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III Appendix

Appendix 1. Searching strategy for this meta-analysis.

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Figure S1. Quality assessment of 24 included randomized controlled trials.

The Cochrane quality risk of bias assessment tool was used with different symbols for various risk of bias levels: green representing low-risk, yellow moderate-risk, and red high-risk.

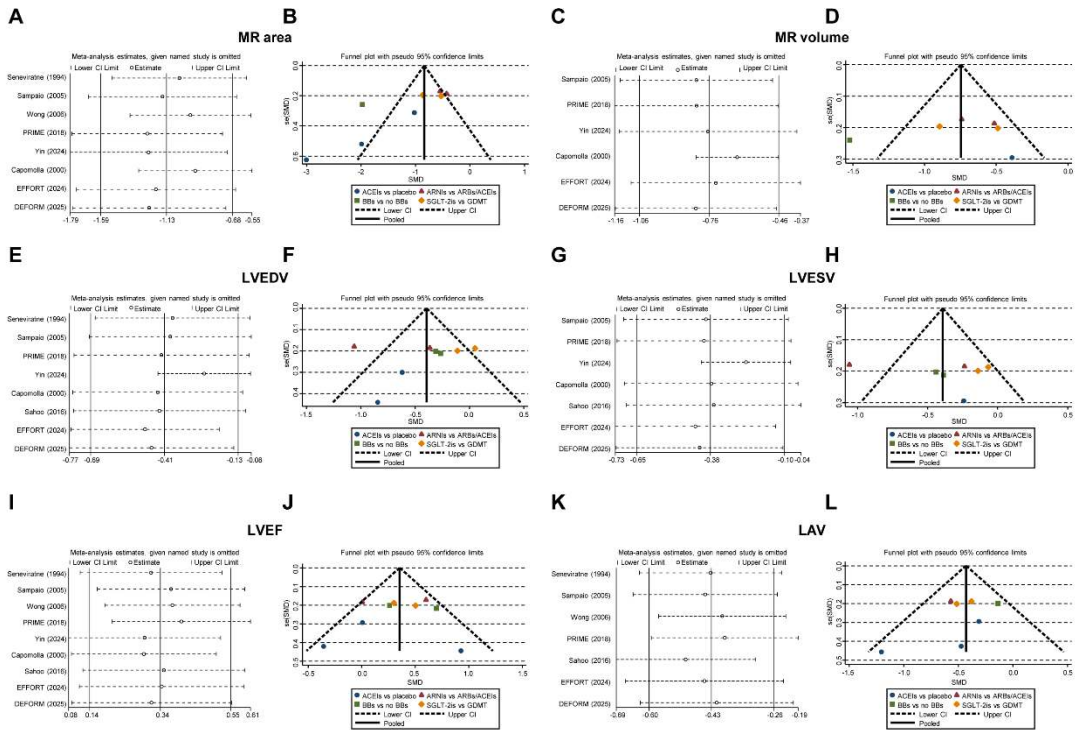

Figure S2. Leave-one-out heterogeneity source screening and publication bias for the meta-analysis on the impact of overall medications on MR regression and left heart improvement.

(A) Sensitivity analysis for meta-analysis on MR area; (B) Funnel plot for meta-analysis on MR area; (C) Sensitivity analysis for meta-analysis on MR volume; (D) Funnel plot for meta-analysis on MR volume; (E) Sensitivity analysis for meta-analysis on LVEDV; (F) Funnel plot for meta-analysis on LVEDV; (G) Sensitivity analysis for meta-analysis on LVESV; (H) Funnel plot for meta-analysis on LVESV; (I) Sensitivity analysis for meta-analysis on LVEF; (J) Funnel plot for meta-analysis on LVEF; (K) Sensitivity analysis for meta-analysis on LAV; (L) Funnel plot for meta-analysis on LAV.

Abbreviations: ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; ARNI, angiotensin receptor and neprilysin inhibitors; BB, beta-blocker; CI, confidence interval; GDMT, guideline-directed medical therapy; LAV, left atrial volume;

LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVESV, left ventricular end-systolic volume; MR, mitral regurgitation; se, standard error; SGLT-2i, sodium-glucose cotransporter-2 inhibitor; SMD, standard mean difference.

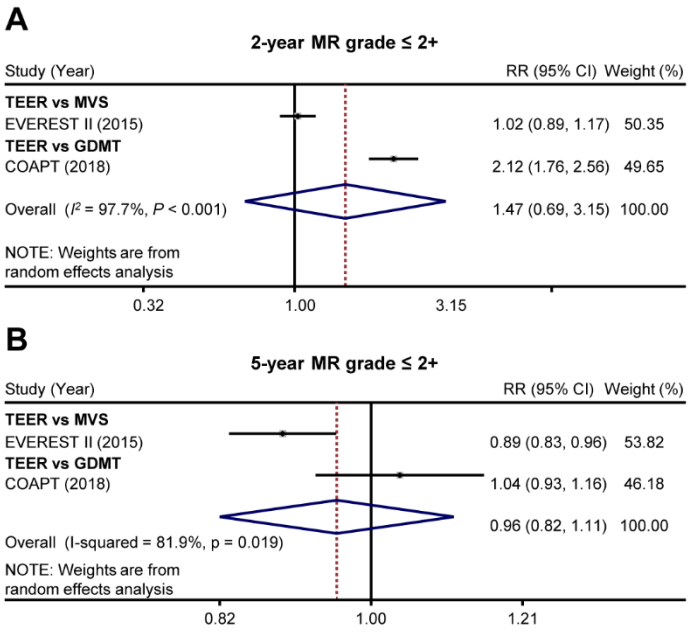

Figure S3. Forest plots for the impact of TEER on MR regression after 2-year (A) and 5-year (B) follow-up compared to MVS and GDMT.

