Supplementary Table S1: Database search strategy after retrieval of relevant SRs

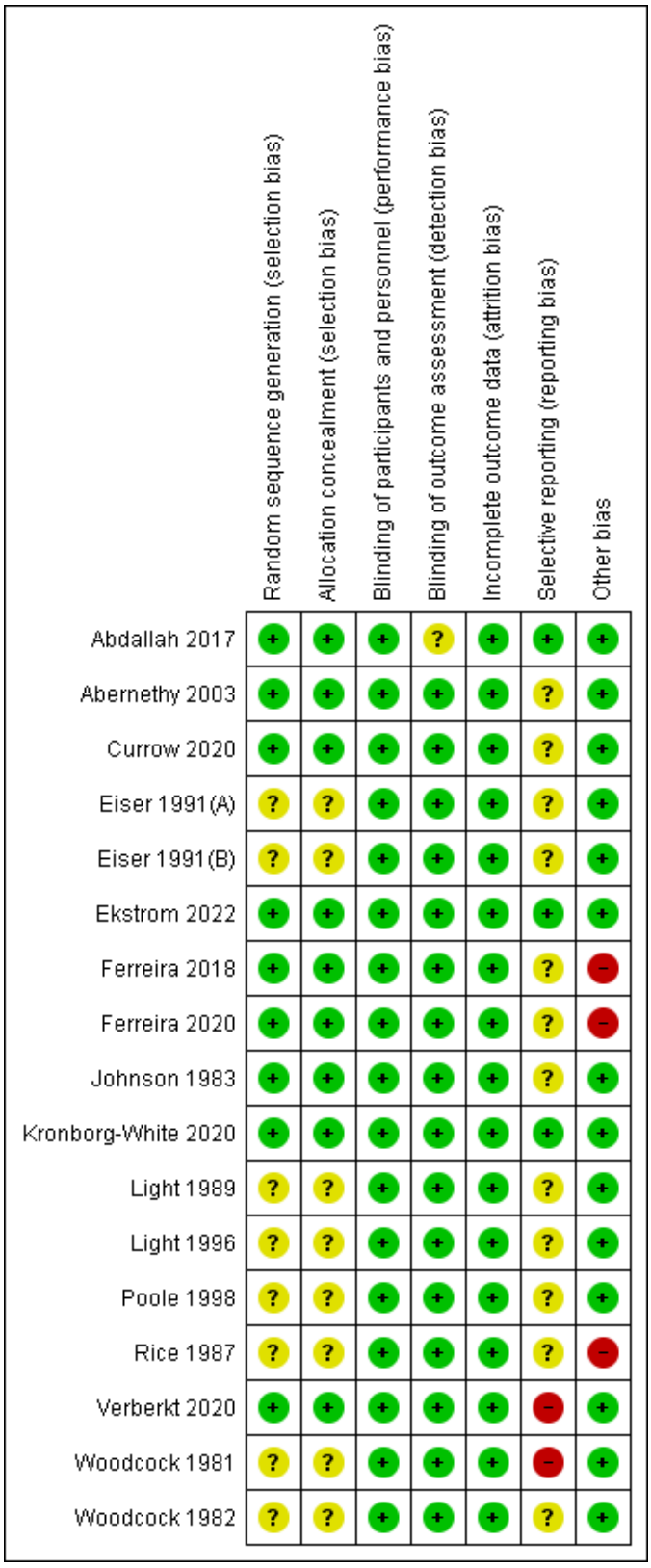
Disease group(s)	Date range	Database
COPD, ILD and bronchiectasis	1st January 2020 to 8th July 2022	MEDLINE, CENTRAL
COPD and bronchiectasis	1st January 2020 to 8th July 2022	EMBASE
ILD	1st January 2019 to 8th July 2022	EMBASE
CF	1st of January 2019 to 8th July 2022	MEDLINE, EMBASE, CENTRAL
PHT	1st January 2015 to 8th July 2022	MEDLINE, EMBASE, CENTRAL

Supplementary Table S2: Relevant prior systematic reviews

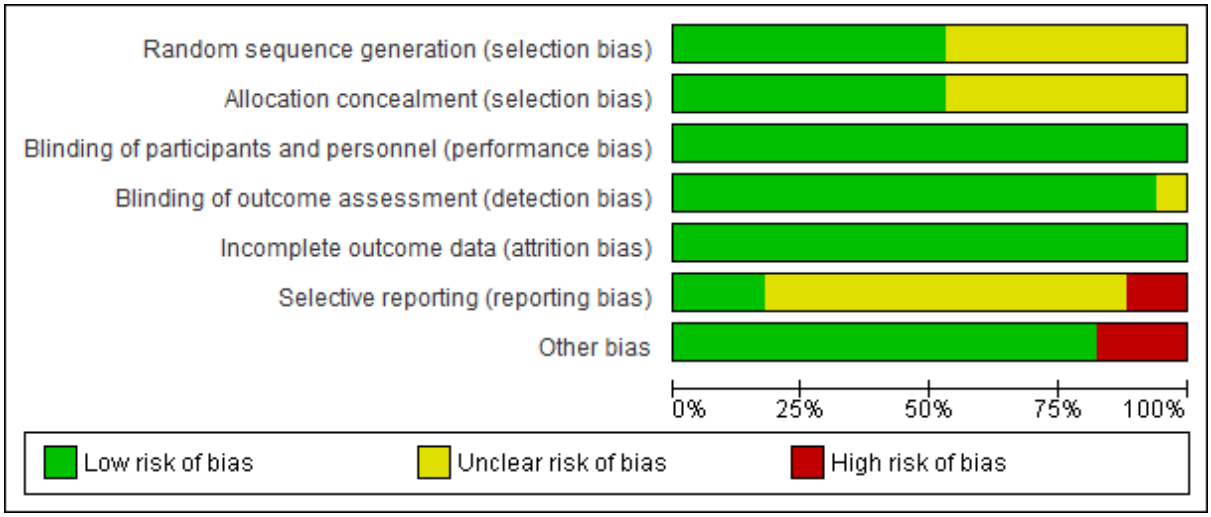
Prior Systematic Review	Relevant Studies
Bajwah, Colquitt [40]	None.
Barnes, McDonald [18]	Abernethy, Currow [51] Eiser, Denman [46] Johnson, Woodcock [47] Poole, Veale [54] Rice, Kronenberg [55] Woodcock, Gross [50]
Ekström, Nilsson [41]	Abernethy, Currow [51] Eiser, Denman [46] Johnson, Woodcock [47] Light, Stansbury [49] Poole, Veale [54] Woodcock, Gross [50] Woodcock, Johnson [56]
Jaiswal, Singh [39]	None.
Yamaguchi, Saif-Ur-Rahman [42]	Abdallah, Wilkinson-Maitland [45] Abernethy, Currow [51] Currow, Louw [31] Kronborg-White, Andersen [53]

