

1 **Supplemental material: Understanding the effectiveness of different exercise training programme**
2 **designs on $\dot{V}O_{2peak}$ in COPD: a component network meta-analysis**

3

4 *Supplementary methods*

5 Exercise intensity was categorised into low, moderate and high intensity as detailed previously (very
6 high intensity in our previous classification was combined into the high intensity group due to
7 limited numbers) [1].

8

9 *Supplementary results*

10 Model 1 included 50 controlled trials involving 1899 participants. Of these, 19 were trials of aerobic
11 training versus usual care or structured education in isolation, 28 were controlled trials in which
12 both arms performed aerobic training in different forms or with different “add-ons”, and three
13 studies had three arms (one compared aerobic training with aerobic training plus inspiratory muscle
14 training versus usual care, one compared lower limb aerobic training with and without the addition
15 of arm cycling versus usual care and one compared addition of either oxygen or helium hyperoxia
16 compared to aerobic training in isolation).

17 Model 2 included 30 studies involving 1210 participants. Of these, 17 were trials of aerobic training
18 versus usual care or structured education in isolation, 10 were controlled trials comparing different
19 forms of aerobic training and three were studies with three arms comparing two different forms of
20 aerobic training with usual care.

21 In model 1, lower limb aerobic training (SMD 0.56 95% CI 0.32;0.81, intervention arms = 86), non-
22 invasive ventilation (NIV) during exercise (SMD 0.55 95% CI 0.04;1.06, intervention arms = 4) and
23 administration of ghrelin alongside exercise training (SMD 1.13 95% CI 0.13;2.14, intervention arms =
24 1) were the effective components at improving $\dot{V}O_{2peak}$ (Figure 2). No other component resulted in
25 significant improvement in $\dot{V}O_{2peak}$.

26 In model 2, moderate to high intensity continuous cycling and walking training modalities and high
27 intensity interval walking and cycling resulted in improvements in $\dot{V}O_{2peak}$ (all $p < 0.05$, Figure 3). There
28 were non-significant improvements in $\dot{V}O_{2peak}$ following water-based callisthenics (SMD 0.41 95% CI -
29 0.26;1.09, intervention arms = 1) and land-based callisthenics (SMD 0.38 95% CI -0.03;0.78,
30 intervention arms = 6). No improvements in $\dot{V}O_{2peak}$ were seen following moderate intensity interval
31 cycling however this was performed by one intervention group. Stair climbing (SMD -0.79 95% CI -
32 1.28;-0.31, intervention arms = 4) and low intensity continuous walking (SMD -0.43 95% CI -0.83;-
33 0.03, intervention arms = 2) appeared to have a detrimental effect on improvements in $\dot{V}O_{2peak}$.
34 Whilst high intensity training modalities resulted in the greatest increase in $\dot{V}O_{2peak}$, the differences
35 compared to moderate intensity training were not significant.

36 For model 1, a sensitivity analysis removing two unconnected studies did not significantly change the
37 results except eccentric cycling was removed from the model. Results did not change significantly
38 after removing two unconnected studies for model 2. Node splitting and examination of net heat
39 plots did not identify significant inconsistency between direct and indirect evidence for model 1 or 2
40 although the number of pairwise comparisons were low.

41 When limiting analysis to RCTs with low risk of bias for blinding of outcome assessors, 22 studies
42 remained in model 1 with aerobic training the only component with a significant impact on change

43 in $\dot{V}O_{2peak}$ (SMD 0.97 95%CI 0.12:1.82) and nine studies remained in model 2 with high intensity
44 continuous walking and high intensity continuous cycling the only components with a significant
45 impact on change in $\dot{V}O_{2peak}$ (SMD 0.94 95%CI 0.02:1.86 and SMD 1.10 95%CI 0.31:1.88). When
46 limiting analysis to studies with high quality of reporting (Consensus on Exercise Reporting Template
47 score ≥ 12), 19 studies remained in model 1 with aerobic training and ghrelin the only components
48 with significant impact on change in $\dot{V}O_{2peak}$ (SMD 0.56 95%CI 0.13:0.99 and SMD 1.13 95%CI
49 0.04:2.22) and 11 studies remained in model 2 with high intensity continuous cycling and high
50 intensity interval walking the only components with a significant impact on change in $\dot{V}O_{2peak}$ (SMD
51 0.77 95%CI 0.31:1.22 and SMD 1.11 95%CI 0.03:2.19).