(A) Comparison of the 2-year outcome in the EVEREST II study[1] and the COAPT study[2]; (B) Comparison of the 5-year outcome in the EVEREST II study[3] and the COAPT study[2].

Abbreviations: CI, confidence interval; GDMT, guideline-directed medical therapy; MR, mitral regurgitation; MVS, mitral valve surgery; RR, relative risk; TEER, transcatheter edge-to-edge repair.

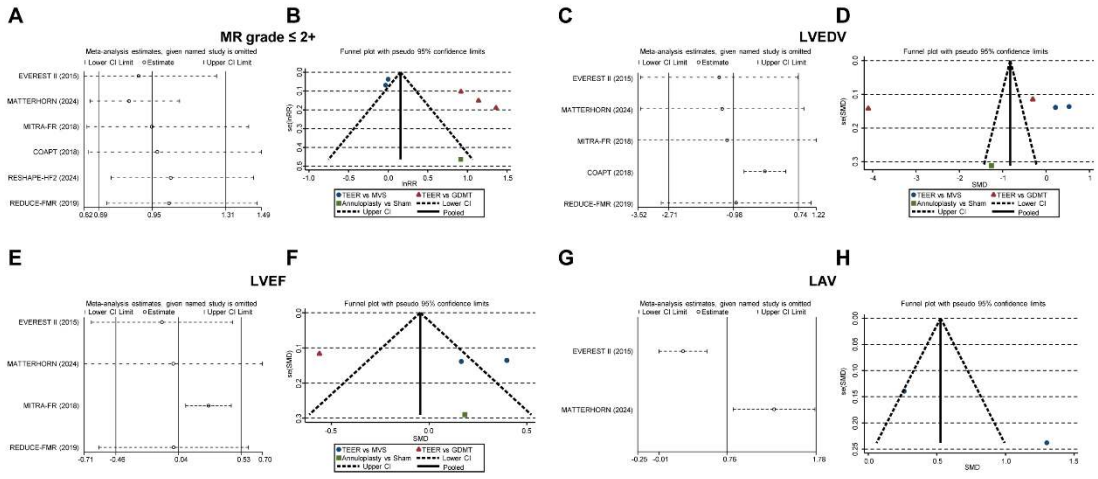

Figure S4. Leave-one-out heterogeneity source screening and publication bias for the meta-analysis on the impact of TMVr on MR regression and left heart improvement.

(A) Sensitivity analysis for meta-analysis on MR grade ≤ 2+; (B) Funnel plot for meta-analysis on MR grade ≤ 2+; (C) Sensitivity analysis for meta-analysis on LVEDV; (D) Funnel plot for meta-analysis on LVEDV; (E) Sensitivity analysis for meta-analysis on LVEF; (F) Funnel plot for meta-analysis on LVEF; (G) Sensitivity analysis for meta-analysis on LAV; (H) Funnel plot for meta-analysis on LAV.

Abbreviations: CI, confidence interval; GDMT, guideline-directed medical therapy; LAV, left atrial volume; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; MR, mitral regurgitation; MVS, mitral valve surgery; RR, relative risk; se, standard error; SMD, standard mean difference; TEER, transcatheter edge-to-edge repair; TMVr, transcatheter mitral valve repair.

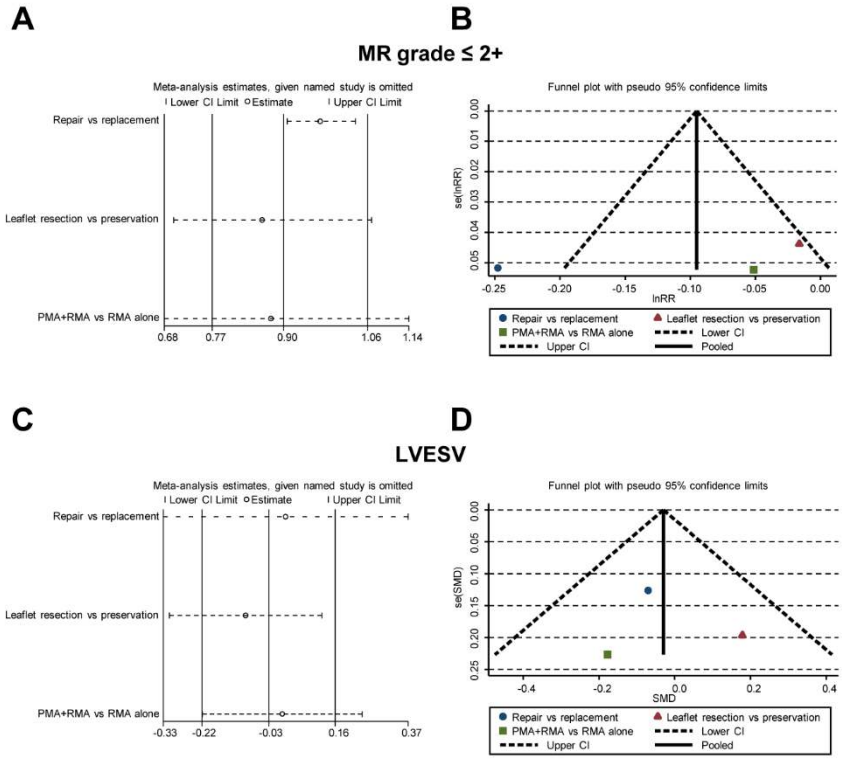

Figure S5. Leave-one-out heterogeneity source screening and publication bias for the meta-analysis on the impact of different types of MVS on MR regression and left ventricular change.

(A) Sensitivity analysis for meta-analysis on MR grade ≤ 2+; (B) Funnel plot for meta-analysis on MR grade ≤ 2+; (C) Sensitivity analysis for meta-analysis on LVESV; (D) Funnel plot for meta-analysis on LVESV.