	Eiser, Denman [46] Ferreira, Louw [52] Johnson, Woodcock [47] Kronborg-White, Andersen [53] Light, Muro [48] Light, Stansbury [49] Poole, Veale [54] Verberkt, Van Den Beuken-Van Everdingen [30] Woodcock, Gross [50] Woodcock, Johnson [56]
Total included relevant studies from prior systematic reviews	Abdallah, Wilkinson-Maitland [45] Abernethy, Currow [51] Currow, Louw [31] Eiser, Denman [46] Ferreira, Louw [52] Johnson, Woodcock [47] Kronborg-White, Andersen [53] Light, Muro [48] Light, Stansbury [49] Poole, Veale [54] Light, Stansbury [49]

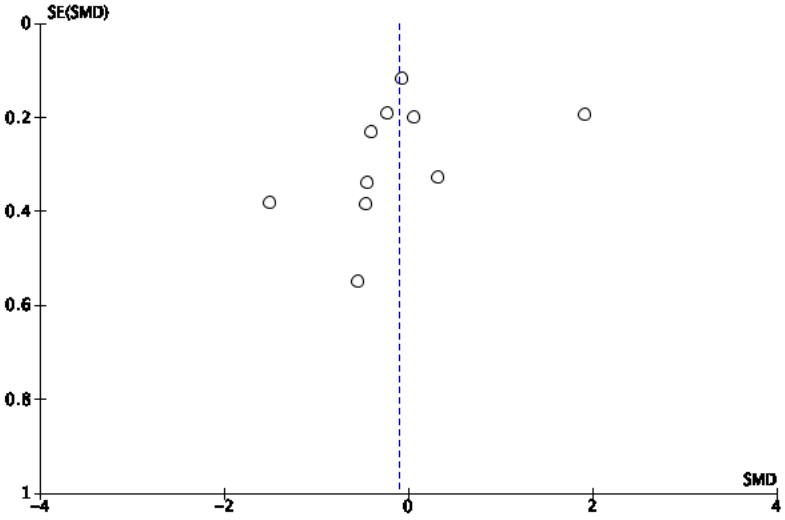
	Woodcock, Gross [50] Woodcock, Johnson [56] Verberkt, Van Den Beuken-Van Everdingen [30]



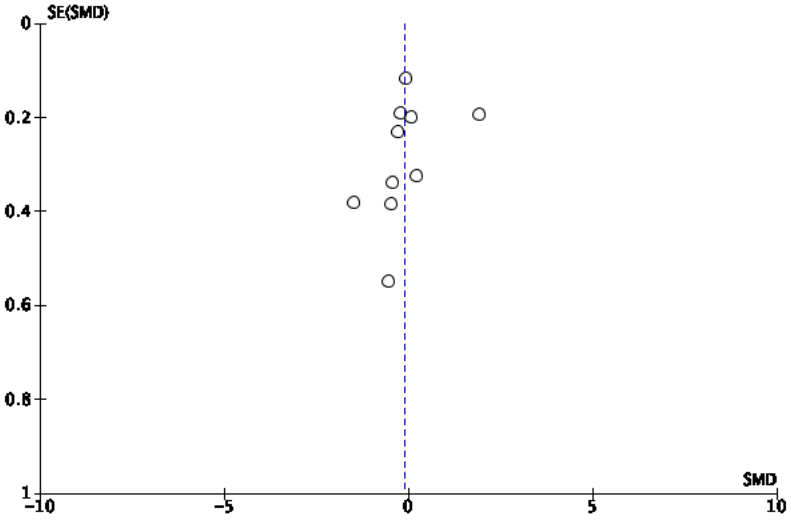
Supplementary Figure S1: Risk of Bias Summary



