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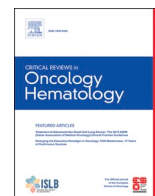
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Adapted physical activity programs for the prevention and treatment of musculoskeletal pain induced by aromatase inhibitors in non-metastatic breast cancer patient: A scoping review

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ABSTRACT

Background: Aromatase inhibitor is associated with a high incidence of Aromatase Inhibitor-Associated Musculoskeletal Syndrome (AIMSS) in postmenopausal women with hormone-sensitive breast cancer.

Objective: This scoping review aims to identify available information regarding the frameworks, models, or strategies of adapted physical activity (APA) programs implemented for the prevention and management of AIMSS.

Methods: Search was realized by two independent reviewers in six databases following PRISMA-ScR guidelines. Data of included articles were extracted, and risk of bias analyzed.

Results: Finally, 14 were included. No study has examined APA in the prevention of AIMSS. There is no solid evidence supporting the impact of APA on the management of AIMSS. However, evidence suggests that an APA program can reduce the worst joint pain and improve the quality of life.

Conclusion: Future research will enlighten clinical practices with the development of personalized APA programs in hormone-sensitive breast cancer.

1. Introduction

1.1. Epidemiology of breast cancer

Breast cancer is the second most common cancer globally, with an incidence of 2.3 million new cases in 2022, accounting for 11.6 % of all new cancer cases (Bray et al., 2024).

It was the most prevalent cancer among women in 157 countries out of 185. In the same year, breast cancer caused approximately 670,000 deaths worldwide, further emphasizing its significant health impact (Bray et al., 2024). According to GLOBOCAN 2022 from the International Agency for Research on Cancer, the 5-year prevalence of breast cancer was estimated to reached 8.2 million people (Ferlay et al., 2024).

1.2. Therapeutic strategies in hormone-dependent breast cancer

Eighty percent of breast cancers are hormone dependent (Nadji et al., 2005; National Cancer Institute, 2022). They are diagnosed at a median age of 63 and over 90 % of these cancers are stage I to III, making them eligible for curative treatment (Pistilli et al., 2020).

For the postmenopausal women with hormone-sensitive breast cancer, the standard adjuvant hormonal treatment is aromatase inhibitor (AI) therapy (Early Breast Cancer Trialists' Collaborative Group, 2015). AI is currently prescribed for five years, but recent guidelines recommend its extension from five to ten years for certain high-risk patient subgroups (Burstein et al., 2019).

1.3. Adherence to treatment and side effects

The prevalence of adherence to this treatment ranges from 50 % to

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91 %, with discontinuation rates ranging from 5 % to 25 % within the first two years of treatment (Murphy et al., 2012). These low level of adherence could be due to the fact that hormone therapy is associated with frequent toxicities (Hyder et al., 2021) and has longer and more detrimental side effects, than chemotherapy, on the quality of life of women with breast cancer, especially those who are postmenopausal (Ferreira et al., 2019).

One important adverse effect is a high incidence of musculoskeletal symptoms collectively termed Aromatase Inhibitor-Associated Musculoskeletal Syndrome (AIMSS) (Beckwée et al., 2017). AIMSS is associated with several symptoms such as arthralgia, joint stiffness, myalgia, muscle weakness, tenosynovitis, carpal tunnel syndrome and loss of bone mineral density (Laroche et al., 2014). These symptoms are linked to pains that decrease treatment adherence for nearly half of patients, with a major impact on clinical efficacy (Hershman et al., 2010). Thus, joint pains would predict early discontinuation of AI therapy (Kadakia et al., 2016). Risk factors and the pathophysiology of AIMSS are still poorly understood (Gupta et al., 2020).

1.4. Pathophysiology of AIMSS

The underlying mechanisms behind the development of AIMSS remain unclear at present.

However, the pathophysiology appears to be linked to estrogen deprivation (Borrie and Kim, 2017; Hershman et al., 2015), particularly affecting the musculoskeletal and nervous systems (Gupta et al., 2020; Hyder et al., 2021). Estrogen is crucial for maintaining the joint and bone health by promoting cartilage regeneration and reducing inflammation (Hyder et al., 2021). AIMSS results from several mechanisms: (i) inflammation and joint degeneration, (ii) alterations in bone and cartilage, and (iii) increased stiffness of tendons and ligaments.

Firstly, estrogen regulates anti-inflammatory cytokines, and its reduction increases in pro-inflammatory cytokines, promoting joint inflammation and causes pain, particularly in the hands, wrists, knees and feet (Tenti et al., 2020). Secondly, estrogen supports bone density and healthy cartilage. Its depletion can cause joint stiffness and cartilage degradation, promoting osteoarthritis-like symptoms (Grigorian and Baumrucker, 2022). Thirdly, reduced estrogen diminished the elasticity of tendons and ligaments, causing increased joint stiffness (Martinez et al., 2022). In addition, lower estrogen levels may increase pain sensitivity, aggravating musculoskeletal symptoms in AI patients (Hyder et al., 2021). Genetic determinants may also influence the likelihood of developing AIMSS (Borrie and Kim, 2017; Stearns et al., 2024).

Although current medical treatments provide some relief, they are often insufficient when used alone. A multidimensional approach is necessary for patients suffering from AIMSS, focusing not just on pharmacological treatments but also on individualized supportive care tailored to each patient's needs. This holistic approach includes physical therapies, psychological support, and personalized care strategies, which have been shown to improve overall patient outcomes and adherence to treatment.

1.5. Adapted physical activity as supportive care

Adapted physical activity (APA) is a supportive care in oncology, as defined by Multinational Association of Supportive Care in Cancer (Scotté et al., 2023), and represents a non-pharmacological therapeutic option. The American College of Sports Medicine recommended regular aerobic and strength training for individuals with cancer (Campbell et al., 2019). Numerous studies have been conducted with breast cancer patients and have shown that physical activity practiced before and/or after breast cancer diagnosis was associated with better overall and specific survival, as well as a reduced risk of recurrence (Friedenreich et al., 2020). APA also has benefits on patients' quality of life and fatigue reduction (Campbell et al., 2019; Cramp and Byron-Daniel, 2012; Mishra et al., 2012; Mustian et al., 2017).

As the cure rate for hormone-sensitive breast cancer rises, more patients on AI experience side effects like AIMSS, posing a growing public health challenge. While abundant literature supports APA benefits in breast cancer is, few studies focus on APA's impact specifically for AIMSS. This scoping review aims to identify and present existing APA frameworks, models, or strategies implemented for preventing and managing AIMSS.

2. Methods

The study was a scoping review to explore the literature breadth on the subject (Arksey and O'Malley, 2005; Munn et al., 2022, 2018), following the PRISMA-ScR "Preferred Reporting Items for Systematic Reviews and Meta-Analyses for Scoping Reviews" guidelines (Tricco et al., 2018) (Supplementary Table 1).