Abbreviations: CI, confidence interval; LVESV, left ventricular end-systolic volume; MR, mitral regurgitation; MVS, mitral valve surgery; PMA, Papillary Muscle Approximation; RMA, restrictive mitral annuloplasty; RR, relative risk; se, standard error; SMD, standard mean difference.

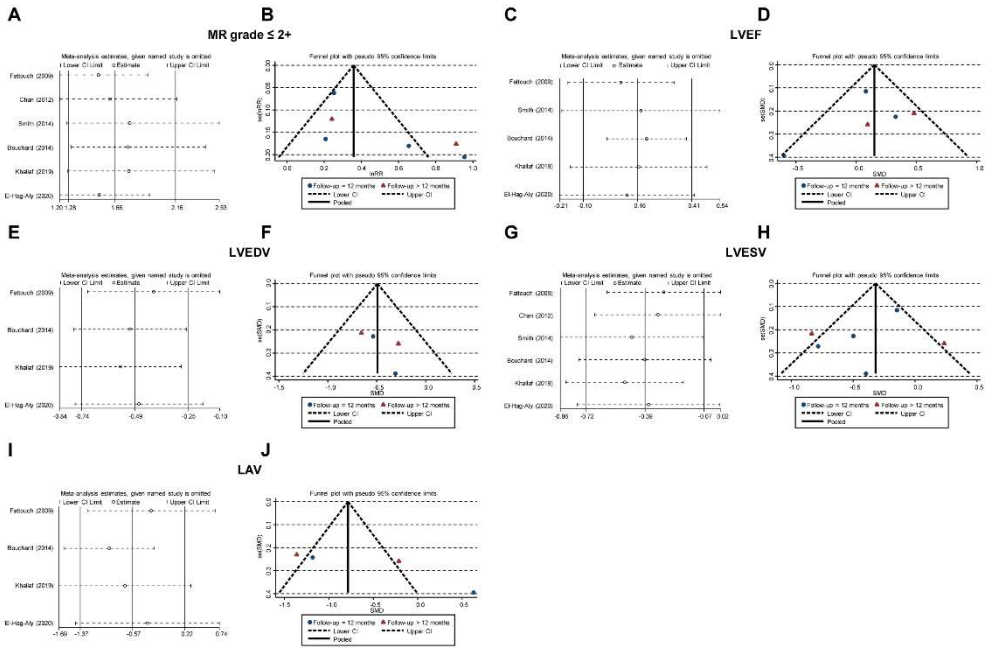

Figure S6. Leave-one-out heterogeneity source screening and publication bias for the meta-analysis on the impact of different types of MVS added to CABG on MR regression and left heart structures to CABG alone.

(A) Sensitivity analysis for meta-analysis on MR grade ≤ 2+; (B) Funnel plot for meta-analysis on MR grade ≤ 2+; (C) Sensitivity analysis for meta-analysis on LVEF; (D) Funnel plot for meta-analysis on LVEF; (E) Sensitivity analysis for meta-analysis on LVEDV; (F) Funnel plot for meta-analysis on LVEDV; (G) Sensitivity analysis for meta-analysis on LVESV; (H) Funnel plot for meta-analysis on LVESV; (I) Sensitivity analysis for meta-analysis on LAV; (J) Funnel plot for meta-analysis on LAV.

Abbreviations: CI, confidence interval; CABG, coronary artery bypass grafting; LAV, left atrial volume; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVESV, left ventricular end-systolic volume; MR, mitral regurgitation; se, standard error; SMD, standard mean difference.

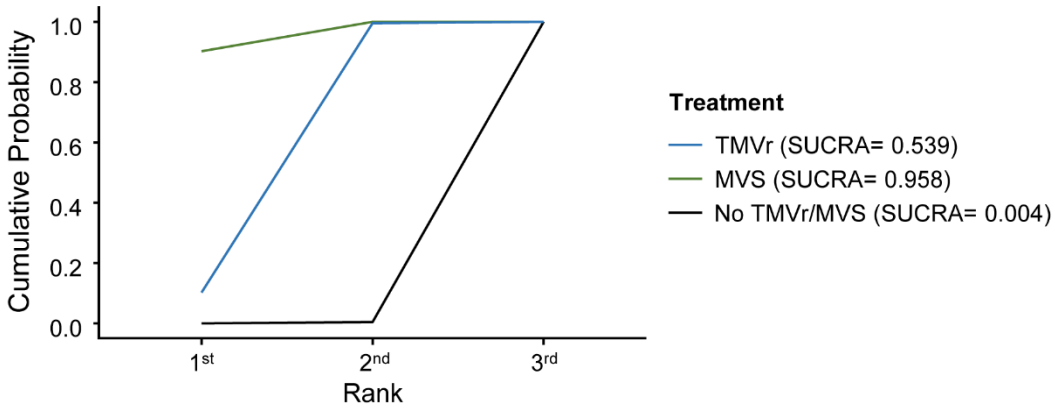

Figure S7. The cumulative probability of the rank for different treatments.

Abbreviations: MVS, mitral valve surgery; TMVr, transcatheter mitral valve repair.

II Supplemental tables

Table S1. Echocardiographic changes and study information of 24 included studies.

