

Supplementary Material

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Supplementary Table 1 Data sources and search strategies

<p>PubMed (n=1934)</p>	<p>((("dipeptidyl peptidase iv inhibitors"[Pharmacological Action] OR "dipeptidyl peptidase iv inhibitors"[MeSH Terms] OR ("dipeptidyl peptidase"[All Fields] AND "iv"[All Fields] AND "inhibitors"[All Fields]) OR "dipeptidyl peptidase iv inhibitors"[All Fields] OR ("dipeptidyl"[All Fields] AND "peptidase"[All Fields] AND "iv"[All Fields] AND "inhibitor"[All Fields]) OR "dipeptidyl peptidase iv inhibitor"[All Fields] OR (((("dipeptidyl peptidase 4"[MeSH Terms] OR "dipeptidyl peptidase 4"[All Fields] OR ("dipeptidyl"[All Fields] AND "peptidase"[All Fields] AND "iv"[All Fields]) OR "dipeptidyl peptidase iv"[All Fields]) AND "inhibitor*"[All Fields]) OR (("dipeptidyl peptidase 4"[MeSH Terms] OR "dipeptidyl peptidase 4"[All Fields]) AND "inhibitor*"[All Fields]) OR ("DPP4"[All Fields] AND "inhibitor*"[All Fields]) OR ("dipeptidyl peptidase iv inhibitors"[Pharmacological Action] OR "dipeptidyl peptidase iv inhibitors"[MeSH Terms] OR ("dipeptidyl peptidase"[All Fields] AND "iv"[All Fields] AND "inhibitors"[All Fields]) OR "dipeptidyl peptidase iv inhibitors"[All Fields] OR "dpp 4 inhibitor"[All Fields]) OR ("dipeptidyl peptidase iv inhibitors"[Pharmacological Action] OR "dipeptidyl peptidase iv inhibitors"[MeSH Terms] OR ("dipeptidyl peptidase"[All Fields] AND "iv"[All Fields] AND "inhibitors"[All Fields]) OR "dipeptidyl peptidase iv inhibitors"[All Fields] OR ("dpp"[All Fields] AND "iv"[All Fields] AND "inhibitor"[All Fields]) OR "dpp iv inhibitor"[All Fields]) OR ("dipeptidyl peptidase iv inhibitors"[Pharmacological Action] OR "dipeptidyl peptidase iv inhibitors"[MeSH Terms] OR ("dipeptidyl peptidase"[All</p>
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	<p>Fields] AND "iv"[All Fields] AND "inhibitors"[All Fields]) OR "dipeptidyl peptidase iv inhibitors"[All Fields] OR "dpp 4 inhibitor"[All Fields] OR ("DPP-4"[All Fields] AND "inhibitor*"[All Fields]) OR ("dipeptidyl peptidase iv inhibitors"[Pharmacological Action] OR "dipeptidyl peptidase iv inhibitors"[MeSH Terms] OR ("dipeptidyl peptidase"[All Fields] AND "iv"[All Fields] AND "inhibitors"[All Fields]) OR "dipeptidyl peptidase iv inhibitors"[All Fields] OR ("dpp"[All Fields] AND "iv"[All Fields] AND "inhibitor"[All Fields]) OR "dpp iv inhibitor"[All Fields]) OR ("DPP-IV"[All Fields] AND "inhibitor*"[All Fields]) OR "DPP-4i"[All Fields])) OR ("alogliptin"[All Fields] OR "anagliptin"[All Fields] OR "dutogliptin"[All Fields] OR "evogliptin"[All Fields] OR "gemigliptin"[All Fields] OR "gosogliptin"[All Fields] OR "linagliptin"[All Fields] OR "omarigliptin"[All Fields] OR "saxagliptin"[All Fields] OR "sitagliptin"[All Fields] OR "teneligliptin"[All Fields] OR "trelagliptin"[All Fields] OR "vildagliptin"[All Fields])) AND ("randomized controlled trial"[Publication Type] OR "controlled clinical trial"[Publication Type] OR "randomized"[Title/Abstract] OR "randomly"[Title/Abstract] OR "random*"[Title/Abstract])) AND (humans[Filter])</p>	
<p>Web of Science (n=2791)</p>	<p>#1</p>	<p>TS= (dipeptidyl peptidase IV inhibitor or dipeptidyl peptidase IV inhibitor* or dipeptidyl-peptidase 4 inhibitor* or DPP4 inhibitor* or DPP 4 inhibitor or DPP IV inhibitor or DPP-4 inhibitor or DPP-4 inhibitor* or DPP-IV inhibitor or DPP-IV inhibitor* or DPP-4i)</p>
	<p>#2</p>	<p>TS=(alogliptin or anagliptin or dutogliptin or evogliptin or gemigliptin or gosogliptin or linagliptin or omarigliptin or</p>

