American Journal of Preventive Cardiology 12 (2022) 100376

Contents lists available at ScienceDirect

American Journal of Preventive Cardiology

journal homepage: www.journals.elsevier.com/american-journal-of-preventive-cardiology

The relationship between anxiety sensitivity and clinical outcomes in cardiac rehabilitation: A scoping review

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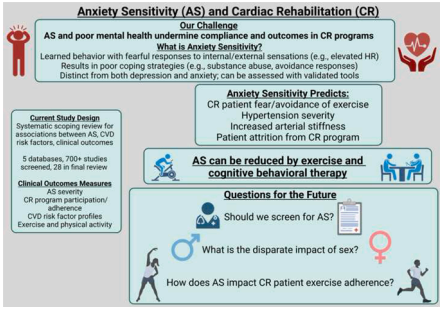
HIGHLIGHTS

- Despite strong evidence, participation in cardiac rehab remains very low.
- Myriad system-level and patient-level barriers persist.
- Anxiety sensitivity is separate from anxiety and depression and can be treated.
- There is a likely link between anxiety sensitivity, exercise, and cardiac rehab.
- Significant gaps remain in our understanding of possible sex-based differences.

GRAPHICAL ABSTRACT



ARTICLE INFO

Keywords:
Anxiety sensitivity
Cardiac rehabilitation
Cardiovascular disease
Exercise
Cardiovascular disease risk factors

ABSTRACT

Background: Despite well-established efficacy for patients with a cardiovascular diagnosis or event, exercise-based cardiac rehabilitation program participation and completion has remained alarmingly low due to both system-level barriers and patient-level factors. Patient mental health, particularly depression, is now recognized as significantly associated with reduced enrollment, participation, attendance, and completion of a cardiac rehabilitation program. More recently, anxiety sensitivity has emerged as an independent construct, related to but distinct from both depression and anxiety. Anxiety sensitivity has been reported to be adversely associated with participation in exercise and, thus, may be important for patients in cardiac rehabilitation. Accordingly, the objective of this study was to conduct a scoping review to summarize the evidence for associations between

Abbreviations: 6MWT, 6-minute walk test; AF, atrial fibrillation; AFSS, atrial fibrillation severity scale; AnxS, anxiety sensitivity; ASI, anxiety sensitivity index; ASI-R, anxiety sensitivity index –revised; ASI-3, anxiety sensitivity index – 3; BMI, body mass index; BP, blood pressure; CBT, cognitive behavioral therapy; CR, cardiac rehabilitation; CVD, cardiovascular disease(s); DT, distress tolerance; GRE, general self-efficacy; HPAPQ, health physical activity participation questionnaire; IPAQ, international physical activity questionnaire; FEQ, fear of exercise questionnaire; LV, left ventricular; MET, metabolic equivalent; MI, myocardial infarction; MVP, mitral valve prolapse; PAM, physical activity measure; RCT, randomized controlled trial; SR, stress reactivity; SUDS, subjective units of distress scale.

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https://doi.org/10.1016/j.ajpc.2022.100376
Received 5 March 2022; Received in revised form 18 August 2022; Accepted 22 August 2022
Available online 31 August 2022

anxiety sensitivity and cardiovascular disease risk factors, exercise, and clinical outcomes in cardiac rehabilitation.

Methods: A formal scoping review, following PRISMA-ScR guidelines, was undertaken. Searches of MEDLINE, Web of Science, CINAHL, PSYCINFO, and Scopus databases were conducted, supplemented by hand searches; studies published through December of 2020 were included. The initial screening was based on titles and abstracts and the second stage of screening was based on full text examination.

Results: The final search results included 28 studies. Studies reported statistically significant associations between anxiety sensitivity and exercise, cardiovascular disease, and participation in cardiac rehabilitation. Many studies, however, were conducted in non-clinical, community-based populations; there were few studies conducted in cardiovascular disease and cardiac rehabilitation clinical patient populations. Additionally, significant gaps remain in our understanding of the sex-based differences in the complex relationships between anxiety sensitivity, exercise and cardiac rehabilitation.

Conclusion: More research is needed to understand specific associations between anxiety sensitivity and clinical outcomes among clinical cardiovascular disease patients and participants in cardiac rehabilitation programs. Treatment of anxiety sensitivity to optimize clinical outcomes in cardiac rehabilitation programs should be investigated in future studies.

1. Background

Cardiovascular diseases (CVD) are the leading cause of death globally [1] and, while mortality rates from CVD have trended downward in the last 30 years [2], the prevalence of people living with CVD has increased, subsequently increasing the associated burden on society [3]. Cardiac rehabilitation (CR) was first established in the 1970s and is supported with strong evidence for improving cardiovascular function, reducing mortality and morbidity related to CVD, and also being cost-effective [4–6]. Unfortunately, despite the overwhelming evidence to support CR, participation and completion of CR in Canada remains discouragingly low. Of patients referred to CR in Alberta, only 50% completed their program, 40% did not attend, and 10% participated but did not complete the program [7]. More discouragingly, in Ontario the number of patients who participate in CR is just 22% of eligible patients [7]. Substantial evidence from myriad studies indicate that both system-level and patient-level factors are barriers that have contributed to the low CR referral, uptake, and completion rates.

System-level barriers to CR have been well studied and include inconsistent and incomplete referral, disparities in referrals, disparities in physical or geographic access to CR centers, and inadequate capacity, including too few CR centers or patient spaces and concentration of centers in urban settings leaving patients in rural areas without access to care [8–10]. With regard to patient-level psychological factors, there is evidence that depression is associated with a worse prognosis for multiple cardiovascular diseases, including increased risk for myocardial infarction (MI), incident coronary heart disease (CHD), and stroke [11–14]. Additionally, multiple studies have established that patients with depression are significantly less likely to complete their CR program [15], which has resulted in the incorporation of routine depression screening into evidence-based guidelines for CR [16]. Although there are fewer studies addressing the impact of anxiety, there is evidence that anxiety is also significantly associated with CVD risk factors such as hypertension, specific types of CVD such as CHD, stroke, and heart failure, and an overall increased risk of CVD mortality [11].