2.1. Identification of research questions

The PICO question was: What Adapted Physical Activity programs (Intervention) may have a positive effect on the prevention and treatment of AIMSS (Outcome) in patients treated with AI for non-metastatic breast cancer (Patient) compared to usual care (Comparison)?

This study aims to answer to the following research questions:

- (i) What are the specific characteristics of APA programs (types, frequencies, and intensities) used to prevent or treat musculoskeletal pains induced by AIs?
- (ii) How is AI-induced pain evaluated?
- (iii) What are the positive or negative effects of these programs?

2.2. Selection of publications

The search was conducted in PubMed, Embase, Cochrane Library, SportDiscus, Web of Science, and Google Scholar in March 2024. The search strategies for each database are presented in Supplementary Table 2.

Inclusion criteria were: (1) publications in English; (2) fully accessible; (3) women treated for breast cancer with aromatase inhibitors; (4) human studies. Exclusion criteria were: (1) male; (2) metastatic breast cancer; (3) association with another therapy such as massage studied during the trial; (4) case reports, conference abstracts, recommendation texts or comments, posters, editorial letters.

Two reviewers (N.P. and F.C.) examined publications based on titles and abstracts. Subsequently, they assessed the full text for inclusion. In case of disagreement, at each stage, they discussed until they reached a consensus.

2.3. Data extraction, summary of results, and evaluation of the quality

For each included publication, key data were extracted: (i) characteristics of the study (design, country, allocation concealment and blinding), (ii) characteristics of the study population (number of participants, inclusion/exclusion criteria, definition of AIMSS, number of participants), (iii) characteristics of the intervention (intervention vs control group, aerobic/resistance/combo, exercise intensity, frequency and duration of sessions, duration of intervention period, supervised versus home-based) and, (iv) characteristics of the outcomes (pain assessment, incidence of AIMSS, Adverse effects, compliance, follow-up period).

The quality of the included study was assessed by both reviewers (N. P. and F.C.) using the National Institutes of Health's study quality assessment tools (National Institut of Health, 2013).

3. Results

3.1. Article selection process

From database searches, 362 publications were identified (Fig. 1). After removing duplicates, 260 were screened based on title and abstract, and 48 articles were retained for full-text evaluation. Finally, 14 articles were included.

3.2. Characteristics of included articles

The characteristics of the included articles are presented in Supplementary Tables 3 and 4.

Seven clinical experimental studies were included (four randomized controlled trials (RCT) (Fields et al., 2016; Irwin et al., 2015; Nyrop et al., 2017; Paulo et al., 2019), one pragmatic controlled trial (Cantarero-Villanueva et al., 2013), two single-arm trial (DeNysschen et al., 2014; Jacobsen et al., 2015) and seven systematic reviews and meta-analyses (Bae et al., 2023; Boing et al., 2020; Lu et al., 2020; Nahm et al., 2018; Roberts et al., 2020; Yang et al., 2017; Zhu et al., 2021).

3.2.1. Characteristics of clinical studies

The characteristics and key results of clinical studies are summarized in Supplementary Table 3. The seven clinical studies were conducted in the United States, the United Kingdom (DeNysschen et al., 2014; Irwin et al., 2015; Jacobsen et al., 2015; Nyrop et al., 2017), Spain

(Cantarero-Villanueva et al., 2013) and Brazil (Paulo et al., 2019). Three were multicentric (Cantarero-Villanueva et al., 2013; Irwin et al., 2015; Nyrop et al., 2017). All trials were open-label trials. Sample sizes ranged from 10 (Jacobsen et al., 2015) to 121 (Irwin et al., 2015) with a median of 40 participants. The mean age was mentioned in six studies and ranged between 61 and 63 years. The majority of trials involved patients only on AI, with one exception, which also included women on tamoxifen (Cantarero-Villanueva et al., 2013). Patients had been on AI therapy for one to six months at the start of the study. Only one study did not include at least moderate arthralgia as an inclusion criterion (Paulo et al., 2019).

Cantarero-Villanueva et al. specified that these pains had to be specifically related to AI, excluding women with previous joint pains such as inflammatory arthritis, chronic pain, and osteoarthritis (Cantarero-Villanueva et al., 2013). All studies excluded women at the metastatic stage.

3.2.2. Characteristics of systematic reviews and meta-analyses

The seven systematic reviews are detailed in Supplementary Table 4. They were published between 2017 and 2023, and all, but one (Nahm et al., 2018), carried out a meta-analysis. The number of included studies in these systematics reviews ranged from three (Bae et al., 2023) to seven (Roberts et al., 2020) and some of them were found in several systematic reviews. For example, one study (Irwin et al., 2015) was included in six out of seven systematic reviews, another (Fields et al., 2016) in five, and a third (Nyrop et al., 2017) in three.

