Supplemental Material

Data S1.

Supplemental Methods

Search strings

Pubmed

PubMed	
Chemotherapy	Anthracyclines[Mesh] OR Chemotherapy, Adjuvant[Majr:NoExp] OR Mitoxantrone[Mesh] OR doxorubicin[Title/Abstract] OR DOX[Title/Abstract] OR Adriamycin[Title/Abstract] OR Daunorubicin[Title/Abstract] OR Cerubidine[Title/Abstract] OR Idarubicin[Title/Abstract] OR Idamycin[Title/Abstract] OR Epirubicin[Title/Abstract] OR Ellence[Title/Abstract] OR Mitoxantrone[Title/Abstract] OR Novantrone[Title/Abstract]
Cardiotoxicity	Cardiotoxicity[MeSH Terms] OR Cardiovascular Diseases[Majr:NoExp] OR Heart Failure[Majr] OR cardiotoxicity[Title/Abstract] OR cardiomyopathy[Title/Abstract] OR cardiomyopathies[Title/Abstract] OR cardiotoxic[Title/Abstract] OR CTRCD[Title/Abstract] OR Cardiac Failure[Title/Abstract] OR Cardiac damage[Title/Abstract] OR Cardiac dysfunction[Title/Abstract] OR Cardiac myopathy[Title/Abstract] OR cardiac apoptosis[Title/Abstract] OR heart failure[Title/Abstract] OR heart toxicity[Title/Abstract] OR heart damage[Title/Abstract] OR heart dysfunction[Title/Abstract] OR myocardial failure[Title/Abstract] OR Myocardial toxicity[Title/Abstract] OR myocardial damage[Title/Abstract] OR myocardial dysfunction[Title/Abstract] OR "ventricular failure"[Title/Abstract] OR "ventricular toxicity"[Title/Abstract] OR "ventricular damage"[Title/Abstract] OR "ventricular dysfunction"[Title/Abstract] OR cardiomyocyte damage[Title/Abstract] OR cardiomyocyte toxicity[Title/Abstract] OR cardiomyocyte dysfunction[Title/Abstract] OR cardiomyocyte apoptosis[Title/Abstract] OR "cardiomyocytes damage"[Title/Abstract] OR "cardiomyocytes toxicity"[Title/Abstract] OR "cardiomyocytes apoptosis"[Title/Abstract] OR "cardiomyocytes dysfunction"[Title/Abstract] OR cardiac injury[Title/Abstract]

	OR heart failures[Title/Abstract] OR heart toxicities[Title/Abstract] OR "ventricular toxicities[Title/Abstract] OR myocardial oxidative damage[Title/Abstract] OR cardiac oxidative damage[Title/Abstract]
Exercise	Exercise[MeSH Terms] OR sports[MeSH Terms] OR Exercise Therapy[MeSH Terms] OR kinesiotherapy[Title/Abstract] OR walking[Title/Abstract] OR weight lifting[Title/Abstract] OR sport[Title/Abstract] OR sports[Title/Abstract] OR ((Physical[Title/Abstract] OR Aerobic[Title/Abstract] OR exercise[Title/Abstract] OR endurance[Title/Abstract] OR fitness[Title/Abstract] OR training[Title/Abstract]) AND (activity[Title/Abstract] OR exercise[Title/Abstract] OR therapy[Title/Abstract] OR program[Title/Abstract] OR training[Title/Abstract] OR conditioning[Title/Abstract] OR activities[Title/Abstract] OR exercises[Title/Abstract] OR therapies[Title/Abstract] OR programs[Title/Abstract] OR trainings[Title/Abstract])) OR ((Activity[Title/Abstract]) AND (program[Title/Abstract] OR conditioning[Title/Abstract])))

Embase

EmBase	
Chemotherapy	'anthracycline antibiotic agent'/exp OR 'cancer chemotherapy'/mj OR 'mitoxantrone'/de OR 'doxorubicin':ti,ab,kw OR 'DOX':ti,ab,kw OR 'Adriamycin':ti,ab,kw OR 'Daunorubicin':ti,ab,kw OR 'Cerubidine':ti,ab,kw OR 'Idarubicin':ti,ab,kw OR 'Idamycin':ti,ab,kw OR 'Epirubicin':ti,ab,kw OR 'Ellence':ti,ab,kw OR 'Mitoxantrone':ti,ab,kw OR 'Novantrone':ti,ab,kw
Cardiotoxicity	'Cardiotoxicity'/exp OR 'cardiovascular disease'/mj OR 'Heart Failure'/exp OR 'cardiotoxicity':ti,ab,kw OR 'cardiomyopathy':ti,ab,kw OR 'cardiomyopathies':ti,ab,kw OR 'cardiotoxic':ti,ab,kw OR 'CTRCD':ti,ab,kw OR 'Cardiac Failure':ti,ab,kw OR 'Cardiac damage':ti,ab,kw OR 'Cardiac dysfunction':ti,ab,kw OR 'Cardiac myopathy':ti,ab,kw OR 'cardiac apoptosis':ti,ab,kw OR 'heart failure':ti,ab,kw OR 'heart

