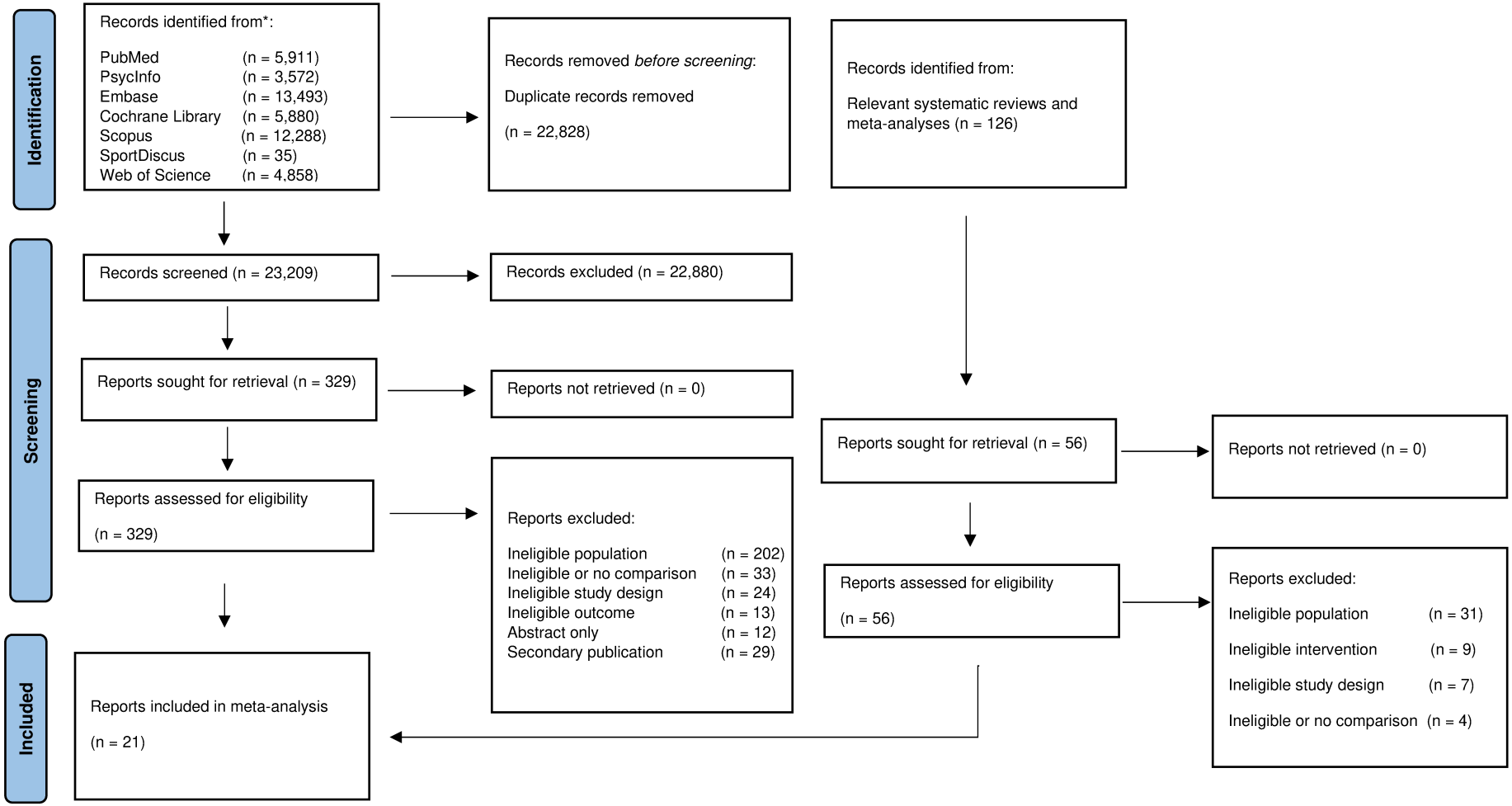
Comparative effectiveness of exercise, antidepressants, and their combination in treating non-severe depression: A systematic review and network meta-analysis of randomized controlled trials

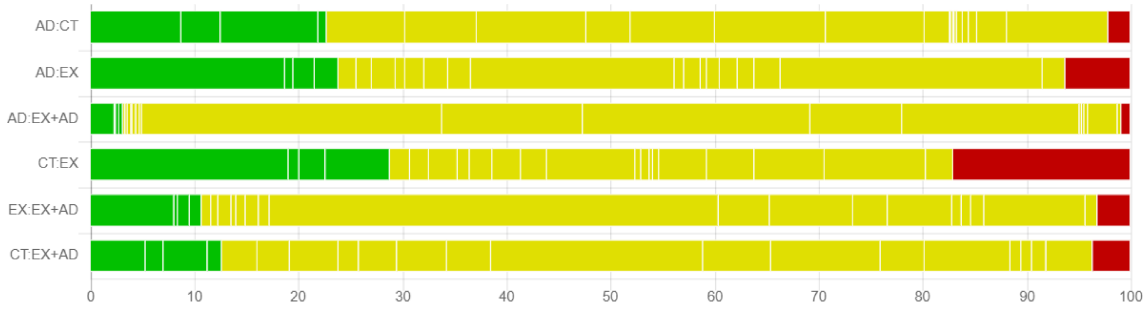
Supplementary Online Content

Recchia F, *et al. Br J Sports Med* 2022;0:1–7. doi: 10.1136/bjsports-2022-105964

