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Cardiovascular and mortality outcomes of DPP-4 inhibitors vs. sulfonylureas as metformin add-on therapy in patients with type 2 diabetes: A systematic review and meta-analysis

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Abstract

Background

Type 2 diabetes significantly increase the risk of cardiovascular disease and mortality. This systematic review and meta-analysis compared cardiovascular and mortality outcomes in type 2 diabetes patients receiving dipeptidyl peptidase-4 inhibitors (DPP-4is) plus metformin versus sulfonylureas (SUs) plus metformin as add-on therapy.

Methods

PubMed, Web of Science, Cochrane Central Register of Controlled Trials, Embase, Google Scholar, and Scopus were searched through January 1, 2025, for studies comparing DPP-4is plus metformin versus SUs plus metformin in type 2 diabetes patients. Outcomes of interest were major adverse cardiovascular events and all-cause mortality. Heterogeneity was assessed using Cochran's Q test and I^2 statistic. Publication bias was evaluated with Begg's and Egger's tests. Study quality was assessed with the Jadad scale (for randomized controlled trials) and the Newcastle-Ottawa Scale (for observational studies).

Results

Twenty-seven studies (2012–2024), encompassing 1,505,821 participants, were included in the analysis. Major adverse cardiovascular events were reported in 21 studies, and all-cause mortality data were available from 19 studies. Meta-analysis revealed a significantly lower risk of both major adverse cardiovascular events (risk

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ratio [RR]: 0.79; 95% confidence interval [CI]: 0.73–0.84; p < 0.001) and all-cause mortality (RR: 0.79; 95% CI: 0.71–0.88; p < 0.001) in patients with diabetes treated with DPP-4 inhibitors plus metformin compared to those treated with SUs plus metformin. No publication bias was detected.

Conclusion

In type 2 diabetes patients treated with metformin, adding a DPP-4is is associated with significantly lower risks of major adverse cardiovascular events and all-cause mortality compared to adding an SUs. These findings underscore the potential cardiovascular benefits of DPP-4is and their role in improving patient outcomes.

Introduction

Type 2 diabetes mellitus (T2DM) is a major global health concern, strongly associated with cardiovascular disease (CVD) [1]. The World Health Organization (WHO) recognizes CVD as the leading cause of death among individuals with diabetes, accounting for over 50% of mortalities [2]. These individuals experience a substantially increased risk of serious cardiovascular complications, including myocardial infarction, stroke, and heart failure [2,3].

Effective blood glucose management through medication is paramount in mitigating the elevated cardiovascular risk associated with diabetes [4]. Maintaining tight glycemic control prevents harmful fluctuations that can damage blood vessels and organs over time. Chronically elevated blood glucose contributes to the development of atherosclerosis, characterized by the accumulation of plaque within the arteries [5]. This arterial narrowing increases the risk of restricted blood flow, thrombosis, and subsequent cardiovascular events such as myocardial infarction and stroke [5,6]. Persistently high glucose levels also damage the endothelium, the protective inner lining of blood vessels, promoting systemic inflammation[6]. These factors significantly contribute to the burden of CVD mortality in individuals with T2DM [7,8].

Given the heightened risk of CVD and mortality in individuals with T2DM, effective glycemic management through pharmacological interventions is essential. While lifestyle modifications play a role in risk reduction, they are often insufficient as the disease progresses [9]. Pharmacological therapies are crucial for achieving and maintaining optimal glycemic control, thereby mitigating the risk of macrovascular and microvascular complications [10].

Metformin is the established first-line treatment for T2DM, demonstrating efficacy in lowering HbA1c levels and exhibiting a favorable safety profile compared to other initial therapies [11]. Studies have shown that metformin, compared to sulfonylureas or insulin, is associated with a reduced risk of cardiovascular events and mortality [12,13]. However, the progressive nature of T2DM, characterized by declining pancreatic beta-cell function, often necessitates the addition of second-line agents to maintain adequate glycemic control over the long term [14].

When metformin monotherapy becomes insufficient, the choice of add-on therapy is critical, considering the potential impact on cardiovascular outcomes and mortality. Sulfonylureas (SUs) and dipeptidyl peptidase-4 inhibitors (DPP-4is) are frequently prescribed as second-line agents in combination with metformin [15–18]. They are often used as adjunctive therapies to metformin to further lower blood glucose levels [18,19]. SUs stimulates insulin secretion from pancreatic beta-cells by binding to and closing ATP-sensitive potassium channels, leading to membrane depolarization and calcium influx, which triggers insulin release. This mechanism can increase the risk of hypoglycemia [20]. DPP-4is, conversely, enhance the levels of incretin hormones, such as glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP). These incretins promote glucose-dependent insulin release and suppress glucagon secretion [21,22], reducing the risk of hypoglycemia compared to SUs. Metformin, a biguanide, primarily reduces hepatic glucose production and improves insulin sensitivity in peripheral tissues. It also modestly reduces intestinal glucose absorption. Unlike SUs, metformin does not directly stimulate insulin secretion and therefore carries a lower risk of hypoglycemia [23,24].

While these medications demonstrate efficacy in glycemic control, concerns remain regarding their long-term safety profiles, particularly concerning cardiovascular outcomes when used as add-on therapy to metformin [25]. Further research is needed to better understand and compare the risks associated with these two drug classes.

Some studies suggest a higher risk of adverse cardiovascular outcomes, including myocardial infarction and stroke, with the use of SUs compared to other antidiabetic medications [25–29]. Some analyses even report increased all-cause mortality with SUs compared to specific alternative treatments [18,27–31]. Conversely, it has been hypothesized that DPP-4is may confer a lower cardiovascular risk when used as add-on therapy to metformin[16,31,32], but further research is required to confirm this hypothesis.

Determining the precise cardiovascular safety profiles of DPP-4is plus metformin versus SUs plus metformin remains an area of ongoing investigation. While some studies indicate a higher risk with SUs [16,25–29], the results across the literature have not been entirely consistent [16,17,31–34]. Further high-quality research is necessary to definitively characterize any potential risks and provide more robust evidence. A recent umbrella review by Bashardost et al. (2023) highlighted the complex relationship between metformin, sulfonylureas, and cardiovascular outcomes, emphasizing the need for careful consideration when selecting add-on therapies [35]. This systematic review and meta-analysis aimed to contribute to this body of knowledge by directly comparing the effects of DPP-4is plus metformin versus SUs plus metformin on cardiovascular outcomes and mortality in patients with T2DM.

Materials and methods

Study design and search strategies

This systematic review and meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [36]. The PRISMA checklist is provided in the supporting information file; S1 Checklist. A comprehensive search strategy was implemented across multiple electronic databases, including PubMed, Web of Science, Cochrane Central Register of Controlled Trials, Embase, Scopus, and Google Scholar. The search encompassed all available data from database inception to January 1, 2025.

The search strategy employed a combination of Medical Subject Headings (MeSH) terms and free-text keywords relevant to the research question. Specific terms included, but were not limited to: “sulfonylureas”, “dipeptidyl peptidase-4 inhibitors”, “DPP-4 inhibitors”, “gliptins”, “metformin”, “cardiovascular outcomes”, “major adverse cardiovascular events”, “MACE”, “myocardial infarction”, “stroke”, “cardiovascular death”, “all-cause mortality”, “mortality”, and “type 2 diabetes”. The full search strategy for each database is available in S2 Table.

Eligibility criteria

Studies were considered eligible for inclusion based on the following criteria:

Population. Adults diagnosed with T2DM.

Intervention/ Exposure. DPP-4is plus metformin.

Comparator. SUs plus metformin.

Outcomes. The primary outcomes of interest were MACE, defined as a composite of myocardial infarction, stroke, and cardiovascular death [37,38], and all-cause mortality.

Study design. Randomized controlled trials (RCTs), prospective and retrospective cohort studies, cross-sectional studies, and case-control studies were eligible for inclusion.

Data availability. Studies were required to report effect estimates (hazard ratios [HR], odds ratios [OR], or risk ratios [RR]) with corresponding 95% confidence intervals (CIs).

Language. No language restrictions were applied. Studies published in languages other than English were translated as needed.

Studies were excluded based on the following criteria

Publication type. Non-original research articles, including reviews, editorials, letters, commentaries, and case reports were excluded.

Intervention/comparator. Studies that investigate DPP-4is or SUs as monotherapy, in combination with other antidiabetic agents (excluding metformin), or that do not directly compare DPP-4is plus metformin to SUs plus metformin.

Duplicate data. In cases of multiple publications reporting on the same or overlapping patient populations, only the most comprehensive and recent publication was included to avoid duplication of data.

Insufficient data. Studies lacking sufficient data to calculate effect estimates (e.g., HRs, ORs, or RRs with corresponding 95% CIs).

Study selection

Following the literature search, all identified records were imported into a citation management software (EndNote) for deduplication. Two independent reviewers screened the titles and abstracts of all identified records against the pre-defined eligibility criteria. Full-text articles of potentially eligible studies were retrieved and independently assessed by the same two reviewers. Discrepancies between reviewers at any stage were resolved through discussion and consensus, with a third reviewer consulted if necessary. A PRISMA flow diagram will be presented to illustrate the study selection process in Fig 1.