Study	Year	Country	Disease and MR criteria	Follow-up (months)	Treatment/ Controls	Sample Size	Mean age (years)	Female ratio (%)	ΔMR area (%)	ΔMR volume (%)	MR grade ≤ 2+ (N, %)	ΔLVEF (%)	ΔLVEDV (%)	ΔLVESV (%)	ΔLAV (%)
Medical therapy vs placebo/no corresponding drugs															
Seneviratne[4]	1994	Australia	Chronic HF with LVEF < 40% and MR area > 5 cm^2	3	ACEI	10	72.3±5.4	0.0	-77.78±27.16	-	-	-39.53±26.74	-4.69±5.47	-	-9.57±15.95
					Placebo	13	71.5±7.2	0.0	-21.11±29.44	-	-	16.67±22.98	1.56±8.59	-	-1.57±18.97
Sampaio[5]	2005	Brazil	Moderate-to-severe MR with area > 40% or 8 cm^2	12	ACEI	26	38±17	35.0	-26.60±27.13	-25.29±35.02	-	-1.56±9.38	-4.69±7.81	-4.76±8.33	-6.25±12.50
					Placebo	21	40±13	53.0	4.44±33.89	-1.81±81.50	-	-1.64±13.11	0.00±7.26	-2.44±10.98	-2.00±15.00
Wong[6]	2006	Canada	At least moderate isolated MR with LVEF > 60%	12	ACEI	12	53.2±2.4	30.4	-6.40±3.50	-	-	-1.10±2.10	-	-	-12.70±11.40
					Placebo	11	Overall	Overall	3.70±3.20	-	-	-0.40±1.80	-	-	5.00±17.60
PRIME[7]	2018	Korea	Chronic HF with LVEF 25%-50% and EROA > 0.1 cm^2 lasting > 6 months	12	ARNI	60	64.7±10.2	43.3	-29.74±48.72	-33.43±41.50	-	7.45±16.62	-11.80±16.31	-14.40±21.32	-14.89±20.91
					ARB	58	60.5±11.8	34.5	-8.57±50.00	-11.98±42.06	-	7.35±14.12	-5.71±17.12	-9.31±21.57	-2.20±23.64
Yin[8]	2024	China	AMI undergoing revascularization with MR area > 8 cm^2	12	ARNI	72	70.0±9.6	43.1	-3.21±2.18	-27.22±15.22	52.8	4.67±4.97	-19.13±13.99	-15.94±10.85	-
					ACEI	70	69.0±10.0	37.1	-1.83±2.81	-13.67±21.02	40.0	1.47±5.67	-4.00±14.54	-3.35±12.88	-
Capomolla[9]	2000	Italy	Chronic HF with LVEF < 50% and MR stroke volume > 30 ml	6	BBs	45	53.0±9.0	-	-80.60±25.37	-71.93±36.80	-	20.83±33.33	-4.93±28.17	-12.26±36.79	-
					No drugs	45	54.0±8.0	-	-13.56±40.68	-6.00±49.00	-	0.00±26.00	3.62±36.23	1.90±36.19	-
Sahoo[10]	2016	India	Moderate-to-severe MR with LVEF > 55%	3	BBs	48	30.2±12.8	64.4	-	-	8.3	0.80±10.32	-7.34±26.83	-12.18±46.37	-2.10±42.50
					Placebo	52	29.6±15.6	77.3	-	-	1.9	-1.97±10.91	4.07±44.14	13.10±66.03	3.46±38.97
EFFORT[11]	2024	Korea	Chronic HF with LVEF 35%-50% and EROA > 0.1 cm^2	12	SGLT-2i	58	65.4±11.5	36.5	-26.32±31.58	-27.00±30.27	-	4.73±9.69	-5.25±12.29	-7.72±15.25	-3.61±17.78
					GDMT	56	67.3±11.0	41.5	15.00±60.00	5.65±41.94	-	1.19±13.57	-6.06±18.28	-6.38±23.76	4.01±22.15

			lasting > 6 months											
DEFORM[12]	2025	China	Moderate-to-severe MR with LVEF <60% and EROA ≥ 0.2 cm^2	3	SGLT-2i	51	62.0±13.7	13.5	-25.00±33.45	-20.78±34.94	-	17.95±27.60	-1.81±24.63	-5.05±34.13	-5.67±10.77
					GDMT	50	65.3±13.9	26.9	-10.38±20.07	-6.7±20.85	-	4.87±24.29	0.81±22.84	-0.61±29.05	-0.97±7.06
TMVr vs non-transcatheter interventions															
EVEREST II[3]	2015	USA+Canada	Grade ≥ 3+ chronic MR with LVEF 25%-60%	12	TEER	181	67.0±12.7	36.5	-	-45.40±26.82	76.2	-5.37±13.17	-15.43±20.43	-7.34±34.75	-4.94±26.64
					MVS	89	64.7±12.6	33.8	-	-	78.7[1]	-10.92±15.51	-27.10±24.92	-11.84±45.97	-38.27±24.23[14]
										75.40±33.79[13]					
MATTERHORN[15]	2024	Germany	EROA ≥ 0.2 cm^2 or MR volume ≥ 30 ml, or MR fraction ≥ 50%	12	TEER	104	70.2±8.1	36.5	-	-	93.3	7.98±28.40	-5.18±40.00	-	-7.82±38.44
					MVS	104	70.9±7.8	43.3	-	-	93.3	3.23±29.03	-13.22±32.43	-	-16.92±30.43
MITRA-FR[15]	2018	France	MR volume ≥ 30 ml or EROA ≥ 0.2 cm^2	12	TEER	97	70.1±10.1	21.1	-48.39±37.03	-52.22±35.40	79.4	-9.01±26.69	-1.47±20.12	-	-
					GDMT	118	70.6±9.9	29.6	-12.90±38.23	-8.89±36.22	20.3	6.08±27.02	5.20±23.41	-	-
COAPT[16]	2018	USA	Grade ≥ 3+ MR with LVEF 20%-50%	12	TEER	302	71.7±11.8	33.4	-	-	65.9	-	-1.90±2.62	-	-
					GDMT	312	72.8±10.5	38.5	-	-	26.3	-	8.95±2.67	-	-
RESHAPE-HF2[17]	2024	Europe	Grade ≥ 3+ MR with LVEF 20%-50%	12	TEER	250	70.0±10.4	22.0	-	-	52.8	-	-	-	-
					GDMT	255	69.4±10.7	17.2	-	-	16.9	-	-	-	-
REDUCE-FMR[18]	2019	Europe	Grade ≥ 2+ MR with LVEF < 50%	12	Annuloplasty	68	70.1±9.7	27.6	-	-17.50±16.91	50.0	0.56±8.13	-5.57±6.38	-4.86±7.66	-
					Sham	20	69.1±8.9	27.3	-	8.71±36.17	20.0	-1.08±11.03	3.47±9.17	5.00±9.14	-
Comparison of different MVS types															
Acker[19]	2014	USA	Severe ischemic MR with EROA ≥ 0.4 cm^2	12	Repair	126	69.0±10.0	38.9	-	-	76.2	-	-	-10.64±41.90	-2.12±26.89
					Replacement	125	68.0±9.0	37.6	-	-	97.6	-	-	-7.61±44.82	-5.5±29.38
CAMRA CardioLink-2[20]	2022	Canada	MR and mitral valve prolapse	12	Resection	54	63.9±10.4	18.5	-	-	94.4	-9.52±8.87	-9.94±10.13	-4.57±16.14	-33.59±34.78
					Preservation	50	66.3±10.8	16.0	-	-	96.0	-5.70±7.98	-13.82±10.14	-7.44±15.98	-32.62±27.59
Nappi[21]	2016	Italy	Severe ischemic MR with EROA ≥ 0.4 cm^2 ischemic MR	12	PMA	40	62.9±7.0	41.7	-	-	92.5	22.57±15.86	-10.69±5.18	-12.17±5.71	-
					RMA	38	64.6±7.4	37.5	-	-	97.4	15.80±8.17	-9.77±5.62	-11.11±6.23	-
MVS+CABG vs CABG alone															
Fattouch[22]	2009	Italy	Moderate ischemic MR with a	32	MVS+CABG	45	64.0±9.0	37.5	-	-	100.0	14.29±21.43	-11.86±12.71	-17.78±14.44	-7.69±14.10

