Supplementary Material

Appendix 1

**Effect of exercise therapy on established and emerging biomarkers in heart failure patients: a systematic review and meta-analysis**

**Melissa J. Pearson, Nicola King and Neil A. Smart**

**Table S1** Excluded studies

**Table S2** Baseline NT-proBNP and BNP concentrations

**Table S3** Exercise intervention details

**Table S4** Biomarker assay

**Table S5** Sensitivity analysis leave-one-out

**Table S6** TESTEX table

**Supplementary Fig. 1a & 1b** Funnel Plots for publication bias

Sample Search Strategy

**Supplementary Table S1** Excluded studies

|  |  |
| --- | --- |
| **Study** | **Reason for Exclusion** |
| Adamopoulos (2014) | Comparison to two different training modalities (aerobic/IMT vs. aerobic/sham IMT), no usual care/no exercise control group |
| Arad (2008) | Single group pre-post study, no usual care/no exercise control group |
| Braith (1999) | Biomarker outcome (ANP) does not meet inclusion criteria |
| Beckers (2008) | Comparison of two different training modalities (CT vs. ET), no usual care/no exercise control group |
| Besson (2013) | Comparison of Eccentric ergometer training to Concentric(standard ergometer) training |
| Caminiti (2011) | Comparison of two different training modalities (Tai Chi vs. Tai Chi/ET), no usual care/no exercise control group |
| Casillas (2016) | Comparison of Eccentric ergometer training to Concentric(standard ergometer) training |
| Ellingsen (2011) SMARTEX | Comparison of three training modalities (HIIT vs. MCT vs. RRE), no usual care/no exercise control group |
| Giallauria (2006) | Authors do not note a specific chronic heart failure diagnosis |
| Giallauria (2008) | Authors do not note a specific chronic heart failure diagnosis |
| Hagglund (2017) | Comparison of two different training modalities (Yoga vs. Hydrotherapy), no usual care/no exercise control group |
| Haseba (2016) | Comparison of exercise with exercise/sauna therapy, no separate usual care/no exercise control group |
| Jiao (2016) | Exercise did not fit inclusion criteria – weight supported training |
| Karavidas (2010) | Comparison of FES in NYHA Class II to NYHA Class III/IV |
| Kiilavuori (1999) | Biomarker outcome (proANP) did not meet inclusion criteria |
| Laoutaris (2008) | Comparison of two different training protocols (HITG IMT vs. LITG IMT), no usual care/no exercise control group |
| Legallois (2016) | Single group pre-post study, no usual care/no exercise control group |
| Lima (2010) | Patients with Chagas cardiomyopathy |
| Municino (2006) | Single group pre-post study, no usual care/no exercise control group |
| Nakanishi (2017) | Single group pre-post study, no usual care/no exercise control group |
| Ozasa (2011) | Machine assisted cycling vs. conventional ET, no usual care/no exercise control group |
| Prescott (2009)(a) | Single group pre-post study, no usual care/no exercise control group |
| Prescott (2009)(b) | All participants previously participated in an exercise rehabilitation program |
| Pritchett (2012) | The exercise group also consisted of dietary changes, no separate exercise only group |
| Radi (2017) | Patients had been hospitalised for acute HF, intervention 1 month |
| Reda (2017) | Patients had decompensated heart failure and intervention < 4 weeks |
| Rengo (2014) | Single group pre-post study, no usual care/no exercise control group |
| Schoenrath (2015) | Single group pre-post study, no usual care/no exercise control group |
| Stout (2012) | Comparison of Exercise + Testosterone vs. Exercise, no usual care/no exercise control group |
| Svealv (2009) | Crossover trail, no separate control group |
| Takagawa (2017) | Single group pre-post study, no usual care/no exercise control group |
| Van Buuren (2017) | Comparison of two different training protocols (EEMS vs. LEMS), no usual care/no exercise control group |
| Yamauchi (2016) | Single group pre-post study, no usual care/no exercise control group |
| Yeh (2013) | Comparison of two different training modalities (Tai Chi vs. Aerobic) no usual care/no exercise control group |

