

Supplementary Table S1 PRISMA 2020 Checklist

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Supplementary Figure S9 Funnel plot for incidence of CKD between PPIs and H2RAs group

Supplementary Table S1 PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	Page 1, 2
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	-
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	Page 1, 2
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	Page 2
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	Page 2
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.	Page 2
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Page 2, Supplementary Table 1
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.	Page 2
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.	Page 3
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 study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	Page 3
	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.	Page 3
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.	Page 3,4

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.	Page 4
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)).	Table 1
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	Page 4
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	Page 4
	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.	Page 4
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	Page 4
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	Page 4
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	Page 3, 4
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	Page 3, 4
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.	Page 4, Supplementary Figure 1
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	Supplementary Figure 1
Study characteristics	17	Cite each included study and present its characteristics.	Page 4, Table 1
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Page 4, Supplementary Table 2, 3

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.	Page 7
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	Page 4, Supplementary Table 2, 3
	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.	Page 7
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	Page 7, 8
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	Page 7, 8
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	Page 4
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	Page 4, Supplementary Table 3, 4
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	Page 8
	23b	Discuss any limitations of the evidence included in the review.	Page 9, 10
	23c	Discuss any limitations of the review processes used.	Page 9, 10
	23d	Discuss implications of the results for practice, policy, and future research.	Page 9, 10
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.	Page 2
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	Page 2
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	Page 2

Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	Page 10
Competing interests	26	Declare any competing interests of review authors.	Page 10
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.	Page 10

Supplementary Table S2 Risk of bias assessment using Newcastle-Ottawa-Scale for observational studies for incidence of CKD between PPIs and non-PPIs group

Study	Selection				Comparability	Exposure			
	Representativeness of the exposed cohort	Selection of the non exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Comparability of cohorts on the basis of the design or analysis	Assessment of outcome	Was followed-up long enough for outcomes to occur	Adequacy of follow up of cohorts	Total score
Lazarus et al (ARIC)	★	★	★	★	★★	★	★	★	9
Lazarus et al (GHS)	★	★	★	★	★★	★	★	★	9
Hart et al	★	★	★	★	★★	★	★	0	8
Rodríguez-Poncelas et al	★	★	★	★	★★	★	★	0	8
Arora et al	★	★	★	★	★★	★	0	★	8
Dos Santos et al	★	★	★	★	★★	★	★	★	9
Zhang et al	★	★	★	★	★★	★	★	★	9
Yang et al	★	★	★	★	★★	★	0	0	7
Moayyedi et al	★	★	★	★	★★	0	★	★	8

Supplementary Table 2 Risk of bias assessment using Newcastle-Ottawa-Scale for observational studies for incidence of CKD between PPIs and H2RAs group

Study	Selection	Comparability	Exposure
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	Representativeness of the exposed cohort	Selection of the non exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Comparability of cohorts on the basis of the design or analysis	Assessment of outcome	Was followed-up long enough for outcomes to occur	Adequacy of follow up of cohorts	Total score
Kweon et al (NHIS-CDM)	★	★	★	★	★★	★	★	★	9
Kweon et al (6-hospital-CDM)	★	★	★	★	★★	★	★	★	9
Lazarus et al (ARIC)	★	★	★	★	★★	★	★	★	9
Lazarus et al (GHS)	★	★	★	★	★★	★	★	★	9
Xie et al	★	★	★	★	★★	★	★	0	8
Pannoi et al	★	★	★	★	★★	★	★	★	9