	toxicity':ti,ab,kw OR 'heart damage':ti,ab,kw OR 'heart dysfunction':ti,ab,kw OR 'myocardial failure':ti,ab,kw OR 'Myocardial toxicity':ti,ab,kw OR 'myocardial damage':ti,ab,kw OR 'myocardial dysfunction':ti,ab,kw OR 'ventricular failure':ti,ab,kw OR 'ventricular toxicity':ti,ab,kw OR 'ventricular damage':ti,ab,kw OR 'ventricular dysfunction':ti,ab,kw OR 'cardiomyocyte damage':ti,ab,kw OR 'cardiomyocyte toxicity':ti,ab,kw OR 'cardiomyocyte dysfunction':ti,ab,kw OR 'cardiomyocyte apoptosis':ti,ab,kw OR 'cardiac injury':ti,ab,kw OR 'heart failures':ti,ab,kw OR 'heart toxicities':ti,ab,kw OR 'ventricular toxicities':ti,ab,kw OR 'myocardial oxidative damage':ti,ab,kw OR 'cardiac oxidative damage':ti,ab,kw
Exercise	'Exercise'/exp OR 'sport'/exp OR 'kinesiotherapy'/exp OR 'sport':ti,ab,kw OR 'sports':ti,ab,kw OR 'walking':ti,ab,kw OR 'weight lifting':ti,ab,kw OR (('Physical':ti,ab,kw OR 'Aerobic':ti,ab,kw OR 'exercise':ti,ab,kw OR 'endurance':ti,ab,kw OR 'fitness':ti,ab,kw OR 'training':ti,ab,kw) AND ('activity':ti,ab,kw OR 'exercise':ti,ab,kw OR 'therapy':ti,ab,kw OR 'program':ti,ab,kw OR 'training':ti,ab,kw OR 'conditioning':ti,ab,kw OR 'activities':ti,ab,kw OR 'exercises':ti,ab,kw OR 'therapies':ti,ab,kw OR 'programs':ti,ab,kw OR 'trainings':ti,ab,kw)) OR (('Activity':ti,ab,kw) AND ('program':ti,ab,kw OR 'conditioning':ti,ab,kw))

Cochrane

#1	MeSH descriptor: [Anthracyclines] this term only
#2	MeSh descriptor: [Chemotherapy, Adjuvant] this term only
#3	MeSh descriptor: [Mitoxantrone] this term only
#4	'doxorubicin' OR 'DOX' OR 'Adriamycin' OR 'Daunorubicin' OR 'Cerubidine' OR 'Idarubicin' OR 'Idamycin' OR 'Epirubicin' OR 'Ellence' OR 'Mitoxantrone' OR 'Novantrone'
#5	MeSh descriptor: [Cardiotoxicity] explode all trees
#6	MeSH descriptor: [Cardiovascular Diseases] this term only

#7	MeSH descriptor: [Heart Failure] explode all trees
#8	"cardiotoxicity" OR "cardiomyopathy" OR "cardiomyopathies" OR "cardiotoxic" OR "CTRCD" OR "Cardiac Failure" OR "Cardiac damage" OR "Cardiac dysfunction" OR "Cardiac myopathy" OR "cardiac apoptosis" OR "heart failure" OR "heart toxicity" OR "heart damage" OR "heart dysfunction" OR "myocardial failure" OR "Myocardial toxicity" OR "myocardial damage" OR "myocardial dysfunction" OR "ventricular failure" OR "ventricular toxicity" OR "ventricular damage" OR "ventricular dysfunction" OR "cardiomyocyte damage" OR "cardiomyocyte toxicity" OR "cardiomyocyte dysfunction" OR "cardiomyocyte apoptosis" OR "cardiomyocytes damage" OR "cardiomyocytes toxicity" OR "cardiomyocytes dysfunction" OR "cardiomyocytes apoptosis" OR "cardiac injury" OR "heart failures" OR "heart toxicities" OR "ventricular toxicities" OR "myocardial oxidative damage" OR "cardiac oxidative damage"
#9	MeSH descriptor: [Exercise] explode all trees
#10	MeSH descriptor: [Sports] explode all trees
#11	MeSH descriptor: [Exercise Therapy] explode all trees
#12	"sport" OR "sports" OR "walking" OR "weight lifting" OR "kinesiotherapy" OR (("Physical" OR "Aerobic" OR "exercise" OR "endurance" OR "fitness" OR "training") AND ("activity" OR "exercise" OR "therapy" OR "program" OR "training" OR "conditioning" OR "activities" OR "exercises" OR "therapies" OR "programs" OR "trainings")) OR (("Activity") AND ("program" OR "conditioning"))
Search	(#1 OR #2 OR #3 OR #4) AND (#5 OR #6 OR #7 OR #8) AND (#9 OR #10 OR #11 OR #12) in Trials

