Effects of aquatic exercises in woman who have undergone surgery after breast cancer: a systematic review with meta-analysis

Running title: Aquatic exercise for breast cancer: a systematic review

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Abstract

Background. Breast cancer (BC) is the most common cancer among women, with an incidence of 310,720 new cases for the year 2024. In addition to survival, quality of life has become an important outcome measure in BC clinical investigations.

Objective. To evaluate the effects of aquatic exercises (AE) on quality of life (QoL), lymphedema, pain, fatigue, and range of motion in breast cancer survivors compared to land exercise and a control group.

Design. Systematic review. Ten databases were searched from inception until February 2024. Risk of bias and certainty of evidence were assessed using the Risk of Bias 2 tool and the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach. Pooled effects were calculated using standardized mean difference (SMD) and 95 % confidence interval (CI).

Results. A total of 1873 studies were identified, 10 were included in the review and four were included in a meta-analyses. Only 30 % (n=3) of the studies were classified as having a low risk of bias. The effect of AE on the emotional subdomains of the QoL was superior to usual care (SMD=0.58, 95 % CI: 0.1, 0.9; I^2=0 %) but the certainty of evidence was rated as very low. When AE was compared with land exercise, no significant differences were found for pain (SMD=1.1; 95 % CI: 1.5, 3.7; I^2=97 %) with the certainty of evidence graded as low.

Conclusions: Although further studies of high methodological quality are needed to provide more robust conclusions, AE may improve QoL outcome and emotional subdomain (ES=0.58) compared to usual care, but the evidence is very uncertain.

Keywords: Aquatic Exercise; Breast Cancer; Hydrotherapy; Lymphedema; Meta-analysis; Systematic Review.

Registration (PROSPERO): CRD42024506498

Word count: 3630

Highlights

- Breast cancer treatments can cause numerous deleterious effects for survivors;
- Aquatic exercises may help reduce complaints arising from cancer treatments;
- Aquatic exercises may improve quality of life in patients with breast cancer compared to usual care.

INTRODUCTION

The number of cancer survivors in the United States has reached 15.5 million, and it is estimated that this number will double by 2040.[1] Breast cancer (BC) is the most common cancer among women, with an incidence of 310,720 new cases for the year 2024.[2] In addition to survival, quality of life (QoL) is an important outcome measure in BC clinical investigations, often reflecting quality health care and highlighting issues related to the deleterious effects of treatments.

Physical exercise is important during the recovery process in BC,[3] with guidelines recommending 150 minutes of moderate-intensity aerobic exercise or 75 minutes of high-intensity exercise per week, plus muscle-strengthening exercise at least twice a week.[4,5] Aquatic exercise (AE) is a safe, non-pharmacological intervention for those recovering from BC. The benefits of AE are obtained, through a combination of fluid mechanics and the characteristics of the environment itself (temperature). For example, shoulder range of motion (ROM), often restricted due to the healing process and/or radiotherapy, can be improved with simple AE and exercises performed with less pain when compared to land exercise. Water temperature (which can improve lymphatic clearance) combined with hydrostatic pressure can reduce lymphedema by approximately 21.4 %, 95 % CI [14.9, 29.8] in individuals three months to 20 years after BC diagnosis.[6]

Five systematic reviews[7-11] investigated the effects of AE compared to usual care for the outcomes: lymphedema,[8,11] fatigue,[7,10,11] pain,[10,11] shoulder ROM,[10] cardiorespiratory fitness,[10] muscle strength,[10] body composition,[10] pulmonary function,[10] and quality of life[10,11] in BC survivors. Two meta-analyses were performed on lymphedema and physical function (QoL) outcomes[9] and no

differences were found between the groups. Notwithstanding the literature to date there remains some controversy on the effectiveness of AE in the management of BC. The results in the literature are inconclusive because primary studies are lacking in methodological quality and previous systematic reviews were unable to extract results while taking into account the risks of bias.

Furthermore, a literature review identified approximately 40 studies that were not located in the cited reviews, clearly identifying the need for an updated review. This review aims to answer the following clinical question: In people with breast cancer, what are the effects of AE on QoL, lymphedema, pain, fatigue, and ROM, compared with land exercises and usual care, after at least eight weeks of treatment?