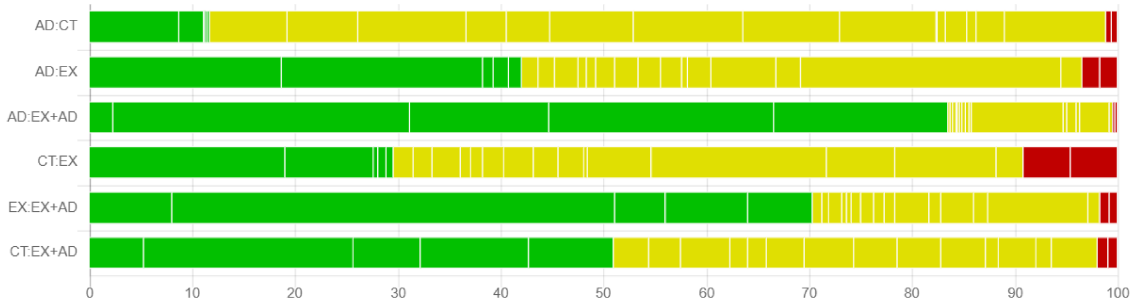
eFigure 1. PRISMA flow chart



eFigure 2. Risk of bias contributions



eFigure 3. Indirectness contributions



eTable 1. Distribution of study characteristics

Comparison	N studies	Participant age (years)	Sex (% women)	Intervention duration (weeks)	Outcome measure
EX:AD	3	< 60	≥ 50%	19	HAM-D
AD:CT	11	< 60	≥ 50%	9	HAM-D
EX:CT	6	< 60	≥ 50%	10	HAM-D
EX+AD:AD	4	< 60	≥ 50%	11	HAM-D
EX+AD:EX	1	< 60	≥ 50%	16	HAM-D

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eTable 2. Meta-regression for direct comparisons

Comparison[a]	N	Coefficient [95% CI]	SE	P value
EX:AD	3			
- Mean age		-0.00 [-0.16 to 0.16]	0.01	0.94
- Mean duration		-0.01 [-0.21 to 0.20]	0.02	0.75
- Proportion of women		-0.02 [-0.39 to 0.36]	0.03	0.67
- Outcome measure		-0.05 [-1.68 to 1.58]	0.13	0.75
AD:CT	11			
- Mean age		0.01 [-0.03 to 0.05]	0.02	0.70
- Mean duration		0.02 [-0.03 to 0.08]	0.02	0.35
- Proportion of women		-0.01 [-0.03 to 0.01]	0.01	0.40
- Outcome measure[b]		NA	NA	NA
EX:CT	6			
- Mean age		0.03 [-0.03 to 0.08]	0.02	0.20
- Mean duration		0.08 [-0.08 to 0.25]	0.06	0.22
- Proportion of women		0.00 [-0.04 to 0.04]	0.01	0.92
- Outcome measure		0.63 [-0.48 to 1.74]	0.40	0.19
EX+AD:AD	4			
- Mean age		0.01 [-0.06 to 0.09]	0.02	0.54
- Mean duration		0.04 [-0.09 to 0.18]	0.03	0.28
- Proportion of women		-0.05 [-0.36 to 0.27]	0.07	0.58
- Outcome measure		-0.49 [-2.03 to 1.06]	0.36	0.31

[a]Meta-regression for the EX+AD:EX comparison could not be performed because only one study was available for that comparison

[b]Meta-regression for this categorical outcome could not be performed because all studies within this comparison used the same outcome measure

eTable 3. Risk of bias for all studies

Study	Randomization process	Deviations from intended interventions	Missing outcome data	Measurement of the outcome	Selection of the reported result	RoB
Bjerkenstedt et al., 2004	Low	Low	Low	Low	Some concerns	Some concerns
Blumenthal et al., 1999	Some concerns	Low	Low	Some concerns	Some concerns	Some concerns
Blumenthal et al., 2007	Low	Low	Low	Low	Low	Low
Danielsson et al., 2014	Low	Low	Low	Low	Some concerns	Some concerns
Detke et al., 2002	Some concerns	Low	Low	Low	Low	Some concerns
Detke et al., 2004	Some concerns	Low	Low	Low	Low	Some concerns
Dunn et al., 2005	Low	Low	Low	Low	Low	Low
Fava et al., 2005	Some concerns	Low	Low	Low	Some concerns	Some concerns
Gastpar et al., 2005	Some concerns	Low	Low	Low	Some concerns	Some concerns
Goldstein et al., 2004	Low	Low	Low	Low	Low	Low
Hemat-Far et al., 2012	Some concerns	Some concerns	Low	Some concerns	Some concerns	Some concerns
Hidalgo et al., 2021	Some concerns	Low	Low	Some concerns	Low	Some concerns
Krogh et al., 2012	Some concerns	High	Low	Low	Low	High
Mao et al., 2015	Low	Low	Low	Low	Low	Low
Mather et al., 2002	Low	Some concerns	Low	Low	Some concerns	Some concerns
McNeil et al., 1991	Some concerns	Some concerns	Low	Some concerns	Some concerns	Some concerns
Moreno et al., 2005	Low	Low	Low	Low	Low	Low
Perahia et al., 2006	Some concerns	Low	Low	Low	Low	Some concerns
Philipp et al., 1999	Some concerns	Low	Low	Low	Some concerns	Some concerns
Sadeghi et al., 2016	Some concerns	Low	Some concerns	Low	Low	Some concerns
Siqueira et al., 2016	Some concerns	Low	Low	Low	Low	Some concerns