Data S2.

References of articles excluded on the basis of full-text screening

All conference abstracts are not shown.

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is this the explanation for the cytoprotection of the heart against oxidative stress-induced redox imbalance in comparison to skeletal muscle cells? *Cell Biochem Funct*. 2007;25:23–32.

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Data S3.

Risk of bias assessment

The risk of bias assessment for the human studies is presented in Figure 2a. The two studies by Kirkham et al.[19,20] were scored as one, since they made use of the same study population and largely the same methodology. These studies were scored as low risk of bias on all items. An exception was the item on performance bias which was scored as 'high', since blinding was not possible due to the nature of the intervention. For Ma, the items on selection bias were scored 'unclear', since no information on the randomization procedure was provided. Performance bias was scored as high risk of bias, similar to the reports by Kirkham et al. Since information on loss of participations was not adequately provided, the risk of attrition bias was rated as high. The item on selective reporting could not be assessed, as no pre-specified protocol was available.

The risk of bias assessment and reporting of quality indicators for the animal studies are presented in Figure 2b and Figure 2c, respectively. Many studies did not adequately report on important aspects of the methodology; hence most items were initially scored as 'unclear'. After contacting authors (response rate: 73%, n=29/40), 127 of the 'unclear' ratings were modified to either 'low' (*n*=109) or 'high' (*n*=18) risk of bias. Risk of selection bias, assessed via entries on random sequences generation, comparability of baseline characteristics and concealment of allocation, were scored low in approximately two-thirds of the studies, 'unclear' in about 25% and high in the remaining studies. Compared to other sources of bias, risk of performance bias comprising entries on random housing and blinding of the trial caregivers and researchers (when possible), was scored high in 14% and 35%, respectively. Risk of detection bias (random outcome assessment and blinding of outcome assessors) were scored relatively low. Drop-outs were inadequately reported in approximately one-fifth of the studies, leading to a high risk of attrition bias in these studies. The item on reporting bias, i.e. whether outcomes were selectively reported, was scored 'unclear' for all studies, since no-preregistered protocols were available.

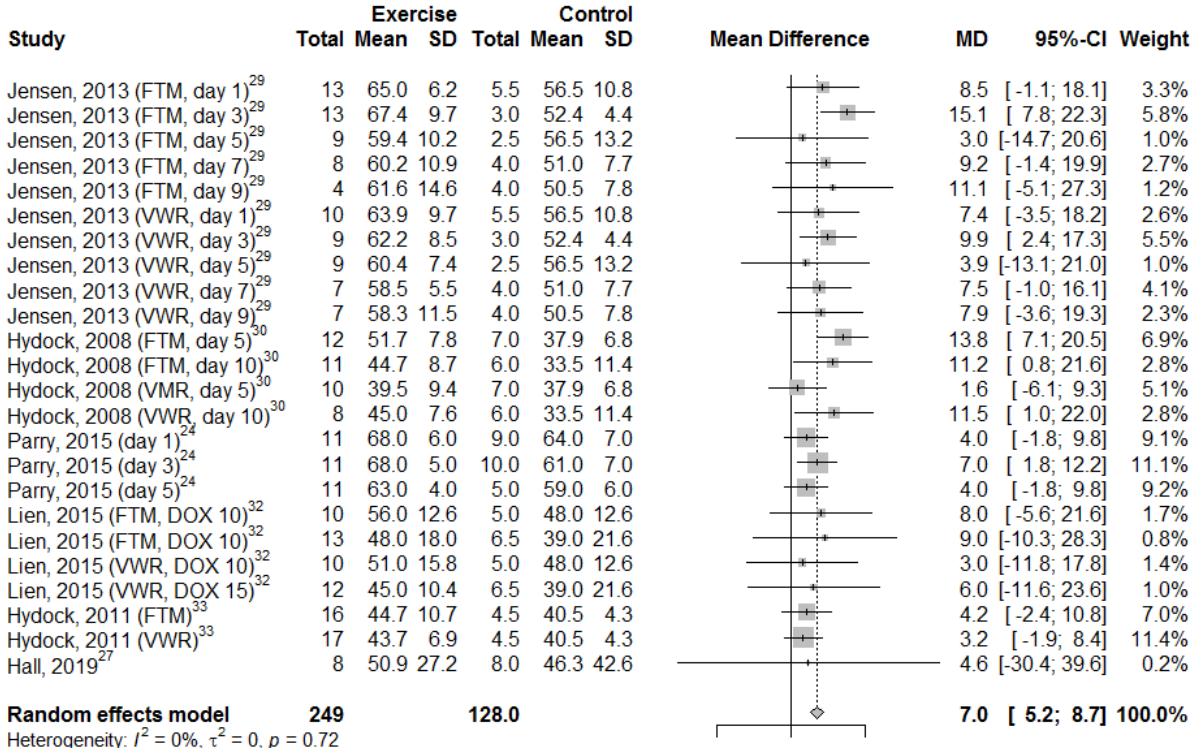
As for the reporting of methodology, none of the studies provided a sample size calculation, and many studies did not mention any form of blinding. Ethical approval was, however, reported in the vast majority of the studies.

