

RESEARCH

Effects and safety of metformin in patients with concurrent diabetes mellitus and chronic obstructive pulmonary disease: a systematic review and meta-analysis

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Abstract

Aim: This study aimed to investigate the effects and safety of metformin in patients with concurrent diabetes mellitus (DM) and chronic obstructive pulmonary disease (COPD).

Methods: PubMed, Embase, Web of Science, the China National Knowledge, and Cochrane Database were searched to find studies that examined the effects and safety of metformin in patients with concurrent DM and COPD. We conducted a meta-analysis with a risk ratio (RR) and assessed the quality of included studies and pooled evidence.

Results: Eight studies were involved. Metformin was associated with lower risk of COPD-related hospitalizations (RR: 0.72, 95% CI: 0.53–0.98; $I^2=89%$) and all-cause mortality (RR: 0.60, 95% CI: 0.36–1.01, $I^2=69%$) in patients with concurrent DM and COPD, but did not increase the risk of hyperlactatemia (RR: 1.14, 95% CI: 0.92–1.41, $I^2=8%$).

Conclusions: Metformin use is associated with lower risk of COPD-related hospitalizations and risk of all-cause mortality without increasing the risk of hyperlactatemia.

Considerations should be given to conduct more high-quality randomized trials involving larger samples.

Key Words

- ▶ metformin
- ▶ diabetes mellitus
- ▶ chronic obstructive pulmonary disease
- ▶ safety
- ▶ meta-analysis

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Introduction

Chronic obstructive pulmonary disease (COPD), a prevalent, preventable, and treatable disorder, is characterized by ongoing respiratory symptoms and incompletely reversible airflow limitation (1). COPD may be linked to an increased risk of diabetes mellitus (DM) due to the sedentary lifestyle and adiposity of COPD patients, the inflammatory processes (2), and the treatment adverse effects associated with the use of high-dose corticosteroids (3). On the other hand, diabetes may aggravate the development and prognosis of COPD by affecting lung physiology, inflammation, and susceptibility to bacterial

infection directly (4). The presence of diabetes among those with COPD is associated with worse outcomes including hospitalizations and mortality (5, 6). As a result, appropriate treatments are urgently needed for patients with concurrent DM and COPD.

Metformin, a typical oral biguanide, is still the first-line therapy for DM (7). Metformin can decrease plasma glucose levels significantly and is widely used due to its safety and low cost. Recently, more and more studies have indicated that metformin might exert positive effects on other diseases such as cancers (8), cardiovascular diseases

(9), liver diseases (10), neurodegenerative diseases (11), and renal diseases (12, 13). In animal models, metformin could limit hyperglycemia-induced bacterial growth by reducing airway glucose permeability (14). Furthermore, metformin attenuates inflammatory responses by inhibiting the production of tumor necrosis factor- α , interleukin (IL)-6, and IL-1, as well as the inflammatory reaction of macrophages while increasing the synthesis of anti-inflammatory cytokines like IL-4 and IL-10 (15, 16). However, metformin has a potential risk of lactic acidosis (17). And hypoxia caused by COPD might aggravate lactic acidosis, which is fatal (18, 19). Although several published studies have reported the use of metformin on patients with concurrent DM and COPD, the results were inconsistent (20, 21, 22, 23, 24, 25). Herein, we conducted this meta-analysis and systematic review to assess the effects and safety of metformin in patients with concurrent DM and COPD.

Methods

This systematic review and meta-analysis followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses guidelines (26). The protocol for the meta-analysis is registered with PROSPERO (CRD42021287378).

