

Comparison of Associations Between Glucocorticoids Treatment and Mortality in COVID-19 Patients and SARS Patients: A Systematic Review and Meta-Analysis

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Research

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Abstract

Background

The response to glucocorticoids treatment may be different between Covid-19 and SARS.

Methods

In this systematic review and meta-analysis, we searched studies on Medline, Embase, EBSCO, ScienceDirect, Web of Science, Cochrane Library, ClinicalTrials.gov, ICTRP from 2002 to October 7, 2020. We used fixed-effects and random-effects models to compute the risk ratio of death in the group receiving glucocorticoids treatment and the control group for COVID-19 and SARS, respectively.

Results

Ten trials and 71 observational studies, with a total of 45935 patients, were identified. Glucocorticoids treatment, was associated with decreased all-cause mortality both in COVID-19 (risk ratio, 0.88; 95% confidence interval, 0.82 to 0.94; $I^2=26\%$) and SARS (0.48; 0.29 to 0.79; 10%), based on high quality evidence, as well as decreased all-cause mortality-including composite outcome of COVID-19 (0.89; 0.82 to 0.98; 0%). In subgroup analyses, all-cause mortality was significantly lower among COVID-19 patients being accompanied by severe ARDS but not mild ARDS, taking low-dose or pulse glucocorticoids, being critically severe but not only severe, being of critical severity and old but not young, being of critical severity and men but not women, non-early taking glucocorticoids and taking dexamethasone or methylprednisolone; but for SARS, lower mortality were observed among those who were taking medium-high dose glucocorticoids, being severe or critically severe, early taking glucocorticoids, and taking dexamethasone or prednisolone.

Conclusions

Glucocorticoids treatment reduced mortality in COVID-19 and SARS patients of critical severity; however, different curative effects existed between the two diseases among subpopulations, mainly regarding sex- and age-specific effects, optimal doses and use timing of glucocorticoids.

Introduction

The coronavirus disease 2019 (COVID-19) and severe acute respiratory syndrome (SARS) are both coronavirus-caused pandemics that broke out in 2019 and 2003, respectively. The SARS epidemic has passed, but COVID-19 is ravaging the world. As of early November 2020, nearly 50 million people have been confirmed with COVID-19, and 1.2 million have been dead of this disease.¹

Glucocorticoids, one of the non-specific immunosuppressants, were the mainstay of immunotherapy during the SARS epidemic, but its role has been a lasting controversy, same in the COVID-19 epidemic. Till July 2020, RECOVERY trial, a large clinical randomized controlled trial (RCT) from the UK, involving 6425

patients, reported an absolute decrease in all-cause mortality of 2.8% in COVID-19 patients receiving a low dose of dexamethasone compared with those receiving usual care.² Lately, a prospective meta-analysis involved 7 RCTs concluded systemic glucocorticoids were associated with decreased all-cause mortality in critically ill patients with COVID-19.³ However, scholars pointed out that removing the RECOVERY trial, the result of that meta-analysis changed to no statistical significance.⁴ Therefore, to obtain a robust product, more ongoing RCTs should be included.

Although evidence has shown severe dysregulated host inflammatory and immunity response is deadly both in COVID-19 and SARS patients⁵⁻⁸, their epidemiology and clinical manifestations are substantial differences due to the subtle differences in pathogenesis.^{9,10} We speculate that the response to glucocorticoids treatment is different between the two diseases. Moreover, which doses, timing, and types of glucocorticoids treatment are more effective, and whether there are any other survival benefit subgroups besides critically ill patients have not been determined. Therefore, we conducted this systematic review and meta-analysis to provide more clues in these undetermined aspects.

Methods

Guidance and Protocol

We followed the standards developed by the meta-analysis of observational studies in epidemiology (MOOSE)¹¹ and preferred reporting items for systematic reviews and meta-analyses (PRISMA)¹² for reporting our study. The protocol for this review and meta-analysis was registered with PROSPERO (CRD42020193823).