		saxagliptin or sitagliptin or teneligliptin or trelagliptin or vildagliptin)
	#3	#1 OR #2
	#4	TS=("randomi?ed trial" OR "randomi?ed" OR "random allocation" OR random* OR "controlled trial" OR "randomized controlled trial")
	#5	#3 AND #4
EMBASE (n=4303)	#1	'dipeptidyl peptidase iv inhibitor' OR 'dipeptidyl peptidase iv inhibitor*' OR 'dipeptidyl-peptidase 4 inhibitor*' OR 'dpp4 inhibitor*' OR 'dpp 4 inhibitor' OR 'dpp iv inhibitor' OR 'dpp-4 inhibitor' OR 'dpp-4 inhibitor*' OR 'dpp-iv inhibitor' OR 'dpp-iv inhibitor*' OR 'dpp-4i'
	#2	alogliptin OR anagliptin OR dutogliptin OR evogliptin OR gemigliptin OR gosogliptin OR linagliptin OR omarigliptin OR saxagliptin OR sitagliptin OR teneligliptin OR trelagliptin OR vildagliptin
	#3	#1 OR #2
	#4	'randomi*ed controlled trial' OR 'randomi*ed trial'
	#5	#3 AND #4
	CENTRAL (n=3326)	#1
#2		("alogliptin" or "anagliptin" or "dutogliptin" or "evogliptin" or "gemigliptin" or "gosogliptin" or

		“linagliptin” or “omarigliptin” or “saxagliptin” or “sitagliptin” or “teneligliptin” or “trelagliptin” or “vildagliptin”) in Title Abstract Keyword
	#3	#1 OR #2
	#4	("randomi?ed trial" OR "randomi?ed" OR "random allocation" OR random* OR "controlled trial" OR "randomized controlled trial") in Title Abstract Keyword
	#5	#3 AND #4

Supplementary Table 2 Eligibility criteria of included studies in the meta-analysis

	Inclusion criteria	Exclusion criteria
Participants	Adults with T2DM	Pregnant women; without T2DM; receiving DPP-4 inhibitors or GLP-1 receptor agonists treatments before the trials
Intervention	DPP-4 inhibitors have been prescribed to patients with T2DM; DPP-4 inhibitors could be used as monotherapy or add-on treatments to other interventions in any dose and frequency.	Co-formulation of fixed-dose combinations of DPP4 inhibitors with other commonly used agents
Comparators	Placebo, non-incretin-based drugs; non-pharmaceutical treatment (e.g., diet and exercise)	Comparison of different members of the DPP-4 inhibitors class; comparison of different dose of one type of DPP-4 inhibitors.
Outcomes	Outcome: overall infection, serious infections,	Without outcome data available

	opportunistic infections and Infection of various systems.	
Study design	randomized controlled, cardiovascular outcome trials (CVOTs)	Reviews or non-CVOTs; cross-over study designs.

T2DM, type 2 diabetes mellitus; DPP-4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1.

Supplementary Table 3 Definition of various systems infection

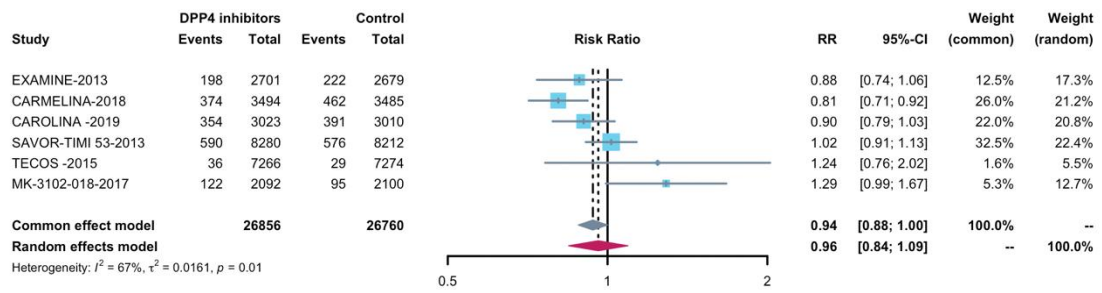
	Definition
Respiratory infection	Influenza, H1n1 influenza, Nasopharyngitis, sinusitis, Acute sinusitis, Chronic sinusitis, Rhinitis, Pharyngotonsillitis, Peritonsillar abscess, Tonsillitis, Viral tonsillitis, Chronic tonsillitis, Pharyngitis, Pharyngitis streptococcal, Ludwig angina, Epiglottitis, Laryngitis, bronchitis, Tracheobronchitis, Bronchiolitis, Bronchitis viral, Respiratory tract infection [RTI], RTI viral, Infective exacerbation of chronic obstructive airways disease, Infective exacerbation of bronchiectasis, upper RTI, lower RTI, Pneumonia, Bronchopneumonia, Lobar pneumonia, Atypical pneumonia, Bronchopulmonary aspergillosis, Pneumonia influenzal, Pneumonia bacterial, Pneumonia staphylococcal, Bronchopulmonary aspergillosis allergic, Pneumonia viral, Lung infection, Pneumonia chlamydial, Pneumonia respiratory syncytial viral, Pneumonia klebsiella, Pneumonia legionella, Pneumonia pneumococcal, Pneumonia streptococcal, Actinomycotic pulmonary infection, Pneumonia necrotizing, Pulmonary sepsis, Enterobacter pneumonia, Lung infection pseudomonal, Pneumonia mycoplasmal, Pulmonary tuberculosis, Infectious pleural effusion, Pleural infection bacterial, Mediastinitis
Urinary tract infection	Urinary tract infection (UTI), Escherichia UTI, UTI fungal, UTI bacterial, UTI pseudomonal, UTI enterococcal, Streptococcal UTI, UTI staphylococcal,