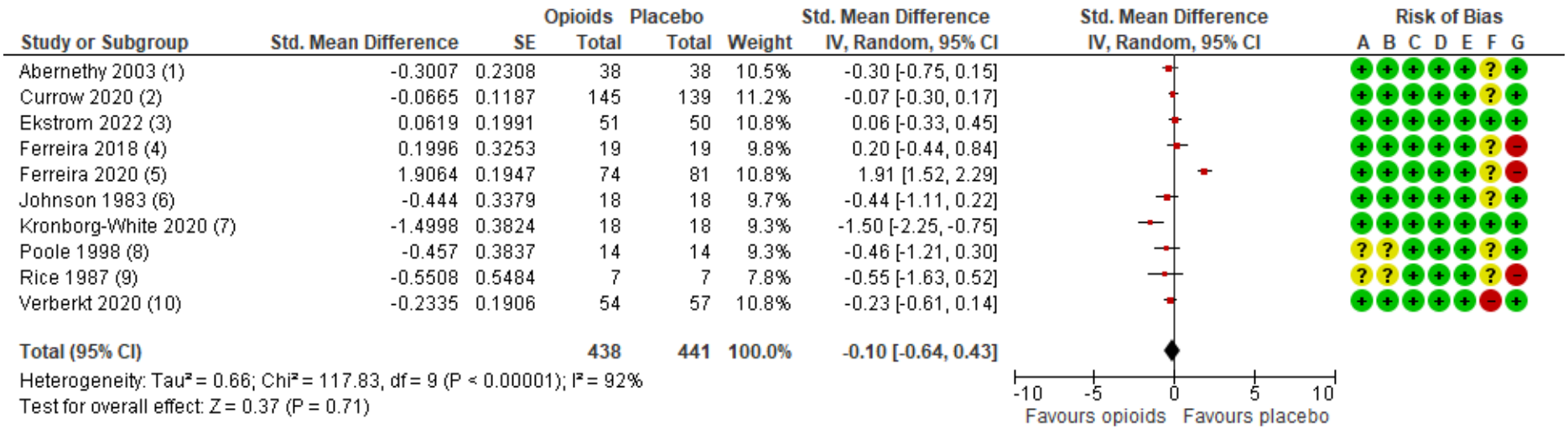
Supplementary Figure S2: Risk of bias domains



Supplementary Figure S3: Funnel plot for at home studies reporting breathlessness pragmatically during daily life



Supplementary Figure S4: Funnel plot for at home studies reporting breathlessness pragmatically during daily life using morning scores when available



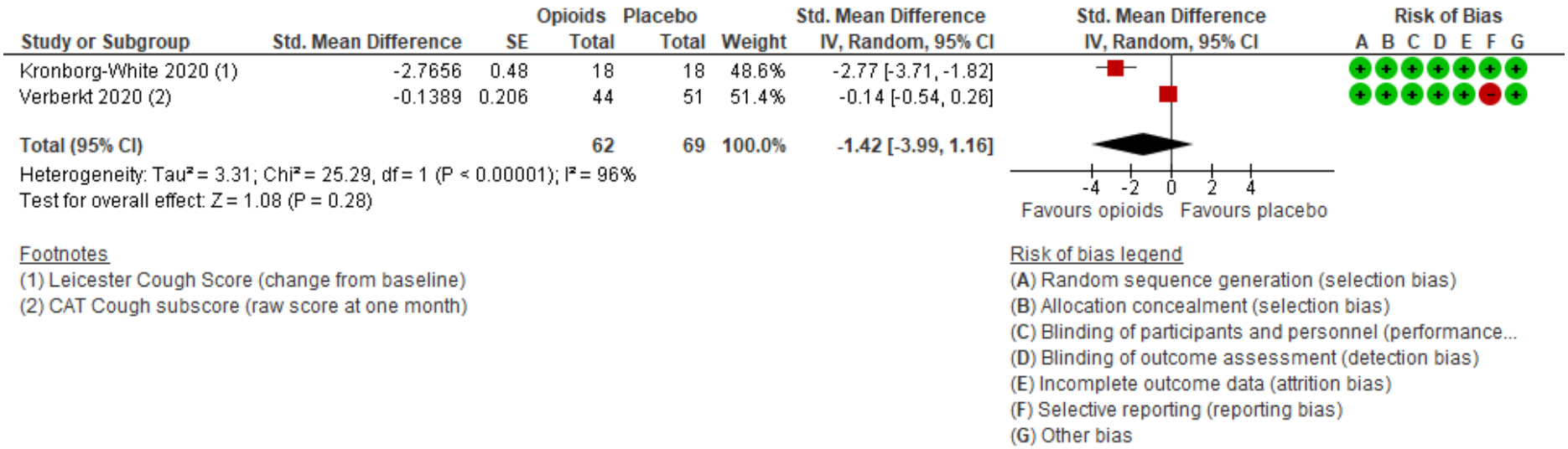
Footnotes

(1) 10cm VAS breathlessness intensity (final morning relative to baseline)
(2) 10cm VAS breathlessness intensity NOW (days 5-7 average of mean morning/evening scores relative to...
(3) NRS intensity of breathlessness (16mg/day dose, days 5 to 7 average scores relative to days -3 to -1 average..
(4) 10cm VAS breathlessness intensity NOW (final evening score relative to baseline)
(5) 10cm VAS breathlessness intensity NOW (days 5-7 average of mean morning/evening scores relative to...
(6) 10cm VAS breathlessness (final early evening relative to baseline from alternating weeks period)
(7) 10cm VAS breathlessness during LAST HOUR (change from baseline to followup)
(8) CRQ Dyspnea subscale (change from baseline to 6-weeks)
(9) 10cm VAS breathlessness during PAST 24 HOURS (change from baseline to followup)
(10) NRS over PAST 24 HOURS (change from baseline to followup)