Anxiety sensitivity (AnxS) has emerged as an independent construct, related to but distinct from both depression and anxiety. Unlike depression or anxiety, AnxS is not a clinical pathology but is defined as a learned cognitive trait that predisposes individuals to fearful misinterpretations of internal processes and sensations, such as elevated heart rate or respiratory rate, and is associated with the development of maladaptive coping strategies (e.g., substance use) or outright avoidance (e.g., avoiding physical activity) [17]. While it is known that individuals with higher levels of AnxS are more likely to develop anxiety related disorders [18–23] and that there is a modest association between AnxS and mood disorders, including depression [20,22], emerging evidence suggests that AnxS can be independently targeted for treatment [17].

The recognition of AnxS as a potential therapeutic target was aided substantially by the development and refinement of psychometrically validated tools to measure and quantify AnxS, particularly the Anxiety Sensitivity Index (ASI). Initially developed in 1986, the original ASI consisted of 16 items, each item being scored from 1 to 4 points, resulting in a total score ranging from 0 to 64 points [24]. A revised and expanded version of the ASI, Anxiety Sensitivity Index-Revised (ASI-R), was published in 1998 and consisted of 36 items [25] and a distinct factor structure [26], though some studies raised concerns about the stability of the proposed factor structure of ASI-R [20]. The Anxiety Sensitivity Index-3 (ASI- 3) was first issued in 2007 and consists of 18 total items representing 3 factors (physical, cognitive, and social concerns), with each item scored from 1-4 points resulting in a total score ranging from 0 to 72 points [27]. Thus far, published evidence supports that the ASI-3 is a more stable, valid, reliable, and multidimensional tool used to assess AnxS in both clinical and non-clinical populations compared to the previously designed measures [28,29]. Most recently, a brief version of the ASI, the Short Scale Anxiety Sensitivity Index (SSASI), has been proposed as a 5-item questionnaire that may be more suitable for screening for AnxS in clinical settings [30]. As each if the tools within the ASI family consist of different number of items, factors, scoring algorithms, and total scores, there is not a scoring categorization scheme that crosses all versions of the ASI; categorization into low, medium, or high AnxS is tool or study dependent.

There is a growing body of scientific studies of the many different aspects of AnxS. Included in this literature are multiple studies that have reported that AnxS may be related to hypertension [31,32] and participation in physical activity [33–36], both of which are central components of CR. Given what is known about the importance of depression and anxiety within CR, and evidence of associations between AnxS and depression, anxiety, hypertension, and participation in exercise, it is reasonable to postulate that AnxS may impact some patients in CR, and this merits further investigation. Therefore, the objective of this study was to conduct a scoping review to summarize what is known about relationships among AnxS and outcomes for patients in CR programs, including the discrete behavioral and traditional cardiovascular disease risk factors that are the focus of treatment and programing in CR (exercise, blood pressure, blood cholesterol, blood glucose).

2. Methods

2.1. Information sources and search strategy

This study was implemented by following standard methodology for conducting a scoping review [37]. A comprehensive literature search was conducted using the following electronic databases: MEDLINE, Web of Science, CINAHL, PsycINFO, and SCOPUS. Multiple searches were conducted in each database using different approaches (e.g., keywords,

subject headings), though search strategies had to be adapted slightly for the particular characteristics of each database (e.g., Medical Subject Terms (MeSH) are available in Medline).

Records retrieved contained the following terms: exercise; cardiovascular disease risk factors; cardiovascular disease; and cardiac rehabilitation were combined with anxiety sensitivity. Additional filters narrowed articles only published in the English language and limited to humans. Where databases did not automatically screen for peer-reviewed literature (CINAHL and PsycInfo), that additional limitation was included. No year restriction was added due to the lack of collective research done on anxiety sensitivity; the search included studies up until December 31st, 2020. The full search strategy is summarized in Table 1.

2.2. Study screening, and inclusion and exclusion criteria

Duplicate studies were identified and removed. Studies then underwent a two-stage screening process. The first screening included titles and abstracts only, and the second screening included full text evaluation. In addition to the above identified filters, studies also were required to be full, peer-reviewed studies to be included in this review. The following studies were excluded from this review:

- Studies not assessing anxiety sensitivity as a covariate or predictor or dependent measure;
- Studies not assessing exercise, blood pressure, blood glucose, blood cholesterol, blood platelets, or cardiovascular disease as outcome measures when reporting associations with anxiety sensitivity;
- Studies focusing on individuals below 18 years of age;
- Conference proceedings or abstracts;
- Although smoking is a key CVD risk factor, all but 1 paper related to smoking were excluded due to the complexity of the literature, as highlighted in 2 recent reviews [38,39], addressing the associations between AnxS and substance disorders, post-traumatic stress disorder, and other psychological constructs that are beyond the scope of this review.

The study selection and screening process is outlined in PRISMA-ScR diagram in Fig. 1.

Table 1
Literature Screening Criteria and Results.

Database	Search Strategy	Initial Filters	Number of Publications
Anxiety Sensitivity AND Exercise			
MEDLINE (Ovid)	Terms with subject heading(s)	English	58
Web of Science	Topic	English	117
CINAHL	Subject Heading	English, Peer-reviewed	34
PsycInfo	Terms with subject heading(s)	English, Peer-reviewed	72
SCOPUS	Article title, Abstract, Keywords	English	101
Anxiety Sensitivity AND CVD Risk Factors*			
MEDLINE (Ovid)	Terms with subject heading(s)	English	27
Web of Science	Topic	English	51
CINAHL	Subject Heading	English, Peer-reviewed	14
PsycInfo	Terms with subject heading(s)/Keyword	English, Peer-reviewed	46
SCOPUS	Article Title, Abstract, Keywords	English	39
Anxiety Sensitivity AND Cardiovascular Disease			
MEDLINE (Ovid)	Title	English	28
Web of Science	Title	English	11
CINAHL	Subject Heading	English, Peer-reviewed	23
PsycINFO	Terms with subject heading(s)/Keyword	English, Peer-reviewed	44
SCOPUS	Title	English	23
Anxiety Sensitivity AND Cardiac Rehabilitation			
MEDLINE (Ovid)	Terms with subject heading(s)	English	1
Web of Science	Topic	English	3
CINAHL	Subject Heading	English, Peer-reviewed	2
PsycINFO	Keyword	English, Peer-reviewed	2
SCOPUS	Article Title, Abstract, Keywords	English	4

* CVD risk factor terms included hypertension, blood cholesterol, blood glucose, metabolic syndrome, blood platelets

3. Results

3.1. Overview of selected studies

As summarized in Fig. 1, of the 700 publications identified, 41 studies remained after initial (title and abstract) screening, 32 studies were screened in stage two (full text), and 28 studies were included in the final review. Most studies were conducted in the United States (*n=18*), with other publications originating from Canada (*n=6*), Italy (n=3), and the Netherlands (*n=1*). Of the 28 final studies, 19 studies (17 primary research studies and 2 review studies) focused on associations between AnxS and exercise, with 9 studies investigating the association between AnxS and exercise and ten studies investigating the impact of exercise on AnxS. Seven studies focused on associations between AnxS and CVD as well as CVD risk factors, and two studies were specific to the association between AnxS and CR. Randomized controlled trials were included in this scoping review (*n=8*), all of which addressed associations between AnxS and exercise. Two studies included female participants only and most exercise-related studies used non-clinical populations. In contrast, the CVD- and CR- related studies primarily focused on clinical populations.