Data S4.

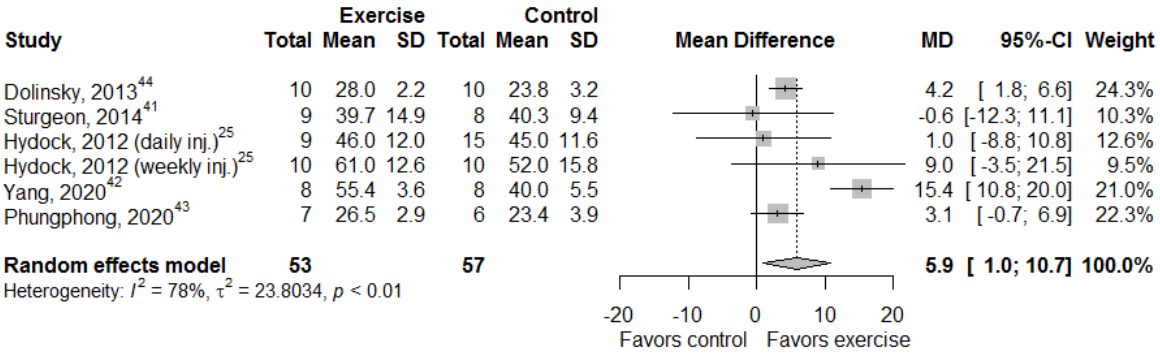
Sub-analysis on the timing of the physical exercise intervention

Forest plot (Figure S1) present the results of the preconditioning physical exercise interventions (i.e. started before DOX treatment) and plot (Figure S2)) presents the results of those interventions given concomitant with DOX administration.

1



2


Study
Exercise Total Mean SD
Control Total Mean SD
Mean Difference
MD 95%-CI Weight
Dolinsky, 2013[44] 10 28.0 2.2 10 23.8 3.2 4.2 [1.8; 6.6] 24.3%
Sturgeon, 2014[41] 9 39.7 14.9 8 40.3 9.4 -0.6 [-12.3; 11.1] 10.3%
Hydock, 2012 (daily inj.)[25] 9 46.0 12.0 15 45.0 11.6 1.0 [-8.8; 10.8] 12.6%
Hydock, 2012 (weekly inj.)[25] 10 61.0 12.6 10 52.0 15.8 9.0 [-3.5; 21.5] 9.5%
Yang, 2020[42] 8 55.4 3.6 8 40.0 5.5 15.4 [10.8; 20.0] 21.0%
Phungphong, 2020[43] 7 26.5 2.9 6 23.4 3.9 3.1 [-0.7; 6.9] 22.3%
Random effects model 53 57 5.9 [1.0; 10.7] 100.0%
Heterogeneity: I^2 = 78%, τ^2 = 23.8034, p < 0.01
-20 -10 0 10 20
Favors control
Favors exercise