52 For model 1, when using a conservative estimate of the correlation coefficient, the effect of the
53 addition of vitamin supplementation to lower limb aerobic training became significant (SMD 0.65
54 95%CI 0.04:1.27) but the results were otherwise unchanged. Using a conservative estimate of the
55 correlation coefficient did not affect the results of model 2.

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235 **eTable 1** - Description of included controlled trials

Study	Group 1 components	Group 2 components	Group 3 components	n	Age	Group 1				Group 2				Group 3			
						Gender (M:F)	FEV ₁ (%pred)	n	Age	Gender (M:F)	FEV ₁ (%pred)	n	Age	Gender (M:F)	FEV ₁ (%pred)	n	Age
Baumann, 2012 [2]	HIIW + Callisthenics + stair climbing + ULRT + Education + Breathing retraining	Usual care		37	63 (11)	23:14	47 (13)	44	65 (8)	24:20	45 (13)						
Borgh-Silva, 2009 [3]	HICW	Usual care		20	67 (10)	13:7	33 (9)	14	67 (10)	12:8	35 (11)						
Borgh-Silva, 2015 [4]	HICW	Usual care		10	67 (7)	7:3	32 (11)	10	66 (10)	5:5	35 (12)						
Duruturk, 2016 [5]	HICC + Education	Usual care	Callisthenics + Education	15	61 (5)	11:4	58 (14)	13	64 (6)	11:2	64 (11)	14	61 (5)	13:1	57(10)		
Emery, 1998 [6]	MICC + MICW + Education + arm cycling	Usual care		25	65 (6)	15:15	43(18)	25	67 (7)	12:13	39 (16)						
Gohl, 2006 [7]	MICC + MICW + ULRT+ LLRT + Education	Usual care		19	63 (7)	6:4	53 (11)	9	63 (9)	7:2	54 (6)						
Lake, 1990 [8]	MICW	Usual care	MICW + arm cycling	6	72 (3)	6:0		7	66 (4)	6:1		7	66 (7)	4:3			
Larson, 1999 [9]	MICC	Usual care	MICC + IMT	14	66 (6)		46 (17)	12	62 (7)		55 (18)	14	68 (6)		46 (17)		
Reardon, 1994 [10]	MICC + MICW + stair climbing + ULRT + Education + IMT + Breathing retraining	Usual care		10	66 (8)	5:5	35 (10)	10	66 (7)	5:5	33 (15)						
Ries, 1995 [11]	MICW + ULRT + Education + Breathing retraining + arm cycling	Education		53	61.5 (8)	42:15		57	64 (6)	45:17							
Troosters, 2000 [12]	HICC + HICW + stair climbing + ULRT + LLRT + arm cycling	Usual care		34	60 (9)	31:6	41 (16)	28	63 (7)	30:3	43 (12)						
Wijkstra, 1996 [13]	HICC + ULRT + Education + IMT + Breathing retraining	Usual care		28	64 (5)	23:5	44 (11)	15	62 (5)	14:1	45 (9)						
Zambom-Ferraresi, 2015 [14]	MICC + ULRT + LLRT	Usual care		14	68 (7)	14:0	44 (12)	8	69 (5)	8:0	40 (5)						