3.2. Associations between anxiety sensitivity and exercise

A total of nineteen studies examined associations between AnxS and exercise – seventeen primary studies and two review studies. Studies were grouped based on the inferred directionality of the association, specifically whether the study examined (a) the associations between AnxS and exercise, or (b) the impact of exercise on AnxS. The eight primary studies reporting on associations between AnxS and exercise [33–35,40–44] and the nine studies describing the impact of exercise on AnxS are summarized in Table 2a [36,45–52]. Two review studies, one examining associations between AnxS and exercise [53] and one examining the associations between exercise and AnxS [54], are summarized in Table 2b. Collectively, these studies suggest that there is a significant inverse association between AnxS and exercise and that increased physical activity significantly reduces AnxS. Evidence also suggests that body mass index (BMI) may play a moderating role in the exercise and AnxS association, as individuals with high AnxS and high BMI have reported less physical activity [34] and greater fear of exercise [43]. Despite the sub-optimal exercise outcomes in individuals with high AnxS, those who were able to participate in exercise demonstrated reductions in AnxS [43]. Additionally, a recent study reported that, among individuals with high AnxS, exercise may lead to smoking abstinence [45]. Finally, associations between AnxS and exercise were similar among both clinical [33,42] and non-clinical study populations [34,35,40,41,43,44,53].

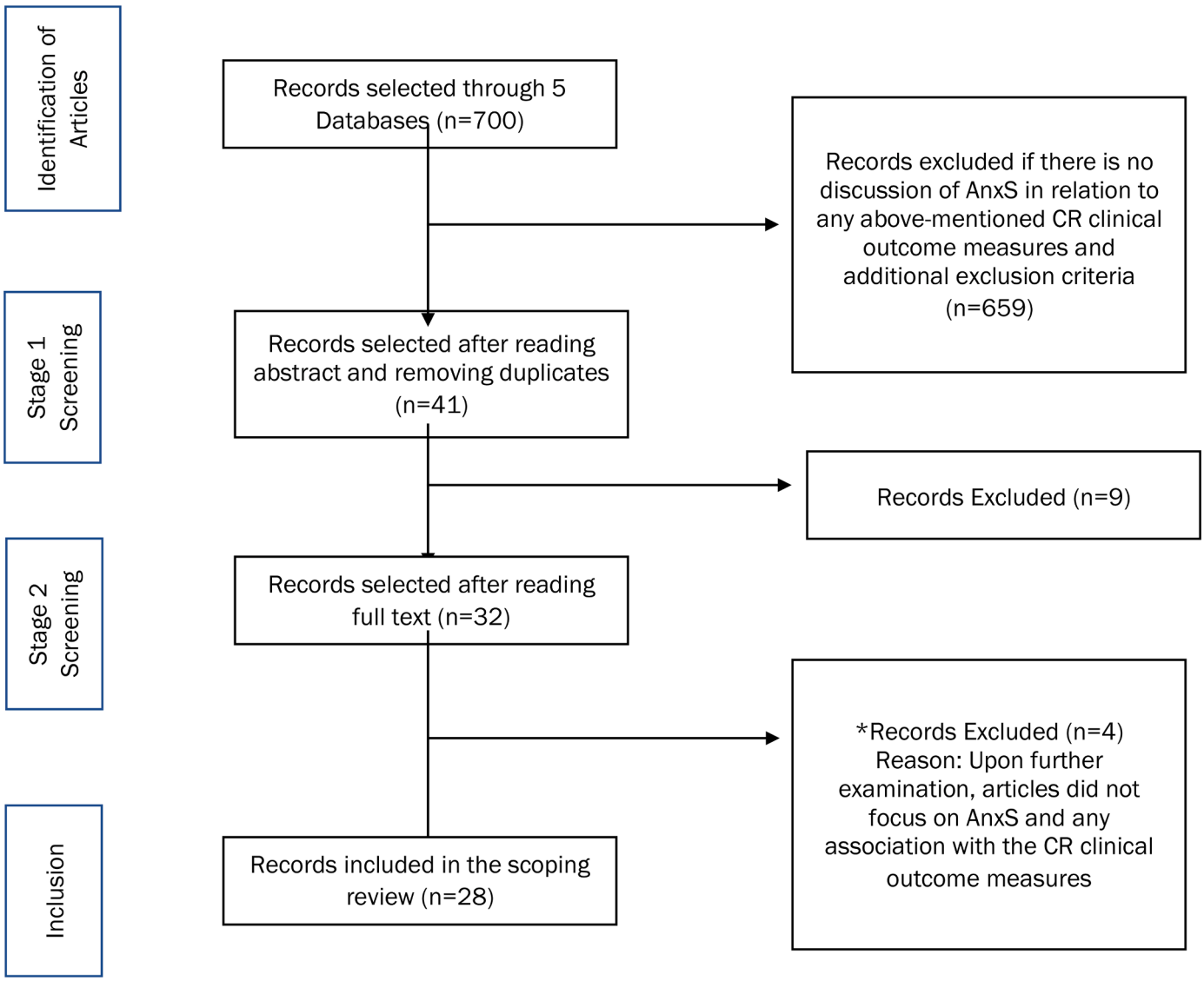

Fig. 1. PRISMA-ScR Flowchart of Search Strategy and Results.