Data extraction

A standardized data extraction form was developed a priori and piloted to ensure consistency and completeness of data collection. Two independent reviewers extracted data from the included studies using the standardized form. Extracted data included study characteristics (author, year, country, study design, sample size, study duration, follow-up duration), participant characteristics (average participant age), intervention and comparator details (number of participants receiving DPP-4is plus metformin, number of participants receiving SUs plus metformin), the list of adjusted variables in each study, and outcome data (effect estimates with 95% CIs). Disagreements were resolved through discussion and consensus, with arbitration by a third reviewer if needed. The completed electronic data extraction form is available in the S2 Table.

Quality assessment

The methodological quality of the included observational studies was appraised using the Newcastle-Ottawa Scale (NOS) [39]. The NOS evaluates the quality of non-randomized studies based on three domains: selection of study groups, comparability of the groups, and ascertainment of exposure and outcome. Each study received a score ranging from zero to nine, with scores below five considered low quality, scores from five to seven considered moderate quality, and scores of eight or higher considered high quality.

Randomized controlled trials (RCTs) were assessed using the Jadad scale [40], an eight-item tool evaluating various aspects of study quality. Jadad scores range from zero to eight, with scores below four indicating low quality, scores from

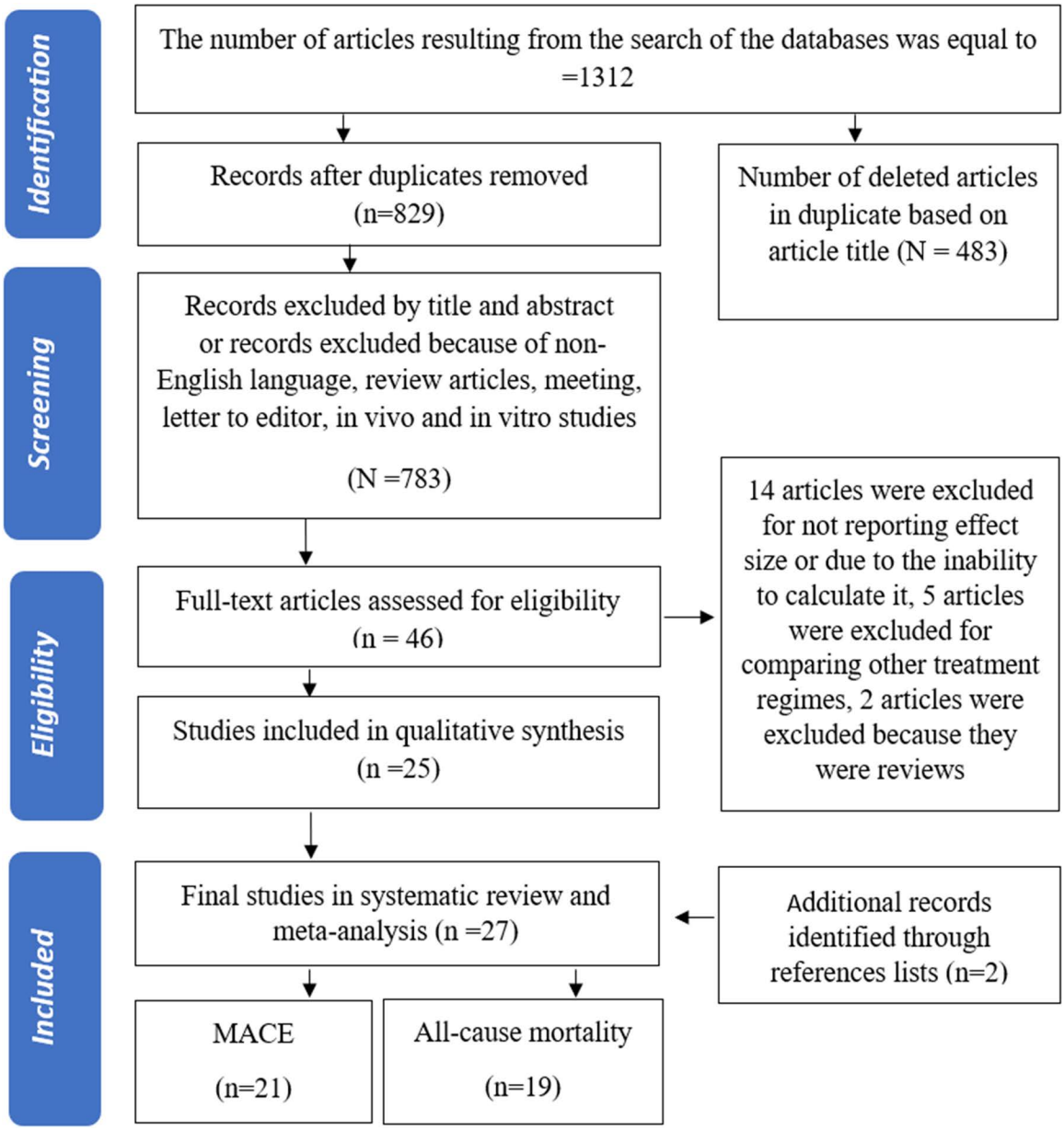

Fig 1. Flowchart depicting the selected studies for meta-analysis.

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four to six indicating moderate quality, and scores of seven or higher indicating high quality. While the quality assessment did not result in the exclusion of any studies, it informed sensitivity analyses exploring the influence of study quality on the meta-analysis results. Meta-regression and subgroup analysis stratified by study quality were performed to assess the robustness of the findings. Quality assessment tools are available in S3 Scales.

Statistical analysis

A rigorous and comprehensive statistical analysis was undertaken to ensure the robustness, validity, and reliability of the synthesized data derived from the included studies. This involved a multi-faceted approach encompassing meta-analysis,

a thorough assessment of heterogeneity, exploration of potential sources of heterogeneity, sensitivity analyses to evaluate the stability of findings, subgroup analyses to explore effect modification, assessment of publication bias, and careful handling of missing data. All statistical procedures were performed with meticulous attention to detail to maintain the highest standards of scientific rigor.

Meta-analysis

The primary objective of this systematic review and meta-analysis was to synthesize the available evidence regarding the comparative effectiveness of DPP-4is and SUs as add-on therapies to metformin in patients with type 2 diabetes. To achieve this, we employed meta-analysis techniques to combine effect estimates from individual studies. Recognizing that studies may report outcomes at different time points, we implemented a strategy to maximize data inclusion without introducing bias. For studies that reported effect estimates separately for different exposure durations, we conducted separate meta-analyses, synthesized these stratified estimates, and calculated overall effects within each study. This approach allowed us to capture the full spectrum of available data while avoiding the artificial inflation of sample size that would result from duplicating participant populations. Similarly, if studies provided results stratified by important covariates, such as sex or age groups, but did not report an overall, we performed meta-analyses to combine these stratified effects into a single pooled estimate. In cases where studies presented raw exposure and outcome group data without a calculated effect size, we utilized Stata software to generate RR estimates with corresponding 95% confidence intervals (CIs). This ensured consistency in the reporting of effect measures across all included studies.

Heterogeneity assessment

A critical aspect of any meta-analysis is the assessment and interpretation of heterogeneity, which refers to the variability in effect estimates across included studies. To address this, we employed a dual approach involving both statistical tests and visual inspection of forest plots. We used Cochran's Q test, a chi-squared-based test specifically designed for meta-analysis, to determine whether the observed differences in effect estimates were statistically significant ($p < 0.10$). This test helps to ascertain whether the observed variation is greater than what would be expected by chance alone. Furthermore, we calculated the I^2 statistic, which quantifies the percentage of total variation across studies that is attributable to heterogeneity rather than sampling error. When substantial heterogeneity ($I^2 \geq 50\%$ or $p < 0.10$ for Cochran's Q test) was detected, we adopted a random-effects model for the meta-analysis [41,42]. This model acknowledges the presence of between-study variation and provides a more conservative estimate of the overall effect. In addition to these statistical tests, we carefully examined forest plots to visually assess the overlap and distribution of confidence intervals across studies. Any study appearing as a potential outlier, with its confidence interval markedly separated from the others, was further investigated through meta-regression, subgroup analyses, and sensitivity analyses to identify potential sources of this heterogeneity.

Exploration of heterogeneity

Meta-regression. To systematically explore the impact of study-level characteristics on the observed heterogeneity, we conducted both univariate and multivariate meta-regression analyses using Stata software. A range of covariates was considered, including study year, study design, sample size, quality assessment score, geographic region, average age of participants, and follow-up duration. These analyses aimed to identify specific factors that might explain the variation in effect estimates across studies [43].

Sensitivity analysis. To evaluate the robustness and stability of our meta-analysis findings, we performed sensitivity analyses by systematically excluding each study one at a time and re-running the meta-analysis. This "leave-one-out" approach helps determine whether any individual study disproportionately influences the overall pooled results. If the

overall effect estimates changes substantially after removing a single study, it suggests that the findings may be sensitive to the inclusion of that particular study [44].