	<p>Pyelonephritis, Pyelonephritis acute, Bacterial pyelonephritis, Pyelonephritis chronic, Pyelonephritis fungal, Pyonephrosis, Cystitis, Cystitis escherichia, Emphysematous cystitis, Urethritis, Kidney infection, Renal abscess, Perinephric abscess, Pyelitis, Ureteritis, Urosepsis</p>
<p>Abdominal and gastrointestinal infection</p>	<p>Gastrointestinal infection, Gastroenteritis, Gastritis viral, Gastroenteritis norovirus, Enteritis infectious, Pseudomembranous colitis, Bacterial diarrhea, Gastrointestinal bacterial infection, Gastrointestinal viral infection, Gastroenteritis shigella, Intestinal sepsis, Clostridium colitis, Clostridium difficile colitis, Diarrhea infectious, Gastroenteritis viral, Campylobacter gastroenteritis, Gastroenteritis clostridia, Enterocolitis infectious, Infectious colitis, Diverticulitis, Peridiverticular abscess, Appendicitis, Appendicitis perforated, Appendiceal abscess, Intestinal gangrene, Colon gangrene, Small intestine gangrene, Abdominal infection, Abdominal abscess, Abdominal sepsis, Abdominal wall infection, Abdominal wall abscess, Peritonitis, Peritonitis bacterial, Fungal peritonitis, Infectious peritonitis, Peritoneal abscess, Abscess intestinal, Anal abscess, Perirectal abscess, Rectal abscess, Helicobacter infection, Helicobacter gastritis, Gastric ulcer helicobacter, Oesophageal candidiasis, Retroperitoneal abscess, Perihepatic abscess, Subdiaphragmatic abscess</p>
<p>Skin structures and soft tissue</p>	<p>Soft tissue infection, Skin infection Cellulitis, Cellulitis staphylococcal, Gangrene, Diabetic gangrene, Gas</p>

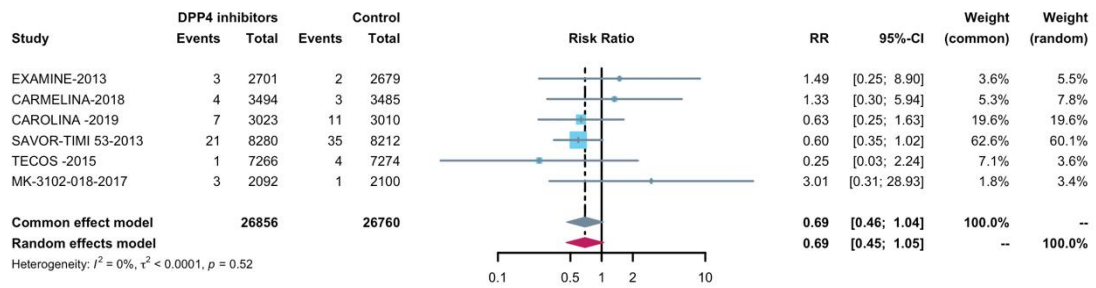
infection	gangrene, Cellulitis gangrenous, Abscess, Abscess limb, Subcutaneous abscess, Groin abscess, Scrotal abscess, Abscess jaw, Abscess neck, Chest wall abscess, Abscess soft tissue, Erysipelas, Carbuncle, Furuncle, Herpes simplex, Herpes zoster, Herpes zoster ophthalmic, Histoplasmosis cutaneous, Pilonidal cyst, Body tinea, Infected dermal cyst, Acarodermatitis, Groin infection, Skin bacterial infection, Staphylococcal skin infection, Infected skin ulcer, Paronychia, Diabetic foot infection, Perineal abscess
Bone infection	Osteomyelitis, Osteomyelitis chronic, Osteomyelitis viral, Osteomyelitis fungal, Arthritis infective, Arthritis bacterial, Septic arthritis streptococcal, Intervertebral discitis, Bursitis infective, Infective spondylitis, Bone abscess
Bloodstream infection	Sepsis, Septic shock, Escherichia sepsis, Thrombophlebitis septic, Staphylococcal sepsis, Bacterial sepsis, Wound sepsis, Sepsis syndrome, Klebsiella sepsis, Neutropenic sepsis, Candida sepsis, Enterococcal sepsis, Clostridium difficile sepsis, Urosepsis, Biliary sepsis, Intestinal sepsis, Post procedural sepsis, Bacteraemia, Acinetobacter bacteraemia, Escherichia bacteremia, Klebsiella bacteraemia, Streptococcal bacteraemia, Enterobacter bacteremia, Enterococcal bacteremia, Pneumococcal bacteremia, Pseudomonas sepsis, Viraemia

