Supplemental Materials

Table S1. All-cause dementia was defined by a narrow Standardized Medical Dictionary for Regulatory Activities (MedDRA) Query (SMQ) of “dementia” including 21 preferred terms.

Table S2. Basic characteristics of 21 cardiovascular and renal outcome trials.

Table S3. Begg’s test and Egger’s test for the effects of DPP-4 inhibitors, GLP-1RAs, and SGLT2 inhibitors on risk of dementia.

Figure S1. The flowchart of the study selection. CENTRAL, Cochrane Central Register of Controlled Trials; DPP-4 inhibitors, dipeptidyl peptidase-4 inhibitors; GLP-1RAs, glucagon-like peptide-1 receptor agonists; SGLT2 inhibitors, sodium-glucose co-transporter-2 inhibitors.

Figure S2. Sensitivity analysis of the effects of novel glucose-lowering drugs on the risk of all-cause dementia (A) and vascular dementia (B) in participants with or without type 2 diabetes. OR, odds ratio; CI, confidence interval; DPP-4 inhibitors, dipeptidyl peptidase-4 inhibitors; GLP-1RAs, glucagon-like peptide-1 receptor agonists; SGLT2 inhibitors, sodium-glucose co-transporter-2 inhibitors.

Figure S3. The funnel plot for the effects of DPP-4 inhibitors, GLP-1RAs, and SGLT2 inhibitors on risk of dementia. DPP-4 inhibitors, dipeptidyl peptidase-4 inhibitors; GLP-1RAs, glucagon-like peptide-1 receptor agonists; SGLT2 inhibitors, sodium-glucose co-transporter-2 inhibitors.

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Outcome	Preferred Terms
All cause dementia	Clinical dementia rating scale score abnormal Corticobasal degeneration Creutzfeldt-Jakob disease Dementia Dementia Alzheimer's type Dementia of the Alzheimer's type, uncomplicated Dementia of the Alzheimer's type, with delirium Dementia of the Alzheimer's type, with delusions Dementia of the Alzheimer's type, with depressed mood Dementia with Lewy bodies Early onset familial Alzheimer's disease Frontotemporal dementia Hippocampal sclerosis Korsakoff's syndrome Mini mental status examination abnormal Mixed dementia Presenile dementia Prion disease Progressive supranuclear palsy Scatolia Senile dementia Variant Creutzfeldt-Jakob disease Vascular dementia
Vascular dementia	Vascular dementia

Table S2. Basic characteristics of 21 cardiovascular and renal outcome trials

Study	NCT	Trial name	No. of patients	Population	Patients with T2D (%)	Mean age (years)	Male (%)	White (%)	Mean duration of diabetes (years)	Comparisons	Median follow-up (years)
Scirica 2013[1]	NCT01107886	SAVOR-TIMI 53	16,492	T2D patients with a history of, or were at risk for cardiovascular events	100	65	67	75	10	Saxagliptin vs Placebo	2.1
White 2013[2]	NCT00968708	EXAMINE	5,380	T2D patients with either an acute myocardial infarction or unstable angina requiring hospitalization within the previous 15 to 90 days	100	61	68	73	7	Alogliptin vs Placebo	1.5
Green 2015[3]	NCT00790205	TECOS	14,671	T2D patients with established cardiovascular disease	100	66	71	68	12	Sitagliptin vs Placebo	3
Gantz 2017[4]	NCT01703208	OMNEON	4,192	T2D patients with established cardiovascular disease	100	64	70	81	12	Omarigliptin vs Placebo	1.8
Rosenstock 2019[5]	NCT01897532	CARMELINA	6,979	T2D patients with high cardiovascular risk	100	66	63	80	15	Linagliptin vs Placebo	2.2
Pfeffer 2015[6]	NCT01147250	ELIXA	6,068	T2D patients who had had a myocardial infarction or who had been hospitalized for unstable angina within the previous 180 day	100	60	70	75	9	Lixisenatide vs Placebo	2.1
Marso 2016[7]	NCT01179048	LEADER	9,340	T2D patients with high cardiovascular risk	100	64	64	78	13	Liraglutide vs Placebo	3.8
Marso 2016[8]	NCT01720446	SUSTAIN-6	3,297	T2D patients with established cardiovascular disease or chronic kidney	100	65	61	83	14	Semaglutide vs Placebo	2.1