Subgroup analysis. We conducted subgroup analyses to delve deeper into potential sources of heterogeneity and to investigate whether the observed association between the type of treatment (DPP-4is plus metformin versus SUs plus metformin) and the risk of MACE or all-cause mortality varied across different study characteristics. Subgroups were defined based on factors such as study year, study design, sample size, quality assessment score, geographic region, average age of participants, and follow-up duration. These analyses provided a more nuanced understanding of the relationship between treatment and outcomes and allowed for more specific interpretations of the findings within particular subgroups [45].

Assessment of publication bias. Publication bias, the tendency for studies with positive or statistically significant findings to be published more frequently than studies with negative or non-significant findings, can distort the results of a systematic review. To mitigate this risk, we assessed publication bias using both graphical and statistical methods. Funnel plots, which plot the effect size of each study against its precision (typically the standard error), were visually inspected for asymmetry. Asymmetry in the funnel plot can suggest the presence of publication bias. In addition to visual inspection, we employed Egger's regression test and Begg's adjusted rank correlation test to statistically evaluate the likelihood of publication bias [42,46].

Missing data. Inevitably, in any systematic review, some studies may have missing data for certain variables. To maintain the integrity and accuracy of our analyses, we adopted a transparent approach to handling missing data. We excluded variables with missing data from specific analyses that required complete datasets. This exclusion was particularly relevant for more complex statistical techniques, such as meta-regression and subgroup analyses, which necessitate fully populated datasets to yield reliable and interpretable results.

Software. All data analyses were performed using Stata 17 software, ensuring rigorous and reliable synthesis of the evidence [47].

Results

Characteristics of included studies

A comprehensive literature search yielded 1,312 articles. After removing 483 duplicates, 829 articles were screened. Based on predefined eligibility criteria, 783 articles were excluded, primarily due to irrelevance to the research question, inappropriate study design, or lack of necessary data. This left 46 potentially eligible studies. Fourteen articles were further excluded for not reporting or enabling the calculation of effect sizes, five were excluded for comparing treatment regimens other than SUs or DPP-4is as add-on therapy to metformin, and 2 articles were excluded because they were reviews. This rigorous screening process resulted in 25 studies that met all inclusion criteria. Reference list screening of these included studies identified two additional eligible articles, yielding a final total of 27 studies included in this systematic review and meta-analysis [15–19,25–34,48–59]. These studies encompassed a total of 1,505,821 participants (Fig 1).

Relationship between DPP-4is plus metformin versus SUs plus metformin on the Risk of MACE

Twenty-one studies, published between 2012 and 2024, investigated the association between DPP-4is plus metformin versus SUs plus metformin and the risk of MACE in individuals with T2DM[15–18,25–29,31–34,48,49,53,55–59]. These studies represented diverse geographic locations, including the USA, UK, Germany, Denmark, Taiwan, South Korea, and Italy. The combined sample size across these studies was 1,219,347 participants (Tables 1–3). The quality assessment scores for the included articles ranged from 6 to 8 (see S2 File for details).

The pooled analysis demonstrated a statistically significant 21% reduction in the risk of MACE among patients receiving DPP-4is plus metformin versus SUs plus metformin. The pooled RR was 0.79 (95% CI: 0.73–0.84; p<0.001) (Fig 2).

Table 1. Characteristics of the studies included in the meta-analysis.

First author	Year	Country	Study design	Study duration	Sample size	DPP-4is plus metformin	SUs plus metformin	Average age	NOS score
Gallwitz B [26]	2012	International*	RCT	2008-2010	1551	776	775	59.8	8
Gitt AK [48]	2013	Germany	Cohort	2010-2011	884	628	256	65.82	8
Mogensen UM [27]	2014	Denmark	Case–control	2007-2011	36230	11138	25092	61	8
Morgan CL [28]	2014	UK	Cohort	2007-2012	12404	6229	6175	60.1	8
Chang YC [49]	2015	Taiwan	Cohort	2009-2011	31343	2242	29101	58	8
Ou SM [29]	2015	Taiwan	Cohort	2009-2013	20178	10089	10089	57.8	8
Seong JM [25]	2015	South Korean	Cohort	2009-2010	327833	74270	253563	58.4	7
Yu OH [30]	2015	UK	Cohort	1988-2012	11807	2286	9521	62.1	7
Eriksson JW [50]	2016	Sweden	Cohort	2006-2013	52760	12024	40736	64.2	7
Hippisley-Cox J [51]	2016	UK	Cohort	2007-2015	167103	32533	134570	65.2	7
Kannan S [52]	2016	USA	Cohort	2008-2013	10906	1487	9419	60.6	7
Zghebi SS [53]	2016	UK	Cohort	1998-2011	7770	1030	6740	62	7
Ha KH [54]	2017	South Korean	Cohort	2013-2015	38205	26623	11582	60.3	8
Ou HT [55]	2017	Taiwan	Cohort	2009-2013	58947	5980	52967	56	7
Vaccaro O [56]	2017	Italy	RCT	2012-2014	3028	1535	1493	62.3	8
Cho YY [19]	2018	South Korean	Cohort	2008-2013	5693	1926	3767	61	6
Hsu PF [31]	2018	Taiwan	Cohort	2004-2015	210449	14306	196143	55.8	7
O'Brien MJ [32]	2018	USA	Cohort	2011-2015	92092	28898	63194	45-65	8
Vashisht R [33]	2018	USA	Cohort	2011-2015	96609	25196	71413	45-65	8
Kim KJ [15]	2019	Korea	Cohort	2008-2013	23635	16803	6832	62.3	7
Raparelli V [16]	2020	USA	Cohort	2011-2017	140783	51678	89105	60	6
Thein D [57]	2020	Denmark	Cohort	2010-2016	24343	15426	8917	61	7
Bazo-Alvarez JC [58]	2021	UK	Cohort	2008-2017	23837	6267	17570	59.2	7
Wang J [17]	2022	Taiwan	Cohort	2007-2013	74634	37317	37317	–	6
Wang H [34]	2023	UK	Cohort	2010-2017	29445	9591	19854	61.3	8
Her AY [18]	2024	South Korea	Cohort	2011-2015	936	468	468	64	7
Franchi M [59]	2024	Italy	Cohort	2015-2018	2416	1208	1208	72	7

*16 countries (Bulgaria, Denmark, France, Germany, Hong Kong, Hungary, India, Ireland, Italy, Netherlands, Norway, Poland, South Africa, Sweden, the UK, and the USA).

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Assessment for publication bias using Begg's test (p = 0.216) and Egger's test (p = 0.865) did not reveal any significant evidence of asymmetry in the funnel plot (Fig 3), supporting the robustness of the observed association.

Meta-regression analysis, exploring the influence of study year, design, sample size, quality assessment score, geographic region, average age of participants, and follow-up duration, revealed that only the study year was significantly associated with heterogeneity (p<0.10) (Table 4). Sensitivity analyses, performed by sequentially removing each study, demonstrated consistent RRs, confirming the robustness of the primary meta-analysis results (Fig 4).

Subgroup analyses stratified by study characteristics revealed variations in the risk of MACE. The RRs were 0.77 (95% CI: 0.62–0.94) for studies conducted in the America and Canada, 0.83 (95% CI: 0.73–0.94) in Europe, and 0.76 (95% CI: 0.71–0.82) in Asia. Further stratification by study year, sample size, average age, study design, follow-up duration, and quality assessment score revealed additional variations in effect estimates (Table 5).

Table 2. Relationship between DPP-4is plus metformin versus SUs plus metformin on the risk of MACE and mortality in included studies.