eTable 4. Indirectness for all studies

Author	Population		Intervention		Outcome		Comparisons	Indirectness
Bjerkenstedt et al., 2005	Low		Low		Low		High	Moderate
Blumenthal et al., 1999	Low		Low		Low		Low	Low
Blumenthal et al., 2007	Low		Low		Low		Low	Low
Danielsson et al., 2014	Low		Low		Low		Low	Low
Detke et al., 2002	Low		Low		Low		High	Moderate
Detke et al., 2004	Low		Low		Low		High	Moderate
Dunn et al., 2005	Low		Low		Low		High	Moderate
Fava et al., 2005	Low		Low		Low		High	Moderate
Gastpar et al., 2006	Low		Low		Low		High	Moderate
Goldstein et al., 2004	Low		Low		Low		High	Moderate
Hemat-Far et al., 2012	High	Female students	Low		Moderate	Self-reported questionnaire	High	High
Hidalgo et al. 2021	High	Elderly	Low		Low		Low	Moderate
Krogh et al., 2012	Low		Low		Low		High	Moderate
Mao et al., 2015	Low		Low		Low		High	Moderate
Mather et al., 2002	Low		Low		Low		Low	Low
McNeil et al., 1991	High	Elderly	Moderate	Somewhat different	Moderate	Self-reported questionnaire	High	High
Moreno et al., 2006	Low		Low		Low		High	Moderate
Perahia et al., 2006	Low		Low		Low		High	Moderate
Philipp et al., 1999	Low		Low		Low		High	Moderate
Sadeghi et al., 2016	Low		Low		Moderate	Self-reported questionnaire	High	Moderate
Siqueira et al., 2016	Low		Low		Low		Low	Low

eTable 5. Confidence in Network Meta-analysis (CINeMA) final report

Comparison	N	Within-study bias	Reporting bias	Indirectness	Imprecision	Heterogeneity	Incoherence	Confidence rating
AD:CT	10	Some concerns	Some concerns	Some concerns	No concerns	Some concerns	No concerns	Moderate
AD:EX	2	Some concerns	Some concerns	Some concerns	Some concerns	No concerns	No concerns	Moderate
EX+AD:AD	5	Some concerns	Some concerns	No concerns	Some concerns	No concerns	No concerns	High
EX:CT	6	Some concerns	Some concerns	Some concerns	No concerns	Some concerns	No concerns	Moderate
EX+AD:EX	1	Some concerns	Some concerns	No concerns	Some concerns	Some concerns	No concerns	Moderate
EX+AD:CT	0	Some concerns	Some concerns	Some concerns	No concerns	No concerns	No concerns	High

eTable 6. Treatment ranking based on the P-score

Treatment	P-score
EX	0.7865
EX+AD	0.7639
AD	0.4489
CT	0.0008

eTable 7. Assessment of inconsistency within comparisons

Comparison	k	Direct	Indirect	Difference	z	P-value
AD:CT	11	-0.33	-0.38	0.05	0.22	0.83
AD:EX	3	0.07	0.19	-0.12	-0.52	0.60
EX+AD:AD	4	0.12	0.09	0.03	0.06	0.95
EX:CT	6	-0.43	-0.48	0.05	0.21	0.83
EX+AD:CT	0	NA	-0.45	NA	NA	NA
EX+AD:EX	1	-0.18	0.12	-0.30	-0.89	0.38

AD: Antidepressants; CT: Control; EX: Exercise; NA: Not available

eTable 8. Sensitivity analyses

Reasons for exclusion	N	EX-AD	Comb-AD	Comb-EX	Comb-CT	EX-CT	AD-CT	I^2
All included	21	-.12 (-.33 to .10)	-.12 (-.40 to .16)	-.00 (-.33 to .33)	-.45 (-.76 to -.14)	-.45 (-.67 to -.23)	-.33 (-.48 to -.19)	46.2%
Participants older than 60	19	-.10 (-.37 to .16)	-.12 (-.41 to .17)	-.02 (-.37 to .34)	-.44 (-.76 to -.12)	-.43 (-.69 to -.17)	-.33 (-.48 to -.18)	49.0%
High Risk of Bias	20	-.20 (-.40 to .00)	-.13 (-.38 to .13)	.07 (-.23 to .37)	-.48 (-.77 to -.20)	-.56 (-.77 to -.34)	-.36 (-.49 to -.23)	31.0%
High Indirectness	19	-.07 (-.29 to .15)	-.11 (-.39 to .17)	-.04 (-.36 to .29)	-.43 (-.74 to -.12)	-.39 (-.62 to -.16)	-.32 (-.46 to -.18)	46.9%
Intervention longer than 12 weeks	18	-.18 (-.58 to .21)	-.29 (-.67 to .09)	-.11 (-.65 to .44)	-.63 (-1.05 to -.22)	-.53 (-.88 to -.17)	-.35 (-.52 to -.17)	52.5%
SD imputed	16	-.17 (-.42 to .09)	-.14 (-.45 to .18)	-.03 (-.34 to .40)	-.41 (-.78 to -.04)	-.44 (-.70 to 0.19)	-.28 (-.50 to .05)	50.4%
Attention/active control comparison	17	-.14 (-.35 to .07)	-.09 (-.39 to .21)	-.05 (-.28 to .38)	-.44 (-.76 to -.11)	-.48 (-.71 to -.25)	-.34 (-.47 to -.22)	32.6%
Passive control comparison	19	-.07 (-.29 to .15)	-.11 (-.39 to .17)	-.04 (-.36 to .29)	-.43 (-.74 to -.12)	-.39 (-.62 to -.16)	-.32 (-.46 to -.18)	46.9%