Search strategy

PubMed, Embase, Web of Science, the China National Knowledge, and Cochrane Database were searched from the date of their inception to October 2021. The following terms were used in the searches: ('Chronic Obstructive Lung Disease' OR 'Chronic Obstructive Pulmonary Disease' OR 'COAD' OR 'COPD' OR 'Chronic Obstructive Airway Disease' OR 'Chronic Obstructive Pulmonary Disease' OR 'Airflow Obstruction, Chronic' OR 'Airflow Obstructions, Chronic' OR 'Chronic Airflow Obstructions' OR 'Chronic Airflow Obstruction' OR 'Pulmonary Disease, Chronic Obstructive') AND ('Dimethylbiguanidine' OR 'Dimethylguanylguanidine' OR 'Glucophage' OR 'Metformin Hydrochloride' OR 'Hydrochloride, Metformin' OR 'Metformin HCl' OR 'HCl, Metformin' OR 'Metformin'). We also scanned the references of included studies to avoid omissions in the search process.

Eligibility criteria and study selection

The inclusion criteria were as follows: (1) observational studies or randomized controlled trials (RCTs); (2) patients

age \geq 18 years; (3) examined the effects of metformin on patients with concurrent DM and COPD; (4) reported at least one clinical outcome among COPD-related hospitalizations, all-cause mortality, and hyperlactatemia. The exclusion criteria were as follows: (1) animal or *in vitro* research; (2) reviews, letters to the editor, or case reports with limited information; (3) duplicate articles.

Two investigators independently screened the titles, abstracts, and full texts of all articles obtained from the search strategy. The studies that met the inclusion criteria were eventually included. If there were any controversies among the reviewers, another author was consulted as the third investigator to achieve an agreement.

Data extracted

The data extraction table was predetermined for two researchers to independently extract data from each included study, including study characteristics (first author, year of publication, study design, sample size), participants' characteristics (gender percentage, mean age), duration of follow-up, and clinical outcomes. Clinical outcomes including COPD-related hospitalizations, all-cause mortality, and hyperlactatemia were further investigated in our study. The 'COPD-related hospitalizations' included hospital admission for acute exacerbation of COPD or respiratory complications during the follow-up period among the participants. The 'all-cause mortality' was calculated as the total number of reported deaths among participants in all included researches. 'Hyperlactatemia' is defined as a serum lactate level of 2 mmol/L or greater (27).

Assessment of study quality and risk of bias

The Newcastle–Ottawa Scale (28) and Critical Appraisal Skills Programme (<http://www.casp-uk.net/>) were used to evaluate the quality of each observational study and randomized controlled trial, respectively.

Statistical analysis

Review Manager software (version 5.3) was used to estimate the risks of bias of the included studies, analyze data, and create plots. I^2 statistics were also calculated to measure inconsistency across studies (29). $I^2 > 75\%$ indicates 'high' heterogeneity, 51–75% 'moderate' heterogeneity, 26–50% 'low' heterogeneity, and 0–25% 'nonsignificant' heterogeneity. Risk ratios (RRs) were calculated for dichotomous variables. The fixed-effects model was used for the meta-analysis if there was low heterogeneity

between the outcomes of each research. If the outcomes of each research showed high heterogeneity, the cause of the heterogeneity was investigated further to exclude the influence of obvious heterogeneity. Sensitivity analysis was performed by deleting one study at a time in order to determine the impact of the deleted study on the combined RR. The publication bias assessment and subgroup analysis were carried out using R language if enough original studies were included.

Results

Search results and description of studies

By executing the search strategy described earlier, a total of 590 articles were found after duplicated records were removed. After screening the title and abstracts, we

downloaded the full texts of 29 records, and 8 studies were ultimately included in our analysis following the eligibility criteria, involving a total of 108,054 participants. Among them, seven were retrospective cohort studies, and one was randomized controlled trial. Four studies assessed the effect of metformin on COPD-related hospital admissions in patients with concurrent DM and COPD, three studies assessed the effect of metformin on all-cause mortality in patients with concurrent DM and COPD, and four studies assessed the influence of metformin on hyperlactatemia in patients with concurrent DM and COPD. The details of the study selection process are shown in Fig. 1, and the characteristics of the studies are shown in Tables 1 and 2. Meta-analysis was performed when same clinical outcomes were reported in more than one study. Overall, the methodological qualities of the researches were moderate.