Eligibility criteria

We considered studies to be eligible if they met the following PICOS criteria (participants, interventions, comparators, outcomes, and study design). The participants of interest included patients (adults/children) who were diagnosed with COVID-19 or SARS. The intervention included any type of glucocorticoids, including but not limited to hydrocortisone, prednisolone, methylprednisolone, prednisone, dexamethasone, and triamcinolone, compared with placebo or usual care (which may have included antiviral, antibiotic and antifungal therapy, intravenous immunoglobulin, or respiratory support, if needed). The primary outcome was all-cause mortality (including 28- or more-day mortality, 14- to 28-day mortality, and 7-day mortality). All-cause mortality rates were used to compute the pooled analysis on 7-day mortality if actual 7-day mortality rates failed to be neither extracted from the published studies nor obtained from study authors. The secondary outcome was the mortality-including composite outcome, including death and mechanical ventilation or intensive care unit (ICU) admission. The definitions of outcomes are presented in Supplementary Table 1. Both RCTs and observational studies (including cohort studies, case-control studies, case series) were included.

Studies were excluded if they were before-after studies, case series with no more than ten patients, overlapping/repeated cohort data, and no or contaminated control design.

Literature search

Two of the authors (J.B.L. and X.L.L.) developed and executed the search strategy of several databases: Medline (Ovid), Embase (Ovid), EBSCO (H.W. Wilson: OmniFile Full-Text Mega), ScienceDirect, Web of Science (All database), Cochrane Library, from 2002 to October 7, 2020. We also searched ClinicalTrials.gov and consulted the WHO International Clinical Trials Registry Platform (ICTRP) to identify any ongoing or unpublished eligible studies. To maximize the search for relevant articles, we reviewed reference lists of identified studies, systematic reviews, and review articles on the same topic. We did not apply language or publication status restrictions. Supplementary Table 2 presents the details of the search strategy.

Study selection

After removing duplicates, two independent groups of four authors (H.Y. and W.Z.; Y.Z. and L.P.W.) screened the titles and abstracts to determine whether the citation met the participants and intervention eligibility criteria. They obtained full texts and then further screened when studies met all the rest eligibility criteria. Disagreements between groups were resolved by consensus, and if necessary, consultation with a third author (Z.W.Z.).

Data collection process

Two independent groups of four authors (H.Y. and W.Z.; Y.Z. and L.P.W.) extracted data from included studies into standard data collection forms and created tables for quality assessment evidence and information. Evidence of severity of illness and administration of glucocorticoids reported in the eligible studies were collected and categorized according to the pre-defined (Supplementary Table 1).

Assessment of risk of bias

Two independent groups of four authors (H.Y. and W.Z.; Y.Z. and L.P.W.) performed the risk of assessment using the Revised Cochrane risk-of-bias tool for randomized trials (RoB 2) and using the Newcastle-Ottawa-Scale (NOS)¹³ for observational studies. The included randomized trials were assessed for (1) randomization process, (2) deviations from intended interventions, (3) missing outcome data, (4) measurement of the outcome, (5) selection of the reported result. Each domain was assessed as low risk, some concerns, or a high risk of bias. The study's overall risk of bias was determined by the highest risk of bias for any criteria. The included observational studies were assessed for (1) selection, (2) comparability, (3) exposure for case-control or outcome for cohort studies. Each domain is composed of 2 to 4 items of criteria, and each criterion was scored in the form of stars. A total score of 8 or 9 was assessed as low risk of bias, 6 or 7 as some concerns, and ≤ 5 as high risk. Disagreements between groups were resolved by consensus, and if necessary, consultation with a third author (Z.W.Z.).