Supplementary Table 4 Risks of bias of individual studies in the meta-analysis

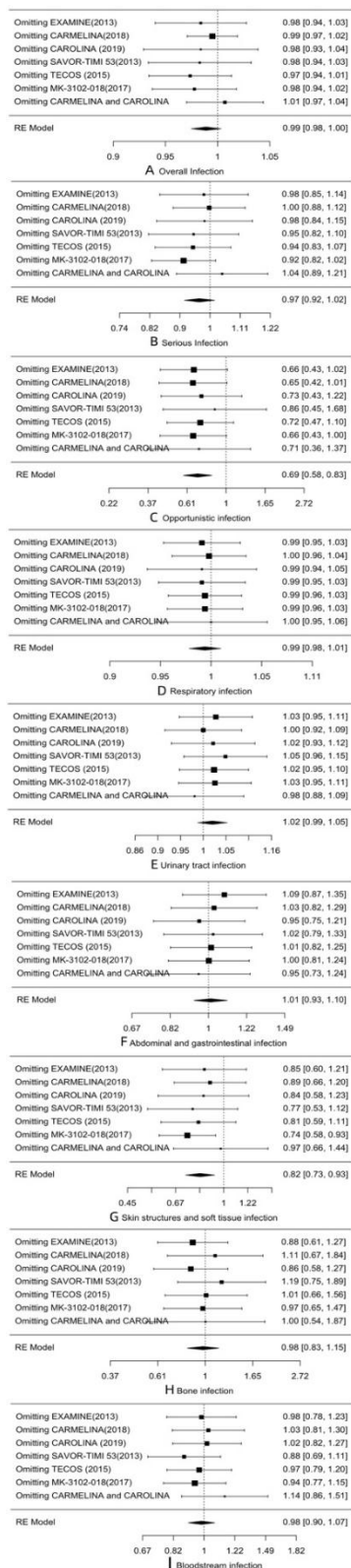
Trials	Domain 1	Domain 2	Domain 3	Domain 4	Domain 5
EXAMINE (2013) (NCT00968708)	low	low	low	some concerns	low
SAVOR-TIMI 53 (2013) (NCT01107886)	low	low	low	low	low
TECOS (2015) (NCT00790205)	low	low	low	low	high
MK-3102-018 (2017) (NCT01703208)	low	low	some concerns	low	some concerns
CARMELINA (2018) (NCT01897532)	low	low	low	low	low
CAROLINA (2019) (NCT01243424)	low	low	low	low	low



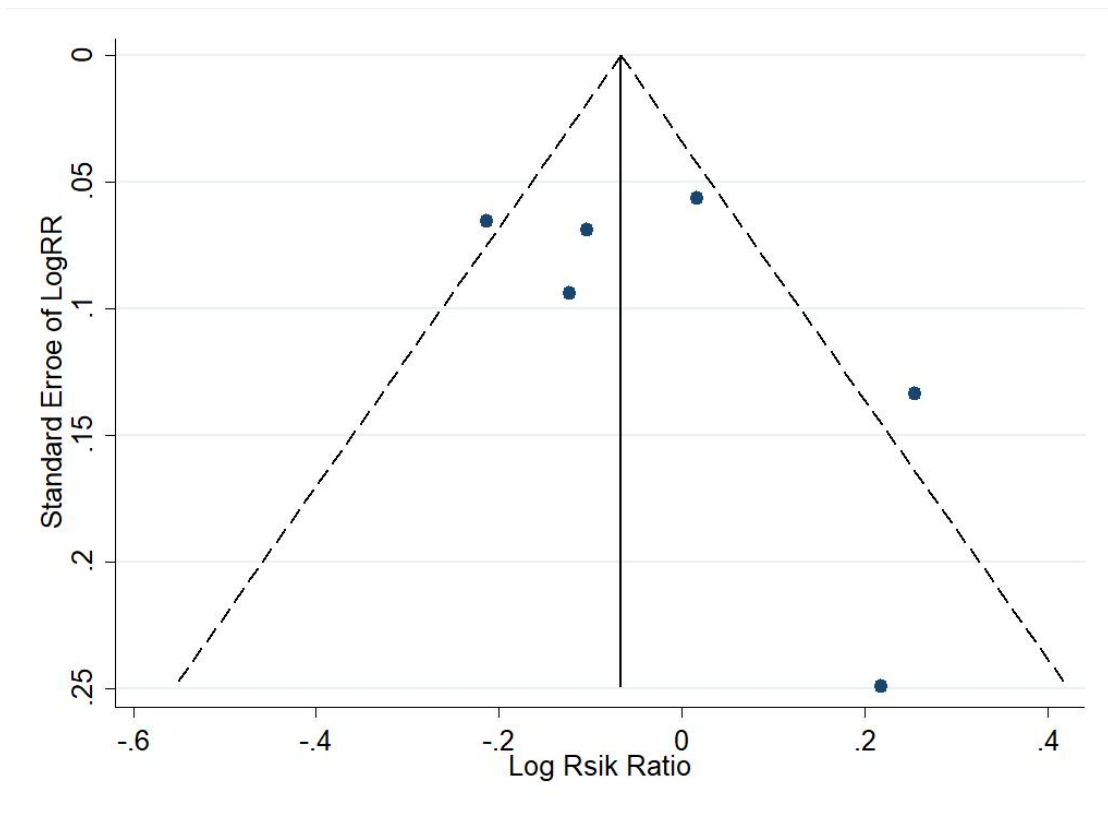
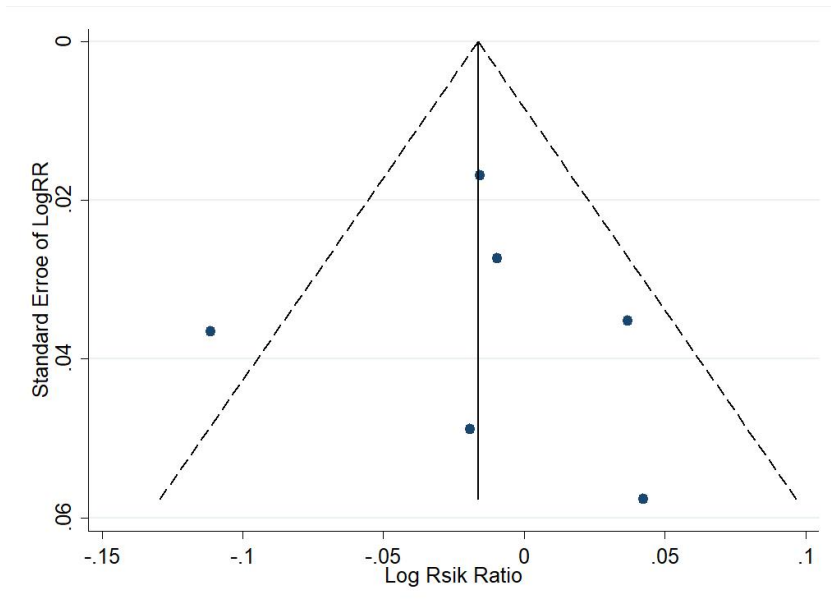
Supplementary Figure 1 Risk of serious infections for dipeptidyl peptidase-4 inhibitors treatment versus control.