Covey, 2014 [15]	HIIC	HIIC + LLRT		27	68 (7)	25:2	39 (9)	28	68 (8)	24:4	41 (10)			
Gigliotti, 2003 [16] (crossover study)	HICC + ULRT + Education	Usual care		20	64 (8)	18:2	42 (12)							
Leite, 2015 [17]	HIIW	Usual care		10	62 (IQR 60-69)		55 (IQR 39-70)	6	62.5 (IQR 57-71)		45 (IQR 38-74)			
O'Donnell, 1995 [18]	HICC + HICW + stair climbing +Breathing retraining + arm cycling	Usual care		30	66 (6)	20:10	38	30	69 (6)	23:7	38			
Serres, 1997 [19]	HIIC + MICW	Usual care		8	60 (2)		49 (12)	6	70 (3)		68 (23)			
Vogiatzis, 1999 [20]	MICC + MICW + Education	Usual care		60	64 (1)	38:22	55 (3)	15	56 (3)	32:28	55 (5)			
Wen, 2008 [21]	MICW	Usual care	HICC	15	67 (7)	14:1	46 (10)	9	66 (10)	9:0	52 (14)	17	68 (7)	17:0 50 (14)
Wadell, 2004 [22]	Callisthenics	Usual care	Water based Callisthenics	14	65 (7)	5:10	53 (12)	12	63 (7)	7:6	49 (12)	15	65 (4)	4:11 56 (11)
Bernard, 1999 [23]	HICC + Breathing retraining	HICC + ULRT +LLRT		15	67 (9)	11:4	39 (12)	21	64 (7)	17:4	45 (15)			
Bianchi, 2002 [24]	MICC + ULRT + LLRT + Education	MICC + ULRT + LLRT + Education + NIV		10	65 (61-69)	10:0	40 (12)	9	64 (61-67)	9:0	48 (19)			
Blanco, 2013 [25]	HIIC + ULRT	HIIC + ULRT + sildenafil		31	65 (8)	26:5	31 (10)	29	66 (8)	28:1	33 (12)			

Borghi-Silva, 2010 [26]	HICW + NIV	HICW + oxygen	14	68 (9)	9:5	34 (10)	14	67 (7)	9:5	33 (7)
Broekhuizen, 2005 [27]	MICC + MICW + swimming	MICC + MICW + swimming + PUFA	32	62 (8)	35:16	36 (15)	31	64 (10)	36:15	38 (15)
Bronstad, 2013 [28]	HICW	MICW	10	65 (8)	7:3	55 (9)	7	65 (5)	5:2	50 (15)
Burdet, 1997 [29]	Moderate intensity exercise, modality unclear	Moderate intensity exercise, modality unclear + growth hormone	8	65 (8)	7:1	42 (12)	8	7:1	67 (10)	37 (15)
Carrieri-Kohlman, 1996 [30]	MICW	MICW + coaching	27	66 (9)	15:12	36 (10)	24	68 (7)	14:10	40 (11)
Costes, 2003 [31]	MICC	MICC + NIV	7	67 (6)	6:1	32 (7)	7	5:2	60 (7)	31 (12)
Creutzberg, 2003 [32]	MICC + MICW + swimming	MICC + MICW + swimming + anabolic steroids	28	67 (7)	28:0	33 (10)	28	28:0	66 (8)	38 (17)
Coppoolse, 1999 [33]	HICC + Callisthenics + Education	HIIC + Callisthenics + Education	10	67 (3)	10:0	37 (18)	9	63 (8)	9:0	36 (10)
Dekhuijzen, 1991[34]	MICC + MICW + Callisthenics + Education + Breathing retraining	MICC + MICW + Callisthenics + Education + Breathing retraining + IMT	20	60 (7)	16:4	52 (17)	20	14:6	58 (8)	47 (14)
Delussu, 2014a [35]	Moderate intensity exercise, modality unclear	Moderate intensity exercise, modality unclear + resistance training, unspecified	35	71 (9)	14:21	61 (14)	30	18:12	74 (6)	59 (18)
Emtner, 2003 [36]	HICC + Education	HICC + Education + oxygen	15	67 (10)	10:5	38 (8)	14	8:6	66 (7)	35 (10)