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eAppendix 1. Search strategy

PubMed

Search	Query
#1	Bupropion[MeSH Terms] OR bupropion[Title/Abstract] OR 34911-55-2[EC/RN Number]
#2	Citalopram[MeSH Terms] OR citalopram[Title/Abstract] OR 59729-33-8[EC/RN Number]
#3	escitalopram[Title/Abstract] OR 128196-01-0[EC/RN Number]
#4	desvenlafaxine[Title/Abstract] OR 386750-22-7[EC/RN Number]
#5	Fluoxetine[MeSH Terms] OR fluoxetine[Title/Abstract] OR 54910-89-3[EC/RN Number]
#6	Fluvoxamine[MeSH Terms] OR fluvoxamine[Title/Abstract] OR 54739-18-3[EC/RN Number]
#7	Milnacipran[Supplementary Concept] OR milnacipran[Title/Abstract] OR levomilnacipran[Title/Abstract]
#8	Mirtazapine[Supplementary Concept] OR mirtazapine[Title/Abstract] OR 4685R51V7M[EC/RN Number]
#9	Nefazodone[Supplementary Concept] OR nefazodone[Title/Abstract]
#10	Paroxetine[MeSH Terms] OR paroxetine[Title/Abstract] OR 61869-08-7[EC/RN Number]
#11	Sertraline[MeSH Terms] OR sertraline[Title/Abstract] OR 79617-96-2[EC/RN Number]
#12	Trazodone[MeSH Terms] OR trazodone[Title/Abstract] OR 19794-93-5[EC/RN Number]
#13	venlafaxine[Title/Abstract] OR 99300-78-4[EC/RN Number]
#14	vilazodone[Title/Abstract] OR 163521-08-2[EC/RN Number]
#15	Vortioxetine[Supplementary Concept] OR vortioxetine[Title/Abstract] OR TKS641KOAY[EC/RN Number]
#16	duloxetine[Title/Abstract] OR 116539-58-3[EC/RN Number]
#17	Antidepressive Agents, Second Generation[MeSH Terms] OR Antidepressive Agents, Second-Generation[Pharmacological Action] OR antidepress*[Title/Abstract]
#18	#1 OR #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 OR #16 OR #17
#19	Depression, unipolar[MeSH Terms] OR Depressive disorders[MeSH Terms] OR depress*[Title/Abstract]
#20	Randomized controlled trial[MeSH Terms] OR Random allocation[MeSH Terms] OR (random*[Title/Abstract] AND (control*[Title/Abstract] OR placebo[Title/Abstract]))
#21	#18 AND #19 AND #20
#22	Exercise[MeSH Terms] OR exercise[Title/Abstract] OR "physical activity"[Title/Abstract] OR aerobic[Title/Abstract] OR training[Title/Abstract] OR lift*[Title/Abstract] OR running[Title/Abstract] OR walk*[Title/Abstract] OR jogging[Title/Abstract] OR swim*[Title/Abstract] OR cycl*[Title/Abstract]
#23	#19 AND #20 AND #22
#24	Adults[MeSH Terms] OR adult*[Title/Abstract]
#25	#21 AND #24
#26	#23 AND #24
#27	#25 OR #26
#28	Filters: Chinese, English, Italian, from 1990 - 3000/12/12

PsycInfo

Search	Query
S1	SU(bupropion) OR AB(bupropion) OR TI(bupropion)