			recent AMI		CABG alone	48	66.0±7.0	35.2	-	-	39.6	4.65±18.60	-3.45±12.93	-4.55±17.05	15.79±19.74
Chan[23]	2012	Europe	Moderate ischemic MR with EROA 0.20-0.39 cm^2, or MR volume 30-59 mL, or MR fraction 30%-49%	12	MVS+CABG	27	70.9±10.5	26.5	-	-79.66±69.49	96.3	-	-	-28.32±32.65	-
					CABG alone	32	70.4±7.9	25.6	-	-28.84±59.87	50.0	-	-	-6.13±24.23	-
Smith[24]	2014	USA+Canada	Multiple coronary artery disease with moderate ischemic MR (EROA 0.20-0.40 cm^2, or the ratio of MR jet area to the left atrial area 20%-40%)	12	MVS+CABG	150	64.3±9.6	29.3	-	-	88.7	11.70±28.12	-	-16.78±47.99	-
					CABG alone	151	65.2±11.3	34.4	-	-	68.9	9.47±26.46	-	-9.49±51.46	-
Bouchard[25]	2014	Canada	Coronary artery disease with ischemic MR graded 2+	12	MVS+CABG	13	69.0±7.0	20.0	-54.36±36.92	-61.43±39.43	92.3	5.91±19.80	-10.98±31.37	-19.06±39.36	11.92±32.41
					CABG alone	14	65.0±12.0	12.5	-80.18±27.31	-81.84±24.93	85.7	23.86±36.99	0.00±39.06	1.74±62.20	-11.37±40.76
Khallaf[26]	2019	Egypt	Moderate ischemic MR with EROA 0.20-0.40 cm^2, or the ratio of MR jet area to the left atrial area 20%-40%	48	MVS+CABG	30	55.3±5.9	43.3	-	-	93.3	12.50±16.67	-4.75±8.36	-4.33±9.45	-3.26±7.67
					CABG alone	30	54.8±5.1	40.0	-	-	73.3	8.00±64.00	-2.63±6.84	-7.00±12.98	-1.22±11.22
El-Hag-Aly[27]	2020	Egypt	Moderate ischemic MR with LVEF ≥ 40% and EROA 0.20-0.40 cm^2	12	MVS+CABG	40	64.4±3.0	20.0	-90.00±13.33	-	97.5	6.91±13.2	-6.48±4.82	-9.20±7.26	-9.85±6.00
					CABG alone	40	63.3±4.0	30.0	-24.14±32.76	-	37.5	2.68±12.55	-3.57±5.97	-4.67±10.57	-0.66±9.21

Continuous variables were expressed as mean±SD, while categorical variables were expressed as n (%).

Data on MR volume, MR severity, and LAV in the EVEREST II trial were obtained from Gucuk's study in 2018, Feldman's study in 2011, and Qasim's study in 2013, respectively.

Abbreviations: ACEI, angiotensin-converting enzyme inhibitors; AMI, acute myocardial infarction; ARB, angiotensin receptor blockers; ARNI, angiotensin receptor and neprilysin inhibitors; BB, beta-blocker; CABG, coronary artery bypass grafting; EROA, effective regurgitant orifice area; GDMT, guideline-directed medical therapy; HF, heart failure; LAV, left atrial volume; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVESV, left ventricular end-systolic volume; PMA, papillary muscle approximation; MR, mitral regurgitation; MVS, mitral valve surgery; RMA, restrictive mitral annuloplasty; SD, standard deviation; SGLT-2i, sodium-glucose cotransporter-2 inhibitor; TEER, transcatheter edge-to-edge repair; TMVr, transcatheter mitral valve repair.

Table S2. Baseline characteristics of MR area, volume, etiology and LVEF.