3.3. Associations between anxiety sensitivity and cardiovascular disease

Results from the seven studies that reported findings on associations between AnxS, CVD, and CVD risk factors are summarized in Table 3. One study reported that high AnxS was associated with an increased likelihood of arterial stiffness and presence of carotid plaques [55]. Additionally, there is evidence of significant associations between AnxS and hypertension, with four studies reporting that individuals with high AnxS were more likely to be hypertensive [32,31,56,57]. Finally, other examples of chronic CVD illnesses associated with higher AnxS included greater symptom burden in individuals with atrial fibrillation and mitral valve prolapse [58,59]. Collectively, then, findings from these studies suggests that AnxS may play a role in increasing cardiovascular risk, though, as several authors have noted, it is unclear if these associations are due to direct psychological effects of AnxS or maladaptive behavioral responses to CVD in individuals with high AnxS, such as less participation in exercise, increased tobacco use, or alcohol abuse [60,61].

3.4. Associations between anxiety sensitivity and cardiac rehabilitation

The summaries of two recent studies assessing the impact of AnxS on participants in CR are included in Table 4. Though the sample sizes for these studies were modest (<70 participants), findings suggested that higher levels of AnxS were associated with lower exercise tolerance [62], greater fear of exercise, [63] and being more likely to not complete centre-based or home-based CR programs [63].

3.5. Highlighting results on sex-based differences

Studies included in this review did not consistently report sex-based differences in baseline characteristics or study outcomes. Of the 28 studies included in this review, only 4 reported sex-based differences. McWilliams and Asmundson (2001) reported that, while males reported higher exercise frequency and self rated fitness compared to women, there were no sex-based differences in ASI total or sub-scale scores [44]. Moshier et al. [35] reported that, while AnxS was negatively associated with vigorous exercise, evidence for the role of sex in mediating the relationship between AnxS and exercise was dependent upon the measurement strategy used for AnxS [35]. In a randomized clinical trial assessing whether a 2-week exercise intervention could successfully reduce AnxS, Medina et al. [48] reported that, while males were observed to have larger initial reductions in response to AnxS (after 1 week), that after the full 2 weeks of the intervention, there were no

Table 2a
Summary of included primary studies reporting on the associations between anxiety sensitivity and exercise.

First Author (Year) (Reference)	Location	Study and Sample Characteristics • Study Design • *n* (% male) • Mean Age (SD) • Study Population	Outcomes • Measurement Instrument Continuous or Categorical Cut-off Values (if used)	Key Findings • Sex-Based Differences
Associations Between Anxiety Sensitivity on Exercise				
Alcantara (2020) (Alcantara et al., 2020)	USA	• Cross-sectional • *n* = 1417 (60.9%) • Mean age= 64.7 (0.35) • Clinical study population: Individuals with MI diagnosis	• AnxS (ASI; categorical) • Physical Activity (single-item question) • ASI cut-off score of 24 based on normative data from general non-cardiac population	• Higher AnxS scores are significantly associated with a decrease in physical activity. • A one-point increase in total AnxS was associated with 2% increased odds of physical inactivity. • Study did not report sex-based differences.
Hearon (2021) (Hearon & Harrison, 2021)	USA	• Longitudinal • *n*= 55 (32.7%) • Mean age= 19.84 (1.07) • Non-clinical study population: College students and community members sample	• AnxS (ASI-3; continuous) • Physical Activity (wGT3X-BT Actigraph) • No reported ASI-3 cut-off score	• Those with higher AnxS scores participated significantly less in aerobic exercise. • Study did not report sex-based differences.
DeWolfe (2020) (DeWolfe, Watt, Romero-Sanchiz, & Stewart, 2020)	Canada	• Cross-sectional • *n*= 802 (21.9%) • Mean age= 20.02 (3.06) Non-clinical study population: post-secondary students	• AnxS (ASI-3; continous) • Physical Activity (2-item Lifestyle Questionnaire) • No reported ASI-3 cut-off score	• AnxS was significantly and negatively associated with self-reported physical activity. • Study reported sex-based differences • Women report less physical activity compared to men. • AnxS plays partial mediation role in relationship between gender and physical activity.
Broman-Fulks (2018) (Broman-Fulks, Abraham, Thomas, Canu, & Nieman, 2018)	USA	• Cross-sectional • *n*= 955 (39.2%) • Mean age= 45.8 (16.22) • Study population: Community members sample recruited from a clinical trial investigating the effects of dietary supplement on physical and psychological health	• AnxS (ASI-3; continous) • No reported ASI-3 cut-off score	• Exercise frequency is significantly negatively associated with AnxS. • AnxS partially mediates relationship between exercise frequency and depression/anxiety scores. • Study did not report sex-based differences.
[§]Hearon (2014) (Hearon, Quatromoni, Mascoop, & Otto, 2014)	USA	• Pilot study; longitudinal • *n*= 32 (37.5%) • Mean age= 43 (15.4) • Non-clinical study population: community sample containing those with normal BMI, obese individuals, normal AnxS, or elevated AnxS	• AnxS (ASI; categorical) • Monitoring activity (Actigraph ActiTrainer) • Clinical ASI cut-off score of 20 established using ASI manual	• In normal weight individuals, high AnxS was associated with greater moderate exercise compared to those with low AnxS. • In obese individuals, high AnxS was associated with less moderate activity compared to those with low AnxS. • Study did not report sex-based differences.
Moshier (2012) (Samantha J. Moshier et al., 2012)	USA	• Cross-sectional • n= 233 (48.9%) • Mean age= 26.0 (13.0) • Study population: Healthy volunteers from Boston University and the surrounding community participated in 1 of 3 studies • Study A: Online web study of undergraduate students (64%); excluded those with suicidal ideation • Study B: Experimental study of eating behaviors (24%); excluded those taking psychiatric medication and a Beck Depression score over 14 • Study C: A questionnaire and interview-based study of motivations and barriers of exercise (12%); excluded those with suicidal ideation	• Physical Activity (IPAQ) • AnxS (ASI; continuous and categorical) • Cut score of 25 established using community sample; cut score of 20 established using ASI manual	• AnxS is significantly associated with vigorous exercise in contrast to moderate exercise and walking. • Elevated AnxS predicts less vigorous exercise. • Vigorous exercise was completed by those with an ASI score of less than 20 (previously established cut-off point for low AnxS is <25) • Study reported sex-based differences. • Sex significantly associated with self-reported vigorous physical activity when AnxS cut score for high vs. low AS was 20 but not 25.
[§]Smits (2010) (Smits, Tart, Presnell, Rosenfield, & Otto, 2010)	USA	• RCT; cross-sectional Exercise group: 20 mins of treadmill exercise, with a target of 70% of each participant's maximum heart rate Control group: no exercise • n=92 (45.5%) • Mean age= 19.43 (1.31) • Study population: Undergraduate students; excluded those with history of panic attacks, substance use disorders within the past 6 months, use of	• AnxS (ASI; continous) • Peak fear (SUDS) • Clinical ASI cut-off score of 25	• Interaction found between BMI, exercise, and AnxS • Fear of arousal sensations reported on the ASI is a predictor of fear of exercise and is significantly greater in those with a higher BMI. • Significantly greater fear of exercise in those with high BMI in individuals with high AnxS. • Study did not report sex-based differences.