**Supplementary Table S2 Baseline Levels NT-proBNP (pg/ml) & BNP (pg/ml)**

|  |  |  |
| --- | --- | --- |
| **Study** | **Baseline NT-proBNP (pg/ml)** | |
|  | **Exercise** | **Control** |
| Ahmad 2014 | 693.7 (276.1, 1725) \* | 778.5 (296.7, 1825) \* |
| Aksoy 2015 (1) | 203.4±154.8  176.2±152.9 | 262.3±215.2 |
| Antonicelli 2015 | 1236 (2038)\*\* | 618 (520)\*\* |
| Berendoncks 2010 | 1216 (530–2887)\* | 833 (373–2477)\* |
| Conraads 2004 | 2124±397 (SE) | 1228±240 (SE) |
| Conraads 2007 | 2325±785 (SE) | 1269±296 (SE) |
| Delagardelle 2008 | 1145±1185  1431±1537 | 1143±1793  1971±2379 |
| Edelmann 2011 | 157±17 | 172±110 |
| Eleuteri 2013 | 853 (87–3772)\*\*\* | 545.6 (62–3312)\*\*\* |
| Guazzi 2012 | 1088.1±447.1 | 1110±312.9 |
| Krishna 2014 | 3965.48±1365.08 | 5495.47±1382.5 |
| Nilsson 2010 (2) | 1412 (753, 2486) \* | 1987 (1108, 3315)\* |
| Marco 2013 | 1677.4±1658.4 | 2212.9±3155.5 |
| Meyer 2004 | 1092±980 | 1075±1067 |
| Passino 2006/2008(3) | 1382±1478 | 1708±1680 |
| Palau 2014 | 983 (325–1932)\* | 1314 (255–1868)\* |
| Sandri 2012 | 1675±354 (SE)  1426±189 (SE) | 1426±189 (SE)  1509±327 (SE) |
| Sarullo 2006 | 3376±3133 | 3285±3012 |
| Wisloff 2007 | 1305±714  1521±1281 | 1321±148 |
|  | **Baseline BNP (pg/ml)** | |
|  | **Exercise** | **Control** |
| Billebeau 2017 | 293 (158,757)\* | 137 (44, 148)\* (n=12) |
| Brubaker 2009 | NR | NR |
| Butterfield 2008 | 355±352 | 646±348 |
| Fu 2013 (4) | 405±  453± | 483± |
| Gary 2011 | 184.4±151.6 | 105.8±159.1 |
| Jonsdottir 2006 | 173.2±180.4 | 122.2±121.8 |
| Karavidas 2008 | 563.5±136.2 | 521.7±9.5 |
| Karavidas 2013 | 646±188 | 668±209 |
| Kato 2017 | 185.6±178.6 | 224.7±180.4 |
| Kawauchi 2017 | 339±291  303±301 | 168±108 |
| Kitzman 2010 | 45±56 | 72±122 |
| Kitzman 2016 | 23.6 (19.4, 39.4)\* | 21.9 (18.2, 26.5)\* |
| Kobayashi 2003 | 281±92 (SE) | 383±89 (SE) |
| Malfatto 2009 | 293±115 | 318±125 |
| Nishi 2011 | 432±451 | 238±130 |
| Norman 2012 | 103.2±108.5 | 175.1±182.1 |
| Parrinello 2009 | 205.2±46.5 | 210.4±51.5 |
| Passino 2006/2008(3) | 193±199 | 194±180 |
| Stevens 2015 | 281±95 (SE) | 285±117 (SE) |
| Yamamoto 2007 | 273.9 (108.1, 658)\* | 177.8 (161.5, 241.7)\* |
| Yeh 2004 | 329±377 | 285±340 |
| Yeh 2011 | 102 (47, 212)\* | 106 (42, 493)\* |

Mean±SD unless otherwise noted, \* Median (IQR), \*\*Median (interval), \*\*\*Median (range)

(1) Converted from fmol/ml (2) converted from pmol/l, (3) Data from Passino 2006 and 2008 consolidated into one dataset.