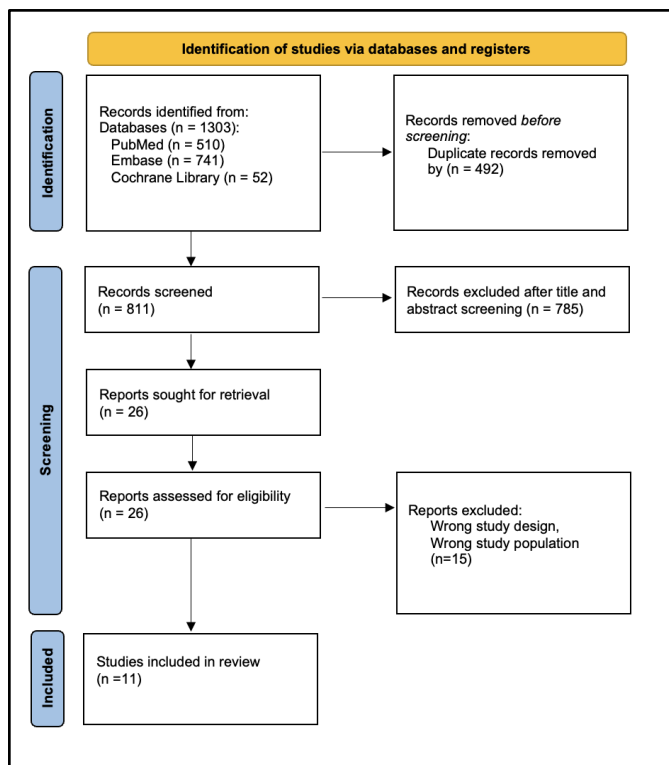
Supplementary Table S3 Certainty of evidence using GRADE approach

No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Certainty (overall score)
Outcome: Incidence of CKD between PPIs and non-PPIs							
8 studies with 9 cohorts	8 observational cohorts, 1 randomised study	not serious	serious	not serious	not serious	none	⊕⊕⊕⊕ very low
Outcome: Incidence of CKD between PPIs and H2RAs							
4 studies with 6 cohorts	Observational	not serious	serious	not serious	not serious	none	⊕⊕⊕⊕ very low

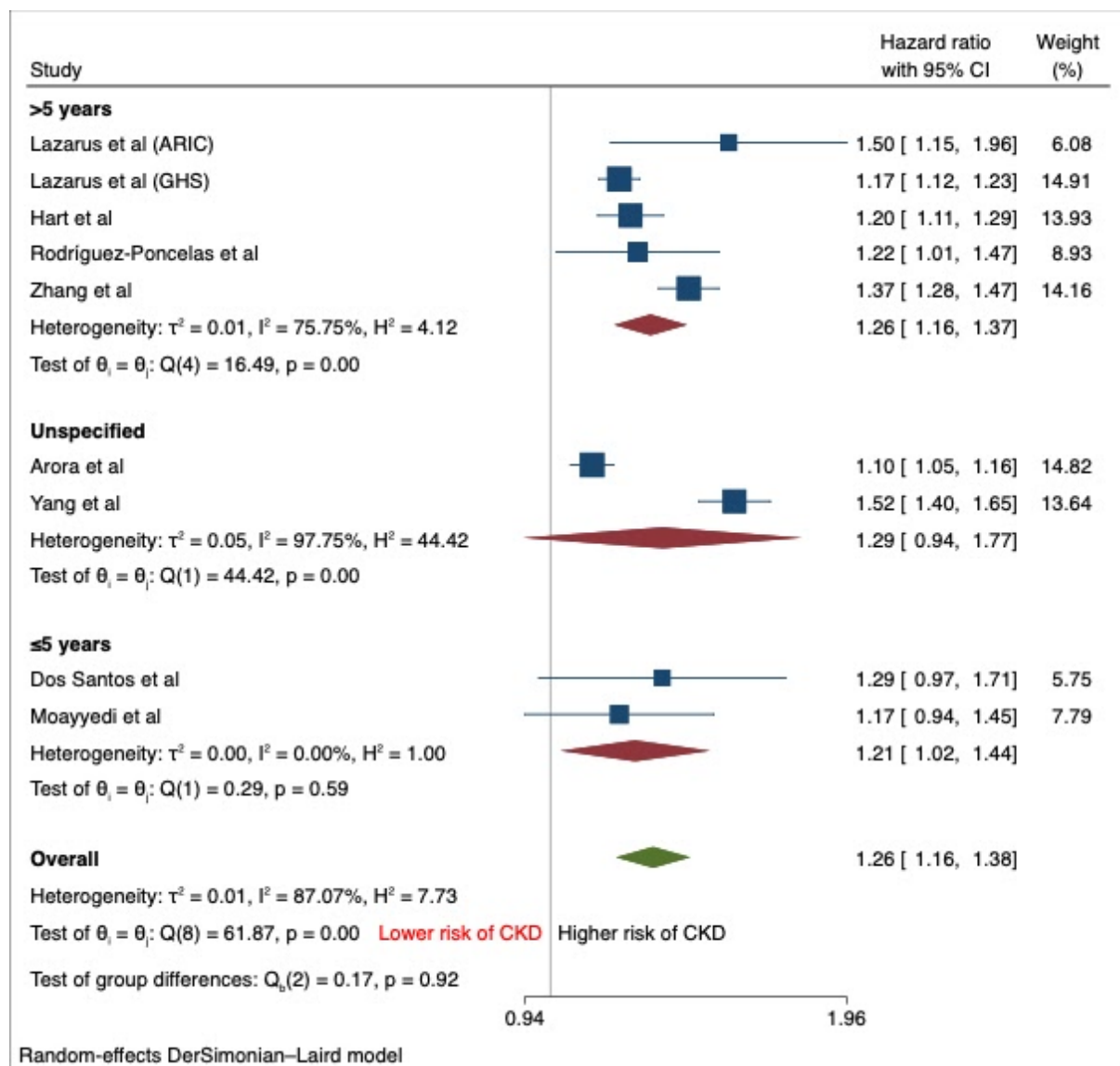
Supplementary Table S4 Covariates adjustment in the included studies