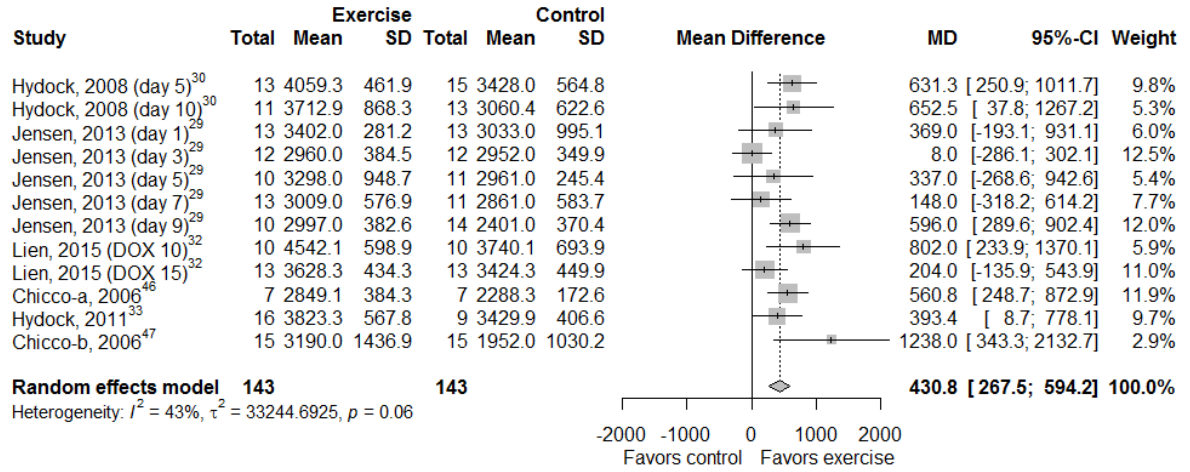
Data S5.

Results on +dP/dt and –dP/dt

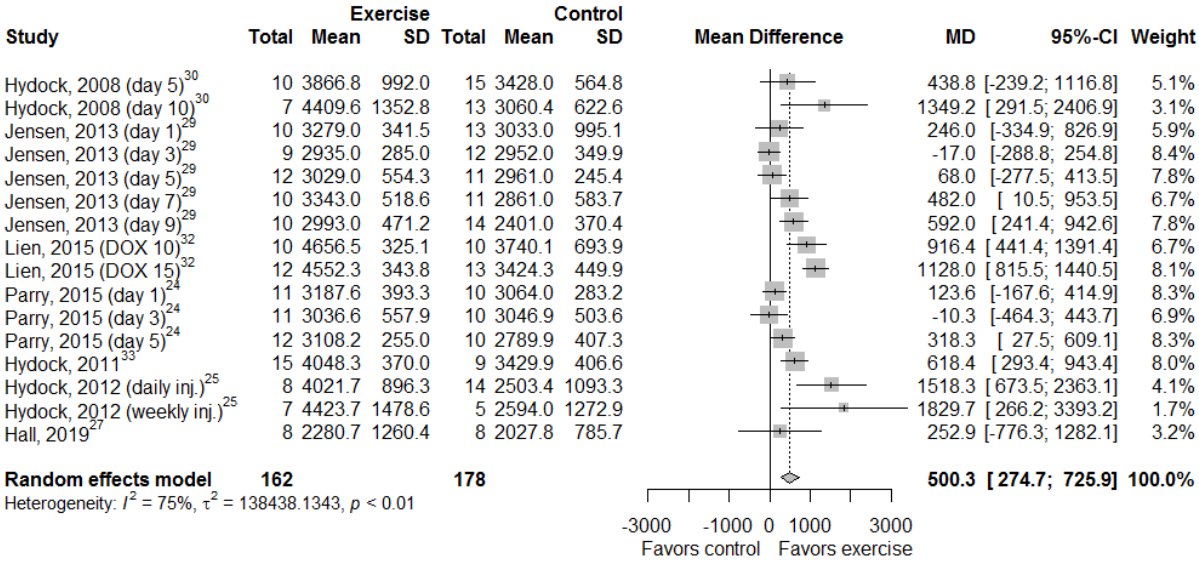
For both +dP/dt and –dP/dt, results are favoring physical exercise groups (Figures S3-S6). In +dp/dt, a pooled analysis of studies using forced exercise interventions demonstrated a MD of 430.8 mm Hg (95CI%: 267.5; 594.1), T^2=21392.1. Results were comparable, yet slighter stronger in the analysis on voluntary exercise interventions; MD of 500.3 mm Hg (95CI%: 274.7; 725.9), T^2=138438.2.

In –dP/dt, a MD of -374.5 (95%CI:-508.9; -240.1), T^2=20895.3, and -407.5 (9%CI: -596.9; -218.1) mm Hg was found for respectively forced and voluntary exercise interventions compared to non-exercised rodents.