First author	Year	Study cohort	Follow up (Year)	Outcomes assessed	Risk Ratio (RR)	
					MACE	All-cause mortality
Gallwitz B [26]	2012	Type 2 diabetes inadequately controlled on metformin	2	MACE, Death	0.49(0.23-1.01)	1.00 (0.14–7.07)
Gitt AK [48]	2013	Patients with type 2 diabetes in which antidiabetic therapy was intensified	1	MACE	1.26(0.44-3.56)	–
Mogensen UM [27]	2014	Type 2 diabetes inadequately controlled on metformin	2.3	MACE, Death	0.57(0.40-0.80)	0.57(0.40-0.80)
Morgan CL [28]	2014	Type 2 diabetes were selected if initiated with combination therapies comprising metformin plus SUs or DPP-4is	1.8	MACE, Death	0.64(0.45-0.93)	0.67(0.49-0.91)
Chang YC [49]	2015	Type 2 diabetes inadequately controlled on metformin	0.74	MACE	0.90(0.74-1.04)	–
Ou SM [29]	2015	All patients with Type 2 diabetes aged 20 years or older	2.5	MACE, Death	0.67(0.59-0.78)	0.63(0.55-0.72)
Seong JM [25]	2015	Type 2 diabetes inadequately controlled on metformin	2	MACE	0.70(0.67-0.74)	
Yu OH [30]	2015	Type 2 diabetes inadequately controlled on metformin	2	Death	–	0.53(0.29-0.97)
Eriksson JW [50]	2016	All patients with T2D in Sweden who initiated second-line treatment	3	Death	–	0.70(0.56-0.87)
Hippisley-Cox J [51]	2016	Type 2 diabetes patients in second antidiabetic drug	3	Death	–	0.62(0.55-0.71)
Kannan S [52]	2016	Patients with DM-2 treated with metformin and an additional anti-diabetic agent.	4	Death	–	1.029 (0.81 - 1.31)
Zghebi SS [53]	2016	All patients with T2Dwho initiated second-line treatment	2.4	MACE	0.78(0.55-1.11)	–
Ha KH [54]	2017	Patients with DM-2 treated with metformin and an additional anti-diabetic agent.	2.3	Death	–	0.84(0.66-1.07)
Ou HT [55]	2017	All patients with T2Dwho initiated second-line treatment	3.3	MACE, Death	0.82(0.69-0.97)	0.82(0.69-0.99)
Vaccaro O [56]	2017	All patients with T2DM aged 50–75 years	2	MACE, Death	0.83(0.54-1.29)	1.10 (0·75–1·61)
Cho YY [19]	2018	All patients with T2Dwho initiated second-line treatment	5.2	Death	–	0.59(0.36-0.98)
Hsu PF [31]	2018	Type 2 diabetes inadequately controlled on metformin	11	MACE, Death	0.78(0.69-0.88)	0.956 (0.847–1.078)
O'Brien MJ [32]	2018	All patients with T2Dwho initiated second-line treatment	1.3	MACE	0.78(0.66-0.93)	–
Vashisht R [33]	2018	All patients with T2Dwho initiated second-line treatment	2.2	MACE	0.89(0.81-0.98)	
Kim KJ [15]	2019	Type 2 diabetes patients in second antidiabetic drug	1.63	MACE, Death	0.67(0.33-1.36)	0.74(0.46-1.18)
Raparelli V [16]	2020	Adults with type 2 diabetes mellitus not controlled with metformin with no prior use of insulin	4.5	MACE	0.64(0.56-0.74)	–
Thein D [57]	2020	Type 2 diabetes patients in second antidiabetic drug	2	MACE, Death	0.82(0.67-0.97)	0.88(0.76-1.01)
Bazo-Alvarez JC [58]	2021	Type 2 diabetes patients in second antidiabetic drug	3.5	MACE, Death	0.94(0.81-1.10)	0.97(0.81-1.16)
Wang J [17]	2022	Type 2 diabetes patients who received DPP-4is or SUs in addition to metformin	2.1	MACE	0.79(0.75-0.82)	–
Wang H [34]	2023	Type 2 diabetes patients who received DPP-4is or SUs in addition to metformin	2.7	MACE, Death	1.02(0.92-1.13)	0.99(0.89-1.09)
Her AY [18]	2024	Type 2 diabetes patients with diabetes and acute myocardial infarction	3	MACE, Death	0.48(0.12-1.90)	0.72(0.41-1.27)
Franchi M [59]	2024	Type 2 diabetes patients who received DPP-4is or SUs in addition to metformin	5.61	MACE, Death	0.78 (0.63-0.97)	0.73 (0.55- 0.98)

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Table 3. Adjusted variables in included studies in the meta-analysis.

First author	year	Adjusted variables
Gallwitz B [26]	2012	–
Gitt AK [48]	2013	–
Mogensen UM [27]	2014	1, 2, 6, 7, 8, 9, 10, 11.
Morgan CL [28]	2014	1, 2, 4, 5, 12, 13, 14, 15, 16.
Chang YC [49]	2015	1, 2, 17, 18, 19, 20, 21.
Ou SM [29]	2015	1, 2, 5, 8, 10, 22, 23, 24, 25, 26, 27.
Seong JM [25]	2015	1, 2, 3, 17, 24, 28.
Yu OH [30]	2015	1, 2, 4, 6, 7, 16, 22, 29, 30.
Eriksson JW [50]	2016	1, 2, 7, 28, 32.
Hippisley-Cox J [51]	2016	–
Kannan S [52]	2016	1, 2, 7, 16, 17, 28, 29, 31, 33.
Zghebi SS [53]	2016	1, 2, 4, 5, 6, 7, 9, 12, 16, 17, 22, 28, 33.
Ha KH [54]	2017	1, 2, 6, 7, 8, 17, 22.
Ou HT [55]	2017	1, 2, 7, 28
Vaccaro O [56]	2017	1, 2, 4, 7, 28, 31, 34.
Cho YY [19]	2018	1, 2, 6, 7,11, 21, 27, 28
Hsu PF [31]	2018	1, 2, 5, 7, 8, 10, 22, 23, 27.
O'Brien MJ [32]	2018	12, 17, 28, 31, 35
Vashisht R [33]	2018	7, 11, 35
Kim KJ [15]	2019	1, 5, 16, 28, 29, 36, 37.
Raparelli V [16]	2020	1, 2, 7, 22, 28, 38, 39.
Thein D [57]	2020	1, 2, 6, 7, 21, 22, 31.
Bazo-Alvarez JC [58]	2021	1, 2, 4, 7, 13, 14, 16, 21, 28, 35, 40.
Wang J [17]	2022	1, 2, 7, 8, 17, 28, 41.
Wang H [34]	2023	1, 2, 4, 5, 7, 12, 14, 15, 16, 20, 21, 22, 28, 33, 42, 43.
Her AY [18]	2024	1, 2, 4, 7,19, 28, 31, 44.
Franchi M [59]	2024	1, 2, 6, 44, 45,46.

1; Age, 2; Sex, 3; age^2, 4; body mass index, 5; diabetes duration, 6; Treatment duration in years, 7; Co-morbidities, 8; Charlson score, 9; Concomitant therapy, 10; income,11; glucose-lowering therapy prior to combination therapy,12; HbA1c, 13; baseline HbA1c, 14; systolic blood pressure (SBP),15; total cholesterol, 16; smoking status, 17; diabetes complication, 18; ischemic heart disease,19; cerebrovascular disease, 20; antiplatelet drugs,21; statin, 22; Index year,23; Urbanization level,24; Hospital level,25; Prescription by diabetes specialists,26; Median Adapted Diabetes Complication Severity Index Score, 27; Antihypertensive drug use, 28; Medications used, 29; alcohol abuse,30; glycated hemoglobin (A1C) levels, 31; cardiovascular risk factors, 32; fragility, 33; ethnicity, 34; Diabetes characteristics,35; sociodemographic characteristics, 36; mean fasting glucose levels, 37; physical activity,38; employment status,39; region,40; history of hypoglycemia,41; coronary revascularization,42; quintiles of Scottish Index of Multiple Deprivation,43; estimated glomerular filtration rate by the Chronic Kidney Disease Epidemiology Collaboration creatinine (CKD-EPI) equation,44; Killip class on admission,45; Cotreatments,46; Comorbidities, 47; Multisource Comorbidity Score.

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Relationship between DPP-4is plus metformin versus SUs plus metformin on the risk of mortality

Nineteen studies, published between 2012 and 2024, examined the association between DPP-4is plus metformin versus SUs plus metformin and all-cause mortality in individuals with T2DM [15,18,19,26–31,34,50–52,54–59]. These studies were conducted in various countries, including the USA, UK, Denmark, Taiwan, South Korea, Sweden, and Italy, with a combined sample size of 733,873 participants (Tables 1–3).

The pooled analysis indicated a statistically significant 21% reduction in all-cause mortality among patients receiving DPP-4is plus metformin versus SUs plus metformin. The pooled RR was 0.79 (95% CI: 0.71–0.88;