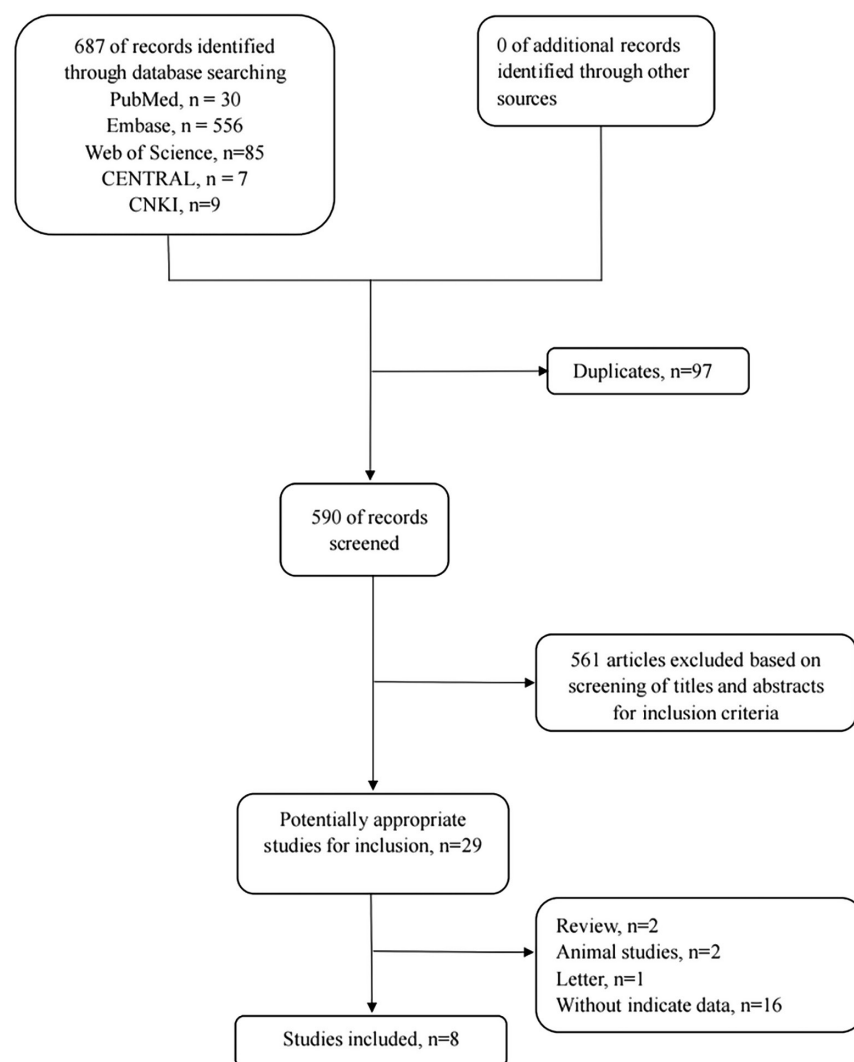


Figure 1
Flowchart of study selection process.

Table 1 Characteristics of the included studies.

Study	Year	Region	Study design	Patients	Sample size (metformin users/metformin non-users)
Hitchings (20)	2015	UK	Retrospective cohort study	COPD with T2DM	130 (51/79)
Dai (49)	2017	China	Randomized control study	COPD with T2DM	140 (70/70)
Yen (22)	2018	Taiwan, China	Retrospective cohort study	COPD with T2DM	Stable COPD: 39,010 (19,505/19,505) exacerbated COPD: 15,442 (7721/7721)
Yen (25)	2020	Taiwan, China	Retrospective cohort study	COPD with T2DM	41,288 (20,644/20,644)
Bishwakarma (23)	2018	America	Retrospective cohort study	COPD with DM	11,260 (3193/8067)
Ho (24)	2019	Taiwan, China	Retrospective cohort study	COPD with T2DM	511 (282/229)
Xu (50)	2020	China	Retrospective cohort study	COPD with T2DM	84 (42/42)
Zhou (51)	2017	China	Retrospective cohort study	COPD with T2DM	189 (97/92)