METHODS

This systematic review and meta-analyses of randomized controlled trials was performed adhering to the guidelines of the Cochrane Collaboration,[12] the PRISMA 2020 Statement,[13] and AMSTAR 2.[14] It was registered with PROSPERO (CRD42024506498).

Data sources and Searches

A total of 10 databases were searched from inception until February 2024: Web of Science (1945), EMBASE (Excerpta Medical Database, 1947), PUBMED (U.S. National Library of Medicine, 1950), CINAHL (Cumulative Index to Nursing and Allied Health Literature, 1982), LILACS (Latin American and Caribbean Health Science, 1982), SPORTDiscus (1985), Cochrane Library

(1988), Scopus (1996), SciELO (Scientific Electronic Library Online, 1998), and PEDro (Physiotherapy Evidence Database, 1999). The keywords used were combined with Boolean operators and are available in the appendix (Supplementary material A).

The search strategy was formulated independently by two researchers for each database, to ensure reliability and reproducibility. Any disagreements were resolved by discussion. Studies were included if they met the following criteria according to the methodology: Population, Intervention, Comparison, Outcome, and Time (PICOT).

(P) Population: women undergoing unilateral surgical treatment after BC;

(I) Intervention: studies were eligible if they included an arm of the treatment dedicated to AE;

(C) Comparison: land exercise and/or usual care;

(O) Outcomes: QoL, lymphedema, fatigue, pain, and ROM;

(T) Time: greater than eight weeks intervention.

Study Selection

After the preliminary searches were completed, each article was examined for relevance and citations checked for additional papers not found in the original search. BC experts were also consulted about additional studies of interest. There were no language restrictions on searches.

Studies that performed AE in the management of women who had undergone surgical treatment for BC were included. AE were defined as: an individual or group intervention where participants were immersed in water in all treatment sessions proposed by the study. Initially the studies were

pooled, according to treatment time, into short-term (8-12 weeks), medium-term (13-24 weeks), and long-term (>24 weeks) and/or comparison.

Outcomes

The primary outcomes of interest were QoL, lymphedema, and fatigue, secondary outcomes were ROM and pain.

Data Extraction and Quality Assessment

Two reviewers independently assessed each included study for risk of bias with the Cochrane Risk of Bias 2 tool for clinical trials (RoB-2),[15] any disagreements were resolved through discussions. The RoB-2 tool examines five main sources of bias: 1) Randomization; 2) Deviations from intended interventions; 3) Missing outcome data; 4) Outcome measurement; 5) Selection of the reported outcome. Bias is classified as “high risk of bias”, “some concerns”, and “low risk of bias”.

To assess the overall certainty of evidence, the Grading of Recommendations Assessment, Development and Evaluation (GRADE) was used.[16] The GRADE tool classifies the certainty of evidence for each result in the following domains: limitations of the studies (risk of bias, according to the recommendations of the Cochrane Collaboration Handbook), inconsistency of results (heterogeneity or variability of results), imprecision (small sample and wide confidence intervals), indirect evidence (comparison of two different treatments with the usual care and not tested face-to-face), and publication bias

(small number of studies and funding sources). The certainty of evidence is classified as follows[17]:

- ✓ High: 75 % of the studies included were considered to be at low risk of bias.
- ✓ Moderate: one of the GRADE domains was not met. More studies are needed to improve the certainty of evidence.
- ✓ Low: two GRADE domains were not met. More research is important.
- ✓ Very low: three GRADE domains were not met. The results of the studies were uncertain.

Data Synthesis and Analysis

Information from the included studies was extracted and presented descriptively. The standardized mean difference was used for analysis of continuous data, with 95 % confidence interval [95 % CI]. Study authors were contacted when more information was needed for effect size (ES) and risk of bias calculations.

All analyses were conducted using the random-effects inverse variance approach proposed by Hartung and Knapp and by Sidik and Jonkman.[18] To assess heterogeneity, the chi-square test was used to verify the studies included in the meta-analysis. Inconsistencies were estimated using the I^2 statistic, where 25, 50, and 75 % were low, moderate, and high heterogeneity thresholds, respectively. Sensitivity analyses were performed by removing the study with the highest “weight” for each cluster, the random effect model was adopted. Statistical analyses were performed using the Comprehensive Meta-analyses v3. Statistical significance was set at 5 %.