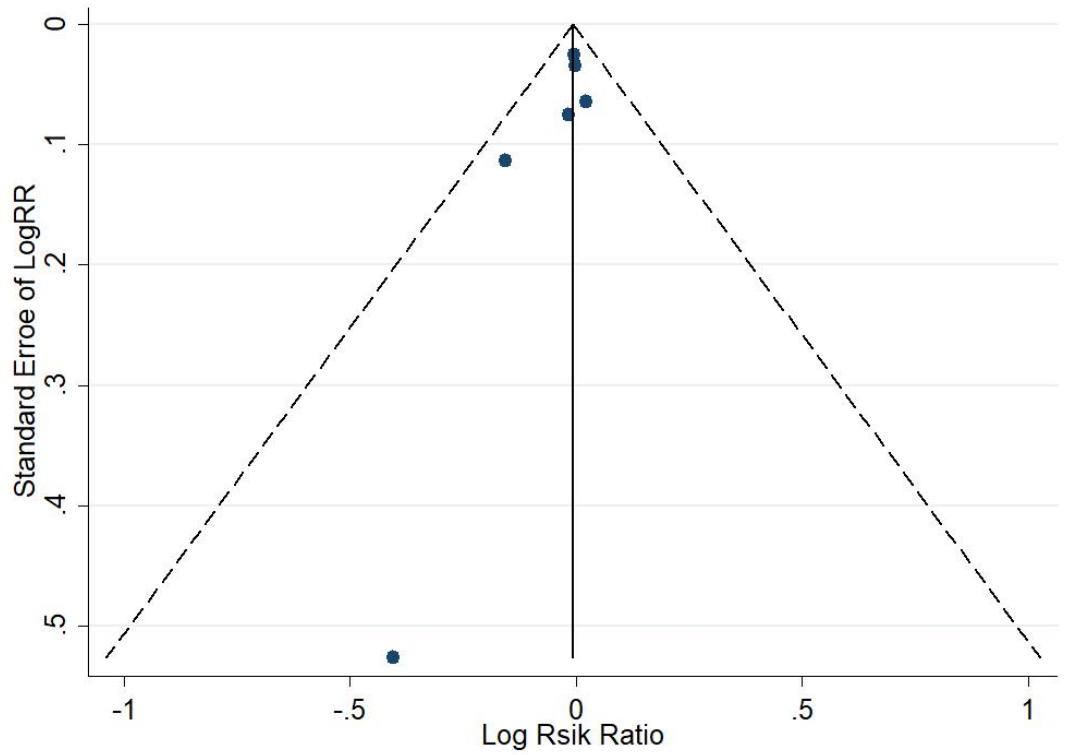
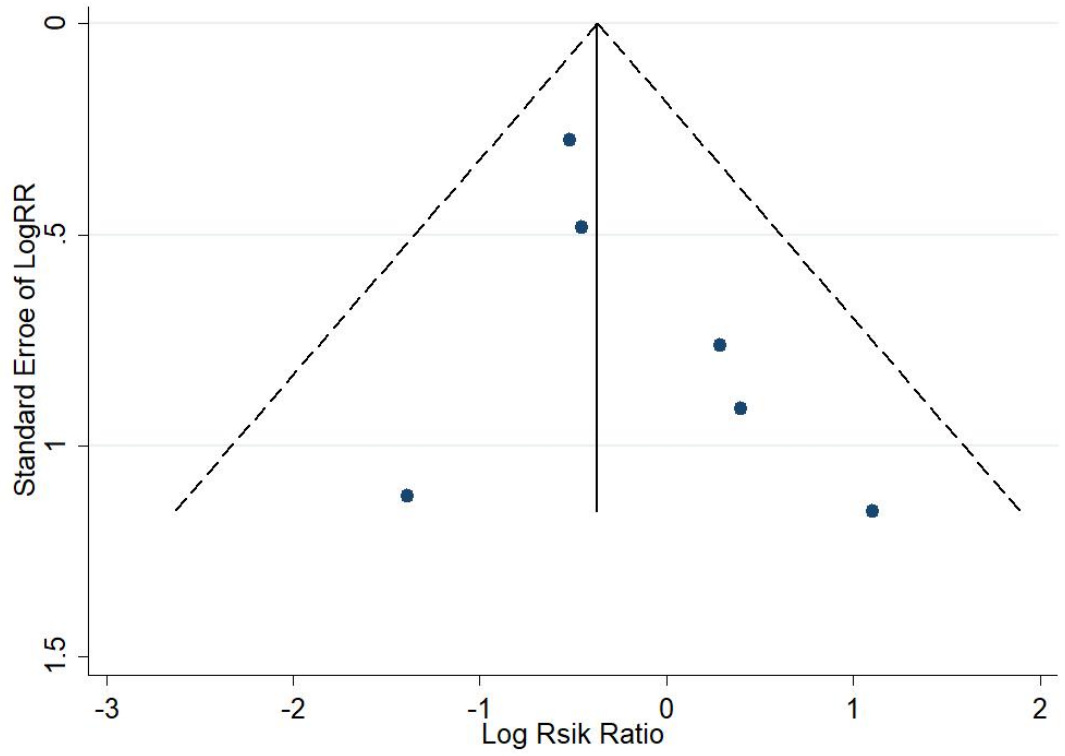