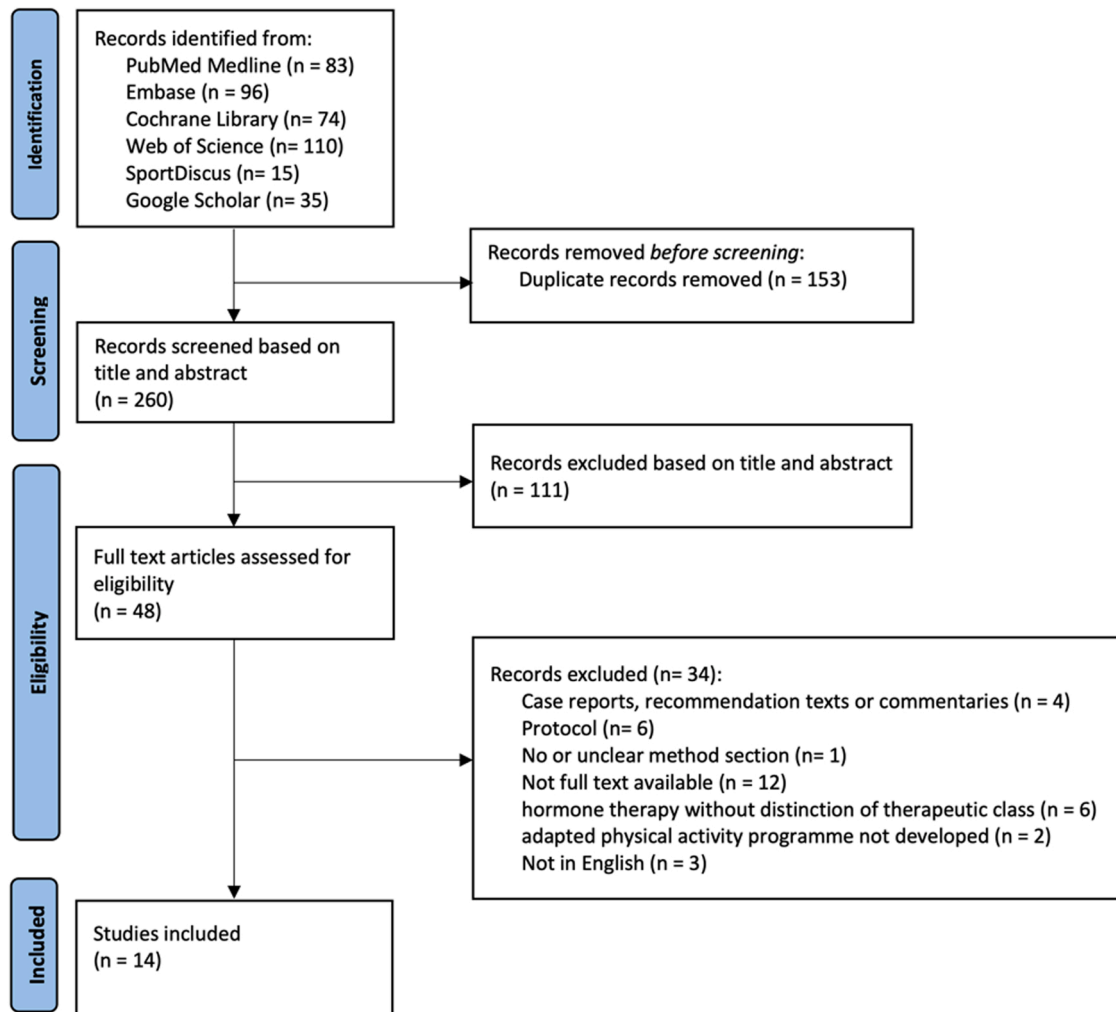


Fig. 1. Flowchart of the scoping review.

The primary objectives of the included studies were different: evaluation of the impact of APA on AIMSS (Roberts et al., 2020; Zhu et al., 2021), management of AIMSS (Nahm et al., 2018; Yang et al., 2017), comparison of the clinical efficacy of therapies, including APA, on AIMSS (Bae et al., 2023), analysis of the effect of an APA program on the quality of life of patients on AI (Lu et al., 2020) and study of the physical abilities of patients on hormone therapy without distinguishing therapeutic class (Boing et al., 2020).

3.3. Summary of results

3.3.1. Characteristics of APA programs

The APA is characterized by several factors, namely Frequency of practice, Intensity, Type and Time of maintenance (FITT) (Barisic et al., 2011) (Fig. 2).

The APAs proposed to patients differed in terms of FITT:

- **Frequency of practice:**
The frequency of practice was between 1 and 5 sessions per week. It was either fixed throughout the study (Cantarero-Villanueva et al., 2013; Irwin et al., 2015; Jacobsen et al., 2015; Nyrop et al., 2017; Paulo et al., 2019), or evolving according to a predetermined program (DeNysschen et al., 2014; Fields et al., 2016).
- **Intensity:**
The intensity was measured in five studies either by subjective perception of effort using the Borg scale (Cantarero-Villanueva et al., 2013), or by the value of maximum heart rate (HRmax) (DeNysschen et al., 2014; Irwin et al., 2015; Paulo et al., 2019), or both (Fields et al., 2016). The relative intensity of APA corresponded to a heart rate of 55–80 % HRmax. Finally, in one study, participants were asked to walk at a safe, comfortable and sustainable pace (Nyrop et al., 2017).
- **Type:**
The type of APA programs was diversified, both in terms of setting, sport and program (aerobic, strength training, or combined). The setting was supervised practice (Cantarero-Villanueva et al., 2013; Jacobsen et al., 2015; Paulo et al., 2019), autonomous (DeNysschen et al., 2014; Nyrop et al., 2017), or mixed (Fields et al., 2016; Irwin et al., 2015). Programs were conducted in specialized centers, outdoors, or at home. Regarding sport, two studies tested an exclusive

walking program (Fields et al., 2016; Nyrop et al., 2017), while others focused on Iyengar yoga (Jacobsen et al., 2015), hydrotherapy (Cantarero-Villanueva et al., 2013), or adapted strength training (DeNysschen et al., 2014; Irwin et al., 2015; Paulo et al., 2019). APA programs could involve aerobic exercises (Nyrop et al., 2017), exercises combining aerobic and strength training activities (Cantarero-Villanueva et al., 2013; DeNysschen et al., 2014; Fields et al., 2016; Irwin et al., 2015; Paulo et al., 2019). Two studies added flexibility exercises to their APA programs (DeNysschen et al., 2014; Paulo et al., 2019) and one proposed neuromotor exercises such as Iyengar yoga (Jacobsen et al., 2015).

- **Time of maintenance:**
The time of maintenance (duration of the session) varied between 30 and 150 min. It was either fixed throughout the study (Cantarero-Villanueva et al., 2013; Irwin et al., 2015; Jacobsen et al., 2015; Nyrop et al., 2017; Paulo et al., 2019) or evolving (DeNysschen et al., 2014; Fields et al., 2016). The total time of APA per week ranged from 150 min (Irwin et al., 2015) to 210 min (Paulo et al., 2019) and the total program duration ranged from 1,5 months (Nyrop et al., 2017) to 12 months (Irwin et al., 2015).

To propose a personalized program, a medical assessment and tests were planned at the beginning. Two studies evaluated cardiorespiratory condition using a standard treadmill maximal oxygen consumption test (DeNysschen et al., 2014; Irwin et al., 2015). In addition, one study incorporated a grip strength test and the "sit-to-stand" test to determine the appropriate training level (three programs with different levels) (DeNysschen et al., 2014).

In addition to the APA program, participants could receive supportive therapies with education through booklets (Fields et al., 2016) or lectures (Paulo et al., 2019), counseling, adjustment strategies (DeNysschen et al., 2014; Nyrop et al., 2017) to aid in behavior change.