Data synthesis

We performed statistical analyses used the meta package in R (version 4.0.1; The R Project for Statistical Computing). Analyses were conducted for the intention-to-treat-based outcomes reported from RCTs and conducted for the narrowest-95%-confidence-interval-based data of risk for outcomes reported from observational studies. We equivalently transformed hazard ratios (HRs)¹⁴ and odds ratios (ORs)¹⁵ into risk ratios (RRs) and log-transform these effect sizes as well as their standard errors first before they were pooled. We used RRs and their associated 95% confidence interval (CI) to assess outcomes, as well as a prediction interval (PI) for the effect of future studies based on present¹⁶, and we considered a 2-tailed P value of less than 0.05 to be statistically significant. We examined heterogeneity using the I^2 test. If non-significant heterogeneity present ($I^2 < 50\%$), we used both fixed-effects and random-effects models to pool outcomes; we used random-effects models when significant heterogeneity was present ($I^2 \geq 50\%$).

The possibility of publication bias was qualitatively visualized through contour-enhanced funnel plots and quantitatively tested through the Egger test. Duval & Tweedie's trim-and-fill procedure was also adopted to estimate the actual effect size when had the "missing" small studies been published.¹⁷

Trial sequential analysis

We performed a trial sequential analysis to explore whether RCTs' cumulative data were adequately powered to evaluate outcomes. Trial sequential analysis¹⁸ (a Java-based software application, version 0.9.5.10) was used to calculate the required information size, and the O'Brien-Fleming approach was adopted to compute trial sequential monitoring boundaries. An optimal information size was calculated based on the event proportion of outcomes in the control arm, 2-sided 5% risk of type I error, 20% risk of type II error (power 80%), and an anticipated relative risk reduction of more than 10% in this study.

Multimodel inference

We performed multimodel inference to examine which possible predictor combinations provide the best fit, and which predictors are the most important ones overall.¹⁹ The "dmetar" package in R was used to calculate the multimodel inference coefficients for each predictor and all predictors and obtain model-averaged importance of the predictors' plot. A total of 7 factors were considered as input predictors: incidence of events in control, the severity of illness, doses of glucocorticoids, types of glucocorticoids, the timing of glucocorticoids, primary data type, and time frame of mortality. No prior knowledge was available on how these predictors are related to effect sizes in our meta-analysis.

Subgroup Analysis

We planned several analyses to test interactions according to the following variables: (1) age (elder [defined as ≤ 65 years plus or minus 5 year] and young [defined as > 65 years plus or minus 5 year]); (2) sex (man and women); (3) incidence of events in control ($\leq 5\%$, 5% to 10%, 10% to 20%, 20% to 40%, 40% to 80%, and 80% to 100%); (4) severity of illness (mild or moderate, severe, critically severe, and severe or

critically severe); (5) acute respiratory distress syndrome (ARDS) (with and without); (6) diabetes (with and without); (7) doses (equivalent methylprednisolone) of glucocorticoids (low dose [< 90 mg/day or < 1.5 mg/kg/day], medium-high dose [90-250mg/day or < 1.5 -4 mg/kg/day], and pulse [250-500 mg/day]); (8) types of glucocorticoids (dexamethasone, hydrocortisone, methylprednisolone, and multiple types); and (9) timing of glucocorticoids (non-early and early [Defined as glucocorticoids therapy within the first 48 hours of admission or within 10 days from illness onset to glucocorticoids therapy]).

Sensitivity analyses

We conducted sensitivity analyses by (1) excluding studies with high, some concerns, or both risks of bias, (2) excluding the largest studies, (3) excluding studies reporting multiple glucocorticoids use, (4) excluding studies identified by clustering-algorithms-dependent Graphic Display of Heterogeneity (GOSH) plots²⁰⁻²³, (5) combining data from RCTs and observational, (6) using odds ratios to assess outcomes.

Results

Eligible studies and study characteristics

Of the 6136 records, 81 studies^{2,24-103} involved a total of 45935 patients were included in the final meta-analysis (Figure 1). Table 1 shows a summary of the included studies. The studies comprised 10 RCTs for COVID-19, including 7898 patients, 59 observational studies for COVID-19 including 26735 patients, and 12 observational studies for SARS including 11302 patients. These studies for COVID-19 reported median mortality of 17% and a median age of 57.4 years among their included patients, and studies for SARS reported median mortality of 6.3% and a median age of 46 years among their included patients. Supplementary Table 3 gives details of those studies.