RESULTS

Supplementary material B provides an overview of the research selection process until inclusion in the meta-analyses (PRISMA Flow Diagram). Database searches identified 1813 studies, of which 41 met the inclusion criteria and 34 were excluded.[19-52]

Therefore, 10 studies[53-62] were considered in this review and, four were included in the meta-analyses.[53-56] The year of publication ranged from 2010 to 2024. The characteristics of the included studies are shown in the Supplementary material C. The descriptive analysis of the results was presented according to the guidelines of the synthesis in systematic reviews[63] and the criterion adopted was the classification of risk of bias.

Characteristics of BC survivors

A total of 505 BC survivors were included, with ages ranging from 44 to 63 years. The stage of cancer diagnosis was reported by 20 % (n=2) of the studies and ranged from I to IIIa. The surgical techniques used were: tumorectomy, lumpectomy, quadrantectomy, mastectomy, or mastectomy associated with breast reconstruction. All survivors had completed chemotherapy or radiation treatments, and many remained on hormone treatment.

The AE group consisted of 235 women, the land exercise group of 147 women, and the usual care of 123 women. The treatment time after mastectomy was reported by 70 % (n=7) of the studies and ranged from six

months to six years. Treatment time ranged from eight to 48 weeks. The weekly frequency of the intervention ranged from one to three times a week and the duration of the sessions ranged from 30 to 60 min. None of the included studies performed the comparison AE *vs*. land exercise *vs*. usual care. All studies performed short-term treatments (between 8-12 weeks). It was not possible to carry out a meta-analysis for medium (13-24 weeks) or long-term treatments, as only one included study used this treatment time (>24 weeks).

Due to the heterogeneity of the studies, subgroup analyses were not possible. Two studies were not included in the meta-analyses due to heterogeneity of treatment and outcomes, and also due to their high risk of bias, which could compromise clinical applicability (external validity). The pilot study by Letellier et al.[58] did not blind the allocation during randomization, as a consequence there were differences in important prognostic variables at baseline. In addition, there were missing data at the end of treatment, which were not corrected by the intention-to-treat analysis principle. Johansson et al.[59], also a pilot study, did not carry out the allocation concealment process, however, this did not lead to problems at baseline, additionally the principle of analysis by intention-to-treat, was not carried out. At the end of the treatment, there was 6 % attrition in the AE group and 21 % in the usual care.

Characteristics of the interventions

The characteristics of the interventions are presented in the Supplementary material D.

Adverse effects

One study found a transient increase in lymphedema in three participants and four participants reported fatigue immediately after AE sessions.[58] In another study,[54] three participants reported discomfort or low-intensity pain/stiffness after an AE session.

Risk of bias assessment

The assessment of the risk of bias using the RoB-2 tool is presented in Figures 1 and 2. For the general classification of bias, 30 % (n=3) of the studies were classified as having low risk of bias, 30 % (n=3) as having some concerns, and 40 % (n=4) as having a high risk of bias. The domain with the most alterations in bias was the randomization process, where 40 % of the studies did not perform this process correctly and in domain two, 50 % of the studies did not perform an intention to treat analysis. Although none of the studies had significant attrition, as with all clinical trials there were some dropouts, and with the existing biases as outlined may have had an effect on outcome, the results therefore, must be interpreted with this in light.

Four studies compared AE with usual care, with 235 participants in the AE group and 123 in the usual care group.[53,54,57,59] Five studies compared AE with land exercise with 235 participants in the AE group and 147 in the land exercise group.[55,56,58,60,61,62]

QoL

Meta-analysis for QoL showed very low certainty of evidence that AE may improve QoL emotional domain (SMD=0.58; 95 % CI [0.1;0.9]; I^2=0 %) compared with usual care (Figure 3). (Supplementary material E)

Due to the heterogeneity of the QoL questionnaires (generic, specific, and outcome measures by domain or general), it was not feasible to perform a meta-analyses to compare AE *vs*. land exercises. Letellier et al.[58] and Odynets et al.[55] investigated QoL through questionnaires such as Functional Assessment of Cancer Therapy Breast Cancer (FACIT-B) and European Organization for Research and Treatment of Cancer Breast Cancer-Specific Quality of Life questionnaire (EORTC QLQ-BR23). Odynets et al.[55] found significant differences for the subdomains: body image ($P<0.01$), breast symptoms ($P<0.05$), and arm symptoms ($P<0.05$). Due to the high risk of bias, the results from Letellier et al.[58] will not be discussed.