Eves, 2009 [37]	MICC + LIW + resistance training, unspecified + Education	MICC + LIW + resistance training, unspecified + Education + Helium-hyperoxia	19	66 (7)	12:7		19	12:7	65 (9)	
Ferreira, 1998 [38]	HICC	HICC + anabolic steroids	7	66 (7)	7:0	49 (16)	10	10:0	70 (5)	41 (14)
Fichter, 1999 [39]	HICC	HICC + oxygen	5	59 (7)	5:0	46 (27)	5	5:0	58 (11)	41 (8)
Fuld, 2005 [40]	MICC + Callisthenics + Education	MICC + Callisthenics + Education + creatine	11	64 (10)	13:7	45 (16)	14	10:8	62 (8)	45 (14)
Hornikx, 2012 [41]	HICC + HICW + ULRT + LLRT + arm cycling + stair climbing	HICC + HICW + ULRT + LLRT + arm cycling + stair climbing + vitamin D	25	69 (6)	19:6	40 (10)	24	67 (8)	19:6	47 (18)
Mador, 2005 [42]	MICC + MICW + Education + Callisthenics	MICC + MICW + Education + Callisthenics + IMT	14	71 (8)		44 (13)	15	70 (8)		45 (21)
Mador, 2009 [43]	HIIC + HIIW + Education	MICC + HICW + Education	21	72 (7)		45 (14)	20	72 (8)		42 (13)
Miki, 2013 [44]	HIIC + Education	HIIC + Education + Ghrelin	10	73 (6)	9:1	33 (11)	10	71 (6)	10:0	32 (9)
Normandin, 2002 [45]	HICC + HICW + Education	Callisthenics + ULRT + Education	20	69 (7)	11:9	43 (16)	20	67 (9)	10:10	56 (20)
Reuveny, 2005 [46]	MICW	MICW + NIV	10	63 (9)	9:1	33 (9)	9	64 (9)	9:0	32 (4)
Rodriguez, 2016 [47]	HIIC	HICC	14	67 (9)	13:1	43 (15)	15	66 (7)	14:1	41 (10)
Rooyackers, 2003 [48]	HIIC + resistance training, unspecified + Education	HIIC + resistance training, unspecified + Education + Eccentric cycling	12	59 (13)	10:2	38 (11)	12	59 (10)	10:2	45 (13)

Scorsone, 2010 [49]	HICC	HICC + oxygen	HICC + Helium hyperoxia	10	68 (7)	7:3	50 (12)	10	67 (9)	7:3	47 (10)	10	67 (9)	9:1	49 (12)
Sivori, 1998 [50]	HICC	HICC + ULRT		14	63 (9)	12:2	35 (17)	14	66 (9)	11:3	37 (11)				
Spielmanns, 2015 [51]	HICC	HICC + oxygen		17	64 (8)		43 (12)	19	64 (8)		44 (10)				
Sykes, 2005 [52]	HICC + ULRT + Education	HICC + ULRT + Education + IMT		17	73 (7)	14:3	44 (12)	20	73 (7)	17:3	40 (13)				
Vallet, 1997 [53]	HIIC + Education	MIIC + Education		12	55 (3)	8:4	54	12	59 (3)	10:2	63				
Varga, 2007 [54]	HICC	HIIC		22	61 (12)	19:3	51 (16)	17	67 (10)	11:6	64 (29)				
Vogiatzis, 2002 [55]	HIIC + Education	MICC + Education		18	67 (2)	14:4	45 (4)	18	69 (2)	16:2	44 (4)				
Vogiatzis, 2005 [56]	HIIC + Education	HICC + Education		10	64 (9)	8:2	44 (19)	9	67 (6)	8:1	39 (18)				
Vonbank, 2012 [57]	HICC + Education	HICC + ULRT + LLRT + Education		12	62 (5)	8:4	58 (19)	12	59 (8)	9:3	51 (20)				
Wang, 2017 [58]	HICC	LIW	HICC + IMT	27	70 (6)		51 (18)	26	70 (6)		58 (19)	28	71 (5)		50 (16)
Wanke, 1994 [59]	HICC	HICC + IMT		21	57 (6)	10:11	48 (17)	21	55 (5)	12:9	44 (19)				

236 HIIC: High intensity interval cycling, HIIW: High intensity interval walking, HICC: High intensity continuous cycling, HICW: High intensity continuous walking,
 237 MIIC: Moderate intensity interval cycling, MICC: Moderate intensity continuous cycling, MICW: Moderate intensity continuous walking, LIW: Low intensity
 238 walking, PUFA: polyunsaturated fatty acids, IMT: inspiratory muscle training, ULRT: upper limb resistance training, LLRT: lower limb resistance training