Study	Mean age (years)	MR area (cm^2)	MR volume (mL)	MR etiology*	LVEF (%)
Medical therapy vs placebo/no corresponding drugs					
Seneviratne (1994)	72	8.6	-	Secondary, functional	29
Sampaio (2005)	40	9.2	240.9	Secondary, functional	63
Wong (2006)	53	4.0	-	Primary, degenerative	60
PRIME (2018)	63	4.0	35.4	Secondary, functional	34
Yin (2024)	70	7.9	55.9	Secondary, ischemic	46
Campolla (2000)	53	11.0	48.5	Secondary, functional	25
Sahoo (2016)	30	-	-	Primary, degenerative	62
EFFORT (2024)	66	4.0	35.3	Secondary, functional	42
DEFORM (2025)	64	5.9	43.9	Secondary, functional	38
TMVr vs non-transcatheter interventions					

MITRA-FR (2018)	70	6.2	45.0	Secondary, functional	33
COAPT (2018)	72	8.1	-	Secondary, functional	31
RESHAPE-HF2 (2024)	70	4.6	35.5	Secondary, functional	32
MVS+CABG vs CABG alone					
Fattouch (2009)	65	4.0	-	Secondary, ischemic	43
Chan (2012)	71	3.9	32.7	Secondary, ischemic	40
Smith (2014)	65	4.0	-	Secondary, ischemic	40
Bouchard (2014)	67	7.7	36.0	Secondary, ischemic	44
Khalaf (2019)	55	4.0	-	Secondary, ischemic	49
El-Hag-Aly (2020)	64	5.9	-	Secondary, ischemic	53

*MR etiology was categorized into 3 types: i) functional MR was defined as mitral valve incompetence due to alterations in LV and LA geometry, dyssynchrony, and imbalances between MV closing and tethering forces; ii) ischemic MR was defined as MR caused by frank

history and coronary angiography evidence of ischemic heart disease with no imaging evidences of primary MR; iii) degenerative MR was defined as primary lesions related to fibroelastic deficiency or myxomatous alterations according to the latest guideline for the management of valvular heart disease[28].

Abbreviations: LVEF, left ventricular ejection fraction; MR, mitral regurgitation.

Table S3. Meta-regression analysis on potential heterogeneity sources in the comparison of MR area changes between overall medications and controls.

Items	Study number	β (95% CI)	*P* value	Adjusted R^2 (%)
Mean age	8	0.004 (-0.087, 0.095)	0.915	0.0
Female ratio	7	-0.002 (-0.073, 0.068)	0.935	0.0
Baseline MR area	8	-0.052 (-1.894, 1.790)	0.941	0.0
Baseline LVEF	8	-0.002 (-0.081, 0.077)	0.947	0.0
MR etiology	8	0.007 (-1.421, 1.436)	0.990	0.0
Sample size	8	0.002 (-0.022, 0.026)	0.837	0.0
Follow-up period	8	0.003 (-0.157, 0.163)	0.965	0.0

Abbreviations: LVEF, left ventricular ejection fraction; MR, mitral regurgitation.

Table S4. Subgroup analysis on potential heterogeneity sources in the comparison of MR area changes between overall medications and controls.

Subgroup	Number of articles	*SMD* (95% CI)	Weight (%)	I^2 (%)	*P* for I^2
Mean age					
≥ 60 years	5	-0.69 (-0.99, -0.39)	66.83	59.6	0.042*
< 60 years	3	-1.88 (-2.82, -0.95)	33.17	80.4	0.006*
Female ratio					
≥39%	3	-0.59 (-0.86, -0.31)	49.85	25.8	0.260
<39%	4	-1.39 (-2.17, -0.61)	50.15	84.3	<0.001*
Baseline MR area					
≥ 6 cm^2	4	-1.34 (-2.13, -0.54)	49.38	87.9	<0.001*
< 6 cm^2	4	-0.92 (-1.49, -0.35)	50.62	82.5	<0.001*
Baseline LVEF					
≥40%	4	-1.11 (-1.70, -0.51)	48.95	80.3	0.002*
<40%	4	-1.17 (-1.97, -0.36)	51.05	90.5	<0.001*

MR etiology					
Non-ischemic	7	-1.26 (-1.79, -0.72)	85.24	86.1	<0.001*
Ischemic	1	-0.55 (-0.88, -0.21)	14.76	-	-
MR etiology					
Primary	1	-3.01 (-4.23, -1.78)	7.39	-	-
Secondary	7	-0.97 (-1.38, -0.55)	92.61	82.6	<0.001*
Sample size					
≥100	4	-0.69 (-0.99, -0.39)	57.99	0.0	0.411
<100	4	-1.88 (-2.82, -0.95)	42.01	71.2	0.015*
Follow-up period					
12 months	5	-0.91 (-1.37, -0.46)	63.49	78.2	0.001*
< 12 months	3	-1.46 (-2.57, -0.34)	36.51	91.0	<0.001*

Abbreviations: LVEF, left ventricular ejection fraction; MR, mitral regurgitation; SMD, standard mean difference.

Table S5. Meta-regression analysis on potential heterogeneity sources in the comparison of MR area changes between ACEI and placebo controls.

Items	Study number	β (95% CI)	*P* value	Adjusted R^2 (%)
Mean age	3	-0.007 (-0.892, 0.877)	0.934	0.0
Female ratio	3	-0.005 (-0.671, 0.661)	0.938	0.0
Baseline MR area	3	0.061 (-7.667, 7.788)	0.937	0.0
Baseline LVEF	3	0.006 (-0.834, 0.846)	0.946	0.0
MR etiology	3	-0.134 (-20.085, 19.817)	0.946	0.0
Sample size	3	0.010 (-1.022, 1.042)	0.922	0.0
Follow-up period	3	0.020 (-3.105, 3.144)	0.950	0.0

Abbreviations: ACEI, angiotensin-converting enzyme inhibitors; LVEF, left ventricular ejection fraction; MR, mitral regurgitation.

Table S6. Subgroup analysis on potential heterogeneity sources in the comparison of MR area changes between ACEI and placebo controls.