(*continued on next page*)

Table 2a (*continued*)

First Author (Year) (Reference)	Location	Study and Sample Characteristics • Study Design • *n* (% male) • Mean Age (SD) • Study Population	Outcomes • Measurement Instrument Continuous or Categorical Cut-off Values (if used)	Key Findings • Sex-Based Differences
		psychotropic medications, and history of medical conditions that could be aggravated by study procedures		
[§]McWilliams (2001) (McWilliams & Asmundson, 2001)	Canada	• Cross-sectional • *n*= 256 (77.0%) • Mean age= 21.2 (6.1) • Study population: Undergraduate students recruited from the Psychology Department	• AnxS (ASI; continuous) • Exercise frequency (# of times participant engaged in strenuous exercise for at least 30 min) • No reported ASI cut-off score	• Study reported sex-based differences. • Men and women differed significantly in exercise frequency and self-rated fitness, but not in AnxS.
Impact of Exercise on Anxiety Sensitivity				
Zvolensky (2018) (Zvolensky et al., 2018)	USA	• RCT; longitudinal Experimental group: Smoking cessation treatment + exercise (three 45 min vigorous intensity sessions per week for 15 weeks – target was 77-85% of maximum heart rate by week 4. Control group: Smoking cessation treatment + wellness education • n= 136 (47.8%) • Mean age= 42.25 (11.2) • Study population: Sample recruited through both community and physician referrals; included only adult daily smokers, with high AnxS, sedentary behavior, and motivated to quit smoking	• AnxS (ASI-3; categorical) • Clinical cut-off score of 20 on the ASI for pre-screen eligibility established using ASI manual • Clinical cut-off score of 23 on ASI-3 established using sample of adult smokers	• Experimental group experienced significantly lower levels of AnxS by 6-month follow-up compared to control group of no exercise. • Lower levels of AnxS were significantly associated with higher smoking abstinence in the exercise treatment group compared to control. • Study did not report sex-based differences.
Moshier (2016) (S. J. Moshier, Szuhany, Hearon, Smits, & Otto, 2016)	USA	• Longitudinal • *n*= 145 (19.0%) • Mean age= 18.8 (1.3) • Non-clinical study population: Students at Boston University	• AnxS (ASI; continuous) • Physical Activity (IPAQ) • No reported ASI cut-off score	• ASI total score is significantly negatively associated with physical activity post-intervention. • ASI total score predicts physical activity post-intervention. • ASI total score predicts METs after one week of physical activity. • Study did not report sex-based differences.
[†]Sabourin (2016) (Sabourin, Watt, Krigolson, & Stewart, 2016)	Canada	• RCT; longitudinal Experimental group: *3-day CBT + 42 10 min group running trials (intensity not mentioned)* Control group: *Provided health education* • *n*= 154 (0%) • Mean age= 18.8 (2.2) • Non-clinical study population: undergraduate female sample either one standard deviation above or below the mean for university women on the ASI (High AnxS vs. Low AnxS)	• AnxS (ASI; continuous) • Clinical cut-off score of 25 on the ASI	• Those with high AnxS in the experimental group (exercise included), demonstrated a significant linear decrease in AnxS. • Those who in the control group showed a similar decline AnxS but eventually leveled off. • Study did not report sex-based differences.
[†]LeBouthillier (2015) (LeBouthillier & Asmundson, 2015)	Canada	• RCT; longitudinal Exercise group: 30 min of vigorous aerobic exercise on a Keiser M3 Series spin cycle – (1) started with a 5 min warm up to reach target of 60% of maximum heart rate; (2) followed by a 10-minute pyramid by increasing resistance every minute for 5 minutes and then decreasing resistance for every minute for another 5 minutes; (3) 10-minute sprint (30 secs of resistance followed by 30 s of recovery at low speed and resistance; (4) 5-minute cool down with little to no resistance. Maintaining 60-80% of maximum heart rate • n= 21 (47.6%) • Mean age= 35.33 (13.3) Control group: Performed a stretching routine consisting of 36 stretches, each held for 45 secs – there was 3 minutes allocated for transitioning between poses • n= 19 (31.6%) • Mean age= 30.95 (11.68)	• AnxS (ASI-3; continuous) • Frequency and intensity of physical activity as well as self-rated fitness (HPAPQ) • No reported ASI-3 cut-off score	• Aerobic group showed greater reductions in AnxS compared to the control group. • Study did not report sex-based differences.

(*continued on next page*)

Table 2a (*continued*)