S2	SU(citalopram) OR AB(citalopram) OR TI(citalopram)
S3	SU(escitalopram) OR AB(escitalopram) OR TI(escitalopram)
S4	SU(Desvenlafaxine) OR AB(Desvenlafaxine) OR TI(Desvenlafaxine)
S5	SU(Fluoxetine) OR AB(Fluoxetine) OR TI(Fluoxetine)
S6	SU(Fluvoxamine) OR AB(Fluvoxamine) OR TI(Fluvoxamine)
S7	SU(Levomilnacipran) OR AB(Levomilnacipran) OR TI(Levomilnacipran)
S8	SU(mirtazapine) OR AB(mirtazapine) OR TI(mirtazapine)
S9	SU(Nefazodone) OR AB(Nefazodone) OR TI(Nefazodone)
S10	SU(Paroxetine) OR AB(Paroxetine) OR TI(Paroxetine)
S11	SU(Sertraline) OR AB(Sertraline) OR TI(Sertraline)
S12	SU(Trazodone) OR AB(Trazodone) OR TI(Trazodone)
S13	SU(Venlafaxine) OR AB(Venlafaxine) OR TI(Venlafaxine)
S14	SU(vilazodone) OR AB(vilazodone) OR TI(vilazodone)
S15	SU(vortioxetine) OR AB(vortioxetine) OR TI(vortioxetine)
S16	SU(duloxetine) OR AB(duloxetine) OR TI(duloxetine)
S17	SU(Antidepressive Drugs, Second-Generation) OR TI(antidepress*) OR AB(antidepress*)
S18	S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17
S19	SU(depression) OR SU(depressive disorder) OR TI(depress*) OR AB(depress*)
S20	SU(randomized controlled trial) OR SU(randomized clinical trial) OR SU(random allocation) OR TI(random* AND control*) OR AB(random* AND control*) OR TI(random* AND placebo) OR AB(random* AND placebo)
S21	S18 AND S19 AND S20
S22	SU(adults) OR TI(adult*) OR AB(adult*)
S23	S21 AND S22
S24	SU(exercise) OR TI(exercise) OR AB(exercise) OR SU(physical activity) OR TI(aerobic) OR AB(aerobic) OR TI(training) OR AB(training) OR TI(lift*) OR AB(lift*) OR SU(running) OR TI(running) OR AB(running) OR TI(jogging) OR AB(jogging) OR TI(walk*) OR AB(walk*) OR TI(swim*) OR AB(swim*) OR TI(cycl*) OR AB(cycl*)
S25	S19 AND S20 AND S24
S26	S22 AND S25
S27	S23 AND S26
S28	#27 Limit date range 1990-2021 AND Limit language: English, Chinese, Italian

Cochrane Library

ID	**Search**
#1	bupropion:ti,ab,kw OR [mh bupropion]
#2	citalopram:ti,ab,kw OR [mh citalopram]
#3	escitalopram:ti,ab,kw OR [mh escitalopram]
#4	desvenlafaxine:ti,ab,kw OR [mh desvenlafaxine]
#5	duloxetine:ti,ab,kw OR [mh duloxetine]
#6	fluoxetine:ti,ab,kw OR [mh fluoxetine]
#7	fluvoxamine:ti,ab,kw OR [mh fluvoxamine]
#8	Levomilnacipran:ti,ab,kw OR [mh levomilnacipran]
#9	mirtazapine:ti,ab,kw OR [mh mirtazapine]
#10	nefazodone:ti,ab,kw OR [mh nefazodone]
#11	Paroxetine:ti,ab,kw OR [mh paroxetine]
#12	sertraline:ti,ab,kw OR [mh sertraline]
#13	Trazodone:ti,ab,kw OR [mh trazodone]
#14	venlafaxine:ti,ab OR [mh venlafaxine]
#15	vilazodone:ti,ab,kw OR [mh vilazodone]
#16	vortioxetine:ti,ab,kw OR [mh duloxetine]

#17	[mh Antidepressive Agents, Second-Generation] OR antidepress*:ti,ab,kw
#18	#1 OR #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 OR #16 OR #17
#19	[mh Depression] OR [mh Depressive Disorder, Major] OR depress*:ti,ab,kw
#20	[mh Randomized Controlled Trials as Topic] OR [mh Randomized Controlled Trial] OR [mh Random Allocation] OR ("randomized controlled"):ti,ab,kw OR ("controlled clinical"):ti,ab,kw
#21	#18 AND #19 AND #20
#22	[mh Adults] OR adults:ti,ab,kw
#23	#21 AND #22
#24	[mh Exercise] OR [mh "physical activity"] OR exercise:ti,ab,kw OR training:ti,ab,kw OR lift*:ti,ab,kw OR aerobic:ti,ab,kw OR running:ti,ab,kw OR walk*:ti,ab,kw OR jogging:ti,ab,kw OR swim*:ti,ab,kw OR cycl*:ti,ab,kw
#25	#19 AND #20 AND #24
#26	#25 AND #22
#27	#23 OR #26 with Publication Year from 1990 to 2021 AND language: English, Chinese, Italian