(4) extracted from graph

**Supplementary Table S3** Detailed Exercise Intervention Characteristics

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Study** | **Modality** | **Duration** | **Sessions/week** | **Total Time**  **per session** | **Intensity** |
| Ahmad 2014 | Aerobic (group based walking, treadmill or cycling) | 3 months | 3 | 15-30 min | 60%HRR and ramped up |
| Aksoy 2015 | Aerobic (Cycle) 2 groups: Interval & Continuous | 10 weeks | 3 | 35 min  (includes 5 min WU & 5 min CD) | Starting power @50%VO2peak, ↑every 2 weeks to power @ 75% VO2peak @ week 10. Interval group - 60s work to 30s recovery (17 cycles) |
| Antonicelli 2016 | Aerobic (cycle) 3 months supervised, 3 months home | 6 months | 3 | 50 min (includes 10min WU & CD) | 20 min @ 60-70%HRmax |
| Berendoncks 2010 | Aerobic and Combined Training | 4 months | 3 | 60 min (includes 5 min WU & CD) | AT intensity 90%HR @ ANT. Initial RM intensity  50% 1RM with an increase to 60% after 2 months |
| Billebeau 2017 | Aerobic (cycle, treadmill or rowers) | 4-6 months | 2 |  | Workload @ VAT |
| Brubaker 2009 | Aerobic (walking & cycle) | 16 weeks | 3 | 60 min (includes WU & CD) | 40-50% HRR (weeks 1-2), increased to 60-70% HRR |
| Butterfield 2008 | Combined Training. 1 x groups session @ hospital (65 min) (45 min circuit) plus daily home-based walking (45 min) | 12 weeks | 7 | >45 min |  |
| Conraads 2007 | Aerobic (cycle & waking) | 4 months | 3 | 60 min (includes 5 min WU & CD) | HR @ 90%VT |
| Conraads 2004 | Combined | 4 months | 3 | 60 min (includes WU & CD) | AT intensity - HR @ 90%VT, RT intensity - 50% 1RM, increased to 60% after 2 months |
| Delagardelle 2008 | Aerobic (cycle & treadmill), Strength, Combined (3 groups) | 13.3 weeks | 3 | 45 min (includes 5 WU) | AT intensity – 60% VO2peak increased to 75%VO2peak  RT intensity – 60% 1RM, increased to 70% 1RM |
| *Rx-DHF Pilot*  Edelmann 2011 & Trippel 2017 | Combined Training, initially aerobic (cycling) weeks 1-4 (20-40 min), with addition of RT @ week 5 | 12 weeks | 2-3 (AT)  2 (RT) | 40 min + | AT: HR @ 50-60% VO2peak (weeks 1-4) ↑HR @ 70% VO2peak 2 week 5, RT @ 60-65%1RM (15 reps) |
| Eleuteri 2013 | Aerobic (cycle) | 3 months | 5 | 40 min  (includes 5 min WU & 5 min CD) | Power & HR @ VAT |
| Fernandez-Silva 2017 | Aerobic (cycle) 2 groups, Interval (1 min: 2 min) and Continuous | 12 weeks | 3 | 40 min  (includes 5 min WU & 5 min CD) | Interval: THR= 1 min @ HR @ RCP, 2 min @ HR @ AT, Continuous: THR = [HR @ RCP + 2 (HR @ AT)]/3 (NB: both groups same average workload @ end 30 min) |
| Fu 2013 | Aerobic (cycle) 2 groups, Intervals 5 x 3 with 3 min recovery (30 min), Continuous (30 min), both programs isocaloric. Supervised | 12 weeks | 3 | 30 min  (+ 3 min WP & 3 min CD) | Interval: 5 x 3 @ 80% VO2peak, 3 min recovery @ 40% VO2peak between each interval  Continuous @ 60% VO2peak |
| Gary 2011 | Combined Training (walking and RT) | 12 weeks | 3 (AT)  2-3 (RT) | 30-60 min  45-60 min | AT intensity- started 50% HRR, increased 70%HRR  RT started @ 2 x 12-15 reps. Increased to 3 x 12-15 reps |
| Guazzi 2012 | Aerobic | 24 weeks | 4 | 40 min | 80% HRR (60% for first 2 weeks) |