Lymphedema

Thidar and Katz-Leurer[53] found no statistically significant differences in the measurement of lymphedema by % Relative Lymphedema Volume (% RVL) (SMD = 0.12; 95 % CI [-0.4;0.7]; $P=0.08$) in the AE *vs*. usual care comparison. Ali et al.[56] included women two years after breast surgery and found statistically significant differences in lymphedema in favor of AE when compared with land exercise ($P<0.001$).

Fatigue

Only one study investigated the effect of AE on fatigue compared to usual care. Cantarero-Villanueva et al.[54] found a statistically significant difference in favor of AE after mastectomy or lumpectomy surgery ($P<0.001$).

316 **Pain**

317

318 One study investigated the effect of AE on pain compared to usual care.
319 Cantarero-Villanueva et al[57] reported a statistically significant difference in neck
320 pain (P<0.001) and shoulder pain (P=0.04)[57] in favor of AE. For the comparison
321 between AE and land exercise, two studies were included in the meta-
322 analysis.[55,56] The evidence is very uncertain about the effect of AE on pain
323 (SMD= 1.10; 95 % CI [-1.54;3.74]; I^2=97 %) compared to land exercise (Figure
324 4). (Supplementary material E).

325

326 **ROM**

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328 Only studies with a high risk of bias investigated this effect with Ali et al.[56]
329 finding statistically significant differences for shoulder flexion (P<0.001) and
330 abduction movements (P<0.001).

331 **DISCUSSION**

332

333 The aim of this review was to determine if AE, of a minimum of eight
334 weeks duration were effective in improving QoL, lymphedema, fatigue, pain,
335 and ROM in BC survivors, when compared with land exercise and usual care.
336 Overall, there is very low certainty evidence regarding the effect of AE. Meta-
337 analyses revealed that AE may improve QoL outcomes compared to usual care
338 but the effect of AE on pain compared to land exercise is still uncertain. Only
339 single studies investigated the effect of AE on fatigue, lymphedema, and ROM.

340 Meta-analyses were pooled by treatment time and short-term results
341 only. For the comparison between AE and usual care, we found very low

certainty of evidence that AE may improve QoL emotional domain (SMD= 0.58; 95 % CI:0.19;0.98; I^2=0). In contrast, when AE was compared with land exercise, we found very low certainty of evidence that AE and land exercise have similar effects on pain.

Women with BC experience physical symptoms and psychosocial distress that negatively affect their QoL.[63] Quality of life consists of several domains, including emotional and physical components. The psychological impact of BC can present in the form of anxiety and depression[64] and a multitude of physical aspects of BC such as distortion of body image due to lack of breast, presence of scars, hair loss, persistent fatigue, functional disability, and post-lymphedema arm care can all impact on QoL.[65]

We found that AE may improve the emotional component of QoL in BC survivors after AE. Cantarero-Villanueva et al.[54] included two important items that may be related to these findings, aerobic activity, which corroborates the findings of a review of reviews published in 2020[66] and group treatment of 10/12 participants. The aquatic environment requires appropriate clothing that challenges and exposes the body and femininity; being in contact with women with the same condition, with or without breast reconstruction, associated or not with lymphedema, can stimulate dialogue, the exchange of experiences, and improve self-acceptance. However, these results should be evaluated with caution, due to the low quality of the evidence.

Lymphedema often presents as a long-term problem post breast reconstruction or breast surgery in BC.[67] Interventions for lymphedema are required at various points along the clinical trajectory and guidelines recommend AE combined with resistance exercise in all phases of treatment, associated with complete decongestive therapy.[68]

Therefore, BC survivors should be encouraged to continue their care at home, with compression bandage, lymphatic drainage, skin care, and water treatment combined with aerobic and resistance exercises added individually for each condition.[69] The study by Thidar and Katz-Leurer[53] proposed aqua lymphatic therapy which had minimal impact on lymphedema. These findings may be explained by the low weekly frequency of sessions (1x per week) and the chronic characteristics of lymphedema (survivors with surgery time of six years), and low exercise intensity. Two of the included studies[55,56] which found statistically significant differences in lymphedema, had an intervention frequency of three times a week.