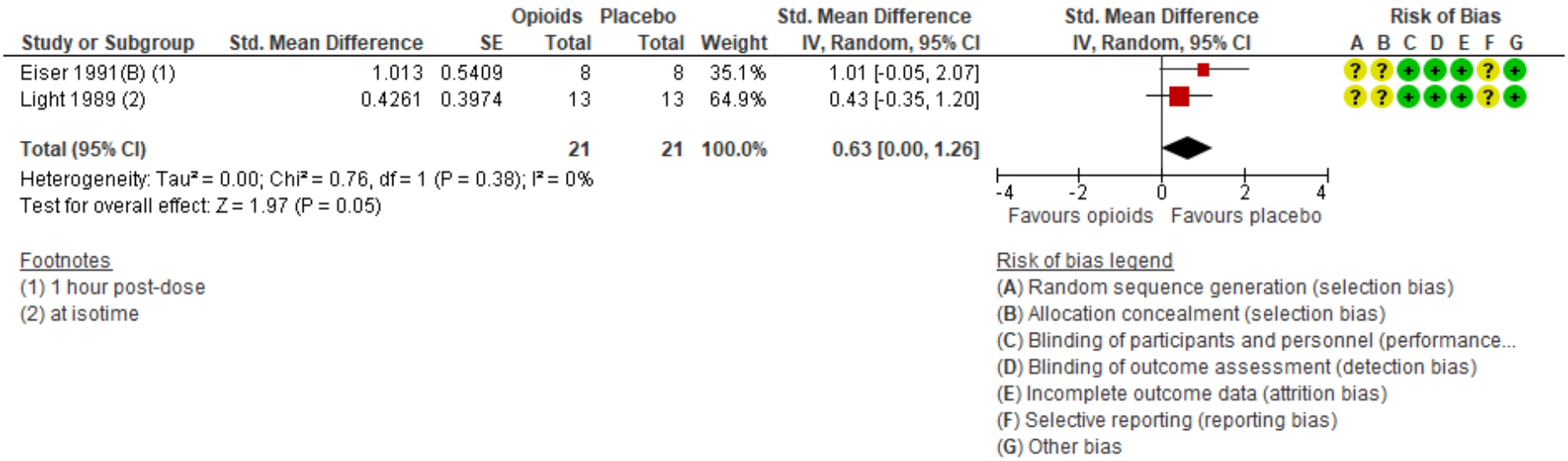
Risk of bias legend

(**A**) Random sequence generation (selection bias)
(**B**) Allocation concealment (selection bias)
(**C**) Blinding of participants and personnel (performance...
(**D**) Blinding of outcome assessment (detection bias)
(**E**) Incomplete outcome data (attrition bias)
(**F**) Selective reporting (reporting bias)
(**G**) Other bias

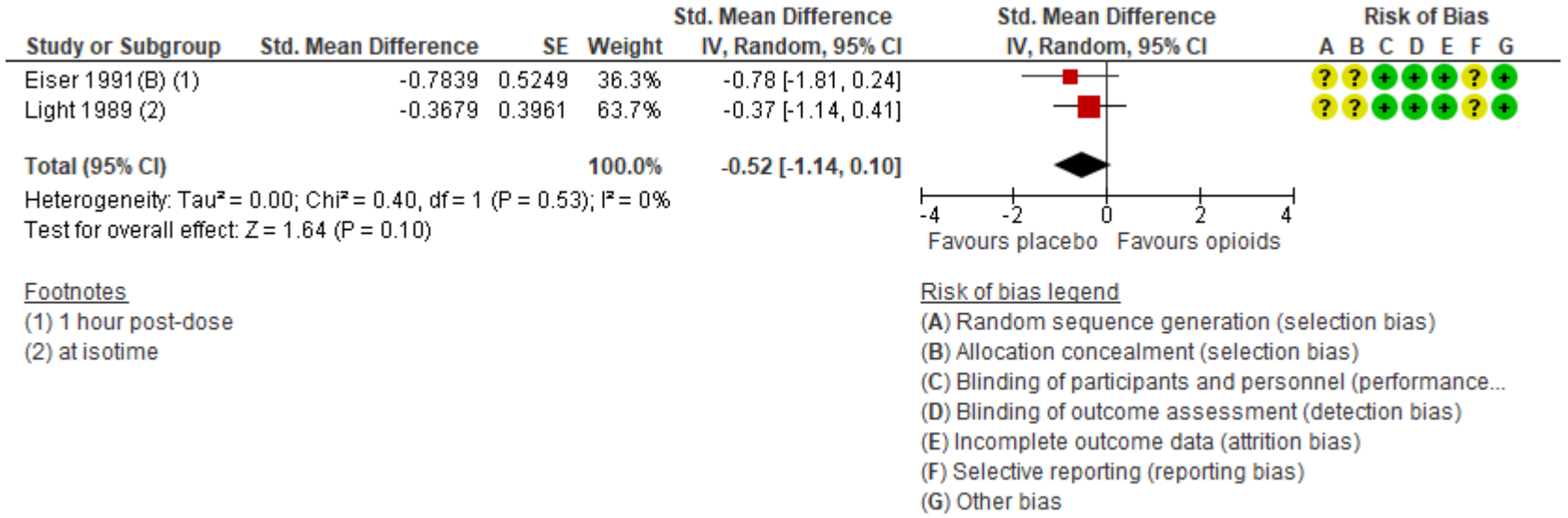
Supplementary Figure S5: At home studies reporting breathlessness pragmatically during daily life using morning scores when available