Regarding the control group, only one study opted for standard care, without an APA program (Irwin et al., 2015). Two studies either offered usual care with biweekly supportive phone calls, an exercise booklet after cancer and daily physical activity journaling (Fields et al., 2016) or invited control group patients to participate in stretching and relaxation classes twice a week without attendance control (Paulo et al., 2019). For two study, the control groups corresponded to participants on a waiting list that could benefit from the program at the end of the study

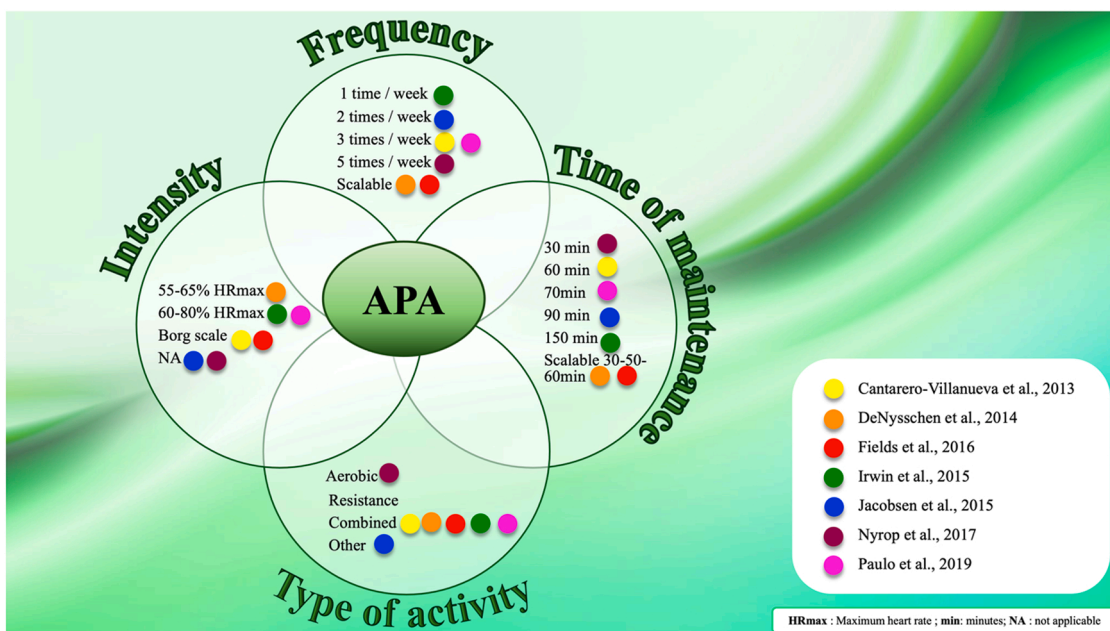


Fig. 2. Frequency of practice, Intensity, Type and Time of maintenance (FITT) of adapted physical activity programs.

(Cantarero-Villanueva et al., 2013; Nyrop et al., 2017).

3.3.2. Description of musculoskeletal pain induced by aromatase inhibitors

The term used to describe musculoskeletal pain induced by AI varied among studies. One study used the generic term "pain" (Paulo et al., 2019), three used the term "arthralgia" or "AI-induced arthralgia" (Bae et al., 2023; Boing et al., 2020; Yang et al., 2017) and 4 used the term AIMSS (Lu et al., 2020; Nahm et al., 2018; Roberts et al., 2020; Zhu et al., 2021).

The components of the pain were described in terms of localization, duration, intensity, quality. The pain was described as bilateral and symmetrical (Bae et al., 2023; DeNysschen et al., 2014; Roberts et al., 2020; Yang et al., 2017; Zhu et al., 2021). The main cited localization was the hands (Bae et al., 2023; DeNysschen et al., 2014; Nahm et al., 2018; Yang et al., 2017) with a decrease in grip strength (Lu et al., 2020). Other joints could be affected such as the hips, lower back, shoulders (DeNysschen et al., 2014; Yang et al., 2017), knees and wrists (Bae et al., 2023; Nahm et al., 2018).

The initial signs appeared 1.6 months (Bae et al., 2023) to 2 months (DeNysschen et al., 2014) after the beginning of AI treatment and disappeared on discontinuation of treatment (DeNysschen et al., 2014).

The intensity of the pain ranged from mild to moderate (Lu et al., 2020) and varied throughout the day with characteristic morning stiffness (Bae et al., 2023; DeNysschen et al., 2014; Roberts et al., 2020; Yang et al., 2017; Zhu et al., 2021). Yang et al. characterized it as diffuse, mixed neuropathic pain and indicated that it should be approached on a bio-psycho-social model (Yang et al., 2017).

3.3.3. Pain assessment

To obtain a comprehensive and objective assessment, pain was evaluated using several scales and questionnaires as shown in Fig. 3.

- Overall pain assessment:

For overall pain assessment, three studies chose unidimensional scales to quantify pain intensity: the Visual Analog Scale (VAS) pain (Nyrop et al., 2017), the body schema (DeNysschen et al., 2014) and the pressure pain threshold (Cantarero-Villanueva et al., 2013). Three studies opted for the Questionnaire Brief Pain Inventory, which evaluates the main dimensions of pain, including intensity, functional disability, social and family impacts and psychological distress (Fields et al., 2016; Irwin et al., 2015; Jacobsen et al., 2015). Self-efficacy in chronic pain management was also measured (Fields et al., 2016).

- Arthralgia assessment:

Regarding musculoskeletal pain, measures assessed pain, stiffness and function of different joints using VAS for joint stiffness (Nyrop et al., 2017), Western Ontario and McMaster Universities Arthritis Index (WOMAC) (Irwin et al., 2015; Jacobsen et al., 2015; Nyrop et al., 2017), Australian Canadian Osteoarthritis Hand Index score (Jacobsen et al., 2015) and Disabilities of the Arm, Shoulder and Hand (Irwin et al., 2015). Grip strength was quantified in one study (Irwin et al., 2015). Impact and repercussions of this type of pain on the patient were also assessed with the Arthritis Impact Measurement Scale modified version (DeNysschen et al., 2014), Rheumatology Attitudes Index (Nyrop et al., 2017) and Arthritis Self-Efficacy Scale subscale (Nyrop et al., 2017).