Supplementary Figures 1 and 2 show a risk bias for RCTs. Seven trials had a low risk of bias, and three trials had a risk of some concerns. Supplementary Tables 4 and 5 show risk bias for observational studies. In case-control studies, two studies reported outcome data with low risk or risk of some concerns, three studies reported outcome data with risk of some concerns, two studies reported outcome data with high risk or risk of some concerns, and 29 studies reported outcome data with high risk. In retrospective cohort studies, 1 study reported outcome data with low risk, 13 reported outcome data with low risk or risk of some concerns, 13 studies reported outcome data with some concerns, four studies reported outcome data with high risk or risk of some concerns, and four studies reported outcome data with high risk.

Primary outcome: all-cause mortality

All 10 RCTs reported all-cause mortality for COVID-19. The overall RR (0.88; 95% CI, 0.82 to 0.94; $I^2=26\%$; PI, 0.81 to 0.95) (Figure 2) revealed an association between glucocorticoids treatment and improved all-cause mortality in COVID-19 patients. There was no statistically significant difference in that association between 7-day, 14- to 28-day, and 28- or more-day mortality. The trial sequential analysis confirmed that

the overall required information size was met for all-cause mortality (Supplementary Figure 3). Similar results were observed for all-cause mortality in all conducted sensitivity analyses (Supplementary Table 6). Funnel plot analysis showed no asymmetry (Supplementary Figure 12), and the Egger test ($P=0.747$) detected no significant small-study effects. A total of 52 observational studies for COVID-19 reported all-cause mortality, and the pooled RR from studies of all risk levels showed an association between glucocorticoids treatment and increased all-cause mortality in COVID-19 patients (RR, 1.32; 95% CI, 1.08 to 1.61; $I^2=99\%$) (Supplementary Figure 5) while result from 11 studies with low risk of bias was similar with that from RCTs (RR, 0.68; 95% CI, 0.5 to 0.94; $I^2=67\%$) (Supplementary Table 6). Funnel plot analysis showed no asymmetry among observational studies reporting all-cause mortality for COVID-19 (Supplementary Figure 14).

A total of 10 observational studies for SARS reported all-cause mortality. Results from studies with low risk of bias revealed a statistically significant association between glucocorticoids treatment and improved all-cause mortality in SARS patients (RR, 0.48; 95% CI, 0.29 to 0.79; $I^2=10\%$; PI, 0.21 to 1.09) (Figure 2). Though the overall RR from studies of all risk levels showed no association between glucocorticoids treatment and all-cause mortality in SARS patients (RR, 1.1; 95% CI, 0.74 to 1.63; $I^2=99\%$) (Supplementary Figure 7), sensitivity analyses excluding studies with a high risk of bias or excluding studies reporting use of multiple glucocorticoids showed a similar result with that from studies with low risk of bias (RR, 0.67; 95% CI, 0.45 to 1; $I^2=97\%$) (Supplementary Table 6)). Funnel plot analysis showed no asymmetry (Supplementary Figure 16), and the Egger test ($P=0.489$) detected no significant small-study effects, and additionally results from the Duval & Tweedie's trim-and-fill procedure (with 5 added studies) were identified with our initial results.

Secondary outcome: mortality-including composite outcome

Evidence from RCTs showed glucocorticoids treatment was associated with significant reduction in all-cause mortality-including composite outcome of COVID-19 (RR, 0.89; 95% CI, 0.82 to 0.98; $I^2=0\%$; PI, 0.69 to 1.15) (Figure 2), especially significant reduction in 28- or more-day mortality-including composite outcome (RR, 0.9; 95% CI, 0.81 to 1; $I^2=40\%$) (Figure 2). In the trial sequential analysis, the cumulative z-curve nearly reached the monitoring boundary, but the number of involved patients failed to meet the required information size of 9347. Sensitivity analyses showed no significantly different results (Supplementary Table 6). Funnel plot analysis showed no significant asymmetry (Supplementary Figure 13), the Egger test ($P=0.403$) detected no significant small-study effects. Additionally, Duval & Tweedie's trim-and-fill procedure (with 2 added studies) showed similar results with the initial ones.