Fatigue is one of the most common and distressing side symptoms of cancer and its treatment and can persist for years after treatment is complete. Fatigue prevalence estimates range from 25 to 99 %, depending on the population, type of treatment, and method of assessment.[70] Exercise-based interventions can reduce inflammatory activity or disrupt pro-inflammatory circuits, thought to contribute to fatigue. Additionally, interventions that increase physical activity could potentially reduce body mass index and increase cardiorespiratory fitness and thereby may improve fatigue.[71] Only one study evaluated fatigue in BC survivors and more studies are needed to determine the effect of AE on fatigue.

Three studies evaluated pain in BC survivors.[54-56] Only Odynets et al.[55] found no significant differences. Cantarero-Villanueva et al.[57] was the only study that included BC survivors without the presence of lymphedema. All studies performed the aquatic treatment at a thermoneutral temperature (31-33 °C) and the treatment time was eight weeks. The evaluation method used by two studies was the VAS,[56,57] one used the McGill Pain Questionnaire Short Form

(MPQSF),[58] and Odynets et al.[55] used the symptoms subdomain of the European Organization for Research and Treatment of Cancer Breast Cancer-Specific Quality of Life questionnaire (EORTC-QLQ-BR23).

The meta-analysis of the pain outcomes did not find differences between AE and land exercise. This result could be related to the high heterogeneity of the studies, such as populations with different pain symptoms, the presence or absence of lymphedema, and risk of bias in the studies. The findings of Letellier et al.[58] should be considered with caution due to the high risk of bias and therefore was not included in the meta-analysis.

The shoulder joint can often present with problems post-breast reconstruction,[65] consequently shoulder ROM is one of the outcomes to consider when treating the patient in the aquatic environment. The aquatic environment can reduce shoulder and cervical joint stress and facilitate movements that are difficult to perform on the ground. Ali et al.[56] found statistically significant improvement in shoulder ROM and reported earlier time to start treatment after surgery (six months).

In general, the sequence of exercises performed by the studies using AE included: warm-up, strength, and mobility exercises, and cool-down/relaxation, following a progression of intensity according to specific guidelines, monitored by the Borg scale. For studies with lymphedema, the proposed treatment was based on the aqua lymphatic therapy proposed by Tidhar and Drouin[21] and consisted of axillary lymph node activation, lymphatic self-drainage, and lymphokinetic exercises. Not all studies recorded the temperature and dimensions of the pool, which is unfortunate as this information is necessary to reproduce the intervention.

Previous literature reviews in this area are replete with methodological weaknesses, the current review included only randomized controlled trials and studies with potential biases in the randomization process were not included in the quantitative analysis due to validity concerns and underestimation or overestimation of results/effect sizes.

Future studies should take into account the recommendations of the current American Cancer Society/American Society of Clinical Oncology Breast Cancer Survivorship Care guidelines regarding the prescription of exercises, with a weekly frequency of at least twice a week. In addition, strength training and aerobic exercises should be included in the treatment and directed to the specific audience. Women with a low risk factor for lymphedema should be treated to reduce pain, limited ROM, and fatigue. Women at a high risk of developing lymphedema (axillary chain resection) should be counseled on the gold standard management of lymphedema, compression therapy, skin care, and lymphatic drainage. Exercises should be offered in an adjuvant way and long-term effects encouraged. It is important to emphasize that specific interventions, such as Bad Ragaz, which has specific movement patterns for the trunk and upper limbs that can help in the treatment of BC survivors should be stimulated. Standardized measurement instruments should be used, such as specific questionnaires for BC and lymphedema.

Finally, methodological rigor must be followed when conducting research, which will lead to better decision making. Quality information is essential so that it can be extracted and assist in the indication, treatment, and improvement in the QoL of BC survivors, for example, following the rules of the CONSORT Statement.

This review was limited by the high variability of the assessment instruments for each outcome, which impacted the meta-analysis (performed with a limited number of studies), precluding sensitivity and subgroup analyses. The low response rate of the authors to the requested information about the studies, such as results in mean and SD, were also responsible for the low number of studies included in the meta-analysis. It is also necessary to interpret meta-analyses with less than five studies and unequal sizes with caution. The certainty of the evidence assessed by GRADE was limited, due to the low inclusion of studies in the meta-analyses, this is not only due to the heterogeneity of the studies in relation to the treatment time combined with the weekly frequency, but also due to the classification of the risk of bias.

Publication bias was not analyzed by funnel plot due to the inclusion of only two studies in the meta-analysis. In addition, two pilot studies were included, with numerous methodological limitations (power, for example). The lymphedema outcome data from the Thidar and Katz-Leurer[53] study were obtained through the study by Yeung and Semciw.[9] Our results refer to the short-term effect, as few studies performed follow-up, making long-term analysis unfeasible.