| Jonsdottir 2006 | Combined (Cycle and circuit RT) | 5 months | 2 | 45 min (includes 10 min WU) | Initial cycle workload @ 50% peak WL, then increased. RT intensity started @20-25%1RM, increased to 35-40%1RM. |
| Karavidas 2008 | FES | 6 weeks | 5 | 30 min | Intensity for visible muscle contraction- 25Hz for 5s than 5s rest |
| Karavidas 2013 | FES | 6 weeks | 5 | 30 min | Intensity for visible muscle contraction- 25Hz for 5s than 5s rest |
| Kato 2017 | Stretching | 4 weeks | 7 | 20 min | Low intensity |
| Kawauchi 2017 | IMT + RT. 2 groups LIPRT & MIPRT | 8 weeks | 7 | 30 min (IMT) | LIPRT - IMT @15% MIP and RT with 0.5 kg. MIPRT - IMT @ 30% MIP and RT @ 50%1RM  RT - 1 x10, then increased to 2x10 reps |
| Kitzman 2010 | Aerobic (walking & cycling) | 16 weeks | 3 | 60 min (includes WU & CD) | 40-50% HRR (weeks 1-2), increased to 60-70% HRR |
| Kitzman 2016 | Aerobic (primarily walking) | 20 weeks | 3 | 60 min | Individualised intensity based on HRR progressed as tolerated |
| Kobayashi 2003 | Aerobic (cycle) | 12 weeks | 4-6 (2-3 per week x 2 per day) | 15 min  (30 min/day) | HR @ VT |
| Krishna 2014 | Yoga. Supervised 3 days, 3 days home | 12 weeks | 6 | 60 min | - |
| Malfatto 2009 | Aerobic (cycle or treadmill) | 12 weeks | 3 | 60 min (includes 15-20 min WU) | 60% VO2peak |
| Marco 2013 | IMT | 4 weeks | 14 (daily x 2) | - | 5 x 10 breaths (100% of their RM) then 1–2 min of unloaded recovery breathing, |
| Meyer 2004 | Aerobic (cycle) | 12 weeks | 4 | 45 min | ANT |
| Nilsson 2010 | Aerobic/Strength (group-based) | 4 months | 2 | 50 min | Included - 3 High intensity intervals @ RPE 15-18 for 5-10 minutes. |
| Nishi 2011 | Aerobic (walking, cycling, callisthenics) | 3 months | 3-5 | 40-60 min | 30-50% HRR |
| Norman 2012 | Combined (AT + RT) | 24 weeks | 3 x AT, 2 x RT | 30 min AT (+15 min WU& CD) | AT: 40- 70% HRR of (RPE 11-14), RT: 8 -10 exercises  1 x 10-15 reps. |
| Palau 2014 | IMT | 12 weeks | 14 (Daily x 2) | 20 min | Started breathing @ 25–30% MIP for 1 week, resistance modified each session according to 25–30% MIP measured. |
| Parrinello 2009 | Aerobic (walking) | 10 weeks | 5 | 30 min | Mild to moderate |
| Passino 2006 | Aerobic (cycle) | 9 months | 3 | 30 min | 65% VO2peak |
| Passino 2008 | Aerobic (cycle) | 9 months | 3 | 30 min | 65% VO2peak |
| Sandri 2012 | Aerobic (cycle) | 4 weeks | 20 (5 days of 4 sessions per day) | 20 min (80 min/day) | 70% symptom limited VO2peak |
| Sarullo 2006 | Aerobic (cycle) | 12 weeks | 3 | 30 min | 60-70% VO2peak |
| Stevens 2015 | Combined: Aerobic 4 x 6-8 (2 min rest), ↑8-12 min @ wk. 6 + RT | 12 weeks | 5 x fortnight | >30 min | Aerobic @ HR@ 2nd VT, RT @ 50-70% 1RM ( 2 x 15, ↑2-3 reps) |
| Wisloff 2007 | Aerobic (treadmill walking), 2 supervised, 1 home per week, 2 groups: AIT & MCT | 12 weeks | 3 | 38 min (AIT) (includes 10 min WU)  47 min (MCT) | Interval: 4x4 @ 90-95%HRpeak, 3 min recovery @ 50-70%HRpeak between intervals  Continuous @ 70-75%HRpeak |
| Yamamoto 2007 | Aerobic (cycle and walking) | 6 months | 3 | 60 min | HR and WL @ VAT and 1 minute before ANT |
| Yeh 2004 | Tai Chi | 12 weeks | 2 | 60 min | NR |
| Yeh 2011 | Tai Chi | 12 weeks | 2 | 60 min | NR |