Embase

#	Searches
1	exp bupropion/ or bupropion.tn,ab,ti. or 34911 55 2.rn.
2	exp citalopram/ or citalopram.tn,ab,ti. or 59729 33 .rn.
3	exp escitalopram/ or escitalopram.tn,ab,ti. or 128196 01 0.rn.
4	exp desvenlafaxine/ or desvenlafaxine.tn,ab,ti. or 93413 62 8.rn.
5	exp fluoxetine/ or fluoxetine.tn,ab,ti. or 54910 89 3.rn.
6	exp fluvoxamine/ or fluvoxamine.tn,ab,ti. or 54739 18 3.rn.
7	exp milnacipran/ or levomilnacipran.tn,ab,ti. or 96847 54 0.rn.
8	exp mirtazapine/ or mirtazapine.tn,ab,ti. or 85650 52 8.rn.
9	exp nefazodone/ or nefazodone.tn,ab,ti. or 82752 99 6.rn.
10	exp paroxetine/ or paroxetine.tn,ab,ti. or 61869 08 7.rn.
11	exp sertraline/ or sertraline.tn,ab,ti. or 79617 96 2.rn.
12	exp trazodone/ or trazodone.tn,ab,ti. or 19794 93 5.rn.
13	exp venlafaxine/ or venlafaxine.tn,ab,ti. or 93413 69 5.rn.
14	exp vilazodone/ or vilazodone.tn,ab,ti. or 163521 12 8.rn.
15	exp vortioxetine/ or vortioxetine.tn,ab,ti. or 508233 74 7.rn.
16	exp duloxetine/ or duloxetine.tn,ab,ti. or 116539 59 4.rn.
17	exp antidepressant agent/ or antidepress*.ti,ab.
18	1 or 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 or 16 or 17
19	exp depression/ or exp major depression/ or depress*.ab,ti,kw.
20	exp randomized controlled trial/ or randomized controlled trial.ab,ti,pt. or randomized placebo trial.ti,ab. or exp randomization/
21	18 and 19 and 20
22	exp exercise/ or exercise.ti,ab. or aerobic.ti,ab. or training.ti,ab. or lift*.ti,ab. or running.ti,ab. or jogging.ti,ab. or walk*.ti,ab. or swim*.ti,ab. or cycl*.ti,ab.
23	19 and 20 and 22
24	exp adults/ or adult*.ti,ab.
25	21 and 24
26	23 and 24
27	25 or 26
28	Limit 27 to yr=1990-Current, English, Chinese, Italian language

Scopus

#	Query
#1	TITLE-ABS-KEY(bupropion OR citalopram OR escitalopram OR desvenlafaxine OR fluoxetine OR fluvoxamine OR milnacipran OR mirtazapine OR nefazodone OR

	paroxetine OR sertraline OR trazodone OR venlafaxine OR vilazodone OR vortioxetine OR duloxetine OR antidepress*)
#2	TITLE-ABS-KEY(depress*)
#3	TITLE-ABS-KEY(randomized controlled trial)
#4	TITLE-ABS-KEY(adult*)
#5	#1 AND #2 AND #3 AND #4
#6	TITLE-ABS-KEY(exercise OR 'physical activity' OR aerobic OR training OR lift* OR running OR walk* OR jogging OR swim* OR cycl*)
#7	#2 AND #3 AND #4 AND #6
#8	#5 OR #7

SportDiscus

Search	Query
S1	(TI(bupropion OR citalopram OR escitalopram OR desvenlafaxine OR fluoxetine OR fluvoxamine OR milnacipran OR mirtazapine OR nefazodone OR paroxetine OR sertraline OR trazodone OR venlafaxine OR vilazodone OR vortioxetine OR duloxetine OR antidepress*)) OR (AB(bupropion OR citalopram OR escitalopram OR desvenlafaxine OR fluoxetine OR fluvoxamine OR milnacipran OR mirtazapine OR nefazodone OR paroxetine OR sertraline OR trazodone OR venlafaxine OR vilazodone OR vortioxetine OR duloxetine OR antidepress*)) OR (SU(bupropion OR citalopram OR escitalopram OR desvenlafaxine OR fluoxetine OR fluvoxamine OR milnacipran OR mirtazapine OR nefazodone OR paroxetine OR sertraline OR trazodone OR venlafaxine OR vilazodone OR vortioxetine OR duloxetine OR antidepress*))
S2	SU(depression or depressive disorder or depressive symptoms or major depressive disorder) OR TI depress* OR AB depress*
S3	SU(randomized controlled trials or rtc or randomised control trials) OR TI(random* AND control*) OR AB (random* AND control*)
S4	SU(adults or adult) OR TI adult* OR AB adult*
S5	S1 AND S2 AND S3 AND S4
S6	SU(exercise or physical activity) OR TI(exercise OR 'physical activity' OR aerobic OR training OR lift* OR running OR walk* OR jogging OR swim* OR cycl*) OR AB(exercise OR 'physical activity' OR aerobic OR training OR lift* OR running OR walk* OR jogging OR swim* OR cycl*)
S7	S2 AND S3 AND S4 AND S6
S8	S5 OR S7

Web of Science

#	Query
#1	TS=(bupropion OR citalopram OR escitalopram OR desvenlafaxine OR fluoxetine OR fluvoxamine OR milnacipran OR mirtazapine OR nefazodone OR paroxetine OR sertraline OR trazodone OR venlafaxine OR vilazodone OR vortioxetine OR duloxetine OR antidepress*)
#2	TS=(depress*)
#3	TS=(random* AND (control* OR placebo))
#4	TS=(adult*)
#5	TS=(exercise OR 'physical activity' OR aerobic OR training OR lift* OR running OR walk* OR jogging OR swim* OR cycl*)
#6	#1 AND #2 AND #3 AND #4
#7	#2 AND #3 AND #4 AND #5
#8	#6 OR #7

eAppendix 2. Additional methodology information

Risk of bias

The Cochrane risk of bias assessment tool (RoB-2) was used to determine the quality of the individual studies.[1] Bias was assessed in the following domains: 1) randomization process, 2) deviations from the intended interventions, 3) missing outcome data, 4) measurement of the outcome, and 5) selection of the reported results. Each domain was assessed as having either low risk of bias, some concerns, or high risk of bias.