Study	Effect size adjustment
Kweon et al (NHIS-NSC)	PSM with gender, age group, index year, post-observation time, Charlson comorbidity index
Kweon et al (6-hospital CDM)	PSM with gender, age group, index year, post-observation time, Charlson comorbidity index
Lazarus et al (ARIC)	Age, sex, race, study center, education, health insurance status, baseline estimated glomerular filtration rate, urinary albumin creatinine ratio, cigarette smoking status, body mass index, systolic blood pressure, diabetes, cardiovascular disease, antihypertensive medication use, and anticoagulant medication use.
Lazarus et al (GHS)	Age, sex, race, eGFR, smoking status, BMI, systolic blood pressure, diabetes, history of cardiovascular disease, antihypertensive medication use, anticoagulant medication use, and statin, aspirin, and NSAID use.
Hart et al	PSM and further adjustment for heart failure, hypertension, hyperlipidemia, H. pylori infection, and use of H2-receptor blockers
Rodríguez-Poncelas et al	Age, gender, impaired fasting glucose, type 2 diabetes, obesity, high-normal blood pressure, hypertension, low-HDL-cholesterol, hightriglycerides level, metabolic syndrome, chronic diseases, tobacco consumption, alcohol consumption, cardiovascular disease, antihypertensive treatment, hypoglucemiant treatment, hypolipemiant treatment, non-steroidal antiinflammatory drugs, other countries origin.
Arora et al	Age, sex, race, GI and pre-PPI comorbidities
Xie et al	Baseline eGFR, age, race, sex, diabetes mellitus, hypertension, cardiovascular disease, peripheral artery disease, cerebrovascular disease, chronic lung disease, hepatitis C, HIV, dementia, gastroesophageal reflux disease, upper gastrointestinal tract bleeding, ulcer disease, H. pylori infection, Barrett esophagus, achalasia, stricture, and esophageal adenocarcinoma.
Dos Santos et al	Age, sex and per capita household income, excessive alcohol consumption, smoking, obesity, cardiovascular disease, diabetes, hypertension, use of NSAIDs, ARBs and ACEs.
Pannoi et al	Age category, sex, baseline eGFR(imputed), Steroids, Clopidogrel, and stratified, Charlson Comorbidity index (CCI), Hypertension, Steroid, and stratified by NSAID, entry year, and hospital visits assumingly different baseline hazard function between NSAID, entry year and hospital visit intervals at baseline

