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

Supplementary methods

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

Supplementary results

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

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

In model 1, lower limb aerobic training (SMD 0.56 95% CI 0.32;0.81, intervention arms = 86), non-invasive ventilation (NIV) during exercise (SMD 0.55 95% CI 0.04;1.06, intervention arms = 4) and administration of ghrelin alongside exercise training (SMD 1.13 95% CI 0.13;2.14, intervention arms = 1) were the effective components at improving V̇O2peak (Figure 2). No other component resulted in significant improvement in V̇O2peak.

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

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

When limiting analysis to RCTs with low risk of bias for blinding of outcome assessors, 22 studies remained in model 1 with aerobic training the only component with a significant impact on change in $\dot{V}O_{2peak}$ (SMD 0.97 95%CI 0.12:1.82) and nine studies remained in model 2 with high intensity continuous walking and high intensity continuous cycling the only components with a significant 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 limiting analysis to studies with high quality of reporting (Consensus on Exercise Reporting Template score ≥12), 19 studies remained in model 1 with aerobic training and ghrelin the only components 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 0.04:2.22) and 11 studies remained in model 2 with high intensity continuous cycling and high intensity interval walking the only components with a significant impact on change in $\dot{V}O_{2peak}$ (SMD 0.77 95%CI 0.31:1.22 and SMD 1.11 95%CI 0.03:2.19).

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

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eTable 1 - Description of included controlled trials

Study	Group 1 components	Group 2 components	Group 3 components	n	Age	Gender (M:F)	FEV_1 (%pred)	n	Age	Gender (M:F)	FEV_1 (%pred)	n	Age	Gender (M:F)	FEV_1 (%pred)
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)				
Borghi-Silva, 2009 [3]	HICW	Usual care		20	67 (10)	13: 7	33 (9)	14	67 (10)	12:8	35 (11)				
Borghi-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)				

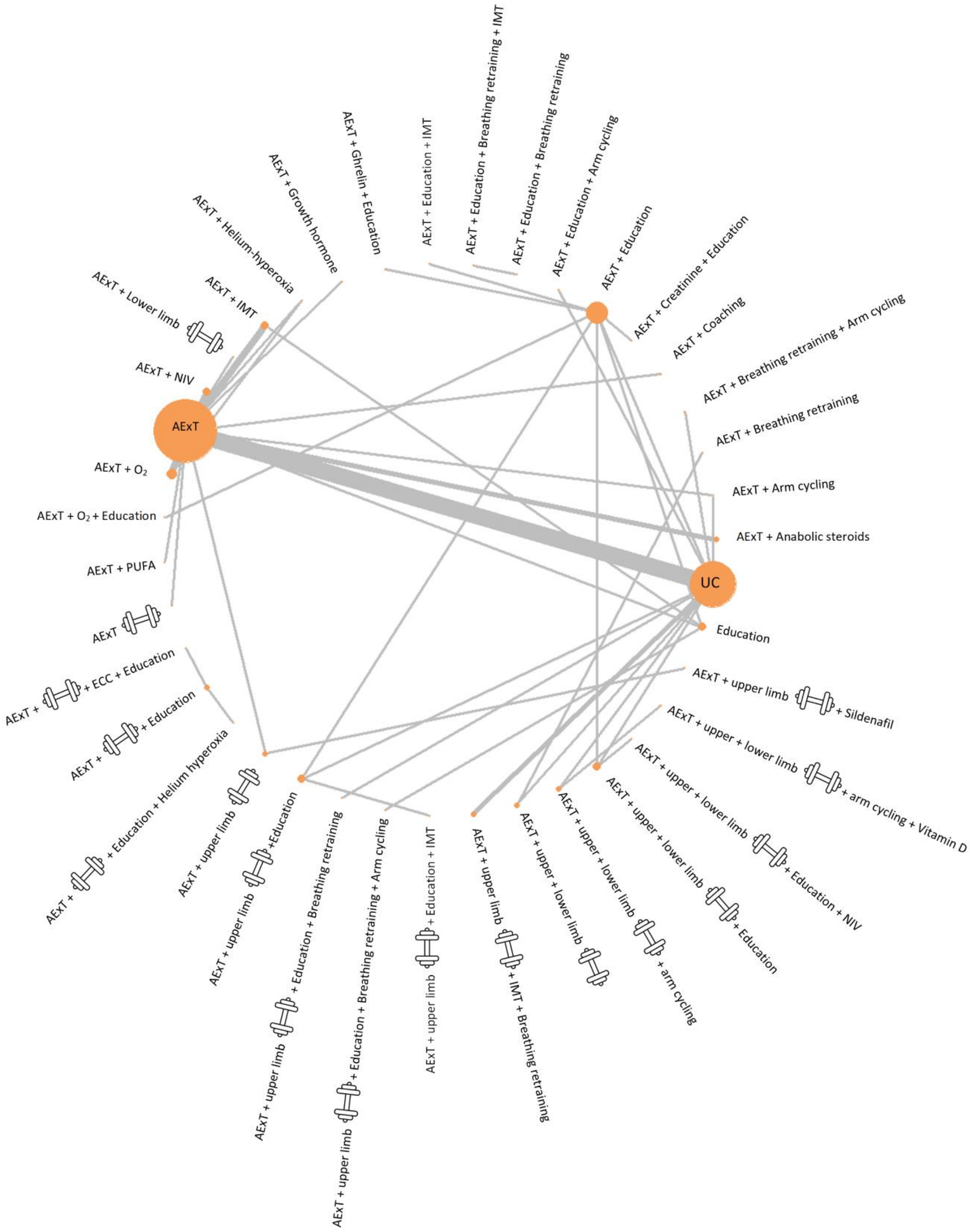
HIIC: High intensity interval cycling, HIIW: High intensity interval walking, HICC: High intensity continuous cycling, HICW: High intensity continuous walking, MIIC: Moderate intensity interval cycling, MICC: Moderate intensity continuous cycling, MICW: Moderate intensity continuous walking, LIW: Low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

eTable 2 – Bias assessment for randomised controlled trials

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
Borghi-Silva (2009) [3]	Unclear	Unclear	High	Unclear	High	Low	Low
Borghi-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
Zambom-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
Borghi-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
Dekhuijzen (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%

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



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

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

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

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