To implement RoB-2, we utilized the Excel template provided in the "Cochrane Handbook for Systematic Reviews of Interventions",[2] which includes "signalling questions" that can be used to assess bias in each domain. Each domain is automatically evaluated by an algorithm based on the signalling questions, as well as subjectively by the author. To avoid the influence of personal bias, the assessment of each domain was strictly based on the output of the algorithm.

1. Bias due to the randomization process was rated "low" if the study allocation sequence was reported as random and there was evidence that the allocation sequence was concealed. Allocation concealment was considered adequate if the allocation was carried out by investigators that were external to the project, or if authors used a form of remote or centrally administered method that ensured allocation concealment (e.g., sealed opaque envelopes). If the strategy for allocation concealment was not clearly reported, the domain was rated as having "some concerns". If both categories were deemed to be inadequately described, the domain was rated "high".

2. Bias due to deviations from the intended interventions was based on whether participants and/or study personnel were blinded to participants' assigned intervention, whether there were deviations from the intervention due to the trial context, and whether an appropriate analysis was used to estimate the effect of the intervention. Bias was rated "low" if all categories were rated as low. Following the Cochrane algorithm, if participants or study personnel were aware of participants' allocated intervention but all other categories were considered as low, the domain was still rated as "low". If there were deviations from the interventions that were suspected to affect the outcome, and if these were not balanced between groups, or if an inappropriate statistical analysis was used that was suspected to substantially impact the outcome, the domain was rated "high". Any other combination was rated as having "some concerns".

3. Bias due to missing outcome data was rated "low" if data were available for all, or nearly all, participants randomized. If there was the possibility that missingness in the outcome was influenced by its true value, the domain was rated "some concerns". If missingness in the outcome was likely influenced by its true value, the domain was rated "high".

4. Bias in measurement of the outcome was rated "high" if the method for measuring the outcome was inappropriate, if it differed between groups, or if it was likely that the assessment was influenced by knowledge of the intervention. It was rated "some concerns" if outcome assessors were aware of the intervention received by participants, but it was not likely that assignment was influenced by knowledge of the intervention. Bias in measurement of the outcome was rated "low" if all categories were considered as low.

5. Bias in selection of the reported result was rated "low" if it was unlikely that the results were selected from multiple measurements or analyses, and data were analysed in accordance with a pre-specified plan. If no pre-specified plan was available but it was unlikely that results were selected from multiple measurements or analyses, the domain was rated "some concerns". If it was suspected that results were selected from multiple measurements or analyses, the domain was rated "high".

Overall risk of bias was rated "low" if all domains were rated "low", it was rated "some concerns" if the study was judged to raise some concerns in at least one domain, but not to be at high risk of bias for any domain, and it was was rated "high" if at least one domain was considered as "high".

Confidence of Network Meta-analysis (CINeMA) rating

We used the CINeMA framework to assess the overall credibility of the results.[3] CINeMA is based on the following domains: 1) within-study bias, 2) reporting bias, 3) indirectness, 4) imprecision, 5) heterogeneity, and 6) incoherence. Within-study bias was evaluated using the RoB-2 tool. Reporting bias for each comparison was coded as "suspected" or "undetected" based on the completeness of the research and availability of published data. Indirectness was assessed as described below. To assess imprecision, heterogeneity, and incoherence, we set the clinically significant effect size to 0.35.[4]

Indirectness

Indirectness was assessed based on recommended guidelines.[5] We evaluated whether studies differed in relation to 1) population, 2) intervention, 3) outcome, and 4) whether a study showed direct evidence for at least one comparison of interest. Study indirectness was coded as "low" if three or more outcomes were considered to be "low" and no more than one was "unclear", and coded as "high" if two or more outcomes were considered to be "high", whereas any other combination was coded as "moderate".