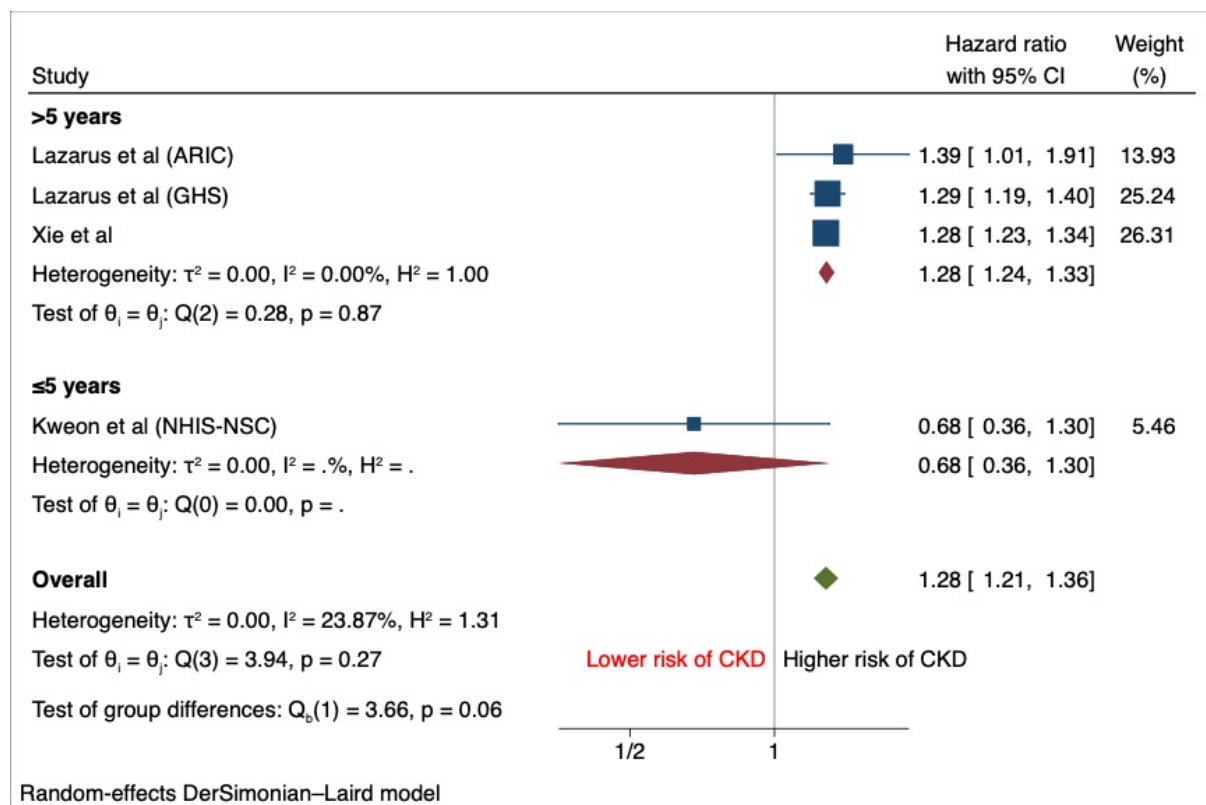
Zhang et al	Propensity-score weighted model with covariates including age, sex (male, female), ethnicity (white people or others), socioeconomic status (the index of multiple deprivation, fifth), smoking status (never smoker, previous smoker, or current smoker), alcohol consumption (daily or almost daily, one to four times a week, one to three times a month, and special occasions only or never), physical activity (low, moderate, or high), fruit and vegetable intake (≥ 5 portions or < 5 portions), body mass index, systolic blood pressure, concomitant comorbidities (hyperlipidemia, diabetes, cardiovascular disease, gastroesophageal reflux disease, and peptic ulcer, yes or no), and medication use (including aspirin, non-aspirin NSAIDs, acetaminophen, antihypertensive drugs, statin, metformin, and H2RAs)
Yang et al	PSM and further adjustment for age, gender, hypertension, gout, CVA, IHD, PAD, CHF, socioeconomic status, urbanization and region
Moayyedi et al	No adjustment



