic evaluation by a mental health professional. Although the effect on cardiac endpoints is as yet unproven, quality of life is improved with depression treatment, and collaborative care with stepped interventions may result in optimal patient outcomes [104].

Anxiety:

Anxiety is a normative response to a potentially life-threatening event, with up to half of hospitalized cardiac patients reporting clinically significant anxiety while in hospital, and this persists in up to 40% of patients after one year [105, 106]. Similarly, the rates of patients meeting criteria for an anxiety disorder reach 18% in patients with heart failure [107] and 26% in ICD patients [78] respectively, with nearly half of the latter population exhibiting significant shock anxiety [108]. Furthermore, in a meta-analysis of 24 studies, Edmondson *et al.* [109] found a 12% prevalence of PTSD among patients with acute ACS, and there is growing evidence that symptoms of posttraumatic stress both worsen the cardiovascular prognosis of patients with CHD [110], and predict all-cause mortality in patients living with an ICD [111].

Although anxiety is more prevalent than, and highly co-morbid with depression [112-114], relatively less is known about anxiety in cardiac patients, although the existing evidence suggests that anxiety disorders per se are less common in this population than sub-clinical levels of anxiety. Anxiety has not been as robust a predictor of cardiac endpoints as depression, and the associations between anxiety and CHD have generally been smaller than those found for depression. Roest *et al.* [115] found that initially healthy participants with elevated anxiety were at increased risk of CHD (HR 1.26; 95% CI: 1.15-1.38) as well as cardiac mortality, and this effect was independent of demographic variables, biological and behavioural risk factors. Notably however, the meta-analytic estimate for the association with CHD was not adjusted for depression. A further meta-analysis examining the prognostic association of anxiety in post-MI patients found that elevated anxiety was predictive of all-cause mortality, cardiac mortality and new cardiac events at three years follow-up [116]. More recently a study of 1411 patients with CHD found that while both depression and anxiety predicted

all-cause mortality 10 years post-PCI, anxiety conferred no additional risk in the case of co-morbid depression [117]. That the effect sizes for anxiety are lower than those for depression raises the possibility that for some cardiac patients, elevated anxiety may in fact be a stimulus for improving health behaviours. While depression has been consistently associated with non-adherence to recommended health behaviours, the evidence is mixed for anxiety [118, 2], and higher anxiety levels have even been associated with a reduction in both mortality and cardiac events 5 years after coronary stenting [119].

Few randomised controlled trials (RCTs) have explicitly targeted anxiety in cardiac patients. The recent Management of Sadness and Anxiety in Cardiology (MOSAIC) trial examined the impact of a 6-month low-intensity collaborative care intervention compared to usual care, in a population of patients hospitalized for acute cardiac illness (*e.g.* ACS, heart failure or arrhythmia) [120]. Cardiac inpatients diagnosed with major depression, generalized anxiety disorder, or panic disorder were blindly allocated to either 6 months of collaborative management [a low-intensity telephone-based multicomponent intervention targeting depression and anxiety disorders (n = 92)] or to 'enhanced usual care' (n = 91), which involved identification of mood/anxiety disorder, serial communication of diagnosis to primary medical providers over 6 months, and provision of emergency care. Interventions were provided by care managers in collaboration with psychiatrists and comprised of psychotherapy and pharmacotherapy on a stepped care basis. Those patients receiving the intervention experienced greater quality of life at 6 months, greater improvements in depressive symptoms and general functioning, and higher rates of treatment of a mental health disorder. However, anxiety scores, disorder response rates and adherence did not differ between groups [120].

Comprehensive CR provides a major therapeutic impetus for patients with CHD, and has been shown to result in significant improvements in anxiety, particularly in those highly anxious at baseline [27, 36]. High levels of anxiety in cardiac patients are often driven by maladaptive beliefs about their heart condition [68], and these misconceptions are frequently targeted during CR, in addition to provision of stress management and relaxation training. As with depression, anxiety levels should be assessed before and after CR with a validated screening tool [121], with specialist psychological support considered as appropriate. Although anxiety disorders may substantially contribute to cardiovascular risk, there is currently no convincing evidence that treating them with psychotherapy and/or pharmacotherapy mitigates this risk, in addition to reducing distress. More RCTs are needed to determine if adjustments to the collaborative care model cited above result in greater improvements in mental health.

