

**Effects of exercise on cardiac function in women receiving anthracycline or trastuzumab treatment for breast cancer: A systematic review and meta-analysis**

**SUPPLEMENTARY MATERIAL**

- Search strategy used for pubmed (Table S1).
- Data extracted from included RCTs, ongoing trials and study protocols (File1).
- Characteristics of the identified ongoing trials (Table S2).
- Forest plot showing the effect of exercise intervention compared to control on E/A ratio (Figure S1).
- Forest plot showing the effect of exercise intervention compared to control on NT-proBNP (Figure S2).

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➤ Search strategy used for pubmed (Table S1).

| <b>MEDLINE via PubMed</b> |   |
|---------------------------|---|
| #1                        | breast neoplasms[MeSH]  |
| #2                        | breast diseases[MeSH]   |
| #3                        | (breast cancer*[tiab] OR breast neoplas*[tiab] OR breast tumor*[tiab] OR breast tumour*[tiab] OR breast carcinoma*[tiab] OR breast malignan*[tiab]) |
| #4                        | #1 OR #2 OR #3  |
| #5                        | chemotherapy[MeSH]  |
| #6                        | anthracycline[MeSH]   |
| #7                        | trastuzumab[MeSH]   |
| #8                        | Antibodies, Monoclonal, Humanized[MeSH]   |
| #9                        | chemotherap*[tiab] OR anthracycline*[tiab] OR trastuzumab[tiab] OR herceptin[tiab]  |
| #10                       | #5 OR #6 OR #7 OR #8 OR #9  |
| #11                       | Exercise [MeSH]   |
| #12                       | Resistance training[MeSH]   |
| #13                       | Exercise therapy[MeSH]  |
| #14                       | ((aerobic OR endurance OR resistance OR strength OR weight OR physical)) AND ((exercise OR training OR sport OR intervention OR program)            |
| #15                       | #11 OR #12 OR #13 OR #14  |
| #16                       | (randomized controlled trial[pt]) OR controlled clinical trial[pt])   |
| #17                       | (randomized[tiab] OR randomly[tiab] OR trial[tiab])   |
| #18                       | #16 OR #17  |
| #19                       | #4 AND #10 AND #15 AND #18  |

➤ Data extracted from included RCTs, ongoing trials and study protocols (File1).

● **The following data was extracted from each RCT:**

- Characteristics of trial: first author name, year of publication, journal name, country, sample size, study register.
- Characteristics of participants: mean age, disease stage and treatment scheme, number of enrolled subjects, number of withdrawals or dropouts.
- Characteristics of intervention: intervention type, sequence, supervision, exercise type, volume, intensity, frequency, length, total number of exercise sessions.
- Safety of intervention.
- Attendance to intervention.
- Compliance of intervention.
- Outcomes of interest (cardiac outcomes, circulating biomarkers).

● **The following data was extracted from each ongoing trials:**

- Characteristics of trial: first author/principal investigator name; study identifier; start planned and completion date; and trial design.
- Characteristics of participants: target sample size; cancer site and stage; and treatment.
- Characteristics of intervention: sequence; supervision; type of training; length; frequency; intensity; volume.
- Outcomes of interest (cardiac outcomes, circulating biomarkers).

● **Sequence was defined according to:**

- Linear approach: standard intensity, frequency, and duration parameters after an initial lead in period, with static increases in session duration.
- Non-linear prescription: nonuniform, alternating exercise doses across the intervention period after an initial lead in.

● **Supervision was defined according to:**

- Supervised: exercise sessions performed under the supervision of a health professional.
- Non-supervised: exercise sessions not monitored (e.g., home-based).

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- Combined: exercise intervention involving supervised sessions and non-supervised sessions.
- **Type of training was defined according to:**
  - Aerobic training: any exercise form that uses large muscle groups which predominately stresses the cardiovascular system (e.g., walking, jogging, cycling).
  - Resistance training: any exercise form that requires a muscle or a muscle group to work against external resistance which predominately stresses the musculoskeletal system (e.g., squats, chest press).
  - Combined training: exercise intervention involving the combination of aerobic exercise and resistance training.
- **Length:** total number weeks/months of intervention.
- **Frequency:** number of exercise sessions per week.
- **Intensity:** percentage of a predetermined physiological parameter such as maximum heart rate obtained from baseline cardiopulmonary exercise test.
- **Volume:** time spend on training, number of sets or repetitions.
- **Total number of exercise sessions:** maximum number of sessions calculated by multiplying length and frequency.
- **Safety of intervention:** reported adverse events which occurred during intervention.
- **Attendance to intervention:** number of exercise sessions attended divided by the total number of planned sessions.
- **Compliance of intervention:** number of exercise sessions performed in line with the planned prescription (i.e., duration and intensity).

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- Characteristics of the identified ongoing trials (Table S2).