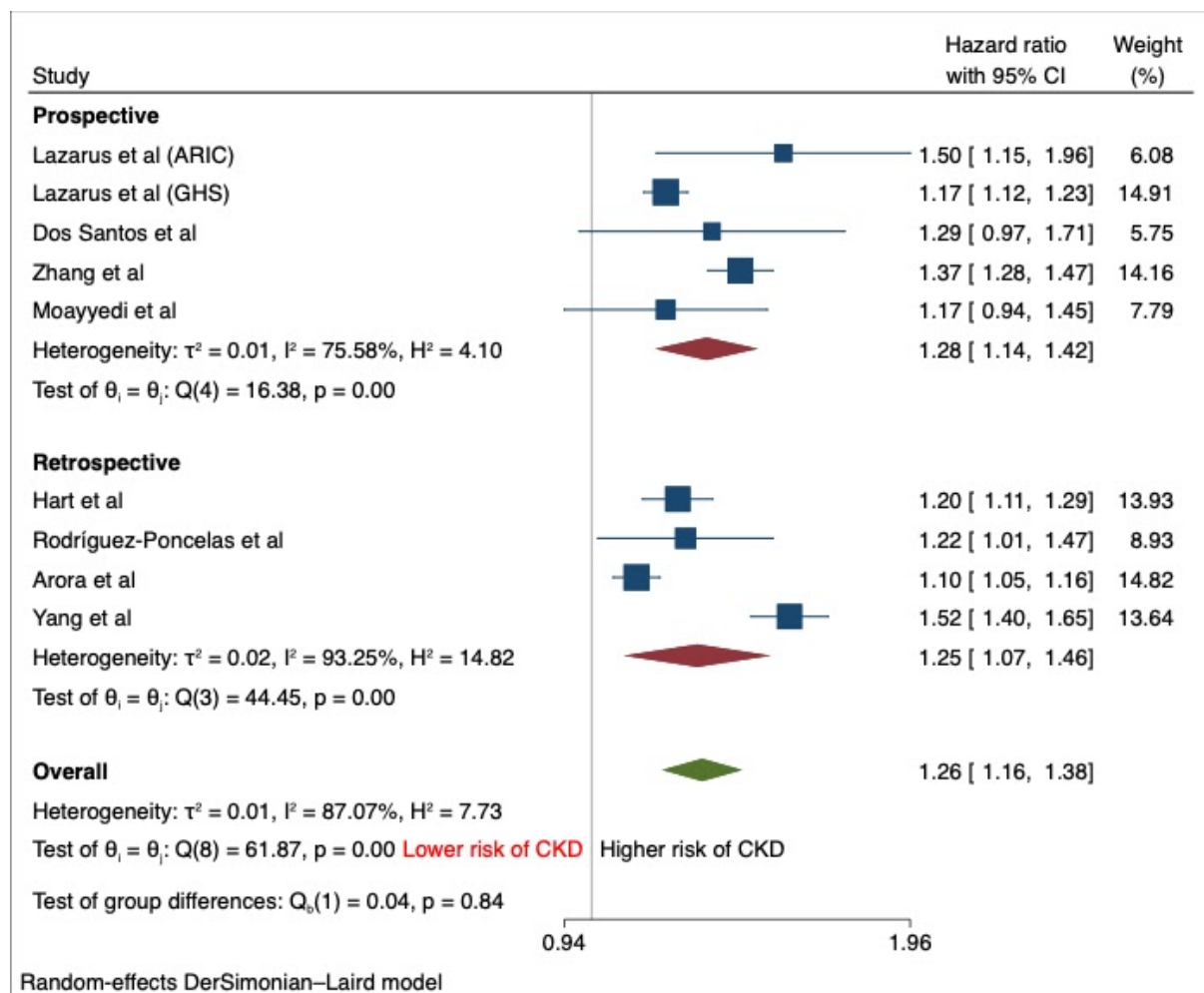
Supplementary Figure S1 PRISMA Flow Diagram