Health-related quality of life:

While quality of life is typically considered an outcome in research studies and practice, more recent research has highlighted how quality of life and health status could be seen as risk factors for prognosis in CVD [2]. The improvement of health-related quality of life (HRQoL) in cardiac patients is considered an important objective of cardiac rehabilitation, and has been increasingly emphasised in cardiac care generally, given that some treatments do not do improve prognosis or are associated with significant psychosocial burden. Studies have also shown that impaired quality of life is predictive of poorer cardiovascular outcomes in patients with CHD and/or heart failure [122-124] although it remains somewhat unclear to what extent this relationship is influenced by disease severity or comorbid affective disorders, which themselves are known to result in poorer cardiovascular outcomes and HRQoL [125]. Although poorer quality of life is associated with less uptake of cardiac rehabilitation [126], patients with CHD or heart failure who do attend experience clear improvements [127]. Lifestyle changes targeted by CR (smoking cessation, increased physical activity, cardioprotective diet) when adopted by cardiac patients, are also linked with better HRQoL [128] . Changes in illness beliefs during CR have also resulted in enhanced HRQoL in this population.

Patients who came to view their heart condition as more understandable, perceived fewer emotional consequences and attributed less symptoms to their illness, experienced better HRQoL upon completing CR [129].
While there are diverse conditions within the spectrum of CVD, often patients receive similar treatments. Therefore, comparison of HRQoL among subgroups has become an important focus. Two HRQoL questionnaires have recently been shown to allow for comparison among different diagnostic groups – the HeartQol and the MacNew [130-132]. The HeartQol, in particular, has demonstrated validity across 22 countries and several languages and has been shown to predict 5-year mortality and cardiac readmissions in patients with ischaemic heart disease [133]. Aside from evaluating the effectiveness of CR, this measure may also aid in identifying patients at higher risk for CVD events and thus inform treatment planning [134].

Sleep and CVD

Sleep was not considered as a risk factor for CVD until relatively recently. The INTERHEART study, for example, conflated sleep with stress by not measuring it directly but rather including it in their measure of stress [3]. However, research over the last decade or so has provided convincing evidence that sleep disturbances independently contribute to poorer cardiovascular health [135, 136], and may represent important novel targets for CVD reduction. Studies examining the association of impaired sleep with cardiovascular health have focused on shiftwork (intermittently misaligned sleep), short and long sleepers, obstructive sleep apnoea (OSA), and more recently, insomnia [137]. A recent systematic review and meta-analysis showed shiftwork to be associated with 23-24% increase in risk for MI and CVD events but not for mortality. All shiftwork schedules other than eveing shifts increased the risk of cardiac events, even after adjusting for behavioural and biomedical risk factors [138]. Meta-analyses have also identified sleep of either long (≥8 to 9 hours) or short (≤ 5 to 6 hours) duration as risk factors for CVD [139]. While it has been posited that longer duration of sleep may be simply a marker of depression or medical co-morbidities [140], the causes of short sleep duration are more varied (*e.g.* insomnia, shiftwork) and often behavioural (*e.g.* poor sleep hygiene, type A behaviour). Short sleep duration has been associated with an increased risk of hypertension in particular 141-142], in addition to neuroendocrine and autonomic dysfunction, inflammation and appetitive factors [143]. Conversely, in a large prospective study of 17887 adults aged 20-65 years and free of CVD at baseline, the addition of sufficient sleep (≥ 7 hours) to four cardioprotective lifestyle factors (sufficient physical activity, healthy diet, moderate alcohol intake and non-smoking) resulted in a 65% lower risk of composite CVD (HR 0·35; 95% CI 0·23-0·52) and an 83% lower risk of fatal CVD (HR 0·17; 95% CI 0·07-0·43)[144].

OSA is characterized by a partial or complete blockage of the upper airway, typically caused by the soft tissue at the back of the throat collapsing during sleep due to lack of muscle tone. Increased sympathetic activity, surges in blood pressure and other mechanisms such as oxidative stress, systemic inflammation, metabolic abnormalities and endothelial dysfunction are thought to contribute to the development of atherosclerosis [145], and OSA has been associated with a 70% relative increased risk of cardiovascular morbidity and mortality [146]. OSA is highly prevalent (~ 66%) but underdiagnosed in cardiac patients [147, 148] and findings suggest that OSA results in decreased cardiac function in patients attending CR, thereby impeding recovery from their cardiac event [148]. Treating OSA in both cardiac and hypertensive patients may result in reduced cardiovascular morbidity and mortality [149, 150] and consequently the importance of routine OSA screening in CR populations has been stressed [147, 151].