First Author (Year) (Reference)	Location	Study and Sample Characteristics • Study Design • *n* (% male) • Mean Age (SD) • Study Population	Outcomes • Measurement Instrument Continuous or Categorical Cut-off Values (if used)	Key Findings • Sex-Based Differences
Medina (2014) (Medina et al., 2014)	USA	• RCT; longitudinal Exercise group: 20 min moderate intensity aerobic exercise three times a week for two weeks – maintain 70% of their respective maximum heart rate • n= 40 (20%) • Mean age= 19.7 (2.3) Waitlist group: no exercise • n= 20 (35%) • Mean age= 22.7 (9.4) • Study population: Undergraduate students and community members; included those with ASI scores of greater than or equal to 25 with no current psychotherapy treatment or no involvement in aerobic exercise more than once a week.	• AnxS (ASI; continuous) • Clinical cut-off score of 25 on the ASI established using ASI manual	• Study reported sex-based differences. • Men showed significantly higher reductions compared to woman mid-treatment – moderating effect of gender on AnxS. • At post-treatment and follow-up, AnxS reductions did not differ significantly between men and women • Potential mechanism is physiological response to exercise being different between sex.
Sabourin (2011) (Sabourin, Hilchey, Lefaivre, Watt, & Stewart, 2011)	Canada	• Cross-sectional • *n*=154 (0%) • Mean age= 19 (2.2) • Non-clinical study population: undergraduate female psychology students; included those who scored 1 standard deviation above or below the mean ASI score for university women (High AnxS vs. Low AnxS)	• AnxS (ASI; categorical) • Assessment of participation in a range of differing intensities of exercise (PAM) • Clinical cut-off score of 35 and 8.5 for high and low, respectively on the ASI. Cut-offs established using sample of undergraduate women	• High AnxS predicted lower levels of exercise • High AnxS group predicted increased barriers to exercise. • Decisional Balance Scale scores mediated the relationship between AnxS and exercise. • Study did not report sex-based differences.
†Broman-Fulks (2008) (Broman-Fulks & Storey, 2008)	USA	• RCT; longitudinal Exercise group: six 20 min aerobic exercise sessions on a treadmill for over two weeks, with no fewer than two and no more than four sessions per week – were asked to maintain 60-90% of their respective maximum heart rate Control group: no exercise • n= 24 (20.8%) • Mean age= 19.04 (1.90) • Non-clinical study population: undergraduate students	• AnxS (ASI-R; continuous) • Clinical cut-off score of 28 on the ASI-R.	• Those in the exercise group demonstrated a significant decrease in AnxS compared to the no exercise group. • Study did not report sex-based differences.
†Smits (2008) (Smits et al., 2008)	USA	• RCT; longitudinal Exercise group #1: six 20 min exercise sessions on a treadmill (three times a week for two weeks) while maintaining 70% maximum heart rate • Mean age= 19.53 (0.35) Exercise group #2: The same exercise treatment as group #1 + cognitive restructuring • Mean age= 19.86 (0.62) Waitlist group: no exercise • Mean age= 22.65 (2.09) • n= 60 (25.0%) • Study population: Undergraduate students and community members; included those with elevated anxiety sensitivity with no current psychotherapy treatment or no involvement in aerobic exercise more than once a week	• AnxS (ASI; continuous) • Clinical cut-off score of 25 on the ASI established using normative data.	• AnxS was reduced significantly in both exercise groups compared to the waitlist group at post-treatment and follow-up measures. • AnxS mediated the relationship between exercise and depression/anxiety, especially in those with high AnxS. • Study did not report sex-based differences.
Broman-Fulks (2004) (Broman-Fulks, Berman, Rabian, & Webster, 2004)	USA	• RCT; longitudinal Exercise group #1: 20 min of high intensity aerobic exercise group consisting of two minutes of stretching, two minutes of treadmill warm-up, and then briskly walk or jog on treadmill maintaining anywhere between 60-90% of maximum heart rate. Participants were encouraged to increase their treadmill speed and heart rates with each subsequent session. n= 29 (21.0%) Mean age= 20.76 (3.16) Exercise group #2: 20 min of low intensity walking, maintaining a maximum of 60% of heart rate maximum	• AnxS (ASI; continuous) • Clinical cut-off score of 25 on the ASI was used for pre-screen eligibility. Cut-off score established using ASI-R manual.	• High intensity group demonstrated significant decline in AnxS scores. • Low intensity group did not show significant decline. • Study did not report sex-based differences.

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Table 2a (*continued*)

First Author (Year) (Reference)	Location	Study and Sample Characteristics • Study Design • *n* (% male) • Mean Age (SD) • Study Population	Outcomes • Measurement Instrument Continuous or Categorical Cut-off Values (if used)	Key Findings • Sex-Based Differences
		• n= 25 (28.0%) • Mean age= 21.64 (6.75) • n_{total}= 54 (24.1%) • Mean age_{total}= 21.17 (5.11) • Non-clinical study population: Student volunteers with elevated AnxS scores		

† RCTs reported in meta-analytic study found in Table 2b;
§ Studies reported in literature review found in Table 2b;
Abbreviations used in Table 2A: AnxS, anxiety sensitivity; ASI, Anxiety Sensitivity Index; ASI-3, Anxiety Sensitivity Index-3; ASI-R, Anxiety Sensitivity Index-revised; BMI, body mass index; CBT, cognitive behavioral therapy; HPAPQ, Health Physical Activity Participation Questionnaire); IPAQ, International Physical Activity Questionnaire; MET, metabolic equivalent; MI, myocardial infarction; PAM, Physical Activity Measure; RCT, randomized controlled trial; SUDS, Subjective Units of Distress Scale

Table 2b
Summary of included review articles reporting on the associations between anxiety sensitivity and exercise.

First Author (Year) (Reference)	Location	Type of Review	Study Purpose and Study Inclusion Criteria	Key Findings Sex-Based Differences
†Jacquart (2019) (Jacquart et al., 2019)	USA	Meta-analysis (6 RCTs of the effect of exercise on AnxS; 28 RCTs total)	• Studies were eligible if they reported findings on an RCT investigating exercise vs. no exercise on four distinct transdiagnostic treatment targets (AnxS, DT, SR, and GRE) using at least one validated outcome instrument measured after the exercise intervention.	• Exercise significantly reduces AnxS. • Effect size of the exercise group vs. control group for reducing AnxS was 0.72. • Study did not report sex-based differences.
§Horenstein (2018) (Horenstein, Potter, & Heimberg, 2018)	USA	Literature Review	• Narrative literature review on the relationships between AnxS and a variety of risk factors for chronic medical conditions. Focus was on adult samples.	• High AnxS scores are significantly associated with less physical activity. • Individuals with hypertension report significantly higher AnxS. • Study did not report sex-based differences.

† Four RCTs are also reported Table 2a of this review and denoted with the same symbol;
§ Select findings of this review are also reported in Table 3a and are denoted with the same symbol;
Abbreviations used in Table 2B: RCT, randomized controlled trials; DT, distress tolerance; SR, stress reactivity; GRE, general self-efficacy

Table 3
Summary of included primary studies reporting on the associations between anxiety sensitivity and cardiovascular disease (CVD) and CVD risk factors.