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| TRIAL INFORMATION   |   |                          | POPULATION TO BE ENROLLED |                       |                 | EXERCISE INTERVENTION |             |  |                      |  | OUTCOMES OF INTEREST                          |                           |
|---|---|--------------------------|---------------------------|-----------------------|-----------------|-----------------------|-------------|--|----------------------|--|---|---------------------------|
| Principal Investigator/<br>Identifier and study protocol<br>reference           | Starting –<br>Planned<br>completion<br>date | Target<br>sample<br>size | Allocation                | Cancer site/<br>Stage | Treatment       | Sequence              | Supervision | Type of<br>training                              | Length/<br>Frequency | Volume/<br>Intensity   | Cardiac<br>outcomes                           | Circulating<br>Biomarkers |
| <b>Trials delivering a single type of training</b>                              |   |                          |                           |                       |                 |                       |             |  |                      |  |   |                           |
| Amy A Kirkham/ [29]; [39]   | October<br>2017–<br>June 2020               | 56                       | RCT                       | BC/ I-III             | AC-T            | Linear                | SP          | Single AE session 24 hours<br>prior to each AC-T |                      | WU: 10 min/ NR<br>CD: 5 min/ NR AT:<br>30 min/<br>70%-75% of<br>HRR  | LVEF; SI;<br>LV<br>volumes;<br>LV mass;<br>CO | NT-proBNP                 |
| Christina Dieli-Conwright/<br>[30]  | Septem<br>2015–<br>Septem<br>2021           | 60                       | RCT                       | BC/ I-III             | AC-T or<br>TC-T | Linear                | SP          | HIIT   | 8 weeks/<br>3 TPW    | WU: 5 min/ 10%<br>PPO<br>CD: 5 min/ 10%<br>PPO<br>HIIT: 7 bouts of<br>1 min at 80%<br>HRR separated<br>by 2 min of<br>active recovery<br>(10% PPO) | LVEF; LV<br>volumes                           | NR                        |
| Roberta Florido/<br>[31]  | January<br>2017–<br>June 2020               | 30                       | RCT                       | BC/ I-III             | AC-T            | Linear                | NS          | Self-selected                                    | NR/ Daily            | WU: NR/ NR<br>CD: NR/ NR<br>Self-selected:<br>10000 steps + 30<br>min of coninuos<br>self-selected<br>exercise/ NR                                 | LVEF; SI                                      | Troponin                  |
| Scott A Grandy/<br>[32]   | January<br>2019–<br>December<br>2022        | 100                      | RCT                       | BC/ I-III             | AC-T            | Non-<br>linear        | NS          | AT<br>(self-<br>selected)                        | 12 weeks/<br>2 TPW   | WU: NR / NR<br>CD: NR / NR<br>AT: 20-40 min /<br>35%-85% HRR   | LVEF; SI                                      | hsTnT;<br>NTproBNP        |
| <b>Trials delivering an exercise intervention combining 2 types of training</b> |   |                          |                           |                       |                 |                       |             |  |                      |  |   |                           |

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|                       |                              |     |     |        |      |        |    |      |                 |   |          |                                       |
|-----------------------|------------------------------|-----|-----|--------|------|--------|----|------|-----------------|---|----------|---------------------------------------|
| Andre La Gerche/ [27] | November 2017– December 2022 | 100 | RCT | BC/ NR | AC-T | Linear | SP | HIIT | 4 months/ 3 TPW | WU: NR / 60%- 80% HRR<br>CD: NR / 60%- 80% HRR<br>HIIT: 4 bouts of 4 min at 80% HRR separated by 2 min active | LVEF; SI | Troponin I; B-type Natriuretic Peptid |
|-----------------------|------------------------------|-----|-----|--------|------|--------|----|------|-----------------|---|----------|---------------------------------------|