239 **eTable 2** – Bias assessment for randomised controlled trials

240


Study	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective outcome reporting (reporting bias)	Other bias
Baumann (2012) [2]	Low	Unclear	High	Low	Low	Low	Low
Borghesi-Silva (2009) [3]	Unclear	Unclear	High	Unclear	High	Low	Low
Borghesi-Silva (2015) [4]	Low	Low	High	Low	Low	Low	Low
Duruturk (2016) [5]	Low	Low	High	Low	Low	Low	Low
Emery (1998) [6]	Low	Low	High	Low	Low	Low	Low
Gohl (2006) [7]	Low	Unclear	High	Unclear	High	Low	Low
Lake (1990) [8]	Unclear	Unclear	High	Unclear	Low	Low	Low
Larson (1999) [9]	Unclear	Unclear	High	Low	Unclear	Low	Low
Reardon (1994) [10]	Low	Unclear	High	Low	Unclear	Low	Low
Ries (1995) [11]	Low	Low	High	Unclear	Low	Low	Low
Troosters (2000) [12]	Low	Low	High	Unclear	Low	Low	Low
Wijkstra (1996) [13]	Unclear	Unclear	High	Unclear	Low	Low	Low
Zamboni-Ferraresi (2015) [14]	Unclear	Low	High	Low	Low	Low	Low
Bernard (1999)	Unclear	Unclear	High	Unclear	Low	Low	Low
Bianchi (2002)	Unclear	Unclear	High	High	High	Low	Low
Blanco (2013)	Unclear	Low	Low	Low	Low	Low	Low
Borghesi-Silva (2010)	Low	Low	High	Unclear	Low	Low	Low
Broekhuizen (2005)	Unclear	Unclear	Low	Low	Low	Low	Low
Bronstad (2013)	Low	Unclear	High	Unclear	High	Low	Low
Burdet (1997)	Unclear	Unclear	Low	Low	Unclear	Low	Low
Carrieri-Kohlman (1996)	Unclear	Unclear	High	Unclear	Low	Low	Low
Coppoolse (1999)	Low	Unclear	High	Unclear	Low	Low	Low
Costes (2003)	High	High	High	Unclear	Low	Low	Low
Covey (2014)	Low	Low	Low	Low	Low	Low	Low
Creutzberg (2003)	Unclear	Low	Low	Low	Low	Low	Low
Dekhuyzen (1991)	Unclear	Unclear	High	Unclear	Low	Low	Low
Delussu (2014)	Unclear	Unclear	High	Unclear	Unclear	Low	Low
Emtner (2003)	Unclear	Unclear	Low	Low	Low	Low	Low
Eves (2009)	Low	Low	Low	Low	High	Low	Low
Ferreira (1998)	Unclear	Unclear	Low	Low	High	Low	Low
Fichter (1999)	Unclear	Unclear	Low	Unclear	Low	Low	Low
Fuld (2005)	Unclear	Unclear	Low	Low	High	Low	Low
Hornikx (2012)	Low	Low	Low	Low	Low	Low	Low
Larson (1999)	Unclear	Unclear	High	Low	High	Low	Low
Mador (2005)	Unclear	Unclear	High	Unclear	Low	Low	Low
Mador (2009)	Unclear	Low	High	Unclear	Low	Low	Low
Miki (2013)	Low	Low	Low	Low	Low	Low	Low
Normandin (2002)	Unclear	Unclear	High	High	Low	Low	Low