Insomnia and OSA are highly co-morbid, and operate synergistically to result in poorer outcomes in both hypertensive and depressed patients [152]. Similarly, although insomnia and short sleep duration are clearly related, they represent different entities, in that insomnia necessitates dissatisfaction with the quality of sleep and the accompanying daytime consequences which may or may not be explained by objectively reduced sleep duration. A recent meta-analysis of 13 prospective studies identified insomnia as a risk factor (RR 1.45, 95% CI 1.29-1.62) for developing or dying from cardiovascular disease [153], and insomnia has also been associated with several adverse cardiometabolic risk factors [154], especially when accompanied by short sleep duration [155]. Chronic insomnia with *objectively measured* short sleep duration is considered to be the most severe biological phenotype of the disorder, particularly with regard to cardiovascular mortality [156], and both hypertension and biomarkers of systemic inflammation (*e.g.* C-reactive protein) have been posited to account for this observed increase in mortality [156, 157, 154].

Importantly, the emergence of DSM-5 Insomnia Disorder (ID) confirmed that insomnia in cardiac patients may no longer be assumed to be merely an associated symptom of depression and anxiety, likely to co-remit. Rather, studies have shown that sleep disturbance typically continues following a depressive episode [158], and residual insomnia symptoms following treatment for depression increase the risk of depressive relapse [159]. Insomnia is highly prevalent in cardiac patients (~ 37%) [160], and poor sleep quality is strongly associated with both depressive symptoms and decreased HRQoL in patients attending CR [161]. Furthermore, in patients recovering from a cardiac event (MI and/or revascularization) sleep disturbance was associated with poorer treatment adherence, and predicted anxiety and depression one year later [162]. These findings suggest that sleep disturbance in cardiac patients may hamper rehabilitative efforts, and demonstrate the importance of sleep evaluation in cardiac care. Consequently, in addition to identifying OSA, it has been strongly recommended that CR programmes should implement brief but comprehensive sleep assessments that discriminate patients who suffer from clinically significant insomnia that could put them at risk for a future major depressive episode [163]. The STOP-BANG [164] and the Insomnia Severity Index (ISI) [165] are recommended as initial CR screening measures for OSA and insomnia respectively. CBT for insomnia (CBT-I) is an effective treatment with an efficacy that is better sustained than pharmacotherapy [166], but access is limited due to the lack of appropriately trained providers [167]. Although it is not yet an established component of cardiovascular care [168], there is emerging evidence that CBT-I improves biomarkers that may contribute to the CVD risk [169]. Looking forward, although sleep disturbance is clearly associated with increased risk cardiovascular disease, large randomized controlled trials are needed to determine whether ameliorating insomnia, or optimizing sleep more generally, improves cardiovascular outcomes. Meeting this challenge may enable sleep to assume its place among “the top 10 modifiable risk factors for cardiovascular disease” [170].

Psychobiological and behavioural pathways linking PSRFs and CVD

A detailed account of the various behavioural and pathophysiological mechanisms linking PSRFs and cardiovascular disease is beyond the scope of the current review. However, a number of common and interrelated pathways have been identified that may serve as plausible explanations for this relationship. The incidence and development of CVD can be brought about by direct physiological effects or indirectly via health behaviours. The psychobiological routes to cardiovascular endpoints can vary according to each PSRF, but collectively include changes in the autonomic nervous system, the endocrine and inflammatory systems, insulin resistance, central adiposity, endothelial and platelet dysfunction [171, 172]. Behavioural pathways include unhealthy diet, lower levels of physical activity, excessive alcohol consumption [173, 174]; reduced adherence to cardioprotective

medications [84], and less engagement with secondary prevention programmes such as smoking cessation and cardiac rehabilitation 86, 87]. Financial barriers to accessing health care post-MI have also been predictive of poorer outcomes [175]. Rather than partial out their individual effects, future research in this area may benefit from investigating the synergistic relationships between PSRFs that may naturally cluster together. For example, a recent prospective study of 4487 adults with CHD provided evidence for a 'perfect storm' conceptual model whereby the confluence of depressive symptoms and concurrent high stress were more predictive of cardiac endpoints at 2.5 years than either PSRF alone [176].

Conclusion

Substantial research has demonstrated the critical importance of PSRFs to quality of life, but also the aetiology and prognosis of CVD. The complex role of PSRFs is highlighted by the fact that they are thought to act on CVD outcomes via indirect and direct mechanisms. Another complicating factors is the interrelatedness of some of the PSRFs highlighted in this review. For example, depression is highly co-morbid with personality, anger, anxiety, poorer HRQoL, sleep disturbance, and even aspects of disease severity, such as left ventricular dysfunction. Large studies are needed to elucidate these relationships, to determine if these are true risk factors, or better seen as risk markers for CVD outcomes. Such studies should also provide a renewed focus on sleep, which could provide a promising avenue for comprehensive behavioural management of related PSRFs and possibly to impact harder endpoints. What is clear from the literature is that the assessment and treatment of such PSRFs do enhance quality of life, and there is a clear ethical obligation to provide such comprehensive, effective psychosocial care.

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