ANT: anaerobic threshold, AIT: aerobic interval training, AT: aerobic training, CD: cool-down, FES: functional electrical stimulation, HR: heart rate, HRR: heart rate reserve, IMT: inspiratory muscle training, LIPRT: low intensity inspiratory muscle training and peripheral resistance training, MCT: moderate continuous training, MIPRT: moderate intensity inspiratory muscle training and peripheral resistance training, MIP: maximal inspiratory pressure, RM: repetition maximum, RT: resistance training, VAT, ventilatory anaerobic threshold, VT: ventilatory threshold, WL: workload, WU: warm-up,

**Supplementary Table S4** Biomarker Assessment

|  |  |  |
| --- | --- | --- |
| **Study** | **Plasma/ Serum** | **Assay/Supplier** |
| **BNP** |  |  |
| Brubaker 2009 | Plasma | Commercially available radioimmunoassay |
| Billebeau 2017 | Plasma | ARCHITECT BNP assay, Abbott Laboratories, Abbot Park, Il, USA |
| Butterfield 2008 | Whole Blood/Plasma | Fluorescence immunoassay, Triage BNP, Biosite Diagnostics Inc., San Diego California |
| Fu 2013 | Plasma | ELISA, USCN Life Science Inc., Burlington, NC |
| Gary 2011 | ? | BNP test, Triage assay |
| Jonsdottir 2006 | Plasma | Immunoradiometric assay (IRMA) kits |
| Karavidas 2008 | Plasma | Immunoassay technique, Triage BNP assay, Biosite Inc., San Diego, California, USA |
| Karavidas 2013 | Plasma | Immunoassay technique, Triage BNP assay; Biosite Inc., San Diego, CA |
| Kato 2017 | Plasma | ? |
| Kawauchi 2017 | ? | Immunoassay, Biosite Diagnostics Inc., San Diego, CA, USA |
| Kitzman 2010 | Plasma | Radioimmunoassay, Phoenix Pharmaceuticals Inc.; Mountain View, Calif. |
| Kitzman 2016 | Plasma | Radioimmunoassay, Phoenix Pharmaceuticals |
| Kobayashi 2003 | ? | Radioimmunoassay |
| Malfatto 2009 | Serum | Triage BNP test, Biosite Ltd, Belfast, United Kingdom |
| Nishi 2011 | Plasma | Immunoradiometric assay for human BNP using a commercial kit, Shionoria |
| Norman 2012 | Plasma | Commercially available immunoflurometric assay , Triage BNP, Biosite Diagnostics, San Diego CA |
| Parrinello 2009 | Plasma | Immunoradiometric assay, Triage; Biosite Diagnostics |
| Passino 2006 | Plasma | BNP was measured by a two-site Immunoradiometric Assay, Shionogi, Japan |
| Passino 2008 | Plasma | BNP was measured by a two-site Immunoradiometric Assay, Shionogi, Japan |
| Stevens 2015 | Plasma | ADVIA Centaur, Siemens Medical Solutions Diagnostics, Munich, Germany |
| Yamamoto 2007 | ? | ? |
| Yeh 2004 | Whole Blood | Fluorescence immunoassay, Biosite Triage BNP Test; San Diego, California |
| Yeh 2011 | Whole Blood | Fluorescence immunoassay, Biosite Triage BNP Test, Biosite Diagnostics, San Diego, California |
| **NT-proBNP** |  |  |
| Ahmad 2014 | Plasma | ELISA, Roche Diagnostics, Indianapolis, IN |
| Aksoy 2015 | Serum | Enzyme immunoassay kits, Biomedica, Bratislava, Slovakia |
| Antonicelli 2016 | Serum | ElectroChemiLuminescence Immunoassay, ECLIA-Cobas, Roche Diagnostics, Rotkreutz, CH |
| Berendoncks 2010 | Plasma | Sandwich immunoassay on Elecsys 2010, Roche Diagnostics |
| Conraads 2004 | Plasma | Sandwich immunoassay on an Elecsys 2010, Roche diagnostics, Mannheim, Germany |
| Conraads 2007 | Plasma | Sandwich immunoassay on an Elecsys 2010, Roche Diagnostics GmbH, Mannheim, Germany |
| Delagardelle 2008 | Serum | Sandwich immunoassay using electro-Chemiluminescence detection on a Modular E170, Roche Diagnostics, Mannheim, Germany |
| Edelmann 2011 | Serum | Commercially available Elecsys proBNP sandwich immunoassay, Elecsys 2010 analyser, Roche Diagnostics, Mannheim, Germany |
| Eleuteri 2013 | Serum | Modular Analytics, Roche Diagnostics |
| Guazzi 2012 | Plasma | ? |
| Krishna 2014 | Serum | Commercially available ELISA kit , Uscn Life Science Inc. |
| Meyer 2004 | Serum | ElectroChemiLuminescence using the automated assay of Roche Diagnostics (Elecsys®proBNP). |
| Nilsson 2010 | Plasma | Elecsys proBNP sandwich immunoassay on Elecsys 2010, Roche Diagnostics, Indianapolis, IN, USA. |
| Palau 2014 | Serum | ? |
| Passino 2006 | Plasma | Measured with an automated electro chemiluminescent immunoassay. |
| Sandri 2012 | Serum | ElectroChemiLuminescence Immunoassay, ECLIA, Roche Diagnostics, Mannheim, Germany) |
| Sarullo 2006 | Plasma | Immunoassay, Roche Diagnostics, Branchburg, New Jersey, USA, was determined on an Elecsys 2010. |
| Wisloff 2007 | Plasma | enzyme immunoassays, Roche Diagnostics, Indianapolis, Ind. |
| **Galectin-3** |  |  |
| Billebeau 2017 | Plasma | ARCHITECT Galectibn-3 assay, Abbott Laboratories, Abbot Park, Il, USA |
| Fernandes-Silva 2017 | Serum | Milliplex MAP kits using Luminex TM xMAP technology, EMD Millipore Corporation, Germany. |
| **sST2** |  |  |
| Billebeau 2017 | Plasma | Test Presage ST2, Critical Diagnostics, San Diego CA, USA |
| **MR-proANP & MT-proADM** |  |  |
| Billebeau 2017 | Plasma | B.R.A.H.M.S. MR-proADM and MR-proANP KRYPTOR, Thermo Fisher Scientific |
| Trippel 2017 | Serum | BRAHMS Kryptor Assays, Thermo Fisher Scientific Clinical Diagnostics B · R · A · H ·M· S GmbH, Hennigsdorf, Germany |
| **CT-proAVP** |  |  |
| Trippel 2017 | Serum | BRAHMS Kryptor Assays, Thermo Fisher Scientific Clinical Diagnostics B · R · A · H ·M· S GmbH, Hennigsdorf, Germany |