				disease of stage 3 or higher or an age of 60 years or more with at least one cardiovascular risk factor							
Holman 2017[9]	NCT01144338	EXSCEL	14,752	T2D patients with or without previous cardiovascular disease	100	62	62	76	12	Exenatide vs Placebo	3.2
Hernandez 2018[10]	NCT02465515	HARMONY	9,432	T2D patients aged at least 40 years with cardiovascular disease	100	64	70	70	14	Albiglutide vs Placebo	1.6
Gerstein 2019[11]	NCT01394952	REWIND	9,901	T2D patients aged at least 50 years with either a previous cardiovascular event or cardiovascular risk factors	100	66	54	76	11	Dulaglutide vs Placebo	5.4
Husain 2019[12]	NCT02692716	PIONEER-6	3,183	T2D patients at high cardiovascular risk	100	66	68	72	15	Oral semaglutide vs Placebo	1.3
Gerstein 2021[13]	NCT03496298	AMPLITUDE-O	4,076	T2D patients with either a history of cardiovascular disease or current kidney disease plus at least one other cardiovascular risk factor	100	72	55	76	NR	Efpeglenatide vs Placebo	2.2
Zinman 2015[14]	NCT01131676	EMPA-REG OUTCOME	7,020	T2D patients with established cardiovascular disease	100	63	72	72	NR	Empagliflozin vs Placebo	3.1
Neal 2017[15]	NCT01032629/ NCT01989754	CANVAS Program	10,142	T2D patients with high cardiovascular risk	100	63	64	78	14	Canagliflozin vs Placebo	2.4
Wiviott 2018[16]	NCT01730534	DECLARE–TIMI 58	17,161	T2D patients had or were at risk for atherosclerotic cardiovascular disease	100	64	63	80	11	Dapagliflozin vs Placebo	4.2

Perkovic 2019[17]	NCT02065791	CREDENCE	4,401	T2D patients with albuminuric chronic kidney disease	100	63	66	67	16	Canagliflozin vs Placebo	2.6
Cannon 2020 [18]	NCT01986881	VERTIS-CV	8,246	T2D patients with atherosclerotic cardiovascular disease	100	64	70	88	13	Ertugliflozin vs Placebo	3.5
McMurray 2019[19]	NCT03036124	DAPA-HF	4,744	Patients with established heart failure and a reduced ejection fraction, regardless of the presence or absence of T2D	41.8	66	77	70	NR	Dapagliflozin vs Placebo	1.5
Heerspink 2020 [20]	NCT03036150	DAPA-CKD	4,304	Patients with chronic kidney disease	67.5	62	67	53	NR	Dapagliflozin vs Placebo	2.4
Packer 2020[21]	NCT03057977	EMPEROR-Reduced	3,730	Patients with class II, III, or IV heart failure and an ejection fraction of 40% or less	49.8	67	76	70	NR	Empagliflozin vs Placebo	1.3

T2D, Type 2 diabetes; CVD, cardiovascular disease; CKD, chronic kidney disease; NR, not reported

Table S3. Begg's test and Egger's test for the effects of DPP-4 inhibitors, GLP-1RAs, and SGLT2 inhibitors on risk of dementia.

	Begg's test	**Egger's test**
DPP-4 inhibitors	0.81	0.27
GLP-1RAs	0.71	0.53
SGLT2 inhibitors	0.76	0.91

DPP-4 inhibitors, dipeptidyl peptidase-4 inhibitors; GLP-1RAs, glucagon-like peptide-1 receptor agonists; SGLT2 inhibitors, sodium-glucose co-transporter-2 inhibitors