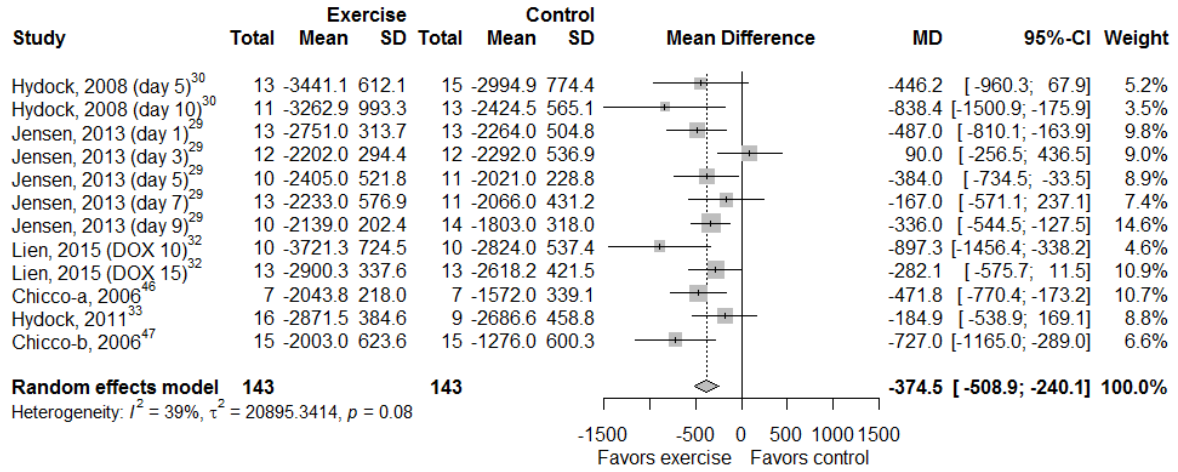
3


Exercise
Control
Study Total Mean SD Total Mean SD
Mean Difference
MD 95%-CI Weight
Hydock, 2008 (day 5)[30] 13 4059.3 461.9 15 3428.0 564.8 631.3 [250.9; 1011.7] 9.8%
Hydock, 2008 (day 10)[30] 11 3712.9 868.3 13 3060.4 622.6 652.5 [37.8; 1267.2] 5.3%
Jensen, 2013 (day 1)[29] 13 3402.0 281.2 13 3033.0 995.1 369.0 [-193.1; 931.1] 6.0%
Jensen, 2013 (day 3)[29] 12 2960.0 384.5 12 2952.0 349.9 8.0 [-286.1; 302.1] 12.5%
Jensen, 2013 (day 5)[29] 10 3298.0 948.7 11 2961.0 245.4 337.0 [-268.6; 942.6] 5.4%
Jensen, 2013 (day 7)[29] 13 3009.0 576.9 11 2861.0 583.7 148.0 [-318.2; 614.2] 7.7%
Jensen, 2013 (day 9)[29] 10 2997.0 382.6 14 2401.0 370.4 596.0 [289.6; 902.4] 12.0%
Lien, 2015 (DOX 10)[32] 10 4542.1 598.9 10 3740.1 693.9 802.0 [233.9; 1370.1] 5.9%
Lien, 2015 (DOX 15)[32] 13 3628.3 434.3 13 3424.3 449.9 204.0 [-135.9; 543.9] 11.0%
Chicco-a, 2006[46] 7 2849.1 384.3 7 2288.3 172.6 560.8 [248.7; 872.9] 11.9%
Hydock, 2011[33] 16 3823.3 567.8 9 3429.9 406.6 393.4 [8.7; 778.1] 9.7%
Chicco-b, 2006[47] 15 3190.0 1436.9 15 1952.0 1030.2 1238.0 [343.3; 2132.7] 2.9%
Random effects model 143 143 430.8 [267.5; 594.2] 100.0%
Heterogeneity: I^2 = 43%, τ^2 = 33244.6925, p = 0.06
-2000 -1000 0 1000 2000
Favors control Favors exercise