Evidence from observational studies of all risk levels showed no significant association between glucocorticoids treatment and all-cause mortality; however, evidence indicated a significant reduction in 28- or more-day mortality-including composite outcome in COVID-19 patients receiving glucocorticoids treatment (RR, 0.53; 95% CI, 0.43 to 0.66; $I^2=83\%$) (Supplementary Figure 6). Sensitivity analyses excluding studies with a high risk of bias confirmed the significant reduction both in 28- or more-day and all-cause mortality-including composite outcome (Supplementary Table 6). No significant small-study

effects were observed among these observational studies reporting the mortality-including composite outcome of COVID-19 (Supplementary Figure 15). Only one observational study reported conflicting data of mortality-including composite outcomes of SARS and pooled RR showed no significant association between glucocorticoids treatment and all-cause mortality in SARS patients (RR, 0.84; 95% CI, 0.17 to 4.3; $I^2=96%$) (Supplementary Figure 8).

Multimodel inference and subgroup analysis

Multimodel inference found that incidence of events in control, doses of glucocorticoids, and types of glucocorticoids were the top three important predictors for all-cause mortality in COVID-19 patients (Supplementary Figure 9). The former two were also the most important predictors for the mortality-including composite outcome of COVID-19 (Supplementary Figure 10). Differently, the types of glucocorticoids became the only most important predictor for all-cause mortality in SARS patients (Supplementary Figure 11).

Subgroup analysis revealed that all-cause mortality was significantly lower in COVID-19 patients with characters of being accompanied by ARDS, taking low-dose or pulse glucocorticoids, being severe or critically severe, being man, and taking dexamethasone or methylprednisolone (Figure 3). Similar results occurred when the mortality-including composite outcome was considered (Figure 4). Some differently, all-cause mortality was significantly lower in SARS patients with characters of taking medium-high dose glucocorticoids, being severe or critically severe, early taking glucocorticoids, and taking dexamethasone or prednisolone (Figure 5). Because 2 of 3 studies for mild or moderate SARS patients reported zero events in both arms, there was no enough power to draw a convincing conclusion in these subgroup patients. Moreover, early taking glucocorticoids seemed to have no significant association with improved mortality in COVID-19 patients until when mechanical ventilation or ICU admission outcome was additionally considered (Figure 4 and 5).

Importantly, pooled effects for COVID-19 and SRAS patients' outcomes strongly correlated to the incidence of events in control. The benefit was only seen among studies that reported more than 20% of the incidence of events in control but was not seen for the incidence of less than 20% (Figure 3, 4, and 5). Pooled effects even showed a significant association between glucocorticoids treatment and worsen mortality reported from studies with the incidence of events in control from 0% to 5% (Figures 3 and 5). We stratified studies according to these incidences to avoid the potential bias caused by the difference of outcome incidence reported in control (Supplementary Figure 17-24). Interestingly, results implied that COVID-19 patients who were critically severe (including severe ARDS) but not only severe (including mild ARDS), and COVID-19 patients who of critical severity were old but not young, or men but not women were more likely to obtain survival benefit from glucocorticoids treatment (Supplementary Figure 17-23, 25).

Discussion

In this meta-analysis of 10 RCTs (including 7898 COVID-19 patients) and 71 observational studies (including 26735 COVID-19 patients and 11302 SARS patients), glucocorticoids treatment was significantly associated with reduced all-cause mortality and mortality-including composite outcome both in COVID-19 and SARS patients. Subgroup analyses demonstrated that among COVID-19 patients, the beneficial effect in our outcomes was associated with being accompanied by severe ARDS but not mild ARDS, taking low-dose or pulse glucocorticoids, being critically severe but not only severe, being of critical severity, and old but not young, being of critical severity and men but not women, non-early taking glucocorticoids and taking dexamethasone or methylprednisolone; among SARS patients, that beneficial effect was associated with taking medium-high dose glucocorticoids, being severe or critically severe, early taking glucocorticoids, and taking dexamethasone or prednisolone. Our findings suggested glucocorticoids treatment's survival benefits both in COVID-19 and SARS patients and its association with the severity of illness; however, there were differences in the other aspects, mainly regarding sex- and age-specific effects, doses, and timing of glucocorticoids treatment.