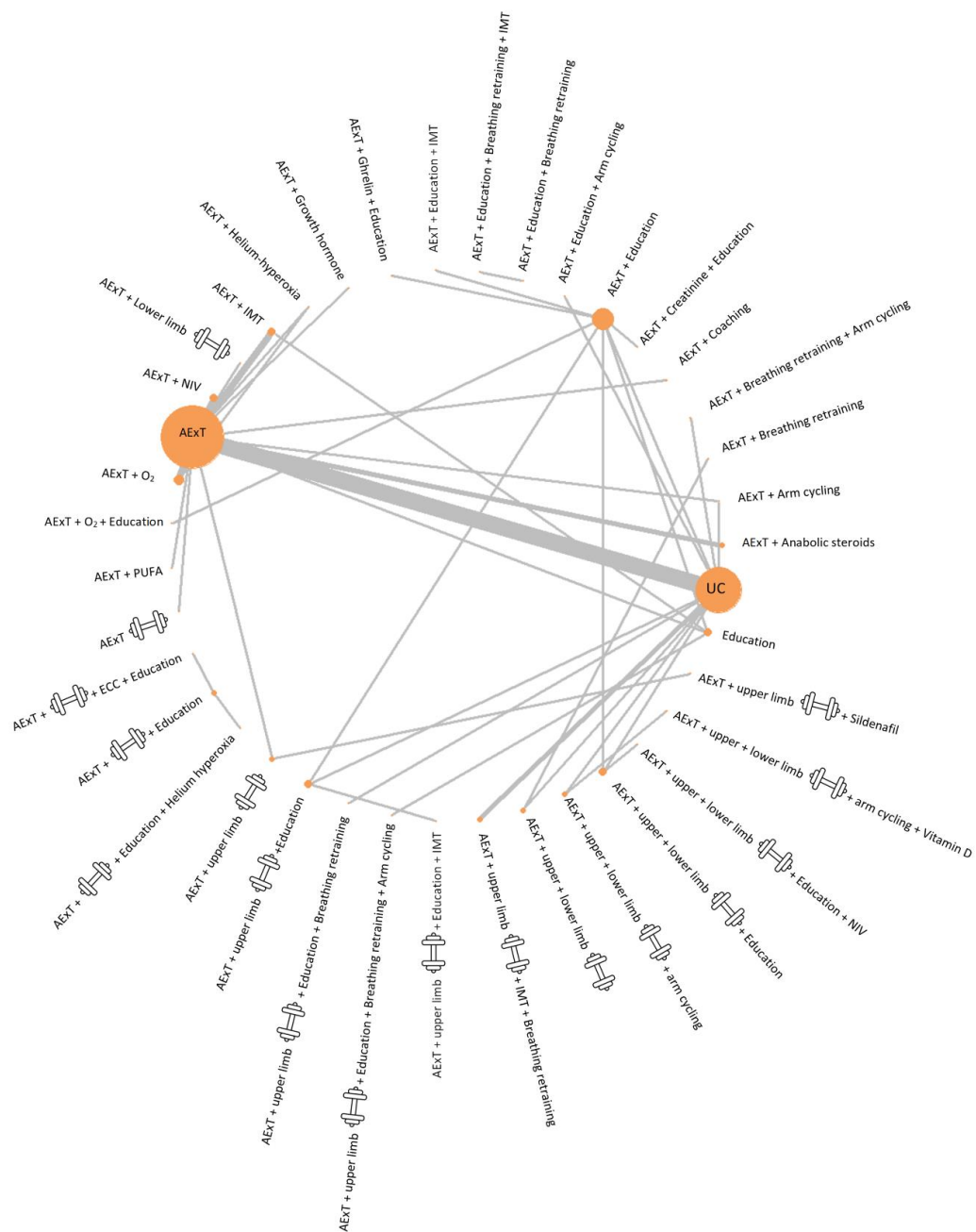
Reuveny (2005)	Low	Low	High	Low	Low	Low	Low
Rooyackers (2003)	Unclear	Unclear	High	Unclear	Unclear	Low	Low
Santos (2015)	Low	Low	High	High	Low	Low	Low
Scorsone (2010)	Unclear	Unclear	Low	Low	Low	Low	Low
Sivori (1998)	Low	Unclear	High	Unclear	High	Low	Low
Spielmanns (2015)	Low	Unclear	Low	High	High	Low	Low
Sykes (2005)	Unclear	Low	High	Low	Low	Low	Low
Vallet (1997)	Unclear	Unclear	Low	Low	Low	Low	Low
Vogiatzis (2002)	Unclear	Unclear	High	Unclear	Low	Low	Low
Vogiatzis (2005)	Unclear	Unclear	High	Unclear	Unclear	Low	Low
Vonbank (2012)	Unclear	Unclear	High	Unclear	Low	Low	Low
Wanke (1994)	Unclear	Unclear	High	Unclear	High	Low	Low
Wen (2008)	Low	Unclear	High	Unclear	High	Low	Low
Wang (2017)	Low	Low	High	Low	Low	Low	Low
Proportion: Low	40%	35%	29%	46%	65%	100%	100%
High	2%	2%	71%	8%	23%	0%	0%
Unclear	58%	63%	0%	46%	12%	0%	0%