1. Sterne JAC, Savović J, Page MJ, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ.* 2019;366:l4898.
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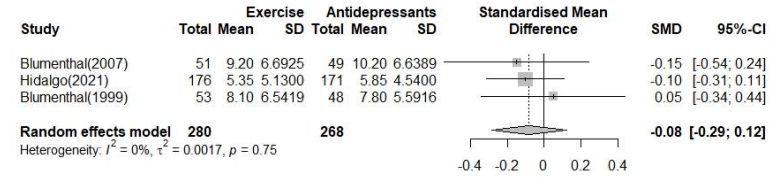
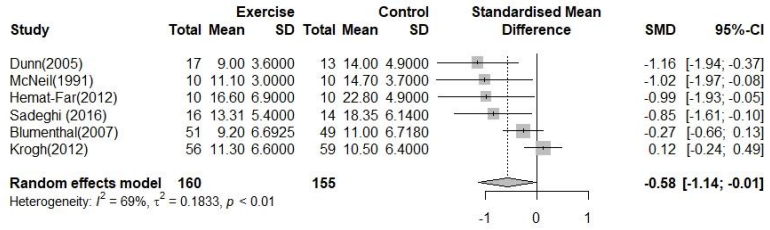
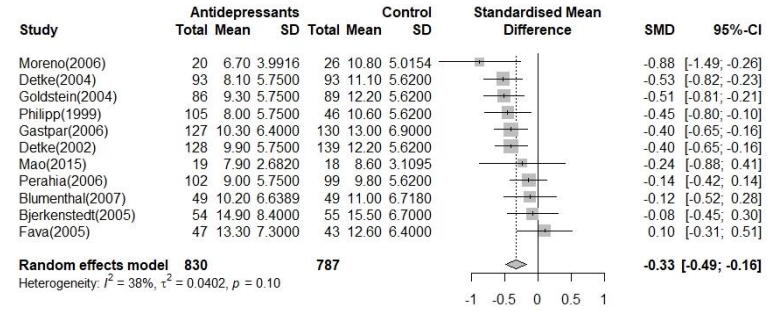
3. Nikolakopoulou A, Higgins JPT, Papakonstantinou T, et al. CINeMA: An approach for assessing confidence in the results of a network meta-analysis. *PLOS Medicine.* 2020;17(4):e1003082.
4. Kroenke K, Stump TE, Chen CX, et al. Minimally important differences and severity thresholds are estimated for the PROMIS depression scales from three randomized clinical trials. *Journal of affective disorders*. 2020;266:100-108. doi:10.1016/j.jad.2020.01.101
5. Guyatt GH, Oxman AD, Kunz R, et al. GRADE guidelines: 8. Rating the quality of evidence--indirectness. *Journal of Clinical Epidemiology*. 2011;64(12):1303-1310.

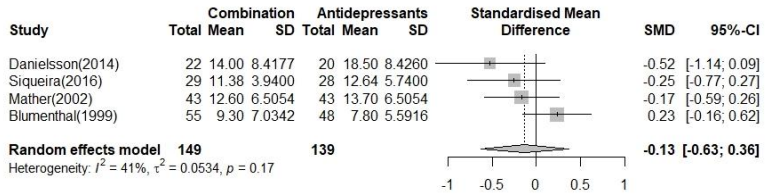
eAppendix 3. Pairwise meta-analyses

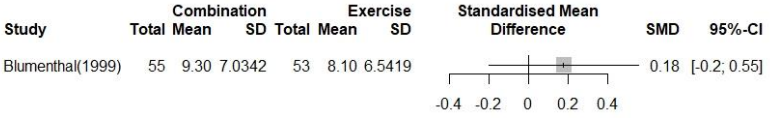
Comparative effectiveness on depressive symptoms from pairwise meta-analyses



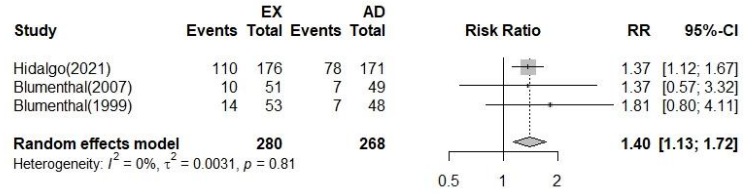


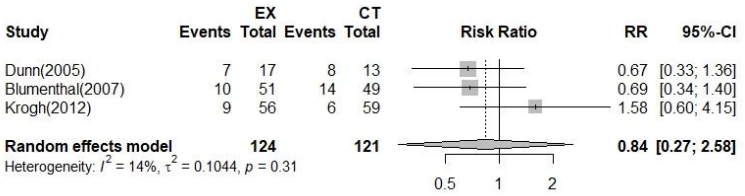


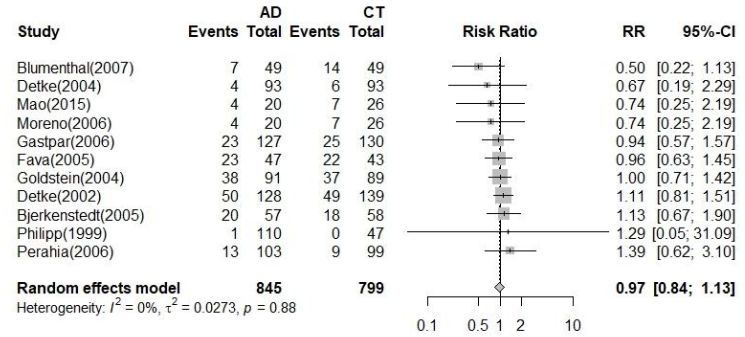


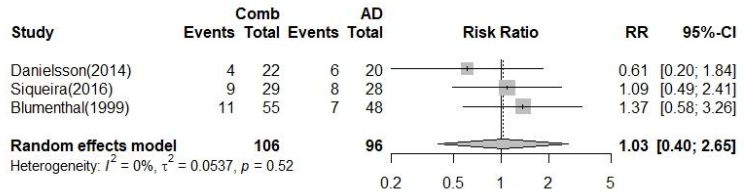


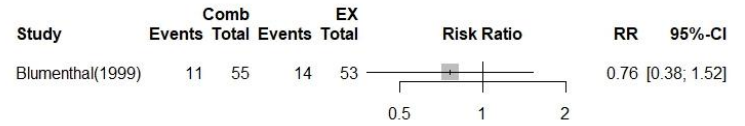
Comparative effectiveness on acceptability from pairwise meta-analyses











eAppendix 4. References

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