Principal findings and comparison with other studies

As of writing this manuscript (early November 2020), 16 meta-analyses^{3,104-118} have examined the use of glucocorticoids in patients with COVID-19 or coronavirus infections. Regarding mortality, 4 meta-analyses^{3,106,111,112,117} included RCTs (1 including 7 RCTs, 3 including 1 or 2 RCTs) and the rest only included observational studies. Of these meta-analyses, 5^{3,104-107} found that glucocorticoids treatment decreased all-cause mortality, 7¹⁰⁸⁻¹¹⁴ found no association between glucocorticoids treatment and all-cause mortality, and the others¹¹⁵⁻¹¹⁸ found glucocorticoids treatment increased all-cause mortality. In general, meta-analyses that supported glucocorticoids treatment mostly identified studies on COVID-19 patients who were severely-ill or with ARDS. The latest meta-analysis³ was a prospective meta-analysis involving seven clinical trials of 1703 critically ill patients with COVID-19. Findings in this meta-analysis showed that administration of systemic glucocorticoids was associated with lower 28-day all-cause mortality (OR based on a fixed-effect meta-analysis, 0.66; 95% CI, 0.53 to 0.82; $I^2=15.6\%$). Results of this prospective meta-analysis without considering other ongoing trials were limited owing to its risk of selective reporting or publication bias. Moreover, the RECOVERY trial² exerted the most influence (comprising 59% patients and contributing 57% of the weight) in that meta-analysis, and if the RECOVERY trial was excluded, results changed to no statistical significance.⁴ Before that study, a single-arm meta-analysis¹⁰⁵ investigated the mortality in COVID-19 patients who were accompanied with ARDS and received glucocorticoids treatment and found that compared to 39% of all-cause mortality among COVID-19 patients with ARDS, glucocorticoids treatment decreased all-cause mortality to 28%. However, the limitation of the single-arm meta-analysis was obvious due to its non-pairwise design. There was one meta-analysis¹¹⁸ investigating glucocorticoids use on mortality in SARS patients alone. The meta-analysis found no association between glucocorticoids treatment and all-cause mortality in SARS patients (RR, 2.56; 95% CI, 0.99 to 6.63; $I^2=77.4\%$). However, results from that meta-analysis were restricted owing to inconsistency (significant heterogeneity across involved studies), published bias (only seven studies), and risk of bias (including observational studies of all risk levels).

The findings of our meta-analysis of the association of glucocorticoids administration with improved all-cause mortality were in line with the recently published results on COVID-19. We further confirmed these findings by including additional 3 RCTs and conducting the sensitivity analysis by excluding the largest trial (RECOVERY trial). Moreover, the results of the trial sequential analysis also reinforced our findings. Besides, we also investigated the effect of glucocorticoids treatment on the mortality-including composite outcome. We found a protective role of glucocorticoids treatment in 28- or more-day mortality-including composite outcomes in COVID-19 patients. Furthermore, results from observational studies with a low risk of bias were like those from RCTs.

Our findings of the survival benefit of glucocorticoids treatment in SARS patients differ from previously published results on SARS. This difference could be explained by identifying more eligible studies and stratifying included studies according to the risk of bias in our meta-analysis. The high risk of bias mainly came from studies reporting multiple glucocorticoids use, which was also confirmed by multimodel inference. After removing these studies of a high risk of bias, survival benefit from glucocorticoids treatment was evident.