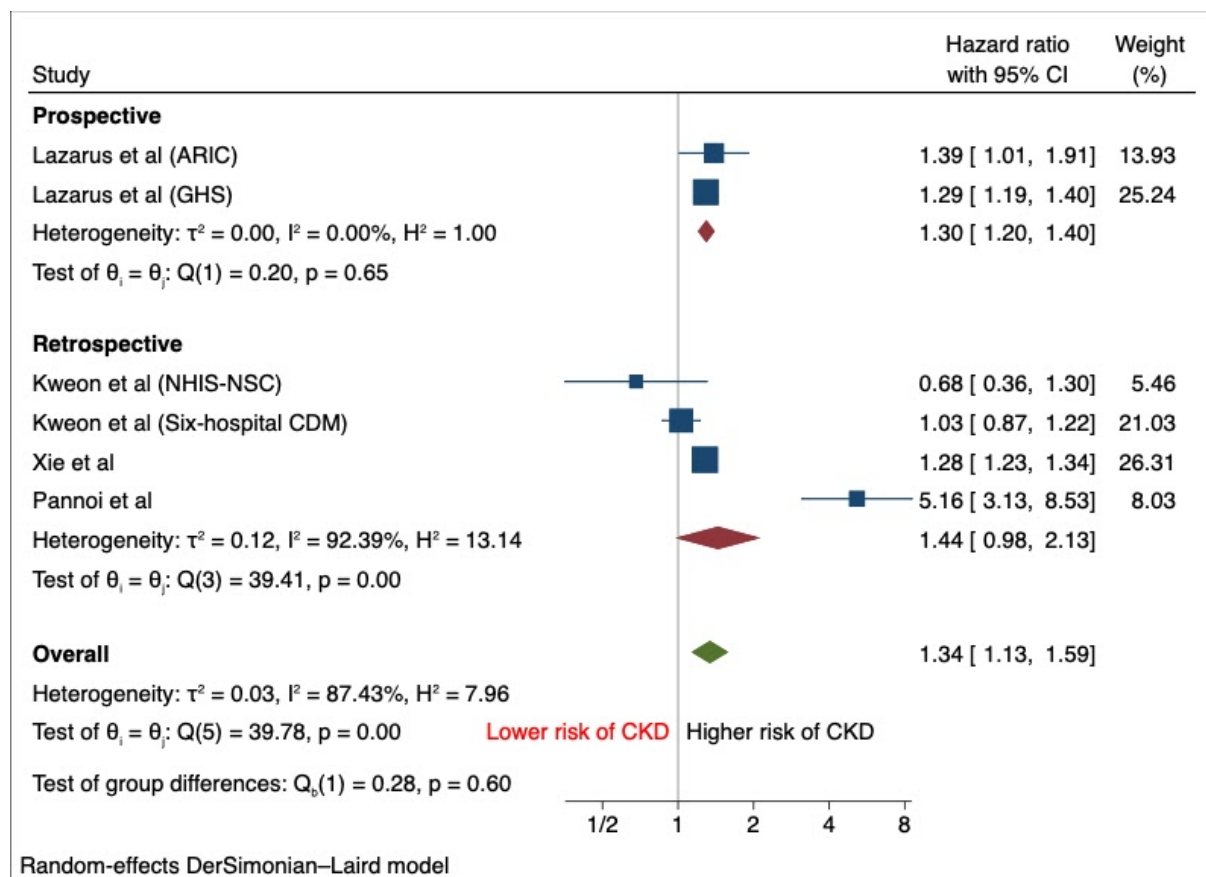
Supplementary Figure S4 Subgroup analysis for incidence of CKD between PPIs and non-PPIs group based on follow-up period