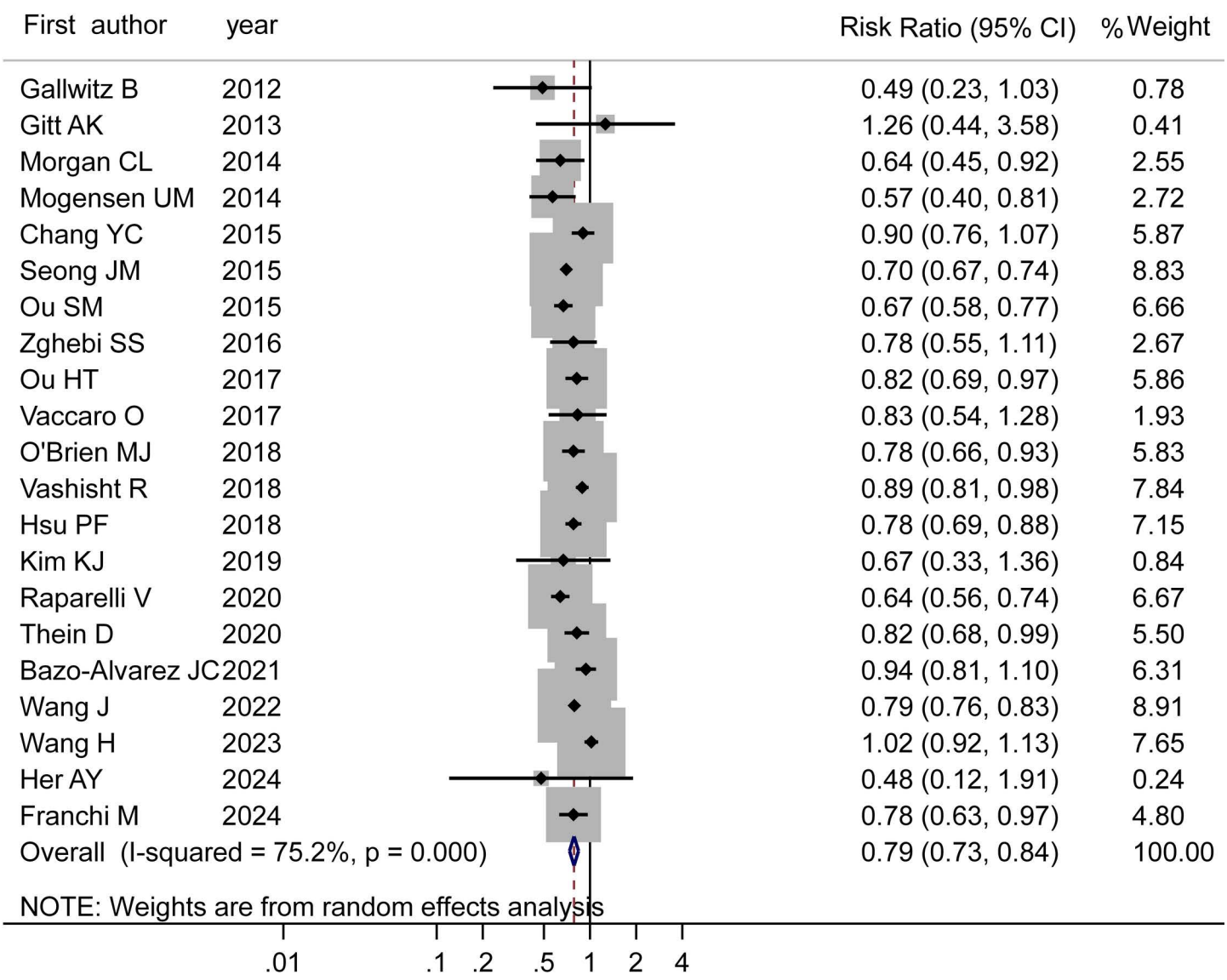

Fig 2. Relationship between DPP-4is plus metformin versus SUs plus metformin on the risk of MACE.

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p<0.001) (Fig 5). No evidence of publication bias was found based on Begg's test (p=0.234) and Egger's test (p=0.346) (Fig 6).

Meta-regression analysis, considering study year, design, sample size, quality assessment score, geographic region, average age, and follow-up duration, showed that study year, study design, geographic region, and average age were significantly associated with heterogeneity (p<0.10) (Table 6). Sensitivity analyses, conducted by sequentially excluding each study, confirmed the stability of the pooled RR (Fig 7).

Subgroup analyses based on study characteristics revealed variations in mortality risk. The RRs were 1.03 (95% CI: 0.81–1.31) in the America and Canada, 0.78 (95% CI: 0.68–0.90) in Europe, and 0.76 (95% CI: 0.62–0.93) in Asia.

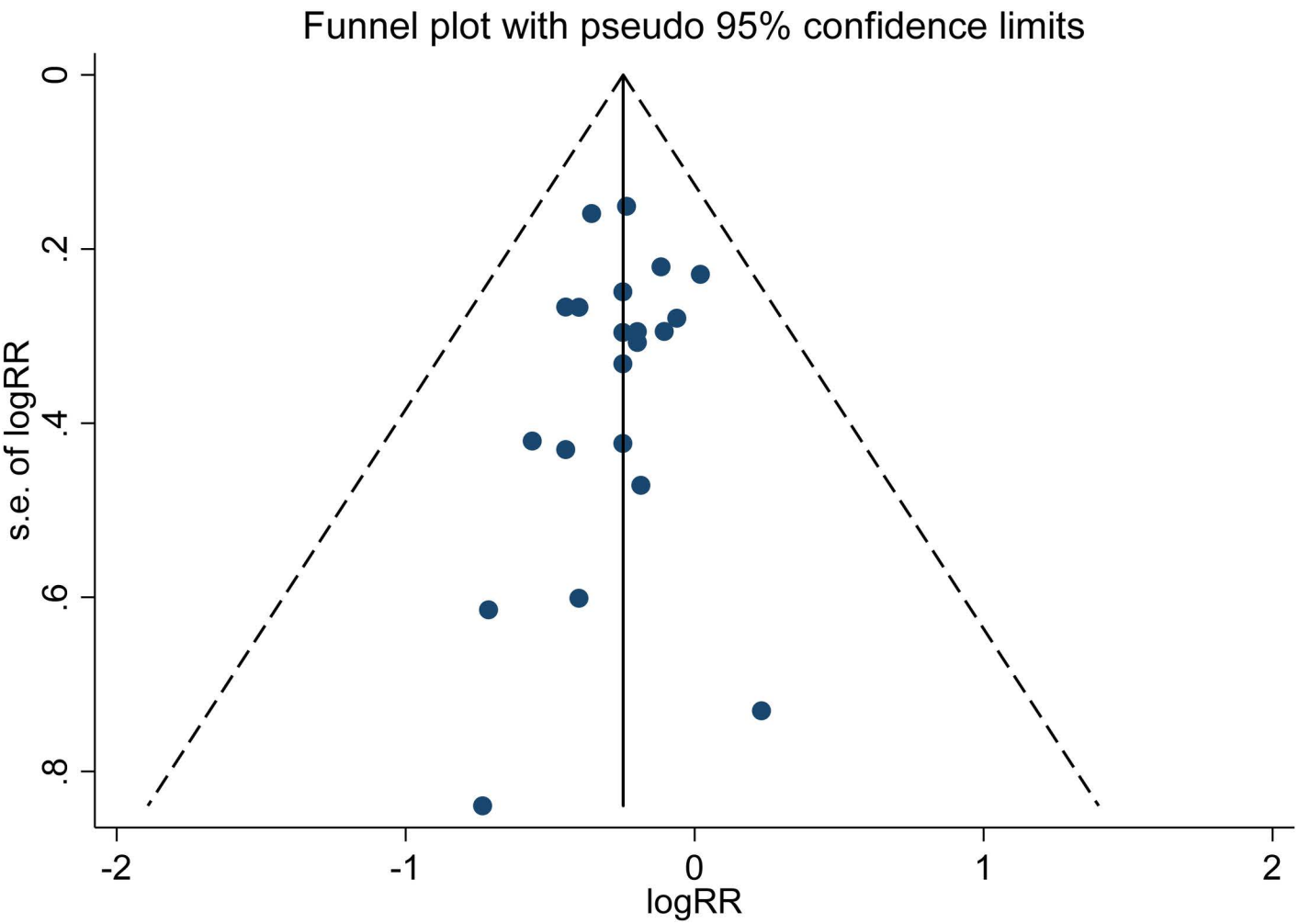

Fig 3. Evaluation of publication bias in meta-analysis studies of the relationship between DPP-4is plus metformin versus SUs plus metformin on the risk of MACE.

https://doi.org/10.1371/journal.pone.0321032.g003

Stratification by study year, sample size, average age, study design, follow-up duration, and quality assessment score revealed further variations (Table 7).

Discussion

This meta-analysis demonstrated that individuals with type 2 diabetes receiving DPP-4is plus metformin experienced a significantly lower risk of MACE versus to those receiving SUs plus metformin. The pooled RR of 0.79 (95% CI: 0.73–0.84; p<0.001) represents a 21% risk reduction. These findings corroborate previous research highlighting the cardiovascular benefits of DPP-4is [27,48,50,53,60]. Similarly, the analysis revealed a statistically significant reduction in all-cause mortality among patients receiving DPP-4is plus metformin versus to those receiving SUs plus metformin, with a pooled RR of 0.79 (95% CI: 0.71–0.88; p<0.001), consistent with prior studies [19,50,51].

Several studies support these findings. Ou et al. (2015) observed lower relative risks of all-cause mortality (RR 0.63, 95% CI: 0.55–0.72), ischemic stroke (RR 0.68, 95% CI: 0.55–0.83), and hypoglycemia (RR 0.43, 95% CI: 0.33–0.56) in a cohort of 10,089 individuals with T2DM treated with DPP-4is plus metformin compared to SUs plus metformin [29]. A

Table 4. Results of meta-regression analysis for the relationship between DPP-4is plus metformin versus SUs plus metformin on the risk of MACE.