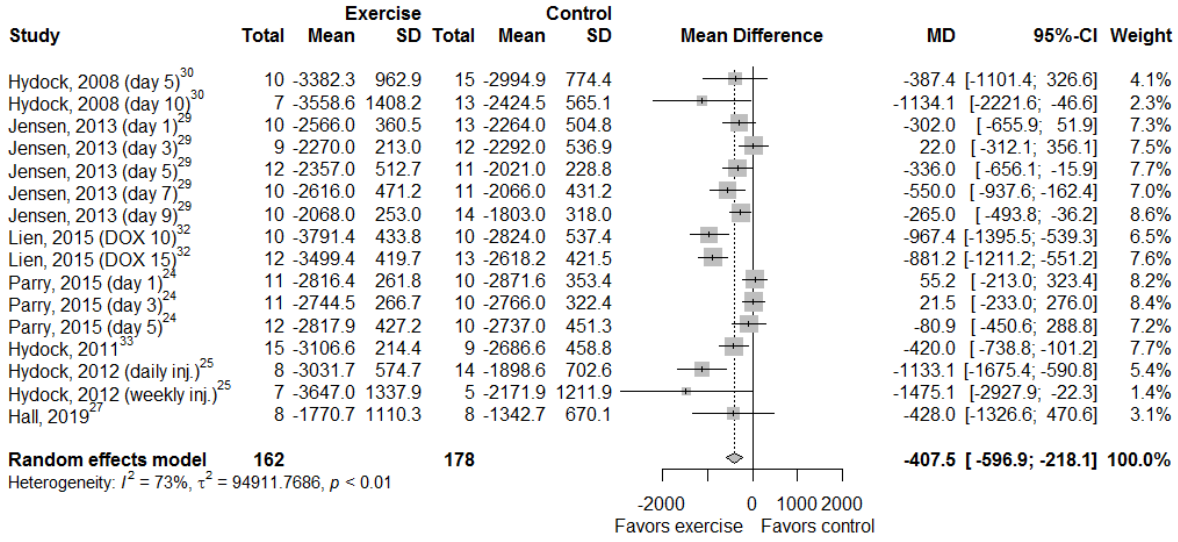
4


Exercise
Control
Study Total Mean SD Total Mean SD
Mean Difference
MD 95%-CI Weight
Hydock, 2008 (day 5)[30] 10 3866.8 992.0 15 3428.0 564.8 438.8 [-239.2; 1116.8] 5.1%
Hydock, 2008 (day 10)[30] 7 4409.6 1352.8 13 3060.4 622.6 1349.2 [291.5; 2406.9] 3.1%
Jensen, 2013 (day 1)[29] 10 3279.0 341.5 13 3033.0 995.1 246.0 [-334.9; 826.9] 5.9%
Jensen, 2013 (day 3)[29] 9 2935.0 285.0 12 2952.0 349.9 -17.0 [-288.8; 254.8] 8.4%
Jensen, 2013 (day 5)[29] 12 3029.0 554.3 11 2961.0 245.4 68.0 [-277.5; 413.5] 7.8%
Jensen, 2013 (day 7)[29] 10 3343.0 518.6 11 2861.0 583.7 482.0 [10.5; 953.5] 6.7%
Jensen, 2013 (day 9)[29] 10 2993.0 471.2 14 2401.0 370.4 592.0 [241.4; 942.6] 7.8%
Lien, 2015 (DOX 10)[32] 10 4656.5 325.1 10 3740.1 693.9 916.4 [441.4; 1391.4] 6.7%
Lien, 2015 (DOX 15)[32] 12 4552.3 343.8 13 3424.3 449.9 1128.0 [815.5; 1440.5] 8.1%
Parry, 2015 (day 1)[24] 11 3187.6 393.3 10 3064.0 283.2 123.6 [-167.6; 414.9] 8.3%
Parry, 2015 (day 3)[24] 11 3036.6 557.9 10 3046.9 503.6 -10.3 [-464.3; 443.7] 6.9%
Parry, 2015 (day 5)[24] 12 3108.2 255.0 10 2789.9 407.3 318.3 [27.5; 609.1] 8.3%
Hydock, 2011[33] 15 4048.3 370.0 9 3429.9 406.6 618.4 [293.4; 943.4] 8.0%
Hydock, 2012 (daily inj.)[25] 8 4021.7 896.3 14 2503.4 1093.3 1518.3 [673.5; 2363.1] 4.1%
Hydock, 2012 (weekly inj.)[25] 7 4423.7 1478.6 5 2594.0 1272.9 1829.7 [266.2; 3393.2] 1.7%
Hall, 2019[27] 8 2280.7 1260.4 8 2027.8 785.7 252.9 [-776.3; 1282.1] 3.2%
Random effects model 162 178 500.3 [274.7; 725.9] 100.0%
Heterogeneity: I^2 = 75%, τ^2 = 138438.1343, p < 0.01
-3000 -1000 0 1000 3000
Favors control Favors exercise