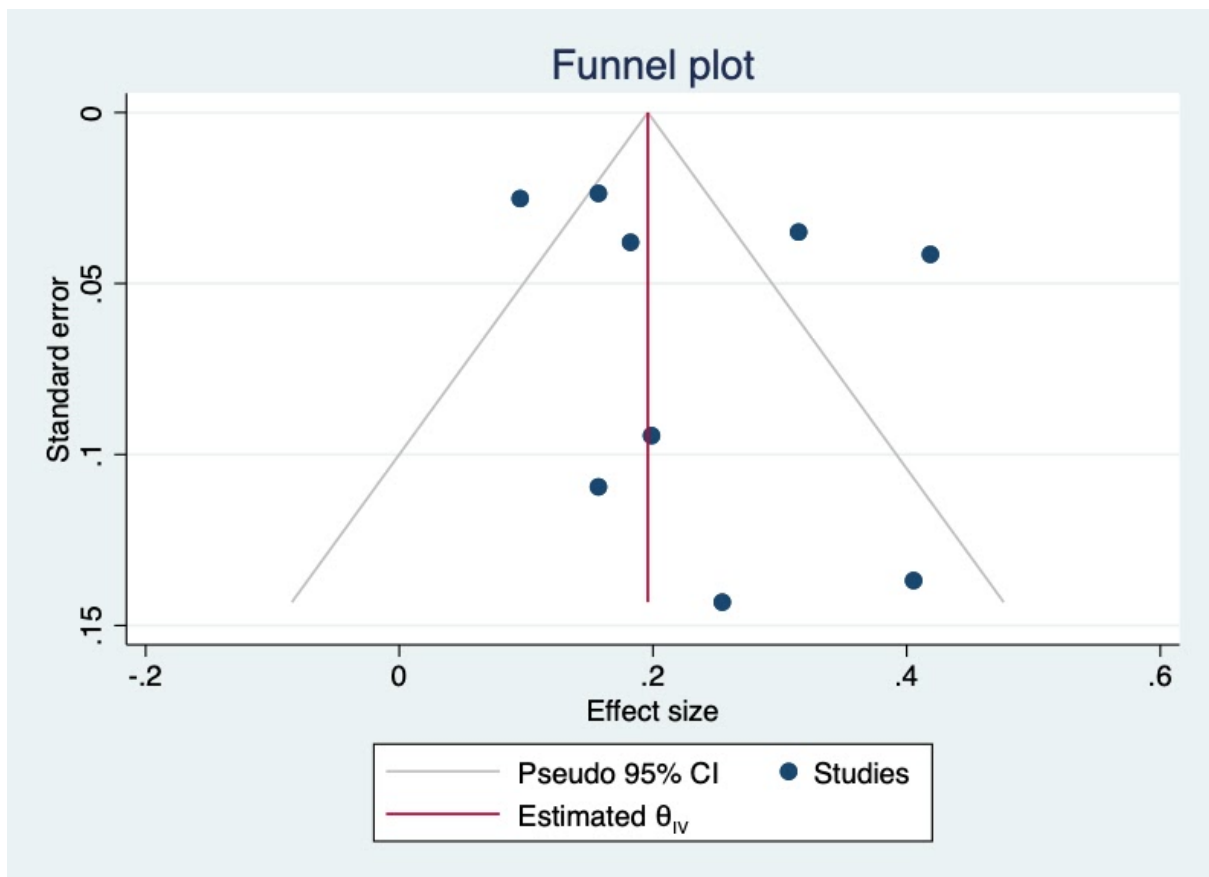
Supplementary Figure S5 Subgroup analysis for incidence of CKD between PPIs and H2RAs group based on follow-up period