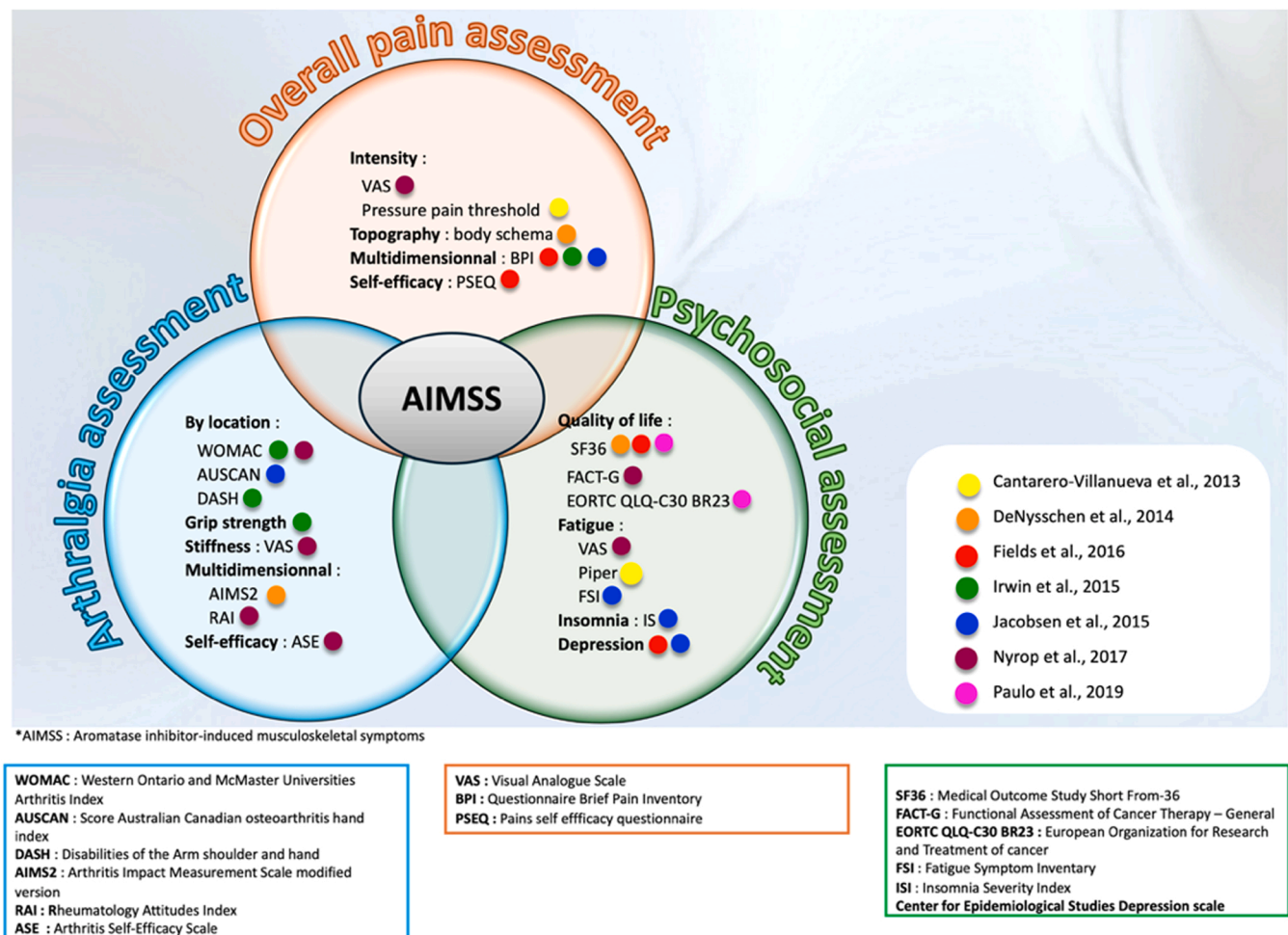


Fig. 3. Methods used to assess pain associated to AIMSS.

- Psychosocial assessment:

For psychological evaluation, studies measured quality of life (DeNysschen et al., 2014; Fields et al., 2016; Nyrop et al., 2017; Paulo et al., 2019), fatigue, insomnia (Jacobsen et al., 2015) and depression (Fields et al., 2016; Jacobsen et al., 2015).

Three studies assess overall pain, musculoskeletal pain and psychosocial impact (DeNysschen et al., 2014; Jacobsen et al., 2015; Nyrop et al., 2017).

3.3.4. Specific effect of APA programs on AIMSS

In all the included studies, the effect of APA programs was determined by self-assessment of pain evolution.

- Joint pain:

Regarding worst joint pain, two studies concluded that APA reduced them. The first demonstrated a decrease in worst joint pain scores by 1.6 points (29 %) at 12 months in the APA group compared to an increase of 0.2 points (3 %) in the control group ($n = 60$; $p < 0.001$) (Irwin et al., 2015).

The second observed a significant improvement in worst joint pain scores (29 % decrease in the APA group versus 3 % increase in the control group, $p < 0.001$), in pain severity and pain interference scores ($p < 0.001$) at the end of the intervention (Nyrop et al., 2017).

These positive results were confirmed in one meta-analysis that concluded to significant evidence for pain scores (Standardized Mean Difference -SMD- = -0.46; 95 % CI: -0.79, -0.13; $p = 0.006$) (Lu et al., 2020) and in another one that demonstrated a reduction of pain in patients exercising and taking AI ($p = 0.05$) (Boing et al., 2020). However, evidence remains uncertain regarding worst pain scores (SMD = -0.23; 95 % CI: -0.78, 0.32) (Roberts et al., 2020).

- Arthralgia:

Regarding arthralgia, APA was linked to a significant decrease in the pain score at 12 months in the APA group compared to increases in the control group ($p < 0.001$) (Irwin et al., 2015). In Roberts et al.'s meta-analysis (Roberts et al., 2020), there was little or no difference in the overall change in stiffness scores (WOMAC) (MD = -0.76; 95 % CI: -1.67, 0.15) and the VAS stiffness score (MD = -0.42; 95 % CI: -2.10, 1.26).

- Quality of life:

An improvement in quality of life related to the APA duration was observed (Paulo et al., 2019). The APA group showed an improvement in global health perception ($p = 0.01$), physical health ($p < 0.001$), bodily pain ($p < 0.001$) and vitality ($p < 0.001$). Their quality of life was also significantly increased at 3 months ($p < 0.001$) compared with the control group ($p = 0.02$) using the European Organization for Research and Treatment of Cancer scale. This improvement was greater after 9 months of training in the APA group than in the control group. On the other hand, another study mentioned a general trend towards improvement in quality of life and depression in both groups (Fields et al., 2016).

Two meta-analyses demonstrated that the level of evidence was very low for the assessment of quality of life (Lu et al., 2020; Roberts et al., 2020).

- Fatigue:

Regarding fatigue, one study found that the APA group did not show significant improvement with the fatigue scale compared to the control group (Cantarero-Villanueva et al., 2013). A second study only evaluated it at the beginning of the study (Nyrop et al., 2017).

- Adverse events related to APA programs:

No adverse events related to APA practice were reported (Cantarero-Villanueva et al., 2013; Fields et al., 2016; Irwin et al., 2015; Nyrop et al., 2017) and adherence to APA varied (> 90 % over six months (Fields et al., 2016) or return to pre-intervention APA levels at six months (Fields et al., 2016). However, all the meta-analyses concluded that, to date, no definitive evidence has been established regarding the impact of APA on AIMSS.

3.3.5. Quality of included articles

Fig. 4 indicates the risk of bias. The risk of bias for systematic reviews and meta-analyses (Fig. 4A) was low, except for one (Nahm et al., 2018), where the risk of bias was moderate to high. The high risk was due to the fact that this review was not conducted by two independent reviewers.

The risk of bias for all interventional (Fig. 4B) and observational studies (Fig. 4C) was moderate to high. In interventional studies, the high risk of bias was associated with the methodology used for open-label trials.