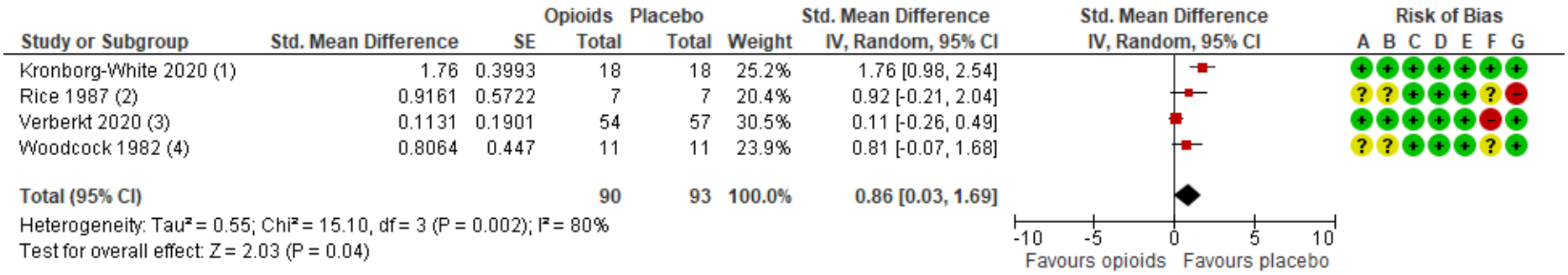
Supplementary Figure S6: At home studies reporting cough



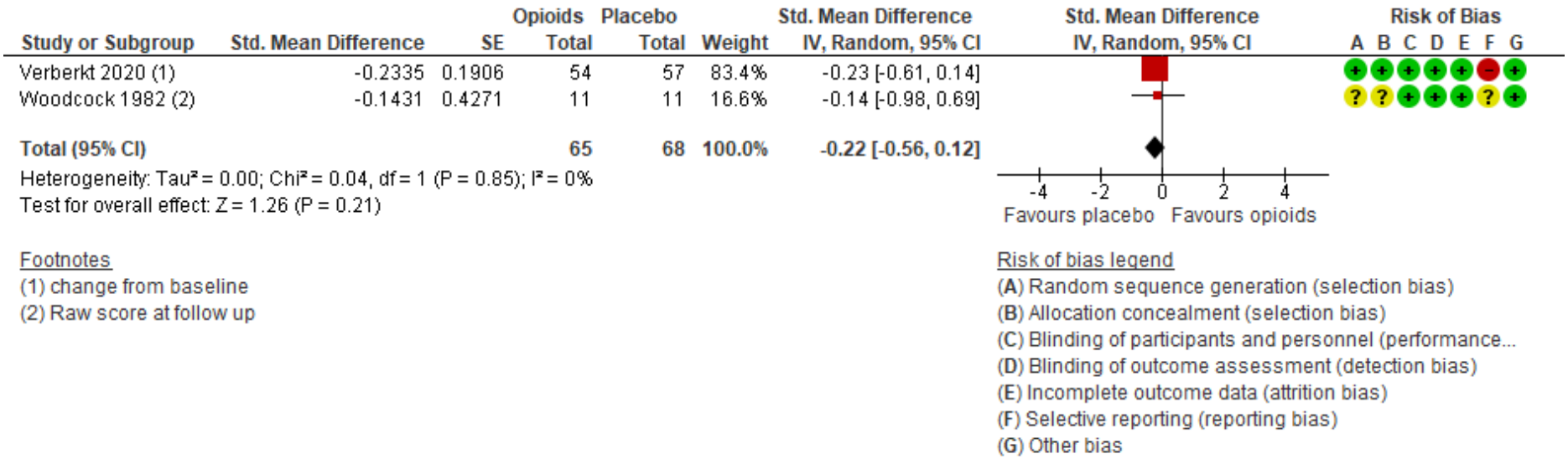
Supplementary Figure S7: Laboratory-based exercise studies reporting arterial blood gases (partial pressure of carbon dioxide)



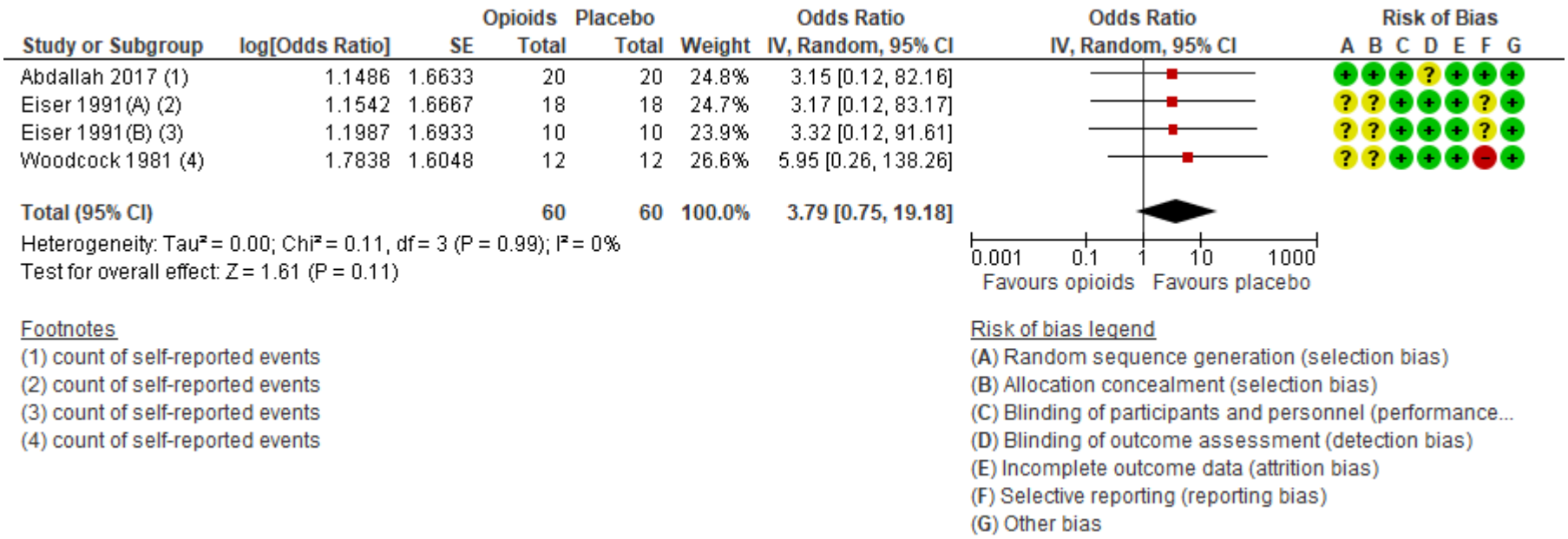
Supplementary Figure S8: Laboratory-based exercise studies reporting arterial blood gases (partial pressure of oxygen)