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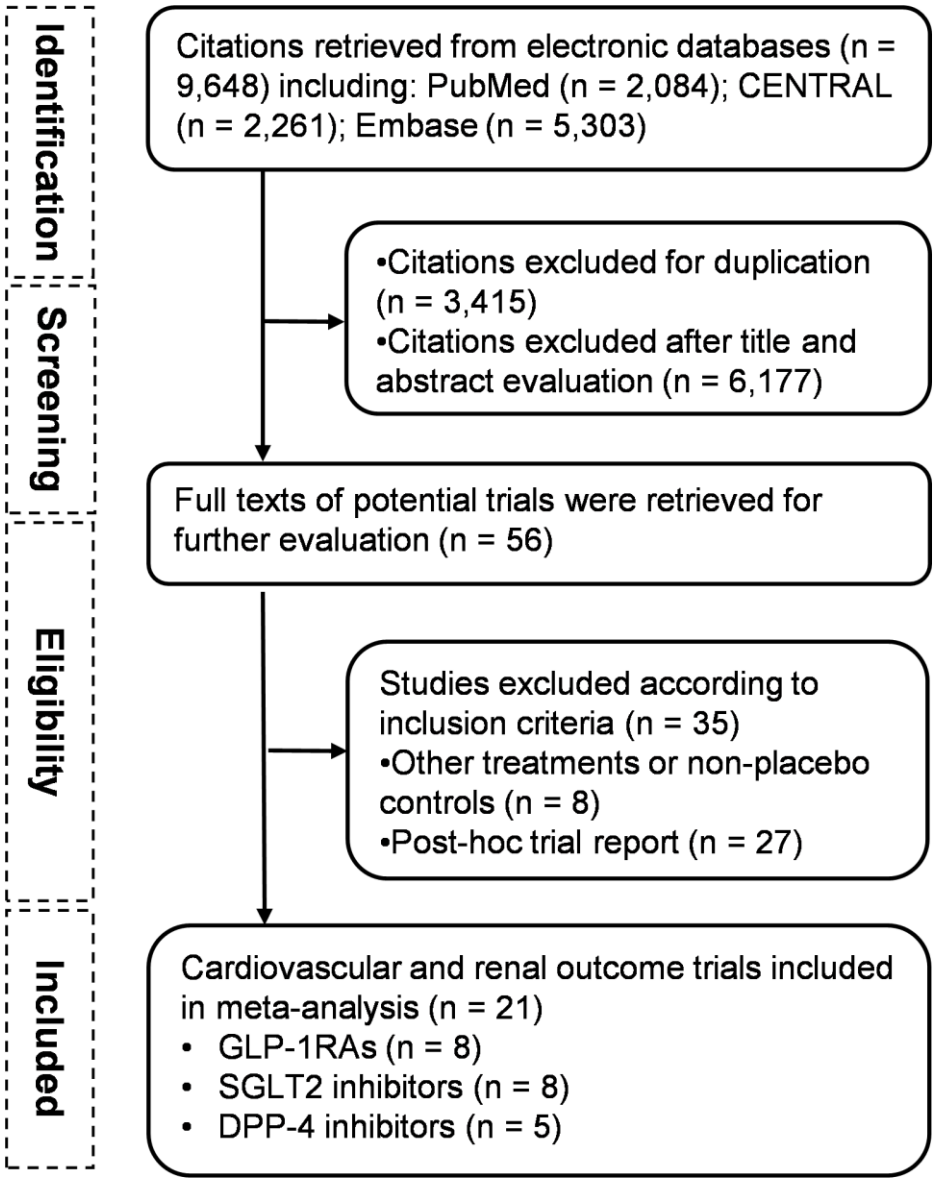

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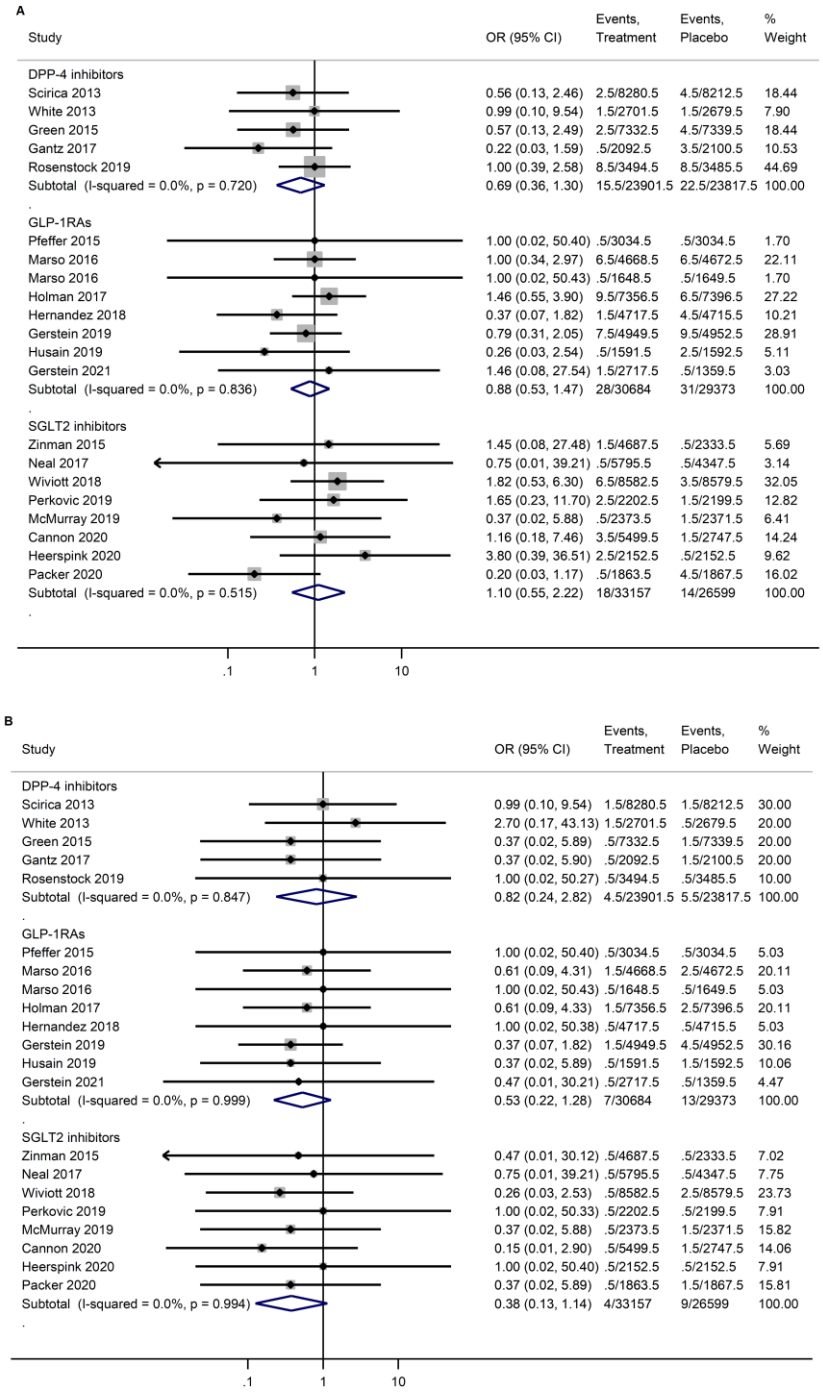