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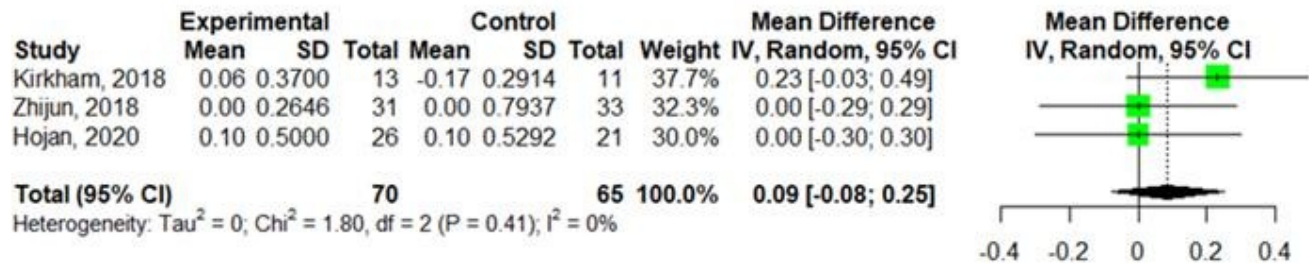
|   |                                       |     |     |                                   |                 |        |           |                            |  | recovery<br>(intensity NR)  |          |                         |
|---|---------------------------------------|-----|-----|-----------------------------------|-----------------|--------|-----------|----------------------------|--|---|----------|-------------------------|
|   |                                       |     |     |                                   |                 |        |           | +                          |  | +   |          |                         |
|   |                                       |     |     |                                   |                 |        |           | RT                         |  | 1-2 sets/ 55-85%<br>of 1-RM   |          |                         |
| Edith Pituskin/ [33]; [40]                            | May 2018–<br>June 2020                | 80  | RCT | BC or<br>lymphoma/<br>early stage | AC-T or<br>TC-T | Linear | SP and NS | AT                         | 2-3months/<br>2 TPW<br>(SP) + 1-<br>2TPW<br>(NS) | WU: NR/ NR<br>CD: NR/ NR<br>AT: 30-60 min/<br>60%-80% peak<br>VO2         | LVEF; SI | BNP,<br>Troponin        |
|   |                                       |     |     |                                   |                 |        |           | +                          |  | +   |          |                         |
|   |                                       |     |     |                                   |                 |        |           | RT                         |  | RT: 1-3 sets/ 10-<br>15 repetitions/<br>moderate                          |          |                         |
| Matthias Wilhelm/<br>[34]                             | May 2019–<br>December<br>2022         | 120 | RCT | BC/ NR                            | AC-T            | Linear | SP        | AT                         | 12 weeks/<br>2 TPW                               | WU: NR/ NR<br>CD: NR/ NR<br>AT: 40 min/<br>moderate                       | LVEF; SI | NT- proBNP;<br>hsTnT    |
|   |                                       |     |     |                                   |                 |        |           | +                          |  | +   |          |                         |
|   |                                       |     |     |                                   |                 |        |           | RT                         |  | RT: NR/ NR  |          |                         |
| Kun-Ling Tsai/ [36]                                   | July 2017–<br>NR                      | 30  | RCT | BC/ I-III                         | AC-T            | NR     | NR        | AT                         | 24<br>sessions/<br>NR                            | NR/ NR  | LVEF     | NR                      |
|   |                                       |     |     |                                   |                 |        |           | +                          |  | +   |          |                         |
|   |                                       |     |     |                                   |                 |        |           | RT                         |  | NR/ NR  |          |                         |
| Pedro Antunes/ [28]; [37]                             | November<br>2018–<br>November<br>2020 | 90  | RCT | BC/ I-III                         | AC-T            | Linear | SP        | AT                         | During CT/<br>3 TPW                              | WU: 5 min/ NR<br>CD: 5 min/ NR<br>AT: 20-30<br>min/50%-85%<br>HRR         | LVEF; SI | NTproBNP                |
|   |                                       |     |     |                                   |                 |        |           | +                          |  | +   |          |                         |
|   |                                       |     |     |                                   |                 |        |           | RT                         |  | RT: 2-3 sets/ 10-<br>12 repetitions/<br>lowest available<br>load to 12-RM |          |                         |
| <b>Integration in cardiac rehabilitation programs</b> |                                       |     |     |                                   |                 |        |           |                            |  |   |          |                         |
| Amparo Gil/<br>[35]                                   | August<br>2018–<br>August 2021        | 340 | RCT | BC/ I-III                         | AC-T or<br>TC-T | NR     | SP        | Participation<br>in a MCRP | NR   | NR  | LVEF; SI | NTproBNP;<br>Troponin I |



## Effects of exercise on cardiac function in women receiving anthracycline or trastuzumab treatment for breast cancer: A systematic review and meta-analysis

Abbreviations: AC-T: anthracycline-based therapy; AE: aerobic exercise; AT: aerobic training; BC: breast cancer; BNP: B-type natriuretic peptide; CD: cooldown; CO: cardiac output; CT: chemotherapy; HIIT: high intensity interval training; HRR: heart rate reserve; hsTnT: high-sensitivity troponin T; LV: left ventricular; LVEF: left ventricular ejection fraction; MCRP: multidisciplinary cardiac rehabilitation program; NR: not reported; NS: non-supervised; NT- proBNP: n-terminal pro-brain natriuretic peptide; PPO: peak power output; RCT: randomized controlled trial; RM: repetition maximum; RT: resistance training; SI: strain imaging; SP: supervised; TC-T: trastuzumab-containing therapy TPW: times per week; WU: warm-up.

➤ Forest plot showing the effect of exercise intervention compared to control on E/A ratio (Figure S1).



➤ Forest plot showing the effect of exercise intervention compared to control on NT-proBNP (Figure S2).