Subgroup	Number of articles	*SMD* (95% CI)	Weight (%)	I^2 (%)	*P* for I^2
Mean age					
≥ 70 years	1	-1.99 (-3.01, -0.97)	32.30	-	-
< 70 years	2	-1.94 (-3.88, 0.00)	67.70	87.6	0.005*
Female ratio					
≥39%	1	-1.02 (-1.64, -0.41)	38.65	-	-
<39%	2	-2.44 (-3.43, -1.45)	61.35	36.0	0.211
Baseline MR area					
> 4 cm^2	2	-1.42 (-2.35, -0.49)	70.95	60.4	0.112
≤ 4 cm^2	1	-3.01 (-4.23, -1.78)	29.05	-	-
Baseline LVEF					
≥60%	2	-1.94 (-3.88, 0.00)	67.70	87.6	0.005*

<60%	1	-1.99 (-3.01, -0.97)	32.30	-	-
MR etiology					
Non-ischemic	2	-1.42 (-2.35, -0.49)	70.95	60.4	0.112
Degenerative	1	-3.01 (-4.23, -1.78)	29.05	-	-
MR etiology					
Primary	1	-3.01 (-4.23, -1.78)	29.05	-	-
Secondary	2	-1.42 (-2.35, -0.49)	70.95	60.4	0.112
Sample size					
≥25	1	-1.02 (-1.64, -0.41)	38.65	-	-
<25	2	-2.44 (-3.43, -1.45)	61.35	36.0	0.211
Follow-up period					
12 months	2	-1.94 (-3.88, 0.00)	67.70	87.6	0.005*
< 12 months	1	-1.99 (-3.01, -0.97)	32.30	-	-

Abbreviations: ACEI, angiotensin-converting enzyme inhibitors; LVEF, left ventricular ejection fraction; MR, mitral regurgitation; SMD, standard mean difference.

Table S7. Meta-regression analysis on potential heterogeneity sources in the comparison of MR volume changes between overall medications and controls.

Items	Study number	β (95% CI)	*P* value	Adjusted R^2 (%)
Mean age	6	0.042 (-5.447, 5.531)	0.984	0.0
Female ratio				
Baseline MR volume	6	-0.005 (-0.687, 0.677)	0.984	0.0
Baseline LVEF	6	-0.036 (-5.208, 5.137)	0.986	0.0
MR etiology	6	0.632 (-21.61, 21.73)	0.994	0.0
Sample size	6	0.014 (-1.887, 1.916)	0.984	0.0
Follow-up period	6	-0.040 (-17.084, 17.004)	0.995	0.0

Abbreviations: LVEF, left ventricular ejection fraction; MR, mitral regurgitation.

Table S8. Subgroup analysis on potential heterogeneity sources in the comparison of MR volume changes between overall medications and controls.

Subgroup	Number of articles	*SMD* (95% CI)	Weight (%)	I^2 (%)	*P* for I^2
Mean age					
≥ 63 years	3	-0.71 (-0.93, -0.49)	53.73	5.7	0.346
< 63 years	3	-0.81 (-1.51, -0.12)	46.27	85.0	0.001*
Baseline MR volume					
≥ 45 mL	3	-0.89 (-1.50, -0.29)	47.00	81.0	0.005*
< 45 mL	3	-0.63 (-0.89, -0.37)	53.00	25.9	0.259
Baseline LVEF					
≥40%	3	-0.74 (-0.98, -0.50)	49.22	1.1	0.364
<40%	3	-0.83 (-1.44, -0.21)	50.78	85.3	0.001*

MR etiology					
Non-ischemic	5	-0.76 (-1.14, -0.38)	81.18	74.4	0.004*
Ischemic	1	-0.74 (-1.08, -0.40)	18.82	-	-
MR etiology					
Primary	0	-	-	-	-
Secondary	6	-0.76 (-1.06, -0.30)	34.91	52.0	0.149
Sample size					
≥100	4	-0.66 (-0.85, -0.48)	71.83	0.0	0.395
<100	2	-0.97 (-2.08, -0.14)	28.17	88.7	0.003*
Follow-up period					
12 months	4	-0.67 (-0.87, -0.47)	67.31	2.2	0.381
< 12 months	2	-1.00 (-2.01, 0.02)	32.69	90.8	0.008*

Abbreviations: LVEF, left ventricular ejection fraction; MR, mitral regurgitation; SMD, standard mean difference.

Table S9. Meta-regression analysis on potential heterogeneity sources in the comparison of postoperative MR grade≤2+ between TMVr and GDMT alone.

Items	Study number	β (95% CI)	*P* value	Adjusted R^2 (%)
Mean age	3	-0.024 (-6.842, 6.795)	0.972	0.0
Baseline MR area	3	-0.016 (-5.283, 5.251)	0.975	0.0
Baseline LVEF	3	0.042 (-11.231, 11.315)	0.970	0.0
MR etiology	3	0.137 (-2.590, 2.863)	0.849	0.0
Sample size	3	0.000 (-0.068, 0.067)	0.966	0.0
Follow-up period	3	0.100 (-1.434, 1.633)	0.806	0.0

Abbreviations: GDMT, guideline-directed medication therapy; LVEF, left ventricular ejection fraction; MR, mitral regurgitation; TMVr, transcatheter mitral valve repair.

Table S10. Subgroup analysis on potential heterogeneity sources in the comparison of postoperative MR grade≤2+ between TMVr and GDMT alone.