Outcomes

COPD-related hospitalizations

Four studies reported COPD-related hospitalizations. Figure 2 shows the forest plots for the effect of metformin on hospital admissions in patients with concurrent DM and COPD. The risk of COPD-related hospitalizations was lower in patients with concurrent DM and COPD taking metformin compared with metformin non-users (RR: 0.72, 95% CI: 0.53–0.98; $I^2 = 89\%$).

All-cause mortality

Data of the all-cause mortality of patients with concurrent DM and COPD were extracted from three studies. Figure 3 shows the forest plots for the effects of using metformin on all-cause mortality in patients with concurrent DM and COPD. As shown in Fig. 3, all-cause mortality was marginally lower in patients with concurrent DM and COPD taking metformin compared with metformin non-users (RR: 0.60, 95% CI: 0.36–1.01, $I^2 = 69\%$).

Hyperlactacemia

Data of hyperlactatemia were extracted from four studies. As shown in Fig. 4, patients using metformin were not at an increased risk of hyperlactatemia compared with metformin non-users (RR: 1.14, 95% CI: 0.92–1.41, $I^2 = 8\%$). There was no statistical significance, although a further sensitivity analysis has been performed.

Sensitivity analysis

Since the pooled results of COPD-related hospitalizations were of high heterogeneity, a sensitivity analysis was conducted for each outcome by excluding one study in return to evaluate the influence of each included

study. After excluding the study (Fu-Shun Yen 2020), the heterogeneity turned out to be moderate (Fig. 5).

Discussion

Several prospective studies showed that COPD appeared to be an important risk factor for the development of type 2 diabetes mellitus (T2DM) after adjusting for possible confounders (2, 30, 31). Recent evidence suggests that hyperglycemia could exacerbate the progression and prognosis of diabetes and increases the mortality associated with COPD (5, 32, 33). Researches about metformin treatment on patients with concurrent DM and COPD have received more attention in recent years, but different trials showed inconsistent results. Zhu *et al.* performed a systematic review to examine the safety and efficacy of metformin in patients with COPD; however, they did not provide statistical evidence to support their findings (34). With eight included studies, our systematic review and meta-analysis first provides a comprehensive assessment of the effect and safety of metformin in patients with concurrent DM and COPD. The patients treated with metformin were associated with lower risk of COPD-related hospitalizations. And it seems that metformin marginally reduces all-cause mortality, although the result is not statistically significant.

Several biological plausibilities are likely related to the demonstrated protective effects of metformin for severe COPD exacerbation. First, COPD is related to increased inflammation and oxidative stress, whereas metformin is shown to exert an anti-inflammatory effect by activating AMP-activated protein kinase (AMPK) (35) and decrease airway remodeling by inducing the production of anti-inflammatory cytokines (36). Additionally, a prospective observational study showed 6-month metformin therapy substantially raised (11%) inspiratory muscle strength

Table 2 Characteristics of the included studies.