Meta-regression REML estimate of between-study variance % residual variation due to heterogeneity Proportion of between—study variance explained Joint test for all covariates With Knapp-Hartung modification					Taue2 =0.005928 I-suuared_res =34.59% Adj R-squared =66.32% Model F (7,11) =2.50 Prob>F =0.0844	
Mean	*Coef.*	*Std. Err.*	*t*	*p>|t|*	*[95% Conf. Interval]*	
The year of study	0.536614	0.015652	3.43	0.006	0.0192096	0.0881131
Study design	-0.02251	0.144277	-0.16	0.879	-0.3402841	0.295259
Sample size	$-4.84e^{-08}$	$3.72e^{-07}$	-0.13	0.899	$-8.68e^{-07}$	$7.71e^{-07}$
Quality score	0.781274	0.0588485	1.33	0.211	-0.0513972	0.207652
Age average	-0.21134	0.0157364	-1.34	0.206	-0.05577	0.0135013
Geographical location	0.066214	0.477616	1.39	0.192	-0.0388085	0.1714365
Follow-up period	-0.01502	0.0150137	-1.00	0.339	-0.0480674	0.0180226
-cons	-107.909	31.42057	-3.43	0.006	-177.0657	-38.75332

https://doi.org/10.1371/journal.pone.0321032.t004

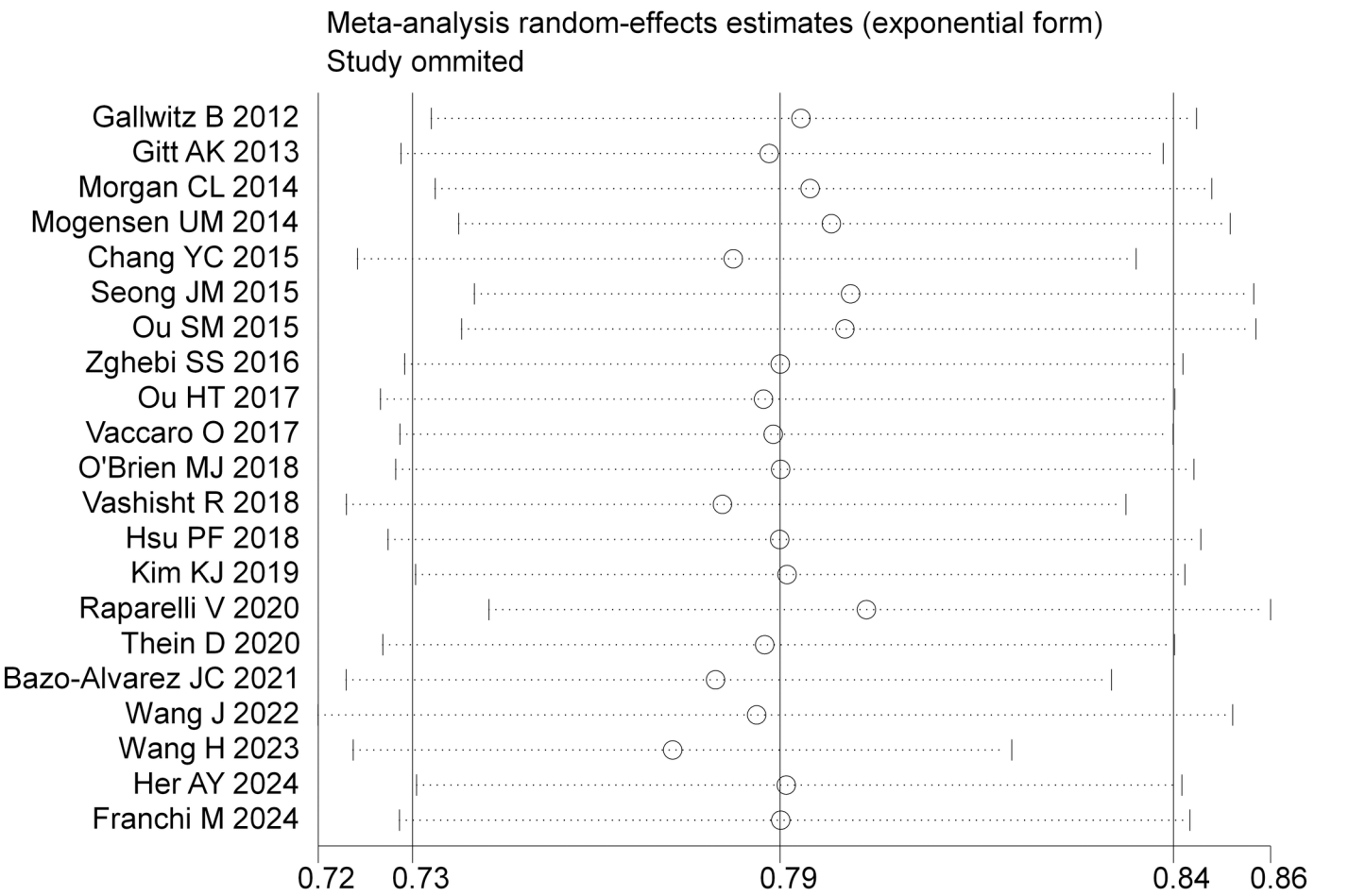

Fig 4. Results of sensitivity analysis for the relationship between DPP-4is plus metformin versus SUs plus metformin on the risk of MACE.

https://doi.org/10.1371/journal.pone.0321032.g004

Table 5. Subgroup analysis of the association between DPP-4is plus metformin versus SUs plus metformin on the risk of MACE.

Characteristics		*Number of studies*	*RR (95% CI)*	*P-value*
Study location	America and Canada	3	0.77(0.62-0.94)	0.012
	Europe	9	0.83 (0.73-0.94)	0.005
	Asia	8	0.76(0.71-0.82)	≤0.001
	International	1	0.49(0.23-1.03)	0.059
Time period	2017 or earlier	8	0.72(0.65-0.80)	≤0.001
	2018 or later	13	0.82(0.76-0.89)	≤0.001
Sample size	<3000	12	0.80(0.70-0.92)	≤0.001
	≥3000	9	0.77(0.71-0.83)	≤0.001
Age average	<60	9	0.79(0.72-0.87)	≤0.001
	≥60	12	0.77(0.69-0.87)	≤0.001
Follow up time	≤2 years	9	0.77(0.69-0.85)	≤0.001
	>2 years	12	0.79(0.73-0.84)	≤0.001
Study design	RCT	2	0.70(0.43-1.13)	0.631
	Cohort	18	0.80(0.74-0.85)	≤0.001
	Case- control	1	0.57(0.40-0.81)	0.001
Quality assessment	Good quality	10	0.80(0.70-0.91)	0.001
	Moderate quality	11	0.77(0.72-0.82)	≤0.001

https://doi.org/10.1371/journal.pone.0321032.t005

meta-analysis by Monami et al. of 115 first-line diabetes treatment studies, including seven RCTs comparing SUs and DPP-4is, reported a significantly lower risk of MACE in the DPP-4is group, primarily driven by a reduction in ischemic strokes [61]. Other meta-analyses have shown similar trends, with one reporting an OR of 0.53 (95% CI: 0.32–0.87) for cardiovascular events with DPP-4is versus SUs [62], and another demonstrating statistically significant increased risks of myocardial infarction, ischemic stroke, cardiovascular mortality, and all-cause mortality with SUs compared to DPP-4is [63]. Network meta-analyses have also suggested a lower risk of myocardial infarction with DPP-4is compared to SUs (OR 0.41, 95% CI: 0.24–0.71) [64] and a lower MACE risk (RR 0.76, 95% CI: 0.59–0.99) [65]. However, a larger network meta-analysis evaluating all glucose-lowering agents found no significant differences in myocardial infarction, cardiovascular mortality, or all-cause mortality between DPP-4is and SUs [66]. It is crucial to note that these studies evaluated these medications as first-line monotherapy or in combination with other agents, not specifically as add-on therapy to metformin.

When DPP-4is are combined with metformin as an adjunctive treatment, they reduce the risk of cardiovascular diseases and mortality through several interconnected mechanisms. Firstly, this combination offers better glucose control compared to adding SUs [67]. Effective blood glucose management mitigates risk factors associated with cardiovascular diseases, such as hypertension, dyslipidemia, and inflammation [29]. Improved glucose control directly contributes to reducing the incidence of cardiovascular diseases and subsequent mortality [17,18]. Secondly, the addition of DPP-4is to metformin carries a lower risk of hypoglycemia compared to SUs [29]. Hypoglycemia can trigger adverse cardiovascular events, including arrhythmias, myocardial infarctions, and strokes [68]. By minimizing the risk of hypoglycemia, the combination of DPP-4is and metformin helps maintain cardiovascular health and reduce mortality risks [68,69]. Additionally, DPP-4is may have unique mechanisms of action that contribute to their protective effect against cardiovascular diseases [70]. These mechanisms could involve modulating the incretin system or other pathways involved in cardiovascular health. Although their precise mechanisms are still under investigation, their impact on reducing cardiovascular risk and mortality is evident [71,72]. Importantly, these reasons are interconnected, and the reduction in cardiovascular diseases directly contributes to the observed