**Supplementary Table S5** Sensitivity Analysis using the leave-one-out approach

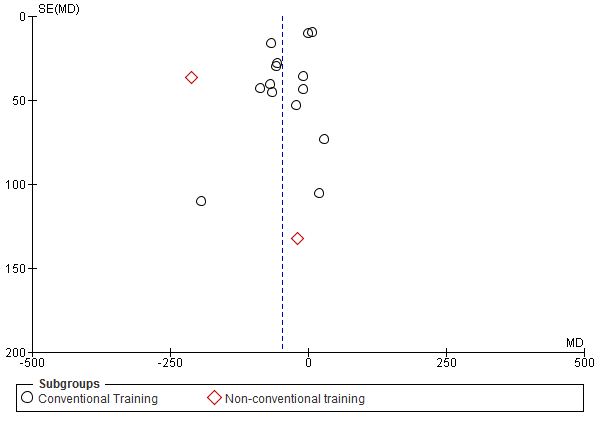
|  |  |  |
| --- | --- | --- |
| **Study removed** | **MD (95% CI)** | ***p*-value** |
| **BNP (pmol/L)** |  |  |
| ***Conventional*** | **-17.17 (-29.56, -4.78)** | **0.007** |
| Butterfield 2008 | -16.86 (-29.86, -3.87) | 0.01 |
| Fu 2013 | -15.64 (-28.79, -2.50) | 0.02 |
| Gary 2011 | -21.79 (-28.91, -14.67) | <0.00001 |
| Jonsdottir 2006 | -19.18 (-32.43, -5.94) | 0.005 |
| Kobayashi 2003 | -17.45 (-30.31, -4.59) | 0.008 |
| Malfatto 2009 | -13.60 (-26.67, -0.53) | 0.04 |
| Nishi 2011 | -15.59 (-27.61, -3.57) | 0.01 |
| Norman 2012 | -17.82 (-31.51, -4.12) | 0.01 |
| Parrinello 2009 | -16.72 (-32.83, -0.60) | 0.04 |
| Passino 2006/2008 | -16.67 (-32.13, -1.22) | 0.03 |
| Stevens 2015 | -16.95 (-29.79, -4.11) | 0.01 |
| ***Non-conventional*** | **-9.92 (-28.03, 8.20)** | **0.28** |
| Karavidas 2008 | -8.91 (-34.77, 16.95) | 0.50 |
| Kato 2017 | -8.26 (-32.05, 15.52) | 0.50 |
| Kawauchi 2017 | -18.28 (-35.05, -1.52) | 0.03 |
| Yeh 2004 | -4.34 (-20.24, 11.56) | 0.59 |
| **NT-proBNP (pmol/L)** |  |  |
| ***Conventional*** | **-32.80 (-56.19, -9.42)** | **0.006** |
| Aksoy 2015 | -54.62 (-74.36, -34.87) | <0.00001 |
| Conraads 2004 | -30.60 (-55.17, -6.03) | 0.01 |
| Conraads 2007 | -34.57 (-59.20, -9.94) | 0.006 |
| Delagardelle 2008 | -35.45 (-59.97, -10.93) | 0.005 |
| Guazzi 2012 | -22.84 (-43.81, -1.86) | 0.03 |
| Meyer 2004 | -35.06 (-59.98, -10.13) | 0.006 |
| Passino 2006/2008 | -30.45 (-54.87, -6.03) | 0.01 |
| Sandri 2012 | -27.53 (-51.75, -3.32) | 0.03 |
| Sarullo 2006 | -30.70 (-53.60, -7.80) | 0.009 |
| Wisloff 2007 | -31.28 (-56.44, -6.12) | 0.01 |
| **Non-conventional** | **-157.47 (-327.64, 12.70)** | **0.07** |
| Krishna 2014 | -19.54 (-277.83, 238.75) | 0.88 |
| Marco 2013 | -212.12 (-283.62, -140.62) | <0.00001 |