CONCLUSION

AE improved the emotional subdomain of QoL when compared with the usual care group. When compared with land exercises, no differences were found for pain. However, there are important concerns in classifying the risk of bias of the included studies and the certainty of the evidence was very low.

Results should be interpreted with caution. No relevant adverse effects that contraindicate AE were reported.

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Declaration of Competing Interest

The authors declare no conflict of interest. There were no conflicts of interest in the nine primary studies included.

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Figure legends:

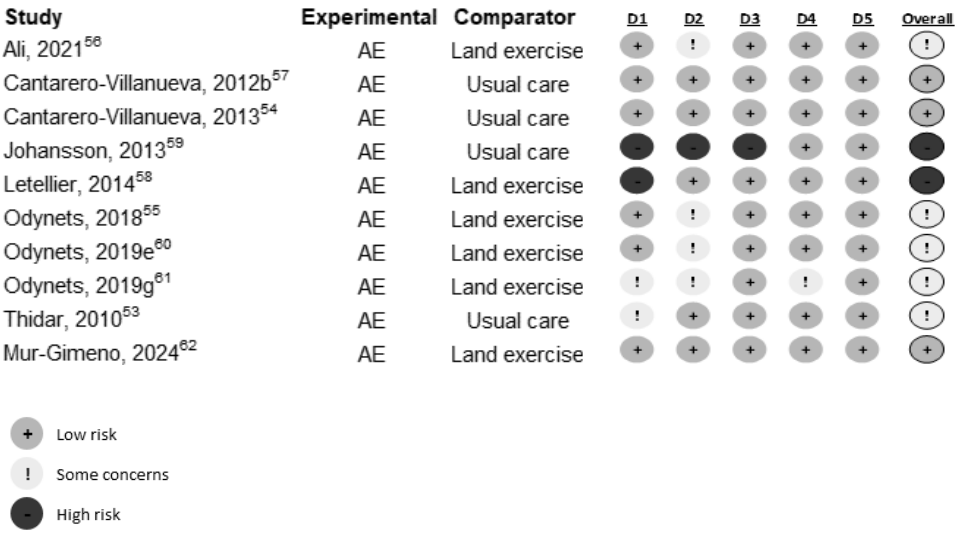


Figure 1. Risk of bias assessment of included studies.