Supplementary Figure S9: At home studies reporting arterial blood gases (partial pressure of carbon dioxide)



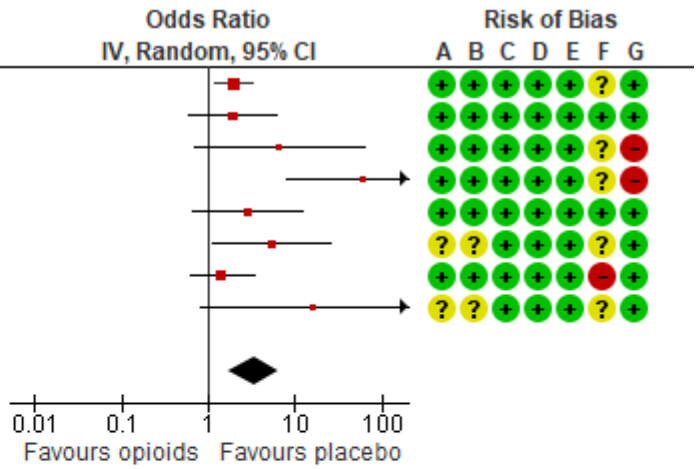
Supplementary Figure S10: At home studies reporting arterial blood gases (partial pressure of oxygen)



Supplementary Figure S11: Laboratory-based exercise studies reporting adverse events (nausea and/or vomiting)

Study or Subgroup	log[Odds Ratio]	SE	Opioids Total	Placebo Total	Weight	Odds Ratio IV, Random, 95% CI
Currow 2020 (1)	0.6699	0.2662	142	137	23.7%	1.95 [1.16, 3.29]
Ekstrom 2022 (2)	0.6568	0.5976	51	50	15.1%	1.93 [0.60, 6.22]
Ferreira 2018 (3)	1.8608	1.1519	19	19	6.7%	6.43 [0.67, 61.47]
Ferreira 2020 (4)	4.0771	1.0342	72	79	7.9%	58.97 [7.77, 447.69]
Kronborg-White 2020 (5)	1.0296	0.7392	18	18	12.1%	2.80 [0.66, 11.92]
Poole 1998 (6)	1.6864	0.8028	16	14	11.0%	5.40 [1.12, 26.05]
Verberkt 2020 (7)	0.3542	0.4341	54	57	19.2%	1.43 [0.61, 3.34]
Woodcock 1982 (8)	2.7589	1.5262	16	16	4.3%	15.78 [0.79, 314.25]
Total (95% CI)			**388**	**390**	**100.0%**	**3.32 [1.70, 6.51]**

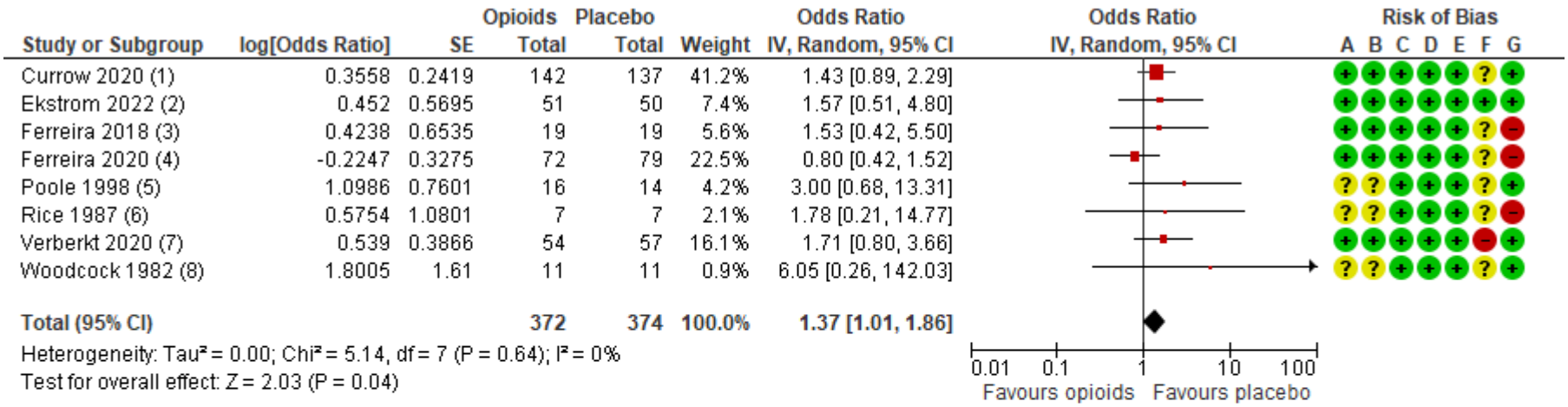
Heterogeneity: Tau² = 0.43; Chi² = 15.07, df = 7 (P = 0.04); I² = 54%
Test for overall effect: Z = 3.50 (P = 0.0005)