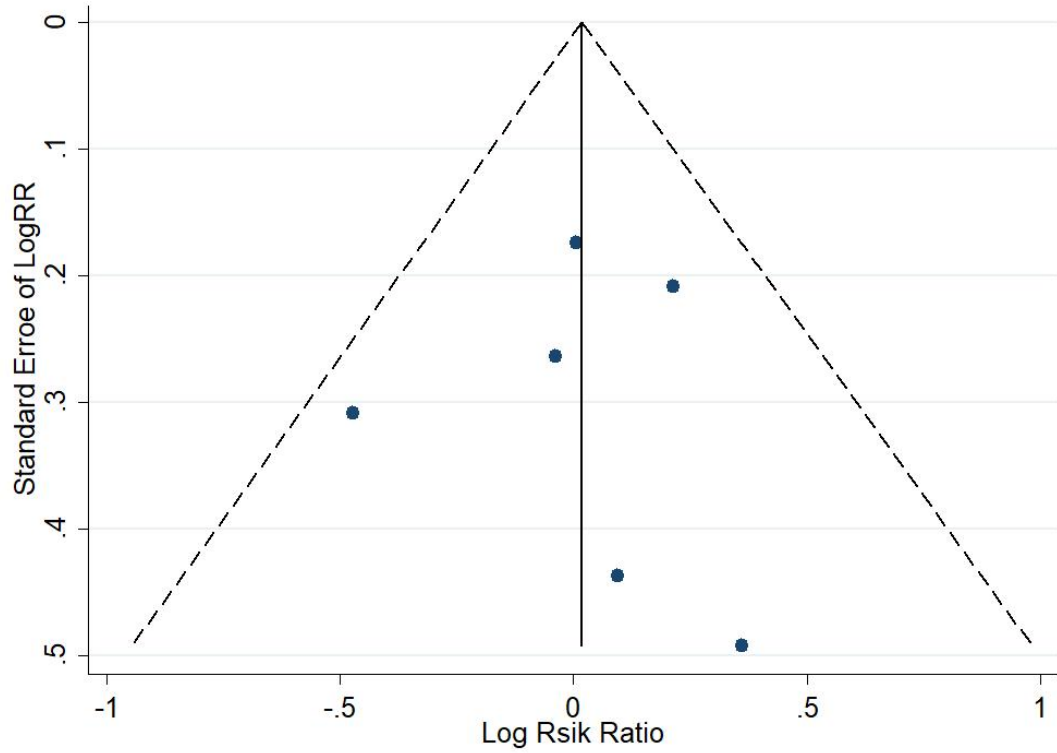
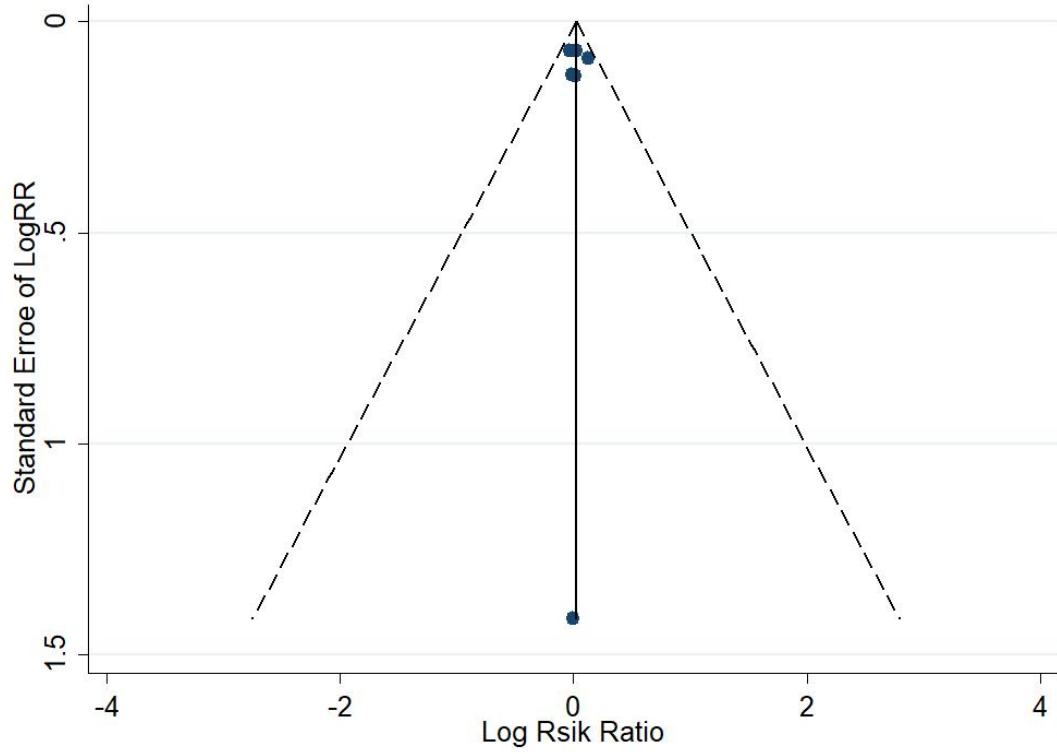
Supplementary Figure 2 Risk of opportunistic infections for dipeptidyl peptidase-4 inhibitors treatment versus control.