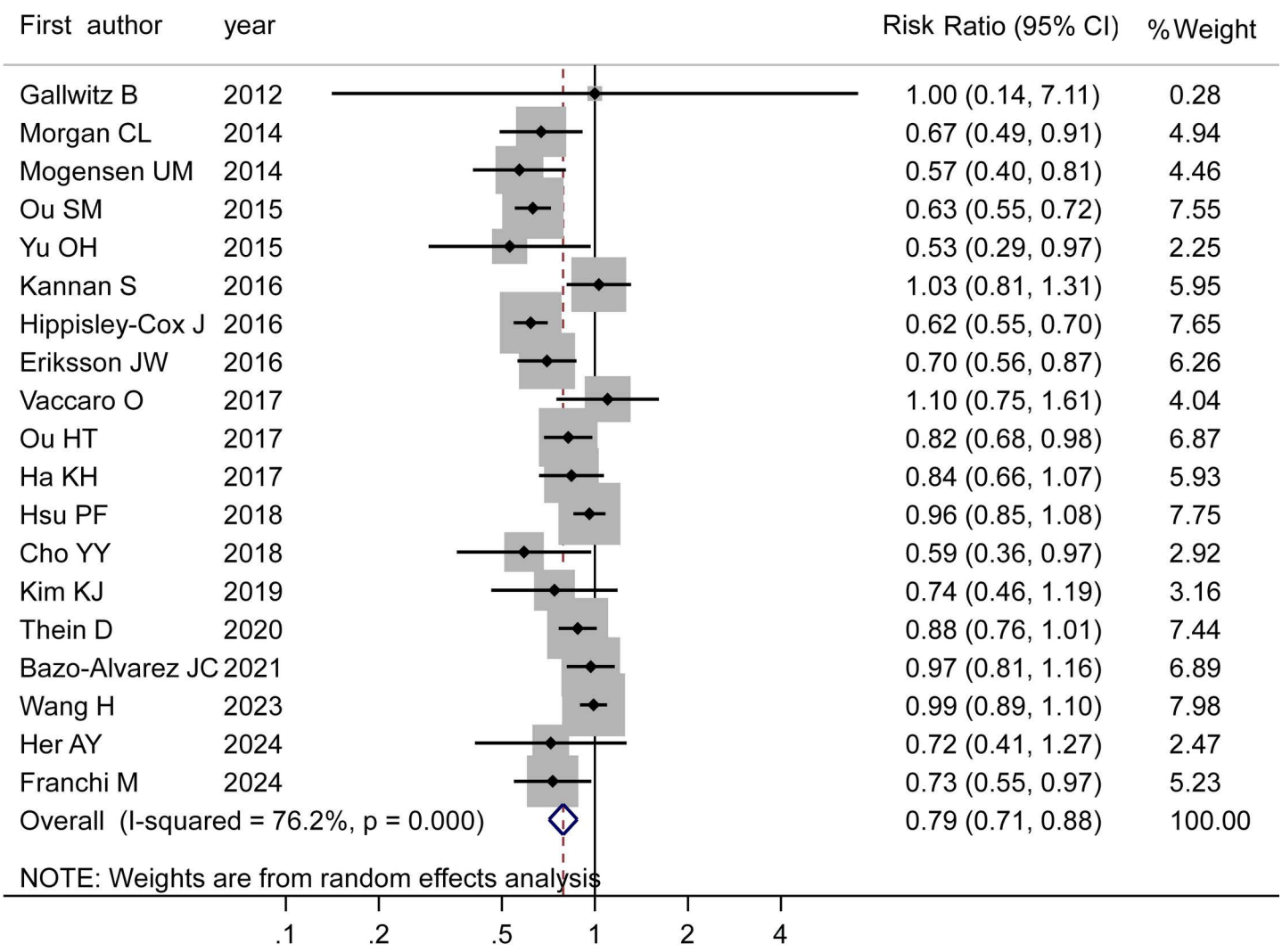

Fig 5. Relationship between DPP-4is plus metformin versus SUs plus metformin on the risk of mortality.

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decrease in mortality rates. However, further research is necessary to fully understand the underlying mechanisms and confirm the observed benefits [72].

While this comprehensive meta-analysis provides compelling evidence suggesting that DPP-4is add-on therapy to metformin may be associated with a lower risk of MACE and all-cause mortality compared to SU add-on therapy, it's crucial to acknowledge the limitations inherent in the predominantly observational nature of the included studies. Observational designs are more susceptible to biases, including residual confounding, which can influence the accuracy of effect estimates. Furthermore, the relatively short average follow-up duration of approximately 3–4 years in the included studies may limit the ability to capture less frequent events and fully assess long-term outcomes.

It is worth acknowledging that the two large randomized controlled trials analyzed in this meta-analysis did not find a statistically significant difference in overall mortality or MACE between the DPP-4is plus metformin treatment groups compared to SUs plus metformin groups [26,56]. However, it is important to note that these trials were not

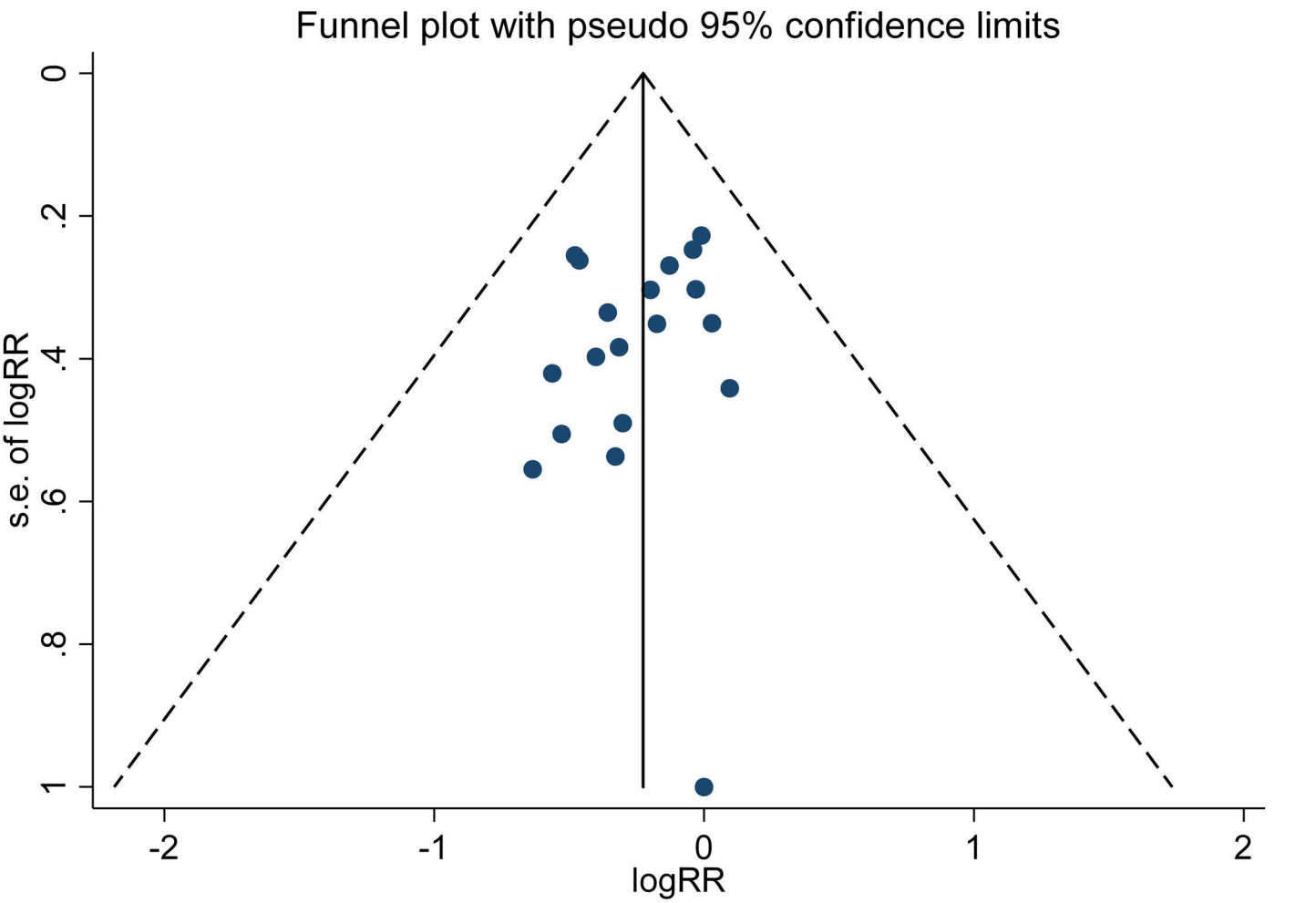

Fig 6. Evaluation of publication bias in meta-analysis studies on the relationship between DPP-4is plus metformin versus SUs plus metformin on the risk of mortality.

https://doi.org/10.1371/journal.pone.0321032.g006

Table 6. Results of meta-regression analysis for the relationship between DPP-4is plus metformin versus SUs plus metformin on the risk of mortality.