Study	Year	Male/total (%)		Age (years)		Duration (years)	Outcomes	NOS
		Metformin users	Metformin non-users	Metformin users	Metformin non-users			
Hitchings (20)	2015	33 (65)	50 (63)	70.5 ± 9.6	74.7 ± 9.6	Not mentioned	All-cause mortality; metabolic acidosis	8
Dai (49)	2017	51 (72.9)	47 (67.1)	67.45 ± 8.26	64.96 ± 10.24	1	All-cause mortality	CASP18
Yen (22)	2018	Stable COPD: 10,253 (52.6) Exacerbated COPD: 5159 (66.8)	10,180 (52.2) 5101 (66.1)	65.4 ± 10.7 Exacerbated COPD: 71.8 ± 11.4	71.8 ± 11.4	Metformin users: 3.19; Metformin non-users: 3.17	All-cause mortality; metabolic acidosis; COPD-related hospitalizations	9
Yen (25)	2020	11,151 (54.1)	11,279 (54.6)	63.9 ± 11.2	63.9 ± 11.2	5.1	COPD-related hospitalizations	9
Bishwakarma (23)	2018	1042 (32.63)	2522 (32.63)	66-74: 1501 (47.01) 75-84: 1400 (43.85) ≥85: 292 (9.15)	2737 (33.93) 3958 (49.06) 1372 (17.01)	2	COPD-related hospitalizations	8
Ho (24)	2019	232 (82)	187 (82)	72.1 ± 9.3	74.0 ± 9.3	2	All-cause mortality	7
Xu (50)	2020	21 (50)	22 (52.4)	60.51 ± 1.55	60.11 ± 1.64	Not mentioned	COPD-related hospitalizations; hyperlactacemia	8
Zhou (51)	2017	53 (54.6)	49 (53.3)	69.4 ± 7.2	69.7 ± 7.5	3	All-cause mortality; hyperlactacemia	8

CASP, Critical Appraisal Skills Programme; NOS, Newcastle-Ottawa scale.

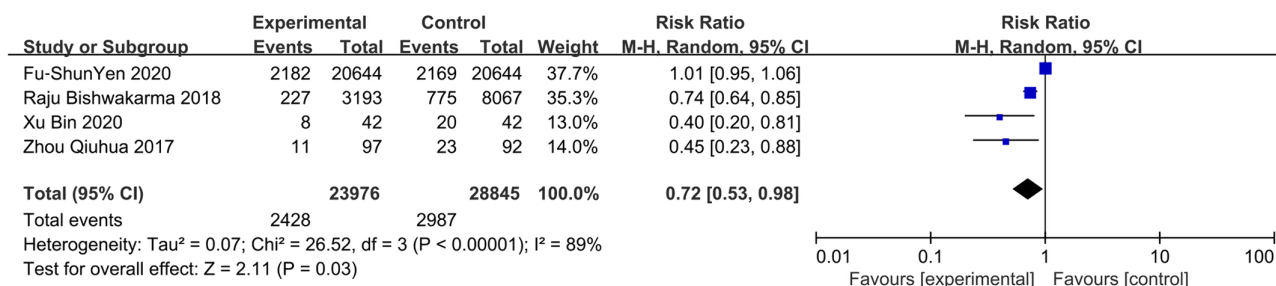


Figure 2
 Forest plot for the effect of metformin on hospital admissions of patients with concurrent DM and COPD.

in patients with moderate-to-severe COPD (37), which indicated metformin might alleviate COPD symptoms worsening by improving respiratory muscle function. Third, insulin resistance is correlated with skeletal muscle dysfunction (38) and chronic systemic inflammation in COPD (39), which further exacerbate airway obstruction. Hence, an alternative reasonable hypothesis is that metformin might induce insulin resistance remission. Our meta-analysis indicated the risk of COPD-related hospitalizations was lower in patients with concurrent DM and COPD taking metformin compared with metformin non-users; however, significant heterogeneity existed. We hypothesized that heterogeneity may be associated with severity of COPD and the duration of metformin administration. Unfortunately, most original studies did not describe the severity of COPD in the patients and we were unable to perform a subgroup analysis of it. Regarding COPD-related hospitalizations, sensitivity analysis suggested that when the study by Fu-Shun Yen (2020) was excluded, heterogeneity decreased from 89% to 57% and RR changed from 0.72 to 0.57, with the results still being statistically significant. We suspect that because the study by Fu-Shun Yen (2020) had a longer follow-up (5.01 years) than the other three studies, the COPD-related hospitalizations were higher regardless of whether the patients were taking metformin or not, which might be one reason for the significant heterogeneity.