Footnotes
(1) count of self-reported events
(2) count of self-reported events
(3) count of self-reported events
(4) count of self-reported events
(5) count of self-reported events
(6) count of self-reported events
(7) count of participants with increase of 2 or more points on symptom NRS relative to baseline
(8) count of self-reported events

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance...
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Supplementary Figure S12: At home studies reporting adverse events (nausea and/or vomiting)



Footnotes

(1) count of self-reported events
(2) count of self-reported events
(3) count of self-reported events
(4) count of self-reported events
(5) count of self-reported events
(6) count of self-reported events
(7) count of participants with increase of 2 or more points on symptom NRS relative to baseline
(8) count of self-reported events

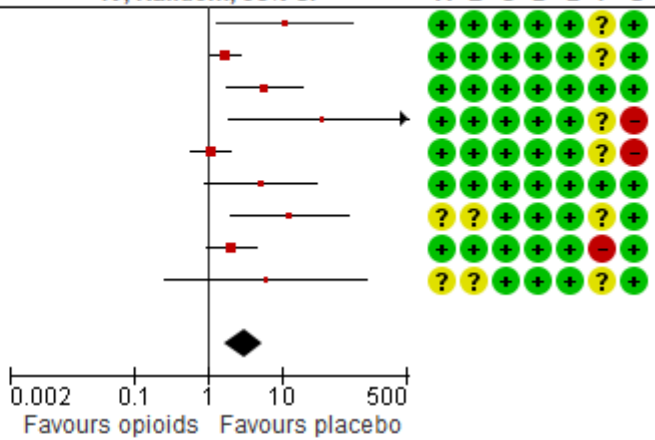
Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance...
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Supplementary Figure S13: At home studies reporting adverse events (drowsiness)

Study or Subgroup	log[Odds Ratio]	SE	Opioids Total	Placebo Total	Weight	Odds Ratio IV, Random, 95% CI
Abernethy 2003 (1)	2.3838	1.0761	48	48	6.1%	10.85 [1.32, 89.38]
Currow 2020 (2)	0.5055	0.2415	142	137	21.7%	1.66 [1.03, 2.66]
Ekstrom 2022 (3)	1.7492	0.6	51	50	12.8%	5.75 [1.77, 18.64]
Ferreira 2018 (4)	3.5635	1.5006	19	19	3.6%	35.29 [1.86, 668.22]
Ferreira 2020 (5)	0.0809	0.3259	72	79	19.5%	1.08 [0.57, 2.05]
Kronborg-White 2020 (6)	1.6275	0.8923	18	18	8.0%	5.09 [0.89, 29.26]
Poole 1998 (7)	2.5337	0.9394	16	14	7.5%	12.60 [2.00, 79.43]
Verberkt 2020 (8)	0.7072	0.3979	54	57	17.6%	2.03 [0.93, 4.42]
Woodcock 1982 (9)	1.8005	1.61	11	11	3.2%	6.05 [0.26, 142.03]
Total (95% CI)			**431**	**433**	**100.0%**	**3.08 [1.69, 5.61]**

Heterogeneity: Tau² = 0.37; Chi² = 18.76, df = 8 (P = 0.02); I² = 57%
Test for overall effect: Z = 3.67 (P = 0.0002)



Footnotes
(1) count of self-reported events
(2) count of self-reported events
(3) count of self-reported events
(4) count of self-reported events
(5) count of self-reported events
(6) count of self-reported events
(7) count of self-reported events
(8) count of participants with increase of 2 or more points on symptom NRS relative to baseline
(9) count of self-reported events

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance...
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Supplementary Figure S14: At home studies reporting adverse events (constipation)

Supplementary Table S3: GRADE certainty of evidence in laboratory-based exercise studies

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	opioids	no opioids	Relative (95% CI)	Absolute (95% CI)		
Breathlessness after exercise (iso-time & iso-load)												
5	randomised trials – all crossover	Serious [a]	Not serious	Serious [b]	Serious[c]	Yes [d]	70	70	-	**SMD -0.50** - 0.84 to -0.16 p=0.004 Favours opioids	⊕◯◯◯ very low	CRITICAL
Breathlessness after exercise (iso-time only)												
3	randomised trials – all crossover	Serious [a]	Not serious	Serious [b]	Serious[c]	Yes [d]	40	40	-	**SMD -0.57** - 1.02 to -0.12 p=0.01 Favours opioids	⊕◯◯◯ very low	CRITICAL
Breathlessness after exercise (iso-load only)												
2	randomised trials – all crossover	Serious [a]	Not serious	Not serious	Serious [c,e]	Yes [d]	30	30	-	**SMD -0.41** -0.92 to 0.11 p=0.12	⊕◯◯◯ very low	CRITICAL
ABG PaCO2 after exercise												
2	randomised trials – all crossover	Serious [f]	Not serious	Serious [b]	Serious [c,g]	Yes [d a]	21	21	-	**SMD 0.63** 0.0 to 1.26 p=0.05	⊕◯◯◯ very low	IMPORTANT
ABG PaO2 after exercise												
2	randomised trials – all crossover	Serious [f]	Not serious	Serious [b]	Serious [c,h]	Yes[d]	21	21	-	**SMD -0.52** -1.14 to 0.10 p=0.10	⊕◯◯◯ very low	IMPORTANT
Adverse events – Nausea or vomiting												

4	randomised trials – all crossover	Serious [a]	Not serious	Serious [b]	Serious [c+]	Yes[d]	60	60	-	**OR 3.79** 0.75 to 19.18 p=0.11	⊕◯◯◯ very low	IMPORTANT

CI: confidence interval; **OR:** risk ratio; **SMD:** standardised mean difference