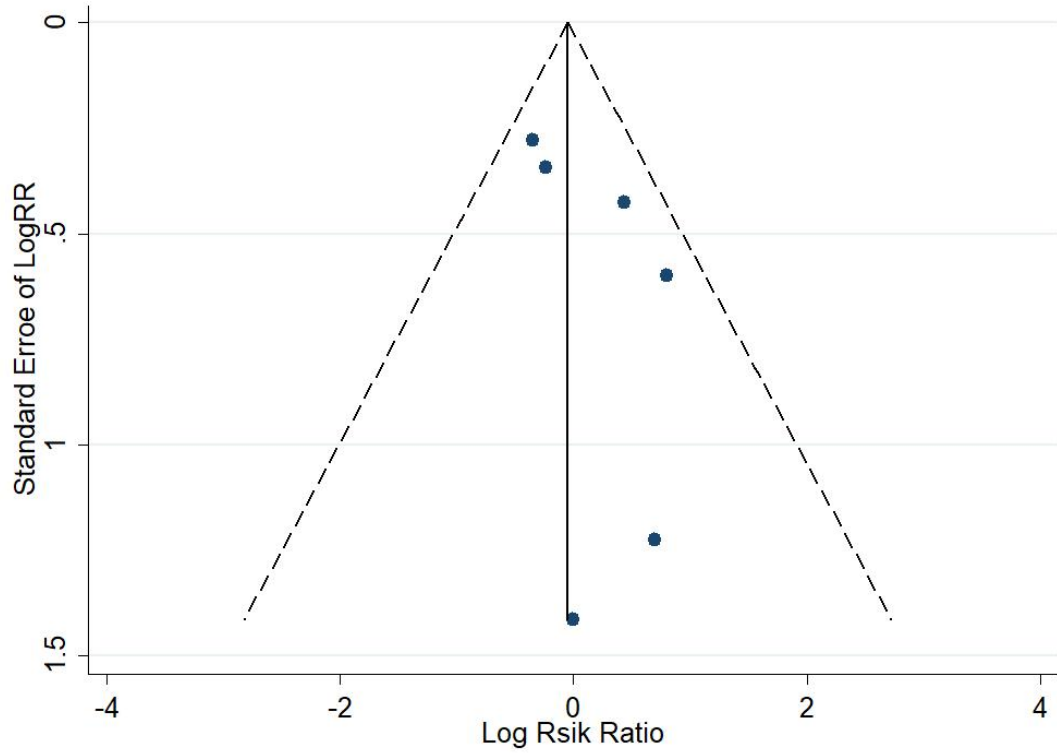
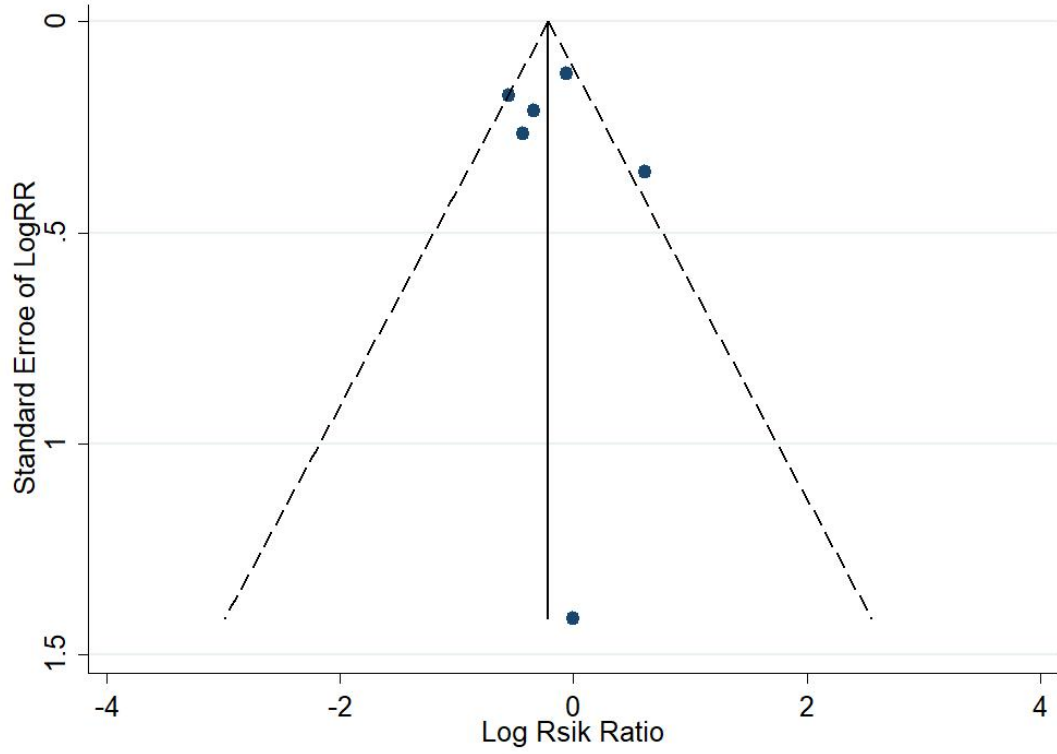