4. Discussion

Early studies in the 1980s, were foundational in demonstrating the safety and benefits of exercise for cancer patients, particularly in managing treatment-related fatigue and improving overall well-being (MacVicar et al., 1989; Winningham et al., 1986). These foundational works laid the groundwork for incorporating exercise into cancer care, reinforcing the importance of physical activity in enhancing both physical and mental health outcomes for cancer survivors. The document published by the American College of Sports Medicine in 2010 marked a turning point by recommending the integration of physical exercise into the care of cancer patients, regardless of the stage of the disease (Schmitz et al., 2010).

Building on this foundation, low adherence to AI among women with early-stage hormone-sensitive breast cancer remains a public health challenge. Early treatment termination leads to higher recurrence, mortality rates, and medical costs. Supportive care like APA is recommended for patients with pain (Campbell et al., 2019), but guidelines on preventing and managing AIMSS with APA are lacking (Roberts et al., 2022). This scoping review aimed to describe APA program characteristics and their impact on AIMSS.

4.1. Benefits of APA on AIMSS

The integration of APA for women with hormone-sensitive breast cancer should be evidence-based and personalized. This scoping review demonstrated that APA improves quality of life and reduces joint but failed to provide formal evidence on APA characteristics on AIMSS.

Firstly, studies suggested that APA during treatment improved AIMSS compared to control groups, with significant reductions in pain ($p < 0.001$) (Irwin et al., 2015; Nyrop et al., 2017). A meta-analysis (Boing et al., 2020), corroborated these findings. Regarding the type of APA, combined training positively influenced pain (Cantarero-Villanueva et al., 2013; DeNysschen et al., 2014; Irwin et al., 2015; Paulo et al., 2019) as described in international APA guidelines (Campbell et al., 2019). However, two systematic reviews found insufficient evidence of APA's impact on AIMSS pain (Boing et al., 2020; Roberts et al., 2020), as noted by Campbell et al., due to pain often being a secondary outcome in RCTs (Campbell et al., 2019). They advocated for research focusing on cancer-related pain. Moreover, AIMSS leads to treatment discontinuation, but this was only considered in one study (Irwin et al., 2015).

Secondly, this scoping review demonstrated that physical activity had benefits on psychosocial assessment and quality of life (Lu et al., 2020; Paulo et al., 2019) consistent with findings of other studies (Hong et al., 2019; Lavallée et al., 2019; Mishra et al., 2012). Five studies favored supervised training programs (Cantarero-Villanueva et al., 2013; Fields et al., 2016; Irwin et al., 2015; Jacobsen et al., 2015; Paulo et al., 2019) with Buffart et al. noting significant quality of life improvements in this type of program (Buffart et al., 2017). Two studies (Fields et al., 2016; Paulo et al., 2019) aligned with international guidelines recommending moderate-intensity aerobic and resistance exercises performed two to three times per week for at least 12 weeks to improve quality of life during and after cancer treatment (Campbell et al., 2019).

However, there was no clear evidence of APA's impact on fatigue,

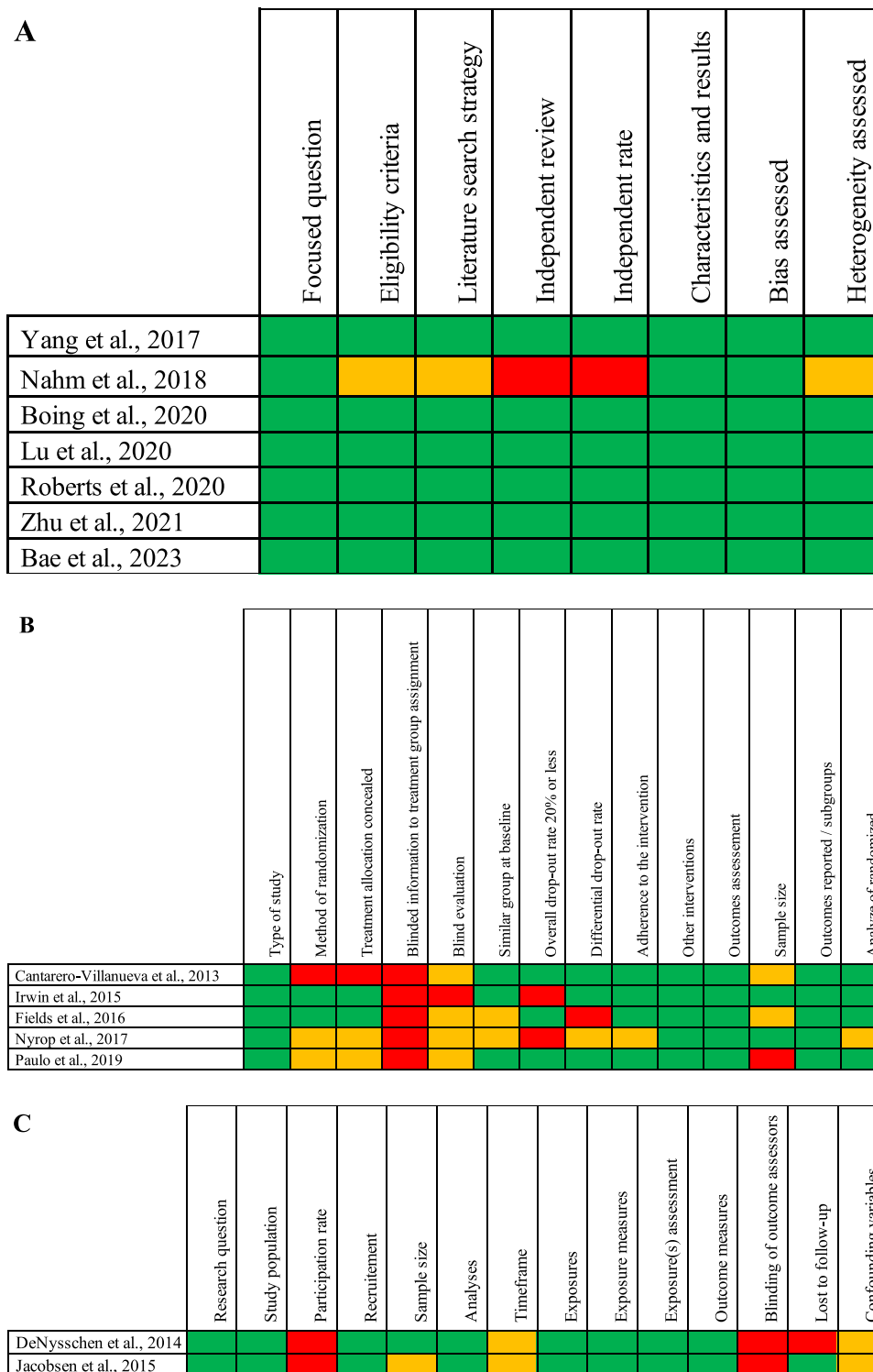


Fig. 4. Risk of bias of the included articles using the NIH quality assessment tool. A: Systematics reviews and meta-analyses. B: Interventional studies. C: Observational studies. In the color code ranking, green color represents low risk of bias, orange color represents moderate risk of bias and red color represents high risk of bias.

despite it being the only treatment proven effective for fatigue (Furmaniak et al., 2016). The European Society for Medical Oncology (ESMO) Clinical Practice Guidelines also recommended APA to improve cancer-related fatigue (Fabi et al., 2020).