Explanations:

a. >=50% of weighting comes from studies with uncertainty or high risk for selection bias and reporting bias

b. All or most studies only include people with COPD

c. Small numbers of patients in the included studies contributes to imprecision in the outcome estimate

d. Most studies had risk of carryover effect due to inadequate washout period in crossover design. The carryover effect is not considered under risk of bias in the ROB1 tool, therefore this was considered separately as an additional consideration.

e. The pooled estimate of the effect of opioids on breathlessness includes both small harm and large benefit

f. All studies have uncertainty regarding for selection bias and reporting bias

g. The pooled estimate of the effect of opioids on ABG $PaCO_2$ includes both large harm and no benefit

h. The pooled estimate of the effect of opioids on ABG PaO_2 includes both large harm and small benefit

i. The pooled estimate of the effect of opioids on nausea or vomiting includes both large harm and no harm

Supplementary Table S4: GRADE certainty of evidence in at home studies

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	opioids	no opioids	Relative (95% CI)	Absolute (95% CI)		
Breathlessness intensity (evening measures or time not stated)												
10	randomised trials – 5 crossover	Not serious [a]	Serious [b]	Not serious	Serious [c]	Yes [d]	438	441	-	**SMD -0.10** -0.64 to 0.44 p=0.71	⊕◯◯◯ very low	CRITICAL
Breathlessness intensity (morning measures or time not stated)												
10	randomised trials – 5 crossover	Not serious [a]	Serious [b]	Not serious	Serious [c]	Yes [d]	438	441	-	**SMD -0.10** -0.64 to 0.43 p=0.71	⊕◯◯◯ very low	CRITICAL
Health-Related Quality of Life												
6	randomised trials – 1 crossover	Not serious [a]	Serious [b]	Not serious	Serious [e]	No	356	359	-	**SMD -0.42** -0.98 to 0.13 p=0.13	⊕⊕◯◯ low	IMPORTANT
Cough												
2	randomised trials – 0 crossover	Not serious	Serious [b]	Not serious	Serious [f]	No	62	69	-	**SMD -1.42** -3.99 to 1.16 p=0.28	⊕⊕◯◯ low	IMPORTANT
ABG PaCO2												
4	randomised trials – 2 crossover	Serious [g]	Serious [b]	Serious [h]	Serious [f]	Yes [i]	90	93	-	**SMD 0.86** 0.03 to 1.69 p=0.04 favours placebo	⊕◯◯◯ very low	IMPORTANT

ABG PaO2												
2	randomised trials – 1 crossover	Serious [j]	Not serious	Serious [k]	Serious [l]	Yes [i]	65	68	-	**SMD -0.22** -0.56 to 0.12 p=0.21	⊕◯◯◯ very low	IMPORTANT
Adverse events - Drowsiness												
8	randomised trials – 4 crossover	Serious [m]	Not serious	Not serious	Serious [n]	No	372	374	-	**OR 1.37** 1.01 to 1.86 p=0.04	⊕⊕◯◯ low	IMPORTANT
Adverse events - Constipation												
9	randomised trials – 4 crossover	Serious [o]	Serious [p]	Not serious	Not serious	No	431	433	-	**OR 3.08** 1.69 to 5.61 p=0.0002 favours placebo	⊕⊕◯◯ low	IMPORTANT
Adverse events – Nausea or vomiting												
8	randomised trials – 3 crossover	Serious [q]	Serious [p]	Not serious	Not serious	No	388	390	-	**OR 3.32** 1.70 to 6.51 p=0.0005 favours placebo	⊕⊕◯◯ low	IMPORTANT

CI: confidence interval; **OR:** risk ratio; **SMD:** standardised mean difference

Explanations:

a. Nearly all studies had an unclear risk regarding selective reporting as most did not publish study protocols before publishing trial outcomes. One study was considered at high risk of bias for selective reporting. However, overall the risk of bias from all domains was considered not serious

b. Significant heterogeneity identified I^2 >80%, which is not explained by differences in study design or study populations

c. The pooled estimate of the effect of opioids on breathlessness includes both strong benefit and moderate harm

d. 3 of the 5 crossover studies had a risk of carryover effect due to inadequate washout period in crossover design. The carryover effect is not considered under risk of bias in the ROB1 tool, therefore this was considered separately as an additional consideration.

e. The pooled estimate of the effect of opioids on QOL includes both small harm and large benefit

f. Small numbers of patients in the included studies contributes to imprecision in the outcome estimate

g. 45% of weighting comes from studies with uncertainty regarding selection bias and 75% of weighting comes from studies with uncertainty or high risk regarding reporting bias

h. 75% of weighting comes from studies with only people with COPD

i. 1 of the 2 crossover studies had a risk of carryover effect due to inadequate washout period in crossover design. The carryover effect is not considered under risk of bias in the ROB1 tool, therefore this was considered separately as an additional consideration.

j. 17% of weighting comes from studies with uncertainty regarding selection bias and 100% of weighting comes from studies with uncertainty or high risk regarding reporting bias
k. Only patients with COPD included in the studies for this outcome
l. The pooled estimate of the effect of opioids on PaO2 includes both moderate harm and small benefit
m. All but 1 study had uncertainty or high risk regarding reporting bias and 30% of the weighting comes from studies with high risk for other bias
n. The pooled estimate of the effect of opioids on drowsiness includes both negligible and large harm
o. 79% of the weighting comes from studies with uncertainty or high risk regarding reporting bias and 23% of the weighting comes from studies with high risk for other bias
p. Significant heterogeneity identified I^2 >50%, which is not explained by differences in study design or study populations
q. 73% of the weighting comes from studies with uncertainty or high risk regarding reporting bias and 15% of the weighting comes from studies with high risk for other bias