Meta-regression **REML estimate of between-study variance** **% residual variation due to heterogeneity** **Proportion of between—study variance explained** **Joint test for all covariates** **With Knapp-Hartung modification**					**Taue2 =0** **I-suuared_res =0.00%** **Adj R-squared =100%** **Model F (7,10) =10.16** **Prob>F =0.0008**	
Mean	***Coef.***	***Std. Err.***	***t***	***p>|t|***	***[95% Conf. Interval]***	
Study design	-0.296033	0.1329793	-2.23	0.050	-0.59233	0.0002625
The year of study	0.0396873	0.0089535	4.43	0.001	0.0197377	0.0596368
Sample size	$-1.19e^{-08}$	$8.15e^{-07}$	-0.01	0.989	$-1.83e^{-06}$	$1.80e^{-06}$
Quality score	0.109591	0.050496	0.22	0.833	-0.1015529	0.1234712
Age average	-0.043568	0.0179665	-2.42	0.036	-0.0836001	-0.0035365
Geographical location	-0.245291	0.071481	-3.43	0.006	-0.4045607	-0.0860216
Follow-up period	0.0216807	0.0233671	0.93	0.375	-0.0303844	0.0737458
-cons	-76.68591	17.92215	-4.28	0.002	-116.619	-36.75287

https://doi.org/10.1371/journal.pone.0321032.t006

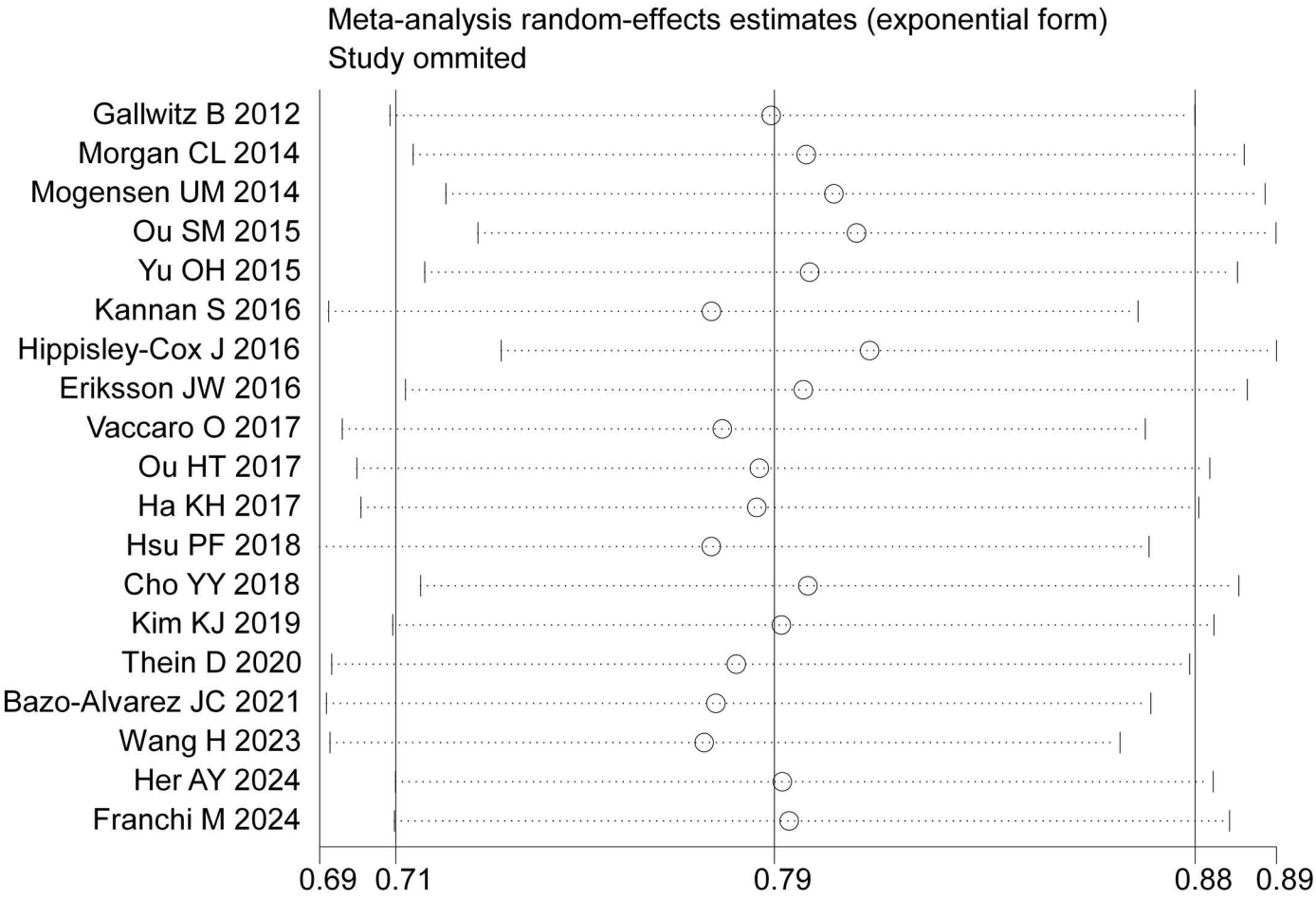

Fig 7. Results of sensitivity analysis for the relationship between DPP-4is plus metformin versus SUs plus metformin on the risk of mortality.

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specifically designed or powered to directly compare the cardiovascular risks associated with these two medication classes.

While further randomized controlled trials with longer follow-up are still needed to definitively establish the cardiovascular safety advantages, the current body of evidence from both observational research and randomized trials suggests that DPP-4is have a similar or potentially lower risk profile compared to SUs when used in combination with metformin. Continued research in larger and longer-term trials is necessary to gain further clarity on any differences in cardiovascular outcomes between these commonly used antidiabetic drug classes.

Clinical implications

This meta-analysis suggests a potential clinical advantage for DPP-4is over SUs in reducing MACE and all-cause mortality when used as add-on therapy to metformin in patients with type 2 diabetes. While current guidelines, including the American Diabetes Association (ADA) Standards of Medical Care [73] and the consensus report from the ADA and the European Association for the Study of Diabetes (EASD) [74], prioritize GLP-1 receptor agonists (GLP-1 RAs) and SGLT2 inhibitors as second-line agents, particularly in patients with or at high risk for atherosclerotic cardiovascular disease (ASCVD), our findings suggest that the role of DPP-4is in this context may warrant

Table 7. Subgroup analysis of the association between DPP-4is plus metformin versus SUs plus metformin on the risk of mortality.

Characteristics		*Number of studies*	*RR (95% CI)*	*P-value*
Study location	America and Canada	1	1.03(0.81-1.31)	0.810
	Europe	11	0.78(0.68-0.90)	0.001
	Asia	6	0.76(0.62-0.93)	0.007
	International	1	1(0.14-7.11)	1.000
Time period	2017 or earlier	8	0.68(0.59-0.78)	≤0.001
	2018 or later	11	0.90(0.84-0.97)	0.004
Sample size	<3000	13	0.81(0.71-0.93)	0.003
	≥3000	6	0.75(0.63-0.90)	0.002
Age average	<60	5	0.83(0.68-1.03)	0.088
	≥60	14	0.77(0.68-0.88)	0.000
Follow up time	≤2 years	6	0.81(0.68-0.97)	0.021
	>2 years	13	0.78(0.68-0.89)	≤0.001
Study design	RCT	2	1.10(0.79-1.59)	0.631
	Cohort	16	0.79(0.71-0.88)	≤0.001
	Case- control	1	0.57(0.40-0.81)	0.001
Quality assessment	Good quality	7	0.78(0.62-0.97)	0.029
	Moderate quality	12	0.80(0.70-0.90)	≤0.001

https://doi.org/10.1371/journal.pone.0321032.t007

reconsideration. Clinical decision-making should be individualized, incorporating patient-specific factors such as cost, contraindications, comorbidities, and patient preferences when choosing between DPP-4is, SUs, or other second-line agents.

Limitations

This review has several limitations that should be considered when interpreting the findings. We observed heterogeneity across the included studies, likely due to variations in study design, population characteristics (e.g., age, comorbidities, baseline cardiovascular risk), and follow-up duration. The inclusion of observational studies introduces the possibility of residual confounding, even after statistical adjustments. Unmeasured or imperfectly measured confounders could influence the observed associations. While our assessment did not reveal statistically significant publication bias, its presence cannot be entirely ruled out. Limited data on specific subgroups restrict the generalizability of our findings to certain populations. Further research is needed to explore the effects of DPP-4is and SUs in diverse patient subgroups. Variations in metformin dosage and background therapies across studies may have influenced the results. Our focus on MACE and all-cause mortality necessitates further research exploring other relevant outcomes, such as microvascular complications (e.g., nephropathy, retinopathy, neuropathy) and quality of life.

Conclusion

This meta-analysis of 27 studies, encompassing over 1.5 million participants, suggests that adding a DPP-4is to metformin in patients with type 2 diabetes inadequately controlled with metformin alone is associated with significantly lower risks of major adverse cardiovascular events and all-cause mortality compared to adding an SU. These findings support the potential preferential use of DPP-4is over SUs as second-line therapy in conjunction with metformin to improve cardiovascular and mortality outcomes in patients with type 2 diabetes. Further research is warranted to elucidate the underlying mechanisms driving these observed benefits and to confirm these findings in diverse populations and with longer follow-up durations.

Supporting information

S1 Checklist. PRISMA 2020 checklist.
(PDF)

S2 Tables. Search strategy and extracted information.
(PDF)

S3 Scales. Study quality assessment scales.
(PDF)

Author contributions

Conceptualization: Refli Hasan, Uliana Y. Chugaeva, Mahdi Mohammadian, Somayeh Zamanifard, Abdollah Mohammadian-Hafshejani.

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Investigation: Refli Hasan, Uliana Y. Chugaeva, Mahdi Mohammadian, Abdollah Mohammadian-Hafshejani.

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Writing – review & editing: Refli Hasan, Uliana Y. Chugaeva, Mahdi Mohammadian, Somayeh Zamanifard, Abdollah Mohammadian-Hafshejani.

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