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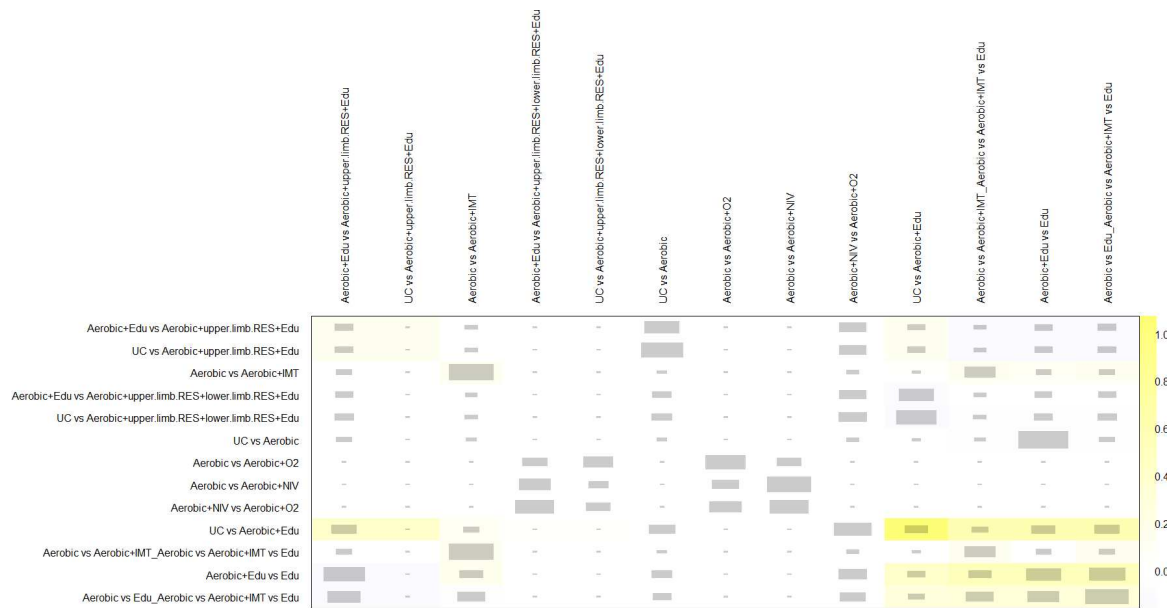
244 **Figure 1** – Network graph of programme components (model 1). : Resistance training, AExT:
245 Traditional lower limb aerobic training, ECC: Eccentric cycling, IMT: Inspiratory muscle training,
246 PUFA: polyunsaturated fatty acids, UC: Usual care. The size of the nodes is proportional to the
247 number of included studies and the thickness of the lines is proportional to the number of
248 comparisons.



249

250 **eFigure 2** – Net heat plot of model 1 once unconnected studies removed.

251 In this plot, the area of a grey square displays the contribution of the direct estimate of one design in
 252 the column to a network estimate in a row. The colours show the change in inconsistency when
 253 relaxing the assumption of consistency for the effects of single designs. The colours on the diagonal
 254 represent the inconsistency contribution of the corresponding design. The colours on the off-
 255 diagonal are associated with the change in inconsistency between direct and indirect evidence in a
 256 network estimate in the row after relaxing the consistency assumption for the effect of one design in
 257 the column. Cool colours (blue) indicate an increase and warm colours (yellow to orange to red) a
 258 decrease, colours in between (yellow) indicate no change: the stronger the intensity of the colour,
 259 the greater the difference between the inconsistency before and after the detachment.



260

261

262 **eFigure 3** – Net heat plot of model 2 once unconnected studies removed.

263 In this plot, the area of a grey square displays the contribution of the direct estimate of one design in
 264 the column to a network estimate in a row. The colours show the change in inconsistency when
 265 relaxing the assumption of consistency for the effects of single designs. The colours on the diagonal
 266 represent the inconsistency contribution of the corresponding design. The colours on the off-
 267 diagonal are associated with the change in inconsistency between direct and indirect evidence in a
 268 network estimate in the row after relaxing the consistency assumption for the effect of one design in
 269 the column. Cool colours (blue) indicate an increase and warm colours (yellow to orange to red) a
 270 decrease: the stronger the intensity of the colour, the greater the difference between the
 271 inconsistency before and after the detachment (yellow represents a low intensity of red i.e. mild
 272 inconsistency).



273

274