**Supplementary Table S6** Assessment of study quality and reporting using TESTEX

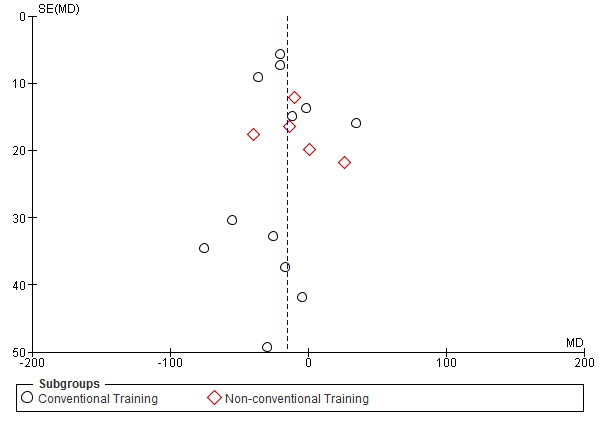
|  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Study | Eligibility Criteria specified | Randomisation details specified | Allocation concealed | Groups similar at baseline | Assessors blinded | Outcome measures assessed >85% participants# | ITT | Reporting between group statistical comparison\* | Point measures & measures of variability | Activity monitoring in control group | Relative exercise intensity reviewed | Exercise volume & EE | Overall TESTEX (/15) |
| ***RCTs*** |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Ahmad (2014)(1) | 1 | 1 | 1 | 1 | 1 | 2 | 0 | 2 | 1 | 0 | 1 | 0 | 11 |
| Aksoy (2015) | 1 | 1 | 0 | 1 | 0 | 0 | 0 | 2 | 1 | 0 | 0 | 1 | 7 |
| Antonicelli (2016) | 1 | 1 | 0 | 1 | 0 | 3 | 0 | 2 | 1 | 0 | 0 | 0 | 9 |
| Brubaker (2009) | 1 | 0 | 0 | 1 | 1 | 2 | 0 | 2 | 1 | 0 | 0 | 1 | 9 |
| Butterfield (2008) | 0 | 0 | 0 | 1 | 0 | 2 | 0 | 2 | 1 | 0 | 0 | 0 | 6 |
| Conraads (2007) | 1 | 0 | 0 | 1 | 0 | 2 | 0 | 2 | 1 | 0 | 1 | 0 | 8 |
| Delagardelle (2008) | 1 | 0 | 0 | 1 | 0 | 2 | 1 | 2 | 1 | 0 | 0 | 0 | 8 |
| Edelmann (2011) | 1 | 1 | 1 | 1 | 0 | 3 | 0 | 2 | 1 | 0 | 1 | 0 | 11 |
| Eleuteri (2013) | 1 | 0 | 0 | 1 | 0 | 3 | 1 | 2 | 1 | 0 | 1 | 1 | 11 |
| Fernandes-Silva (2017) | 1 | 1 | 1 | 1 | 0 | 0 | 0 | 2 | 1 | 0 | 1 | 0 | 8 |
| Fu (2013) | 1 | 0 | 0 | 1 | 0 | 2 | 0 | 2 | 1 | 0 | 1 | 1 | 9 |
| Gary (2011) | 1 | 1 | 0 | 1 | 0 | 3 | 1 | 2 | 1 | 0 | 1 | 1 | 12 |
| Guazzi (2012) | 1 | 1 | 0 | 1 | 0 | 1 | 1 | 0 | 1 | 0 | 1 | 0 | 7 |
| Jonsdottir (2006) | 1 | 0 | 0 | 1 | 0 | 2 | 0 | 2 | 1 | 0 | 0 | 0 | 7 |
| Karavidas (2008) | 1 | 1 | 1 | 1 | 1 | 2 | 1 | 2 | 1 | 0 | 0 | 0 | 11 |
| Karavidas (2013) | 1 | 1 | 1 | 1 | 1 | 2 | 1 | 2 | 1 | 0 | 0 | 0 | 11 |
| Kawauchi (2017) | 1 | 1 | 1 | 1 | 0 | 1 | 0 | 2 | 1 | 0 | 0 | 0 | 8 |
| Kitzman (2010) | 1 | 0 | 0 | 1 | 1 | 3 | 1 | 2 | 1 | 0 | 0 | 1 | 11 |
| Kitzman (2016) | 1 | 1 | 1 | 1 | 1 | 3 | 0 | 2 | 1 | 0 | 0 | 0 | 11 |
| Kobayashi (2003) | 1 | 0 | 0 | 1 | 0 | 3 | 1 | 2 | 1 | 0 | 0 | 0 | 9 |
| Krishna (2014) | 1 | 1 | 1 | 1 | 1 | 0 | 0 | 2 | 1 | 0 | 0 | 0 | 8 |
| Malfatto (2009) | 1 | 0 | 0 | 1 | 0 | 1 | 1 | 2 | 1 | 0 | 1 | 0 | 8 |
| Marco (2013) | 1 | 1 | 1 | 1 | 1 | 2 | 1 | 2 | 1 | 0 | 0 | 0 | 11 |
| Meyer (2004) | 1 | 0 | 0 | 1 | 0 | 1 | 0 | 2 | 1 | 0 | 1 | 0 | 7 |
| Nilsson (2010) | 1 | 1 | 0 | 1 | 0 | 2 | 0 | 1 | 1 | 0 | 0 | 0 | 7 |
| Norman (2012) | 1 | 0 | 0 | 1 | 0 | 3 | 0 | 2 | 1 | 0 | 0 | 0 | 9 |
| Palau (2014) | 1 | 0 | 0 | 1 | 1 | 2 | 0 | 2 | 1 | 0 | 0 | 0 | 8 |
| Parrinello (2009) | 1 | 0 | 0 | 1 | 0 | 1 | 1 | 2 | 1 | 0 | 0 | 0 | 7 |
| Passino (2006) | 1 | 0 | 0 | 1 | 1 | 1 | 0 | 2 | 1 | 0 | 1 | 0 | 8 |
| Passino (2008) | 1 | 0 | 0 | 1 | 1 | 2 | 0 | 2 | 1 | 0 | 1 | 0 | 9 |
| Sandri (2012) | 1 | 1 | 0 | 1 | 0 | 3 | 1 | 2 | 1 | 0 | 0 | 0 | 10 |
| Sarullo (2006) | 1 | 1 | 1 | 1 | 1 | 3 | 0 | 2 | 1 | 0 | 0 | 0 | 11 |
| Stevens (2015) | 1 | 0 | 0 | 1 | 0 | 2 | 0 | 2 | 1 | 0 | 0 | 0 | 7 |
| Trippel (2016) (2) | 1 | 1 | 1 | 1 | 0 | 3 | 0 | 2 | 1 | 0 | 0 | 0 | 10 |
| Wisloff (2007) | 1 | 1 | 1 | 1 | 0 | 3 | 0 | 2 | 1 | 0 | 1 | 0 | 11 |
| Yeh (2004) | 1 | 1 | 1 | 1 | 0 | 2 | 1 | 2 | 1 | 1 | 0 | 0 | 11 |
| Yeh (2011) | 1 | 1 | 1 | 1 | 1 | 3 | 1 | 2 | 1 | 0 | 0 | 0 | 12 |
| ***Non- Randomised/Retrospective*** |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Berendoncks (2010) | 1 | 0 | 0 | 1 | 1 | 1 | 0 | 2 | 1 | 0 | 0 | 0 | 7 |
| Billebeau (2017) | 1 | 0 | 0 | 1 | 0 | 1 | 0 | 2 | 1 | 0 | 1 | 0 | 7 |
| Conraads (2004) | 1 | 0 | 0 | 1 | 0 | 1 | 0 | 2 | 1 | 0 | 0 | 0 | 6 |
| Nishi (2011) | 1 | 0 | 0 | 1 | 0 | 2 | 0 | 2 | 1 | 0 | 0 | 0 | 7 |
| Yamamoto (2007) | 1 | 0 | 0 | 1 | 0 | 2 | 0 | 2 | 1 | 1 | 0 | 0 | 8 |