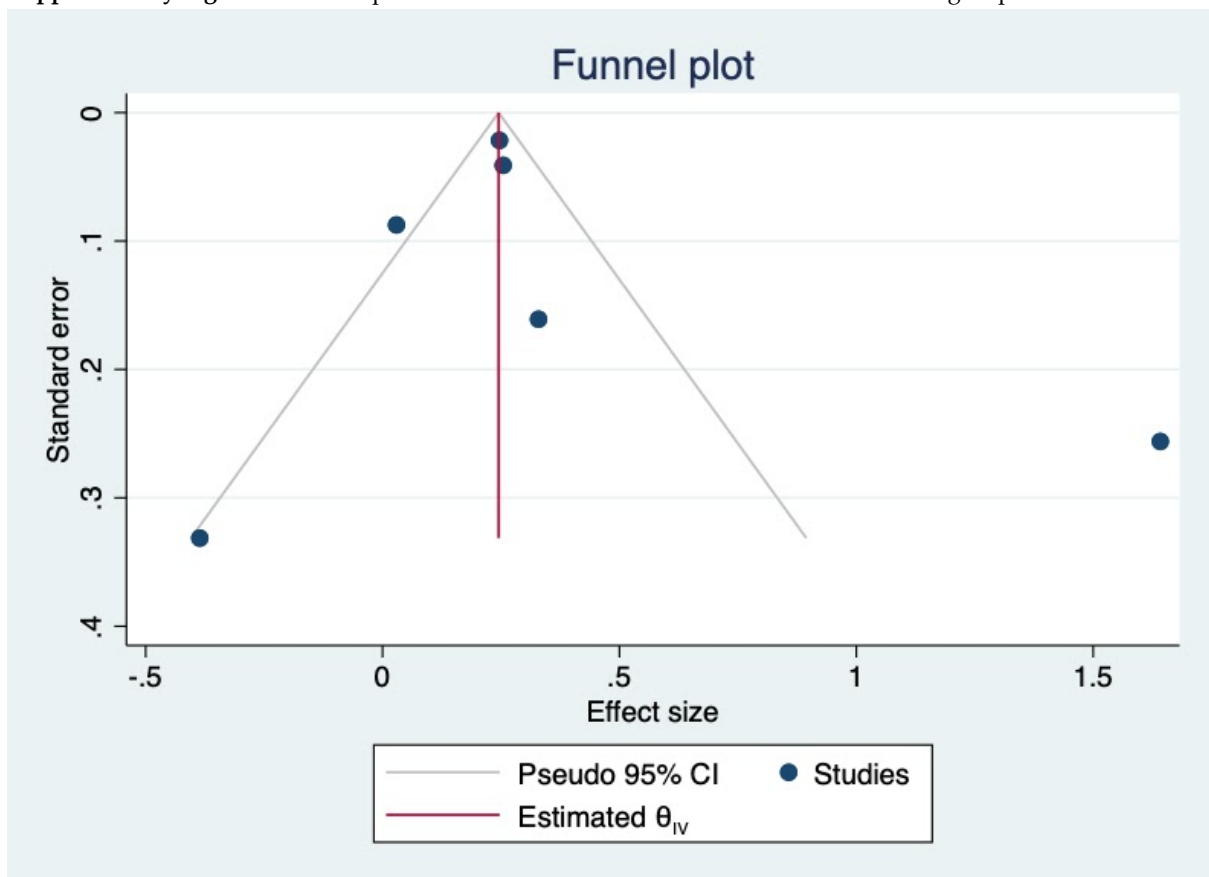
Supplementary Figure S6 Subgroup analysis for incidence of CKD between PPIs and non-PPIs group based on study design



Supplementary Figure S7 Subgroup analysis for incidence of CKD between PPIs and H2RAs group based on study design



Supplementary Figure S8 Funnel plot for incidence of CKD between PPIs and non-PPIs group



Supplementary Figure S9 Funnel plot for incidence of CKD between PPIs and H2RAs group

