

Supplementary material

Supplementary Table 1 Search strategy

PubMed ((diet OR nutrition) OR (exercise OR "physical activit*" OR workout) OR (lifestyle) OR (metformin) OR (GLP-1 RAs) OR (exenatide) OR (liraglutide) OR (albiglutide) OR (dulaglutide) OR (lixisenatide) OR (semaglutide) OR (tirzepatide) OR (SGLT2 inhibitors) OR (gliflozins) OR (dapagliflozin) OR (empagliflozin) OR (canagliflozin)) AND ((diabetes)) AND ("Clinical Trials as Topic"[Mesh] OR "randomized controlled trial"[pt] OR "controlled clinical trial"[pt] OR randomized[tiab] OR placebo[tiab] OR randomly[tiab] OR trial[tiab])

Filters applied: from 2000/1/1 - 2024/07/31

CENTRAL ((diet OR nutrition) OR (exercise OR "physical NEXT activit" OR workout) OR (lifestyle) OR (metformin) OR (GLP-1 RAs) OR (exenatide) OR (liraglutide) OR (albiglutide) OR (dulaglutide) OR (lixisenatide) OR (semaglutide) OR (tirzepatide) OR (SGLT2 inhibitors) OR (gliflozins) OR (dapagliflozin) OR (empagliflozin) OR (canagliflozin)) AND (diabetes)

with Cochrane Library publication date from Jan 2000 to Jul 2024, (Word variations have been searched)

Scopus TITLE-ABS-KEY ((diet OR nutrition) OR (exercise OR "physical activit*" OR workout) OR (lifestyle) OR (metformin) OR (GLP-1 RAs) OR (exenatide) OR (liraglutide) OR (albiglutide) OR (dulaglutide) OR (lixisenatide) OR (semaglutide) OR (tirzepatide) OR (SGLT2 inhibitors) OR (gliflozins) OR (dapagliflozin) OR (empagliflozin) OR (canagliflozin) AND (diabetes)) AND (LIMIT-TO (DOCTYPE , "ar")) AND (LIMIT-TO (LANGUAGE , "English")) AND (LIMIT-TO (PUBYEAR , 2024) OR LIMIT-TO (PUBYEAR , 2023) OR LIMIT-TO (PUBYEAR , 2022) OR LIMIT-TO (PUBYEAR , 2021) OR LIMIT-TO (PUBYEAR , 2020) OR LIMIT-TO (PUBYEAR , 2019) OR LIMIT-TO (PUBYEAR , 2018) OR LIMIT-TO (PUBYEAR , 2017) OR LIMIT-TO (PUBYEAR , 2016) OR LIMIT-TO (PUBYEAR , 2015) OR LIMIT-TO (PUBYEAR , 2014) OR LIMIT-TO (PUBYEAR , 2013) OR LIMIT-TO (PUBYEAR , 2012) OR LIMIT-TO (PUBYEAR , 2011) OR LIMIT-TO (PUBYEAR , 2010) OR LIMIT-TO (PUBYEAR , 2009) OR LIMIT-TO (PUBYEAR , 2008) OR LIMIT-

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TO (PUBYEAR , 2001) OR LIMIT-TO (PUBYEAR , 2000))

Supplementary Table 2 Subgroup and sensitivity analyses for metformin's overall effect intervention

Subgroup Analyses									
Factor	Subgroup	No of studies	OR (95% CI)	P-value	Cochran's Q statistic	Cochran's Q statistic P-value	I ² (95% CI)	P-value test of difference	
Similar countries	Scotland, UK	2	0.32 (0.08, 1.39)	0.13	0.00	0.98	0% (N/A)	0.12	
	Netherlands	2	1.06 (0.70, 1.62)	0.77	0.00	0.96	0% (N/A)		
Follow-up	Included	1	1.06 (0.62, 1.80)	0.84	N/A	N/A	N/A	0.58	
	Not included	3	0.82 (0.40, 1.86)	0.59	2.38	0.50	0% (0, 89%)		
Gender	Male more than female	2	0.75 (0.26, 2.16)	0.60	1.86	0.17	46% (N/A)	0.63	
	Female more than male	2	1.03 (0.53, 2.00)	0.94	0.49	0.49	0% (N/A)		
Mean age	More than 60 years	2	0.32 (0.08, 1.39)	0.13	0.00	0.98	0% (N/A)	0.12	
	Less than 60 years	2	1.06 (0.70, 1.62)	0.77	0.00	0.96	0% (N/A)		
Central adiposity as risk factor	Included	1	0.32 (0.06, 1.64)	0.17	N/A	N/A	N/A	0.17	
	Not included	3	1.04 (0.69, 1.58)	0.84	0.49	0.78	0% (0, 41%)		
	Included	1	0.33 (0.01, 8.50)	0.51	N/A	N/A	N/A	0.51	

Prediabetes and/or HY as risk factor	Not included	3	0.99 (0.366, 1.48)	0.96	1.96	0.38	0% (0, 87%)	
Metformin's daily dosage	1000 mg	2	1.06 (0.70, 1.62)	0.77	0.00	0.96	0% (N/A)	0.31
	1700 mg	1	0.32 (0.06, 1.64)	0.17	N/A	N/A	N/A	
	2000 mg	1	0.33 (0.01, 8.50)	0.51	N/A	N/A	N/A	
Intervention's duration	Up to 6 mo	2	1.06 (0.70, 1.62)	0.77	0.00	0.96	0% (N/A)	0.31
	Up to 12 mo	1	0.33 (0.01, 8.50)	0.51	N/A	N/A	N/A	
	Up to 24 mo	1	0.32 (0.06, 1.64)	0.17	N/A	N/A	N/A	

Sensitivity Analyses

Factor	Subgroup	No of studies	OR (95% CI)	P-value	Cochran's Q statistic	Cochran's Q statistic P-value	I ² (95% CI)
Effect of RCT with the largest sample size	Lower sample size	3	0.82 (0.40, 1.68)	0.59	2.17	0.34	8% (0, 33%)
Effect of RCTs with follow-up	Without follow-up	3	0.82 (0.40, 1.68)	0.59	2.17	0.34	8% (0, 33%)
Effect of RCTs without drop-out	With drop-out	2	0.32 (0.08, 1.39)	0.13	0.00	0.98	0% (N/A)

No, number; OR, odds ratio; CI, confidence interval; UK, United Kingdom; N/A, not applicable; mg, milligram; mo, months; HY, hypertension; RCT, randomized controlled trial.

Supplementary Table 3 Meta-regression for T2DM OR in metformin's overall interventions

Covariate	No of Studies	Coefficient b (95% CI)	SE	P-value	t
Studies' duration (mo)	4	0.002 (-0.09208, 0.09608)	0.048	0.965	0.05
Baseline risk	4	9.993 (2.51756, 17.46844)	3.814	0.12	2.62

T2DM, Type-2 Diabetes Mellitus, OR, odds ratio; No, numbers; CI, confidence interval; SE, standard error; mo, months