Our meta-analysis showed metformin seems to be associated with lower risk of all-cause mortality, although the effect was slight. As airflow restriction worsens, the degree of inflammation worsens in patients with COPD, who are more susceptible to multisystem diseases. Compared with those with mild disease, cardiovascular and other comorbidities are more common in patients with moderate and severe illness (6, 40). All comorbidities could increase mortality risk. Metformin could improve endothelial oxidative stress levels and attenuate hyperglycemia-induced inflammation, decreasing the incidence of cardiovascular comorbidities (41). Additionally, metformin decreases the occurrence of other comorbidities by activating AMPK (42, 43, 44, 45), eventually leading to lower all-cause mortality.

Metformin interferes with mitochondrial respiratory oxidation and inhibits gluconeogenesis of a variety of substrates, such as glycerol lactate pyruvate and amino acids (19). Metformin is thought to reduce gluconeogenesis from alanine, pyruvate, and lactate, and lactic acid levels may increase under certain conditions (46). Although metformin-associated lactic acidosis is an extremely rare condition, cases continue to be reported and its linked mortality rate is close to 50% (47). Metformin increases the risk of lactic acidosis when patients are in a hypoxic condition; type A tends to arise when tissue perfusion or blood oxygenation is lacking (47, 48). Patients with

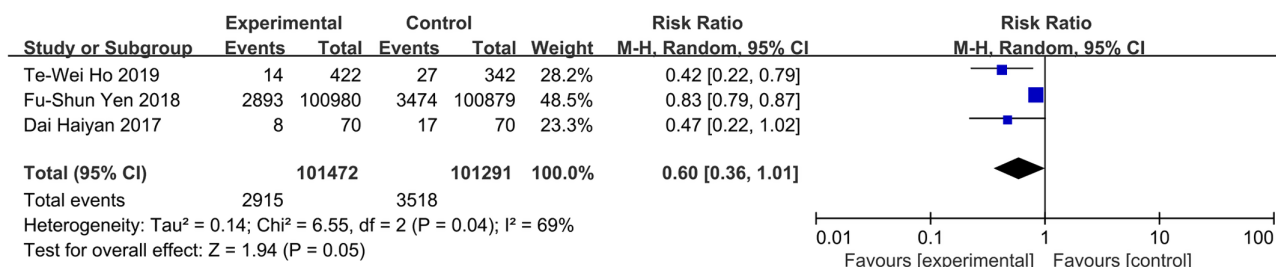


Figure 3
 Forest plot for the effect of metformin on all-cause mortality of patients with concurrent DM and COPD.

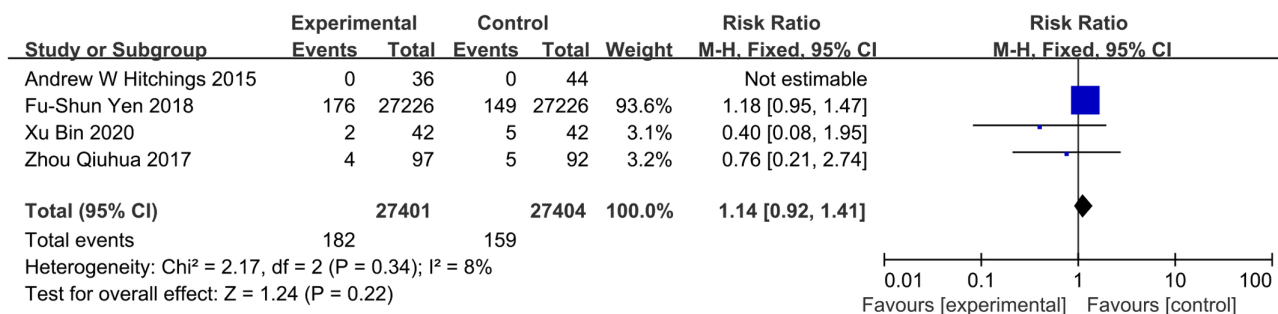


Figure 4 Forest plot for the influence of metformin on hyperlactatemia of patients with concurrent DM and COPD.

severe COPD are often accompanied by hypoxemia, which restricts the clinical use of metformin among patients with concurrent DM and COPD. However, our meta-analysis demonstrated that metformin use for COPD did not increase the risk of hyperlactatemia. Metformin is still the drug of choice for patients with concurrent DM and COPD when excluding other contraindications.