In this scoping review, few studies examined APA’s effect on fatigue (Cantarero-Villanueva et al., 2013; Jacobsen et al., 2015; Nyrop et al., 2017). One reported that there had a lack of fatigue data (Nyrop et al.,

2017). The other two (Cantarero-Villanueva et al., 2013; Jacobsen et al., 2015) found no significant benefit due to non-compliance with ESMO guidelines (Fabi et al., 2020).

4.2. Clinical and methodological heterogeneity

The clinical and methodological heterogeneity of the experimental

studies made it impossible to identify the ideal recommendations for the APA program. There was considerable variability in the definition and evaluation of AIMSS and the characteristics of APA programs.

Firstly, patients presented different symptoms of AI-induced musculoskeletal pain without a specific pattern, leading to discordant descriptions (Gupta et al., 2020; Hyder et al., 2021). Terms like "pain" (Paulo et al., 2019), "arthralgia" or "AI-induced arthralgia" (Bae et al., 2023; Boing et al., 2020; Yang et al., 2017) and AIMSS (Lu et al., 2020; Nahm et al., 2018; Roberts et al., 2020; Zhu et al., 2021) were used. Pain was variably described as nociceptive (Boing et al., 2020; Irwin et al., 2015; Jacobsen et al., 2015; Nyrop et al., 2017) or neuropathic (Yang et al., 2017). A patient with AI-induced arthralgia was defined as one who met four major criteria and at least three minor criteria (Niravath, 2013). The major criteria were: (1) Currently taking AI therapy, (2) Joint pain which has developed or worsened since starting AI therapy, (3) Joint pain improves or resolves within 2 weeks of stopping AI therapy, (4) Joint pain returns upon resuming AI. The minor criteria were: (1) Symmetrical joint pains, (2) Pain in hands and/or wrists, (3) Carpal tunnel syndrome, (4) Decreased grip strength, (5) Morning stiffness, (6) Improvement in joint discomfort with use or exercise. No study adopted this definition, and currently, there is still no uniform definition of this syndrome (Hershman et al., 2015; Roberts et al., 2022). This may be because there is no pathognomonic result to diagnose AIMSS. As a result, the need for further research on predictive factors and the pathophysiology of this syndrome, which remains unknown, was underlined (Hershman et al., 2015; Roberts et al., 2022). A deeper understanding of these mechanisms is essential for developing effective therapeutic strategies in the proactive management of AIMSS.

Secondly, women with AIMSS experience varied pain in intensity, quality, and duration, impacting physical function, psychological state, quality of life, and treatment adherence. However,

accurately assessing AIMSS remains challenging due to the subjective nature of pain evaluations using questionnaires and scales used in clinical trials (Vader et al., 2021). Important symptoms like arthralgia and morning stiffness were inconsistently measured across studies (DeNysschen et al., 2014; Irwin et al., 2015; Jacobsen et al., 2015; Nyrop et al., 2017). The diversity of evaluation scales complicates objective comparison in meta-analyses (Boing et al., 2020; Lu et al., 2020; Roberts et al., 2020; Zhu et al., 2021). Developing standardized, objective measures specific to AIMSS is crucial for future research.

Thirdly, APA programs varied widely in FITT parameters. Recommended APA for cancer patients includes supervised sessions lasting three months, 2–5 times weekly, with progressive intensity and both aerobic and muscle-strengthening exercises. Session duration can vary from 10 to 20 min to 40–60 min (Campbell et al., 2019; Rock et al., 2022). Only two studies followed these recommendations (Irwin et al., 2015; Paulo et al., 2019).

Heterogeneity could result from insufficient evidence and guidelines on systemic, pharmacological, and non-pharmacological therapies, including APA, for the prevention or treatment of AIMSS (Roberts et al., 2022).

4.3. Adherence and maintenance of APA

4.3.1. Relationship between pain and APA

Cancer pain, whether caused by the disease itself or its treatment, is one of the most dreaded complications in cancer patients (Snijders et al., 2023). Psychological factors, such as anxiety, depression, and fear, strongly influence the perception of pain, and the effectiveness of its treatment (Fallon et al., 2018). Unrelieved pain increases the risk for psychological distress, creating a feedback loop that exacerbates suffering (Syrjala et al., 2014). For breast cancer patients, especially those undergoing AI therapy, issues like kinesiophobia (fear of movement) further compound pain and limit physical activity, hampering recovery (Malchrowicz-Moško et al., 2024). Studies show that incorporating psychological support, cognitive-behavioral strategies, and

tailored exercise programs can reduce pain, improve mental health, and enhance adherence to treatment (Antoni et al., 2022; Ashton and Oney, 2024; Jassim et al., 2023).

APA is recommended for preventing and managing AIMSS due to its health benefits (Gupta et al., 2020). However, participation rates were low: 25 % (Fields et al., 2016) and 34 % (Irwin et al., 2015). Patients often experience pain, a common inclusion criterion in six out of seven exploratory studies (Cantarero-Villanueva et al., 2013; DeNysschen et al., 2014; Fields et al., 2016; Irwin et al., 2015; Jacobsen et al., 2015; Nyrop et al., 2017). Studies suggested pain could induce sedentary behavior due to psychological factors like kinesiophobia (Sullivan et al., 2001; Vlaeyen and Linton, 2000). Addressing this, initiating APA early the care pathway in prevention or during the acute phase of AIMSS could be beneficial. Research shows physical activity may prevent chronic pain and improve pain tolerance (Árnes et al., 2023).

4.3.2. Initial assessment and personalized APA program

APA programs must tailor to the patient's health, comorbidities, and treatment. Guidelines for cancer survivors recommend a personalized assessment before starting APA (Campbell et al., 2019).

This interdisciplinary assessment, beginning at diagnosis, should evaluate current physical activity levels, motivations, barriers, and functional abilities (Bluethmann et al., 2015).

While studies required medical evaluations for physical activity safety, only two included baseline medical assessments (DeNysschen et al., 2014; Irwin et al., 2015). APA aims to maintain physical activity throughout treatment, adapting the amount to patient needs, though not always aligning with guidelines. Integration into the patient's care pathway should be patient-centered, considering barriers like life expectancy, employment, family problems etc. (Cheifetz et al., 2015).

Despite uncertainties, patient-centered APA management is crucial.