First Author (Year) (Reference)	Location	Study and Sample Characteristics	Outcomes	Key Findings
		• Study Design • *n* (% male) • Mean Age (SD) • Study Population	• Measurement Instrument Continuous or Categorical Cut-off Values (if used)	• Sex-Based Differences
Alcantara (2014) (Alcantara et al., 2014)	USA	• Cross-sectional • *n*= 88 (22.7) • Mean age= 64.65 (8.06) • Clinical study population: Patients with uncontrolled hypertension	• AnxS (ASI; categorical) • BP medication adherence (Electronic Pill box) • Clinical cut off score of 36 on the ASI, established using clinically significant anxiety levels	• Patients with high AnxS had a significantly higher relative risk of BP non-medication adherence compared to those with low AnxS. • Nearly double the patients with high AnxS were non-adherent compared to those with low AnxS. • Study did not report sex-based differences.
[§]Seldenrijk (2013) (Seldenrijk et al., 2013)	The Netherlands	• Cross-sectional • *n*= 635 (34.5) • Mean age= 46.7 (12.0) • Clinical study population: Patients with lifetime depressive and/or anxiety disorder but with sub-clinical CVD	• AnxS (ASI; continuous) • No reported ASI cut-off score	• Those with higher ASI scores demonstrated a significantly increased likelihood of the presence of carotid plaque and increased arterial stiffness. • Repeated analysis of only healthy participants showed significantly stronger associations between high AnxS and more plaques and increased stiffness. • Anxiety and depression partially mediate association between AnxS scores and increased stiffness. • Study did not report sex-based differences.
[§]Chiaie (2011) (Chiaie et al., 2011)	Italy	• Cross-sectional Experimental group: Hypertensive hospitalized patients that were negative for any Axis I or II disorders sand negative for comorbid severe medical conditions • n=196 (48.5) • Mean age= 61.46 (19.01) Control group: Normotensive hospitalized patients, negative for Axis I&II disorders, and negative for comorbid severe medical conditions • *n*= 96 (50.0) • Mean age= 62.35 (11.22)	• AnxS (ASI; continuous) • Blood pressure (mercury sphygmomanometer) • No reported ASI cut-off score	• Individuals with hypertension report significantly higher levels of AnxS. • Study did not report sex-based differences.
Ong (2006) (Ong et al., 2006)	Canada	• Cross-sectional • *n*= 93 (66) • Mean age= 61.88 (12.04) • Clinical study population: Adult patients with a primary diagnosis of AF, normal ventricular function, and at most, mild valvular disease	• AnxS (ASI; continuous) • Perceived AF episode frequency and AF symptom burden (AFSS) • No reported ASI cut-off score	• AnxS was associated with significantly greater AF symptom severity • AnxS significantly predicted AF symptom severity • Study did not report sex-based differences.
[§]Norman (2005) (Norman & Lang, 2005)	USA	• Cross-sectional • *n*= 267 (49.6) • Mean age= 47.5 (16.1) • Clinical study population: Participants recruited from Veterans' Administration and 3 university based primary care clinics	• AnxS (ASI; continuous) • Assessment of chronic illness diagnosis (demographic questionnaire) • No established ASI cut-off score	• Approximately one-third of all patients had diagnoses of 2 or more chronic illness. • The physical dimension of AnxS was significantly associated with high cholesterol, heart disease, and hypertension. • Study reported sex-based differences. • No significant results on role of sex in relationship between AnxS and chronically physically ill individuals
Delle Chiaie (1996) (Delle Chiaie et al., 1996)	Italy	• Cross-sectional Experimental group: MVP out-patients, referred to cardiologists for multiple palpitation events • *n*= 18 (44.4) • Mean age = 30.5 (9.3) Control group: Healthy individuals with the presence of MVP ruled out • *n*= 20 (60.0) • Mean age = 26.3 (4.3)	• AnxS (ASI; continuous)	• AnxS was significantly higher in the group with MVP patients. • Study did not report sex-based differences.
	Italy	• Cross-sectional • *n*= 40 (62.5)	• AnxS (ASI; continuous) • Hypertension (assessed prior to enrollment)	

(*continued on next page*)

Table 3 (*continued*)

First Author (Year) (Reference)	Location	Study and Sample Characteristics	Outcomes	Key Findings
		• Study Design • *n* (% male) • Mean Age (SD) • Study Population	• Measurement Instrument Continuous or Categorical Cut-off Values (if used)	• Sex-Based Differences
[§]Pagotto (1992) (Pagotto, Fallo, Fava, Boscaro, & Sonino, 1992)		• Age range: 22-67 • Clinical and non-clinical study population: (1) Patients with mild to moderate essential hypertension; (2) Participants with normal blood pressure ranges	• No established ASI cut-off score	• Patients with essential hypertension reported significantly higher levels of AnxS compared to healthy, normotensive control group. • Study did not report sex-based differences.

[§] Studies reported in the literature review found in Table 2b;
Abbreviations used in Table 3: AF, atrial fibrillation; AFSS, Atrial Fibrillation Severity Scale; BP, blood pressure; MVP, mitral valve prolapse

Table 4
Summary of included primary studies reporting on the association between anxiety sensitivity and cardiac rehabilitation.

First Author (Year) (Reference)	Location	Study and Sample Characteristics	Outcomes	Key Findings
		• Study Design • *n* (% male) • Mean Age (SD) • Study Population	• Measurement Instrument Continuous or Categorical Cut-off Values (if used)	• Sex-Based Differences
Kraemer (2021) (Kraemer, Carroll, Clair, Richards, & Serber, 2021)	USA	• Cross-sectional • N_{total} = 69 Cardiovascular sample: • *n*= 52 (67.3%) • Mean age= 61.41 (12.94) Pulmonary sample: • *n*= 17 (58.8%) • Mean age= 70.18 (8.68) • Clinical study population: Individuals with cardiovascular and/or pulmonary conditions	• AnxS (ASI-3; continuous) • Functional exercise tolerance (6MWT) • Other variables of interest included assessment of depressive and anxiety symptoms • No established ASI-3 cut-off score	• Greater levels of AnxS-physical concern subscale were significantly associated with poorer exercise tolerance • Study did not report sex-based differences.
Farris (2018) (Farris, Bond, Wu, Stabile, & Abrantes, 2018)	USA	• Cross-sectional • *n*= 69 (68.1%) • Mean age= 65.6 (10.9) • Clinical study population sample: Patients with unstable angina, myocardial infarction, heart failure, LV assist device, recent percutaneous coronary intervention, heart valve repair or replacement, heart bypass or transplant surgery	• AnxS (ASI-3; continuous) • Fearful belief about negative consequences of exercise (FEQ) • Other variables of interest included assessment of major depression and generalized anxiety • Clinical cut-off score of 23 and 17 for high and moderate, respectively, on the ASI-3. Cut-off scores established using normative data from undergraduate students and daily cigarette smokers.	• AnxS was significantly related to fear of exercise • Patients on average completed 5.3 weeks of the 12-week program • Study did not report sex-based differences.