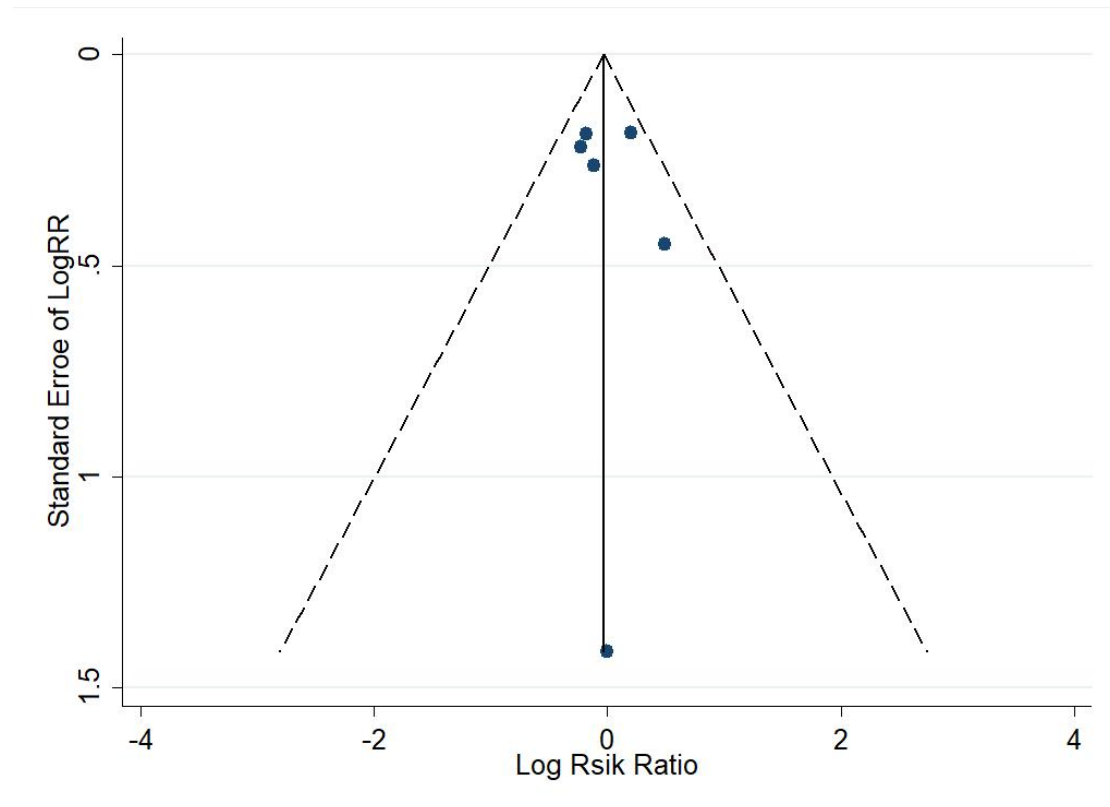
Supplementary Figure 3 Sensitivity analyses by omitting each trial one by one and removing studies with Linagliptin.











Supplementary Figure 4 Funnel plot of all eligible studies. A: Funnel plot of studies included for the association between DPP4i and the risks of overall infection; B: Funnel plot of studies included for the association between DPP4i and the risks of serious infection; C: Funnel plot of studies included for the association between DPP4i and the risks of opportunistic infection. D Funnel plot of studies included for the association between DPP4i and the risks of respiratory infection. E Funnel plot of studies included for the association between DPP4i and the risks of urinary tract infection. F Funnel plot of studies included for the association between DPP4i and the risks of abdominal and gastrointestinal infection. G Funnel plot of studies included for the association between DPP4i and the risks of skin structure and soft tissue infection. H Funnel plot of studies included for the association between DPP4i and the risks of bone infection; I Funnel plot of studies included for the association between DPP4i and the risks of bloodstream infection.