Five studies adapted APA program to each patient's physical conditions (Cantarero-Villanueva et al., 2013; DeNysschen et al., 2014; Fields et al., 2016; Irwin et al., 2015; Paulo et al., 2019), adjusting doses even if not always meeting recommended training volumes (Campbell et al., 2019; Rock et al., 2022). Adaptation aligns with the FITT-VP framework from the American College of Sports Medicine (Piercy et al., 2018), emphasizing individualized programs considering physical condition, treatment, preferences, and barriers (Vallance et al., 2010). While mentioned in studies, specific evaluations of these adaptations were lacking.

4.3.3. Intervention strategies to maintain APA

Even if this scoping review concluded to the benefits of APA for patients on AI, challenges such as patient reluctance to engage in regular exercise persist (Elshahat et al., 2021). Personalized support strategies, including counseling, motivational interviewing, and behavior adjustment therapies, have been shown to improve compliance and reduce pain (DeNysschen et al., 2014; Fields et al., 2016; Nyrop et al., 2017). For instance, regular telephone calls provided encouragement and explanations that lead to better pain management and higher adherence to physical activity regimens (Fields et al., 2016).

Emerging technologies, such as telehealth and mobile health (mHealth) platforms, offer promising solutions for overcoming these barriers. Studies have demonstrated the effectiveness of telehealth in delivering APA programs, improving patient adherence to exercise regimens, and enhancing physical and mental well-being (Garcia-Roca et al., 2024; Henkin et al., 2023; Peng et al., 2022). mHealth applications allow real-time tracking of physical activity and symptoms, providing personalized feedback that supports behavior change. These tools also integrate motivational and cognitive-behavioral strategies to address barriers such as kinesiophobia (fear of movement), helping patients stay engaged in their treatment (Qin et al., 2022).

These data are in accordance with the British Association of Sport and Exercise Sciences (BASES) and Exercise and Sport Science Australia (ESSA) that recommend including exercise in cancer care and to

integrate support for behavior change (Campbell et al., 2012). It has been observed that increased levels of intrinsic motivation are associated with higher levels of physical activity in women affected by breast cancer (Brunet et al., 2013). Moreover, key psychological factors such as pain-related fear, catastrophizing and avoidance are critical, modifiable factors in preventing and managing disability related to chronic musculoskeletal pain, including AIMSS. Healthcare professionals have an important role to play in disseminating positive, evidence-based beliefs about musculoskeletal pain to patients (Caneiro et al., 2021).

Motivational interviews (Pudkasam et al., 2021) and therapeutic patient education (TPE) are effective approaches for addressing these psychological barriers. A study focusing on breast cancer notably demonstrated that supervised APA programs, integrated with TPE and motivational interviewing, significantly improved cardiorespiratory capacity in breast cancer patients, underscoring the long-term benefits of tailored, supportive interventions (Rogers et al., 2015). Such is essential for sustaining APA engagement and maximizing its therapeutic benefits.

4.3.4. Research perspectives related to the integration of APA into the care pathway

Cancer patients tend to not adhere to APA guidelines recommending exercise during treatment. They decrease their activity during treatment and fail to regain their initial level once treatment is finished (Littman et al., 2010). This decrease in APA also has repercussions on the mortality rate of patients (Lee, 2019). For sedentary women, the American College of Sports Medicine roundtable report concluded that physical activity, initiated after diagnosis, reduced the risk of cancer-specific mortality (Patel et al., 2019). One study reported, at 6-month follow-up, a decrease in physical activity with a return to pre-intervention levels (Nyrop et al., 2017). Long-term maintenance of regular APA adoption by cancer patients is challenging to achieve (Jankowski et al., 2014). The difficulty in adhering to APA guidelines may be also explained by the complex process of integrating evidence-based research into routine clinical practice, where it is crucial to consider not only the intervention but also the "real," meaning the context, patients, caregivers, and their reactions, which are true agents of change (Schmitz et al., 2019).

Guidelines (Campbell et al., 2019; Schmitz et al., 2019; Stout et al., 2021) aim to integrate PA experimentation with implementation strategies to improve program adoption, implementation, and sustainability (Proctor et al., 2013). Triangulating data from quantitative and qualitative methods enhances study validity and reliability, particularly for complex symptoms like AIMSS (Piggin, 2020). Mixed-method research combines narrative accounts of pain experiences with generalizable quantitative data (Vader et al., 2021).

4.4. Limitations

This scoping review, conducted following the PRISMA-ScR process, has limitations. Firstly, there is limited literature on the subject, with the last interventional study from 2019. Secondly, the median sample size of the studies was relatively small (median = 40). Thirdly, several studies were pilot or feasibility studies, or single-arm studies limiting statistical power. Fourthly, blinding of participants and healthcare professionals was not possible due to the intervention's nature. Finally, significant study heterogeneity in experimental context, sample size, follow-up duration, exercise types, and measurement methods precludes determining the optimal APA dose, type, and timing for AIMSS management in breast cancer care pathways.

Despite study limitations, the evidence presented is promising. No serious adverse events from APA practice were reported, consistent with literature (Niemeijer et al., 2020). Over four decades, hundreds of trials on physical activity in oncology have improved understanding of physical activity's benefits on function and quality of life in survivors, and the safety and feasibility of programs. However, studies specifically

on APA's impact on AIMSS are limited due to requirements for larger samples, longer follow-ups, and gaps in predictive factors and pathophysiology knowledge.

5. Conclusion

Currently, there is insufficient data to support specific recommendations on the prevention and management of AIMSS through APA. However, given the encouraging results observed indicate significant potential in this area. Future research should aim to include larger and more diverse sample sizes to enhance the generalizability of findings, particularly for postmenopausal women with hormone-sensitive breast cancer. Additionally, adopting rigorous methodologies, including well-defined APA protocols and standardized evaluation metrics, will be critical for assessing efficacy and comparability between studies. Finally, post-intervention follow-up of patients should last for 5 years to obtain data on optimal therapeutic adherence to AI and the long-term adoption of regular physical activity.

A focus on uncovering the mechanisms of AIMSS and identifying patient-specific factors could help tailor personalized interventions, improving treatment outcomes. Moreover, translating research findings into clinical practice through the development of practical and reproducible implementation frameworks is essential. This will facilitate the integration of APA programs into routine care by addressing feasibility, cost-effectiveness, and long-term sustainability in real-world healthcare settings. Such advancements will offer the necessary evidence to optimize APA programs for managing AIMSS, ultimately improving the quality of life for breast cancer patients undergoing hormone therapy.

CRedit authorship contribution statement

Nathalie Piazzon: Conceptualization, Methodology, Investigation, Data curation, Writing – original draft. **Marion Cortet:** Writing – review & editing. **Elise Verot:** Writing – review & editing. **Florence Carrouel:** Conceptualization, Methodology, Investigation, Data curation, Writing – original draft. All authors have read and agreed to the published version of the manuscript.

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Appendix A. Supporting information

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