5


Exercise
Control
Study Total Mean SD Total Mean SD Mean Difference MD 95%-CI Weight
Hydock, 2008 (day 5)[30] 13 -3441.1 612.1 15 -2994.9 774.4 -446.2 [-960.3; 67.9] 5.2%
Hydock, 2008 (day 10)[30] 11 -3262.9 993.3 13 -2424.5 565.1 -838.4 [-1500.9; -175.9] 3.5%
Jensen, 2013 (day 1)[29] 13 -2751.0 313.7 13 -2264.0 504.8 -487.0 [-810.1; -163.9] 9.8%
Jensen, 2013 (day 3)[29] 12 -2202.0 294.4 12 -2292.0 536.9 90.0 [-256.5; 436.5] 9.0%
Jensen, 2013 (day 5)[29] 10 -2405.0 521.8 11 -2021.0 228.8 -384.0 [-734.5; -33.5] 8.9%
Jensen, 2013 (day 7)[29] 13 -2233.0 576.9 11 -2066.0 431.2 -167.0 [-571.1; 237.1] 7.4%
Jensen, 2013 (day 9)[29] 10 -2139.0 202.4 14 -1803.0 318.0 -336.0 [-544.5; -127.5] 14.6%
Lien, 2015 (DOX 10)[32] 10 -3721.3 724.5 10 -2824.0 537.4 -897.3 [-1456.4; -338.2] 4.6%
Lien, 2015 (DOX 15)[32] 13 -2900.3 337.6 13 -2618.2 421.5 -282.1 [-575.7; 11.5] 10.9%
Chicco-a, 2006[46] 7 -2043.8 218.0 7 -1572.0 339.1 -471.8 [-770.4; -173.2] 10.7%
Hydock, 2011[33] 16 -2871.5 384.6 9 -2686.6 458.8 -184.9 [-538.9; 169.1] 8.8%
Chicco-b, 2006[47] 15 -2003.0 623.6 15 -1276.0 600.3 -727.0 [-1165.0; -289.0] 6.6%
Random effects model 143 143 -374.5 [-508.9; -240.1] 100.0%
Heterogeneity: I^2 = 39%, τ^2 = 20895.3414, p = 0.08
-1500 -500 0 500 1000 1500
Favors exercise Favors control

6


Exercise
Control
Study Total Mean SD Total Mean SD Mean Difference MD 95%-CI Weight
Hydock, 2008 (day 5)[30] 10 -3382.3 962.9 15 -2994.9 774.4 -387.4 [-1101.4; 326.6] 4.1%
Hydock, 2008 (day 10)[30] 7 -3558.6 1408.2 13 -2424.5 565.1 -1134.1 [-2221.6; -46.6] 2.3%
Jensen, 2013 (day 1)[29] 10 -2566.0 360.5 13 -2264.0 504.8 -302.0 [-655.9; 51.9] 7.3%
Jensen, 2013 (day 3)[29] 9 -2270.0 213.0 12 -2292.0 536.9 22.0 [-312.1; 356.1] 7.5%
Jensen, 2013 (day 5)[29] 12 -2357.0 512.7 11 -2021.0 228.8 -336.0 [-656.1; -15.9] 7.7%
Jensen, 2013 (day 7)[29] 10 -2616.0 471.2 11 -2066.0 431.2 -550.0 [-937.6; -162.4] 7.0%
Jensen, 2013 (day 9)[29] 10 -2068.0 253.0 14 -1803.0 318.0 -265.0 [-493.8; -36.2] 8.6%
Lien, 2015 (DOX 10)[32] 10 -3791.4 433.8 10 -2824.0 537.4 -967.4 [-1395.5; -539.3] 6.5%
Lien, 2015 (DOX 15)[32] 12 -3499.4 419.7 13 -2618.2 421.5 -881.2 [-1211.2; -551.2] 7.6%
Parry, 2015 (day 1)[24] 11 -2816.4 261.8 10 -2871.6 353.4 55.2 [-213.0; 323.4] 8.2%
Parry, 2015 (day 3)[24] 11 -2744.5 266.7 10 -2766.0 322.4 21.5 [-233.0; 276.0] 8.4%
Parry, 2015 (day 5)[24] 12 -2817.9 427.2 10 -2737.0 451.3 -80.9 [-450.6; 288.8] 7.2%
Hydock, 2011[33] 15 -3106.6 214.4 9 -2686.6 458.8 -420.0 [-738.8; -101.2] 7.7%
Hydock, 2012 (daily inj.)[25] 8 -3031.7 574.7 14 -1898.6 702.6 -1133.1 [-1675.4; -590.8] 5.4%
Hydock, 2012 (weekly inj.)[25] 7 -3647.0 1337.9 5 -2171.9 1211.9 -1475.1 [-2927.9; -22.3] 1.4%
Hall, 2019[27] 8 -1770.7 1110.3 8 -1342.7 670.1 -428.0 [-1326.6; 470.6] 3.1%
Random effects model 162 178 -407.5 [-596.9; -218.1] 100.0%
Heterogeneity: I^2 = 73%, τ^2 = 94911.7686, p < 0.01
-2000 0 1000 2000
Favors exercise Favors control