Abbreviations used in Table 4: 6MWT, 6-minute walk test; LV, left ventricular; AnxS, Anxiety Sensitivity; ASI-3, Anxiety Sensitivity Index-3; FEQ, Fear of Exercise Questionnaire.

sex-based differences in the total reduction in AnxS [48]. Finally, in a large sample (n=802) of post-secondary students, DeWolfe et al. [41] reported that AnxS was significantly and inversely related to self-reported physical activity, and that female students reported significantly less physical activity and significantly greater anxiety sensitivity compared to male students [41]. Using insights from mediation analysis, DeWolfe et al. [41] concluded that there is a significant, indirect effect of sex on physical activity via AnxS [41].

4. Discussion

This scoping review summarized studies examining associations between AnxS and outcomes for patients in CR programs, including the discrete behavioral and traditional CVD risk factors that are the focus of treatment and programing in CR (exercise, blood pressure, blood cholesterol, blood glucose). While the overall number of studies was limited, particularly those studies with participant samples directly relevant to CR patient populations, important associations between AnxS and CR therapeutic outcomes were identified.

Of particular relevance to CR is that individuals with high AnxS participate in physical activity less than individuals with low to moderate AnxS. More encouragingly, despite lower level of physical activity and exercise associated with high AnxS, evidence shows that participating in just a two-week exercise intervention has the ability to reduce AnxS significantly compared to no exercise at all. However, in two studies of CR-specific patient populations, AnxS was reported to be associated with fear of exercise, and lower rates of participation in and completion of CR. As exercise is a cornerstone of CR, further study into the role AnxS may play in participation or completion of CR is warranted. Additionally, an important limitation of the current literature is that most studies included young, healthy individuals, often post-secondary students; understanding the relationship between AnxS and exercise in a CR-relevant population sample (older, less healthy) merits further investigation.

The Anxiety Sensitivity Index 3 (ASI-3) has emerged as a reliable and valid tool for measuring AnxS [64] and AnxS-related outcomes, including the onset of anxiety and depression [65]. As our understanding of the importance of addressing depression and anxiety in CR has evolved, it is now standard-of-care to screen for these conditions at the time of CR intake [16]. The potential value of routine AnxS assessment merits further investigation, as high AnxS may also contribute to both sub-optimal attendance and clinical outcomes for those enrolled in CR. The recent development of the Short Scale Anxiety Sensitivity Index (SSASI) [30] may aid in a screening-type approach for AnxS at CR intake.

Several studies have demonstrated that Cognitive Behavioral Therapy (CBT) approaches that target AnxS may be effective at reducing AnxS and the associated maladaptive or avoidance strategies. At least one study has reported that individuals who participate in CBT are able to reduce levels of AnxS significantly more than those who do not participate in CBT [51]. Other studies have suggested that reducing AnxS may have an impact on other psychological disorders, such as moderating the risk for anxiety-related symptoms [66–68]. Thus, reducing AnxS through targeted intervention is a potential gateway to improving outcomes from CR by reducing the fears associated with cardiac-related sensations, increasing physical activity, and increasing quality of life indicators in those suffering from a cardiovascular diagnosis or event.

Currently, significant gaps remain in our understanding of the sex-based differences in the complex relationships between AnxS, exercise and CR. While some studies have reported sex-based differences in AnxS, the evidence is yet inconclusive regarding sex-based differences in AnxS in the general population [69]. Likewise, there is inconsistent evidence, often from non-comparable studies, on the role of sex-based differences in the relationship between AnxS and exercise, often because studies do not account for baseline differences in exercise participation or AnxS. As the current literature reports that women are less likely to complete CR compared to men [70], it will be both necessary and important that future studies aim to address the substantial knowledge gap on the role of sex in the relationship between AnxS and clinical outcomes in CR.

4.1. Strengths and limitations

This is the first known review to systematically review and summarize associations between AnxS and a broad array of CVD risk factors and therapeutic targets and clinical outcomes of key importance to CR programs. A broad range of sources were searched in order to ensure the inclusion of studies from multiple and interdisciplinary fields. Collectively, results highlight important relationships between AnxS and exercise, CVD, and CR completion.

This review contains several limitations. AnxS is measured differently in different studies and different studies also use different cut-off points to classify patients as having “high”, “medium”, or “low” AnxS. Additionally, all searches were limited to papers in the ‘English language’, potentially excluding some articles that may have been otherwise relevant. Finally, we did not attempt to evaluate the quality of individual studies.

5. Conclusion

The current literature supports the presence of associations between AnxS and a broad array of CVD traditional and behavioral risk factors, therapeutic targets, and clinical outcomes of key importance to CR programs, including participation in and completion of CR. Future studies should expand our current knowledge to better understand the impact of exercise on AnxS in a CR populations, as well as the impact of AnxS on achieving other key therapeutic targets in CR, including blood pressure, independent of associations with exercise. Prospective, longitudinal studies will be needed to better understand the utility of screening for AnxS, or developing treatment strategies for AnxS for patients in CR with high levels of AnxS. Additionally, future studies should aim to fill the substantial gap in knowledge regarding the sex-baed differences in the complex relationships between AnxS, exercise, and CR. A better understanding of the role of AnxS in CR will likely be beneficial CR practitioners and researchers as they seek additional ways to improve CR participation, completion, and outcomes.

Authors’ contributions

- EO made substantial contributions to the: conception and design of this study; the acquisition, analysis, and interpretation of studies including in this review; and the drafting and revising of this manuscript.
- PLP made substantial contributions to the: conception and design of this study; the interpretation of studies including in this review; and the revising of this manuscript.
- NS made substantial contributions to the: conception and design of this study; the interpretation of studies including in this review; and the revising of this manuscript.
- JCF made substantial contributions to the conception and design of this study and the revising of this manuscript.
- SJF made substantial contributions to the: conception and design of this study; the analysis, and interpretation of studies including in this review; and the revising of this manuscript.

Ethics approval and consent to participate

Not applicable. This study is a scoping review of previously published peer-reviewed literature and does not report on or involve the use of any animal or human data or tissue. Thus, ethics approval was not required.

Consent for publication

Not applicable. This study does not contain data from any individual person.

Availability of data and materials

Not applicable.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Funding

The authors declare that no funding was used to complete this study. NS receives research support from the Program in Experimental Medicine in the Department of Medicine, Schulich School of Medicine and Dentistry, University of Western Ontario.

Acknowledgments

The graphical abstract was completed using BioRender (www.biorender.com), for which a publication license was obtained.

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