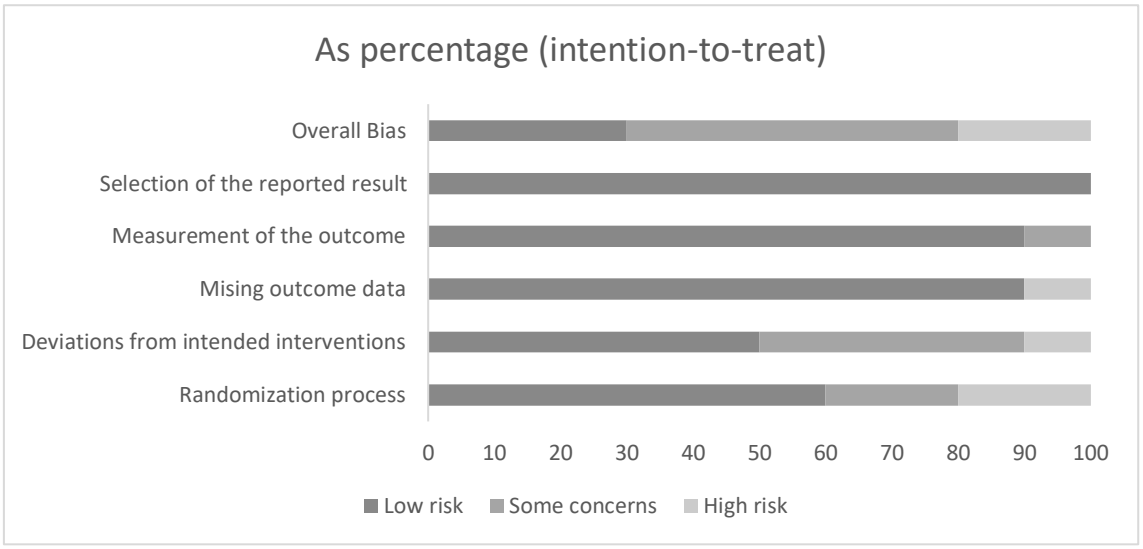
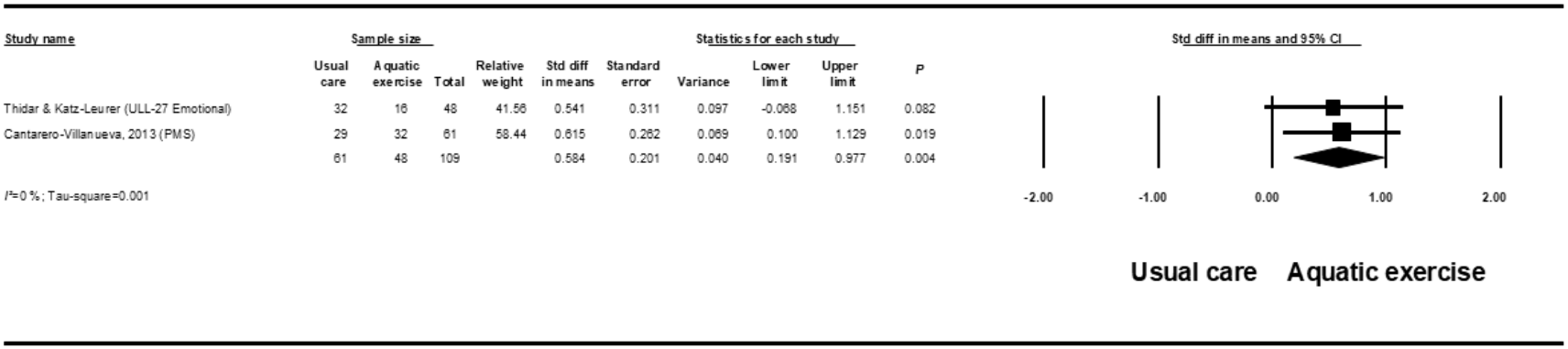
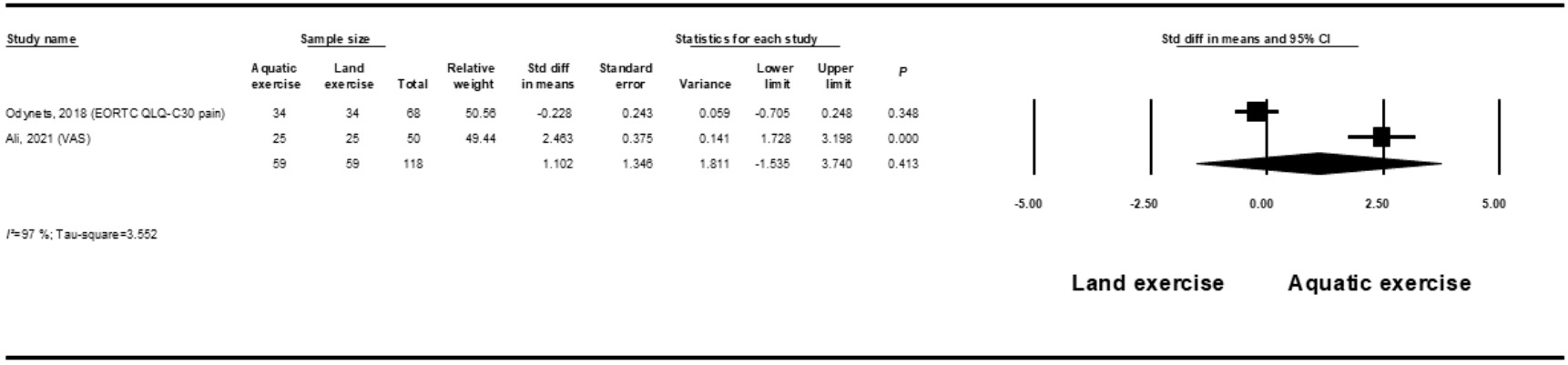


Figure 2. Percentage of bias by domains.



Quality of life outcome: usual care vs. aquatic exercise

Figure 3**.** Outcome meta-analysis quality of life - emotional subdomain (aquatic exercise *vs*. usual care).



Pain outcome: land exercise vs. aquatic exercise

Figure 4. Pain outcome meta-analysis (aquatic exercises *vs*. land exercises).