Key: total out of 15 points. Legend: #three points possible—one point if adherence >85%, one point if adverse events reported, one point if exercise attendance is reported. \*Two points possible—one point if primary outcome is reported, one point if all other outcomes reported. TESTEX, Tool for the assessment of Study quality and reporting in Exercise. 0 awarded if no mention was made of this criteria or if it was unclear whether criteria was meet. If ITT was not specifically mentioned, but it was noted that no participants withdrew and all analysed 1 point was awarded.

**Fig. S1a Funnel Plot NT-proBNP**



**Fig. S1b Funnel Plot BNP**



**Example Search Strategy**

|  |  |
| --- | --- |
| EMBASE |  |
| 1 | ‘heart failure’: ab, ti, kw |
| 2 | ‘exercise’: ab, kw |
| 3 | ‘exercise’/exp OR ‘exercise’ |
| 4 | ‘aerobic exercise’/exp OR ‘aerobic exercise’ |
| 5 | ‘endurance training’/exp OR ‘endurance training’ |
| 6 | ‘resistance training’/exp OR ‘resistance training’ |
| 7 | ‘tai chi’/exp OR ‘tai chi’ |
| 8 | ‘yoga’/exp OR ‘yoga’ |
| 9 | ‘functional electrical stimulation’/exp OR ‘functional electrical stimulation’ |
| 10 | ‘neuromuscular electrical stimulation’/exp OR ‘neuromuscular electrical stimulation’ |
| 11 | ‘inspiratory muscle training’/exp OR ‘inspiratory muscle training’ |
| 12 | ‘respiratory muscle training’/exp OR ‘respiratory muscle training’ |
| 13 | ‘kinesiotherapy’/exp OR ‘kinesiotherapy’ |
| 14 | ‘physiotherapy’/exp OR ‘physiotherapy’ |
| 15 | ‘heart rehabilitation’/exp OR ‘heart rehabilitation’ |
| 16 | #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 |
| 17 | ‘biological marker’: kw |
| 18 | ‘biological marker’/exp OR ‘biological marker’ |
| 19 | ‘natriuretic factor’/exp OR ‘natriuretic factor’ |
| 20 | ‘brain natriuretic peptide’/exp OR ‘brain natriuretic peptide’ |
| 21 | ‘amino terminal pro brain natriuretic peptide’/exp OR ‘amino terminal pro brain natriuretic peptide’ |
| 22 | ‘atrial natriuretic peptide’/exp OR ‘atrial natriuretic peptide’ |
| 23 | ‘suppression of tumorigenicity 2’/exp OR ‘suppression of tumorigenicity 2’ |
| 24 | ‘soluble ST2 protein’/ exp OR ‘soluble ST 2 protein’ |
| 25 | ‘galectin 3’/exp OR ‘galectin 3’ |
| 26 | ‘troponin’/exp OR ‘troponin’ |
| 27 | ‘copeptin’/exp OR ‘copeptin’ |
| 28 | ‘adrenomedullin’/exp OR ‘adrenomedullin’ |
| 30 | #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 |
| 31 | #1 AND #16 AND #30 |