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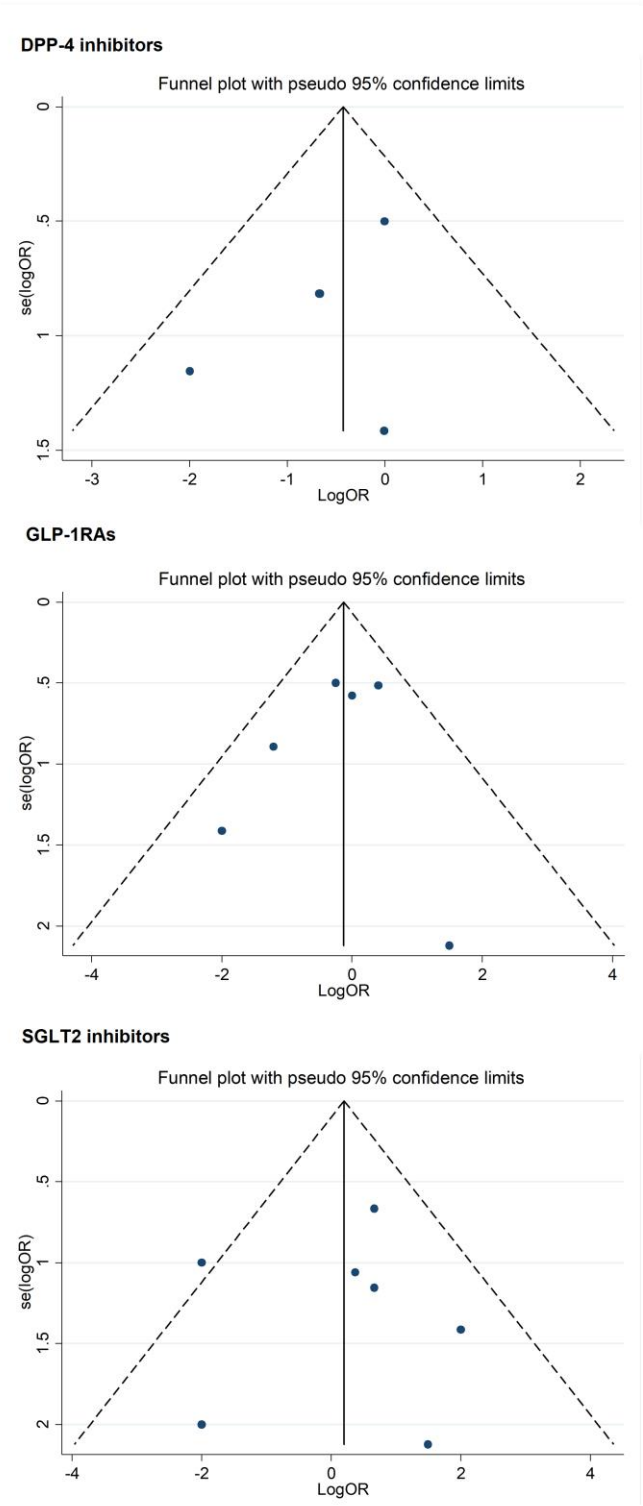

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