Subgroup	Number of articles	*RR* (95% CI)	Weight (%)	I^2 (%)	*P* for I^2
Mean age					
≥ 70 years	2	3.04 (1.98, 4.68)	67.86	76.3	0.040*
< 70 years	1	3.13 (2.33, 4.21)	32.14	-	-
Baseline MR area					
≥ 5 cm^2	2	3.04 (1.98, 4.68)	67.86	76.3	0.040*
< 5 cm^2	1	3.13 (2.33, 4.21)	32.14	-	-
Baseline LVEF					
≥32%	1	3.90 (2.69, 5.66)	25.63	-	-
<32%	2	2.73 (2.20, 3.37)	74.37	32.8	0.222
MR etiology					
Non-ischemic	3	3.02 (2.35, 3.88)	100.00	57.4	0.096
Ischemic	0	-	-	-	-

MR etiology					
Primary	0	-	-	-	-
Secondary	3	3.02 (2.35, 3.88)	100.00	57.4	0.096
Sample size					
≥400	2	2.73 (2.20, 3.37)	74.37	32.8	0.222
<400	1	3.90 (2.69, 5.66)	25.63	-	-
Follow-up period					
12 months	3	3.02 (2.35, 3.88)	100.00	57.4	0.096
< 12 months	0	-	-	-	-

Abbreviations: LVEF, left ventricular ejection fraction; MR, mitral regurgitation; RR, relative risk.

Table S11. Meta-regression analysis on potential heterogeneity sources in the comparison of postoperative MR grade≤2+ between MVS+CABG and CABG alone.

Items	Study number	β (95% CI)	*P* value	Adjusted R^2 (%)
Mean age	6	0.002 (-0.067, 0.071)	0.932	0.0
Baseline MR area	6	0.018 (-0.184, 0.219)	0.820	0.0
Baseline LVEF	6	0.004 (-0.097, 0.104)	0.920	0.0
MR etiology	6	0.127 (-0.203, 0.457)	0.367	0.0
Sample size	6	0.000 (-0.003, 0.003)	0.774	0.0
Follow-up period	6	0.000 (-0.022, 0.022)	0.982	0.0

Abbreviations: CABG, coronary artery bypass grafting; LVEF, left ventricular ejection fraction; MR, mitral regurgitation; MVS, mitral valve surgery.

Table S12. Subgroup analysis on potential heterogeneity sources in the comparison of postoperative MR grade≤2+ between MVS+CABG and CABG alone.

Subgroup	Number of articles	*RR* (95% CI)	Weight (%)	I^2 (%)	*P* for I^2
Mean age					
≥ 65 years	3	1.80 (1.15, 2.81)	47.15	80.3	0.006*
< 65 years	3	1.54 (1.10, 2.15)	52.85	83.5	0.002*
Baseline MR area					
> 4 cm^2	2	1.78 (0.76, 4.12)	30.38	90.6	0.001*
≤ 4 cm^2	4	1.62 (1.20, 2.18)	69.62	82.9	0.001*
Baseline LVEF					
≥45%	2	1.79 (0.81, 3.98)	32.45	91.4	0.001*
<45%	4	1.63 (1.17, 2.26)	67.55	83.0	0.001*
MR etiology					
Non-ischemic	0	-	-	-	-
Ischemic	6	1.66 (1.28, 2.16)	100.00	82.8	<0.001*

MR etiology					
Primary	0	-	-	-	-
Secondary	6	1.66 (1.28, 2.16)	100.00	82.8	<0.001*
Sample size					
> 60	3	1.99 (1.13, 3.50)	50.24	91.6	<0.001*
≤ 60[2]	3	1.42 (1.08, 1.86)	49.76	58.1	0.092
Follow-up period					
12 months	4	1.63 (1.17, 2.26)	66.18	81.3	0.001*
> 12 months	2	1.76 (0.85, 3.65)	33.82	91.8	<0.001*

Abbreviations: LVEF, left ventricular ejection fraction; MR, mitral regurgitation; RR, relative risk.

III Appendix

Appendix 1. Searching strategy for this meta-analysis.

No.	Search terms
#1	(((((("Mitral Valve Insufficiency"[Mesh]) OR (mitral valve insufficiency)) OR (Mitral Insufficiency)) OR (Mitral Regurgitation)) OR (Mitral Valve Incompetence)) OR (Mitral Valve Regurgitation)
#2	((("Randomized Controlled Trial" [Publication Type]) OR (Clinical Trials, Randomized)) OR (Trials, Randomized Clinical)) OR (Controlled Clinical Trials, Randomized)
#3	#1 AND #2
#4	((((((((((medical therapy) OR (optimal medical therapy)) OR (guideline directed medical therapy)) OR (angiotensin-converting enzyme inhibitors)) OR (ACEI)) OR (angiotensin II receptor blocker)) OR (ARB)) OR (Angiotensin Receptor-Neprilysin Inhibitor)) OR (ARNI)) OR (beta-blockers)) OR (sodium-glucose cotransporter 2 inhibitor)) OR (sglt2 inhibitor)) OR (sglt-2i)
#5	(((((mitral valve surgery) OR (mitral valve repair)) OR (mitral valve replacement)) OR (mitral valve annuloplasty)) OR (transcatheter mitral valve repair)) OR (transcatheter edge-to-edge repair)
#6	#4 OR #5
#7	#3 AND #6

Appendix 2. PRISMA 2020 Checklist.

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	1
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	7-8
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	8
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	9
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	9
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	9, Appendix
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	10
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	10
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each	9-10

Section and Topic	Item #	Checklist item	Location where item is reported
		study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	11-12
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	10
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	11
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	11
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	11
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	11
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	11
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	12
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	12
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	12
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	11

Section and Topic	Item #	Checklist item	Location where item is reported
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	13
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	13, Figure 1
Study characteristics	17	Cite each included study and present its characteristics.	13
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	13
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	14-18
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	14-18
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	14-17
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	14-17
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	14-17
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	14-17
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	14-18
DISCUSSION			

Section and Topic	Item #	Checklist item	Location where item is reported
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	19
	23b	Discuss any limitations of the evidence included in the review.	24-26
	23c	Discuss any limitations of the review processes used.	25
	23d	Discuss implications of the results for practice, policy, and future research.	19-24
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	28
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	28
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	28
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	28
Competing interests	26	Declare any competing interests of review authors.	29
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	29

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

IV References

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