Our study first provides significant statistical evidence to assess the effect and safety of metformin on the patients with concurrent DM and COPD, which guides the medical treatments in patients with concurrent DM and COPD. Our meta-analysis demonstrates for the first time that the use of metformin in patients with concurrent DM and COPD is associated with lower COPD-related hospitalizations and the risk of all-cause mortality without increasing the risk of hyperlactatemia. These findings affirmed the metformin's active role in treatment for COPD. Subgroup studies could be carried out in the future to determine the appropriate dosing and duration of metformin therapy. However, several limitations should be acknowledged. First, the number of papers that were qualified for inclusion in our meta-analysis was limited and most of them were retrospective observational studies. Despite the fact that two included studies used propensity score matching to balance confounding factors and promote comparability, we were only able to obtain crude data from the original

articles. Therefore, the influence of confounding factors on the results cannot be ruled out. Second, since the heterogeneity in the studies should not be overlooked when analyzing the results, a sensitivity analysis was done to ensure the reliability and stability of our findings. Finally, there may be publication bias since assessment and subgroup analysis could not be performed because not enough original studies were included.

Conclusions

In summary, this review and meta-analysis suggests that metformin use in patients with concurrent DM and COPD is associated with lower risk of COPD-related hospitalizations and all-cause mortality without increasing the risk of hyperlactatemia. Metformin is safe and well-tolerated in patients with concurrent DM and COPD. To prove and update the therapeutic efficacy of metformin in patients with concurrent DM and COPD, further high-quality RCTs and well-designed researches with larger sample populations are still needed.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

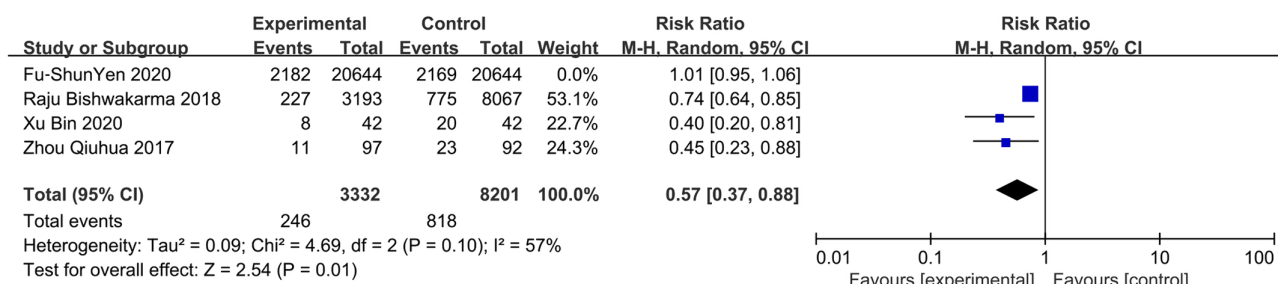


Figure 5 Sensitivity analysis.

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Data availability statement

All data generated or analyzed during this study are included in this article and its supplementary material files. Further enquiries can be directed to the corresponding author.

Author contribution statement

Z T L, M G Y, C J X, and L D conceived and designed the study. M G Y, Z T L, and R Z contributed to acquisition of data, quality assessment, and design of statistical analyses. M G Y and Z T L interpreted the data and wrote the first draft of the study. Z T L, M G Y, C J X, and R Z performed significant revisions. All authors contributed to critical revision of the report for important intellectual content and approval of the final version to be published.

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