Another important difference in our meta-analysis is that we systematically compared the differences in the effects of glucocorticoids treatment on mortality between COVID-19 and SARS patients across subgroups defined by patient characteristics before receiving glucocorticoids treatment, by disease severity, and by details of glucocorticoids regimen. We assessed optimal doses, types and timing of treatment, and other potential benefit subgroups by separately showing evidence across different levels of risk of bias from RCTs and observational studies. Results indicated that the old or men being critically severe or with severe ARDS were more likely to obtain survival benefit from glucocorticoids treatment among COVID-19 patients; however, there was no evidence to support sex- or age-specific effect in SARS patients. Moreover, medium- or long-term types of glucocorticoids were associated with improved mortality both in COVID-19 and SARS patients. Regarding doses, COVID-19 patients were likely to benefit from low-dose or pulse glucocorticoids treatment; however, SARS patients may be more likely to benefit from medium-high dose glucocorticoids treatment. As for treatment timing, benefits likely preferred to early taking glucocorticoids in SARS patients; however, no strong evidence supported early taking glucocorticoids in COVID-19 patients. In brief, optimal glucocorticoids regimens were different between COVID-19 and SARS patients, especially regarding sex- and age-specific effects, doses, and treatment timing.

Strengths And Limitations

This systematic review and meta-analysis have several methodological strengths. We followed the recommendations of the MOOSE statement and PRISMA statement, including a priori protocol. This meta-analysis of all-cause mortality on COVID-19 met the optimum size in trial sequential analysis and was robust despite sensitivity analyses. We collected evidence from RCTs and observational studies, provided prediction intervals, and explored other predictors or confounding factors for all-cause mortality by multimodel inference. Through the systematic comparison of COVID-19 and SARS, we assessed

potential benefit subgroups and the optimal regimens of glucocorticoids treatment. Considering potential bias caused by the various outcome incidence in control reported by studies, systematic subgroup analyses were also conducted across different outcome incidence levels in control.

Our study has limitations. First, the results of this meta-analysis on SARS were all from observational studies. Clinical heterogeneity is inevitable in these studies, including doses, types, timing, and therapy duration. Regarding statistical heterogeneity, the results of studies on SARS included in our analysis were variable, with a high degree of detected heterogeneity for the primary outcome of all-cause mortality ($I^2=98\%$), justifying by use of random-effects models when pooling data of all levels of risk of bias. By only the inclusion of studies with a low risk of bias, heterogeneity could be resolved but with a significant change in the primary outcome. Most studies with a high risk of bias reported multiple glucocorticoids use, which was the most important contributor to heterogeneity in the meta-analysis on SARS. There was a little heterogeneity ($I^2=26\%$) when pooling data of RCTs on COVID-19. This heterogeneity came from only one trial³², which reported pulse use of glucocorticoids. GOSH plots identified this trial, and by the exclusion of this trial, heterogeneity could be eliminated without significant change in the primary outcome.

Second, though funnel plots showed no asymmetry no matter among RCTs or observational studies, no matter for primary or secondary outcomes, publication bias may exist when subgroup analyses were conducted. Some subgroup analyses failed to be conducted due to limited data. To ensure the quality of results, we analyzed RCTs and observational studies separately; however, this may increase publication bias in subgroup analyses.

Third, prevalent time from 16 years, treatments and diagnostic techniques for virus pneumonia have evolved. Therefore, the medical and technical background should be considered when comparing treatment effects on SARS and COVID-19. For example, the severity of illness or clinical classification differed between SARS and COVID-19. For SARS, there was no strict distinction between severe and critically severe, which brings us difficulty in interpreting related results.

Implications for practice

For many years and even today, glucocorticoids have aroused much controversy in treating viral pneumonia, including H1N1, SARS, MERS, and COVID-19. Historically, there was almost no hard evidence to support glucocorticoids treatment in this pneumonia. Even reviews and meta-analyses of this treatment indicated increased mortality, delayed viral clearance, and increased risk of superinfection.^{119,120} Therefore, WHO suggests glucocorticoids use only under special circumstances i.e., septic shock or bronchoconstriction, however, based heavily on empirical evidence. Until the completion of the RECOVERY trial of COVID-19 therapy, the largest relevant RCT announced at present, from which evidence supported glucocorticoids treatment in critically ill COVID-19 patients who were on mechanical ventilation or oxygen support, we're looking at glucocorticoids therapy again. Though at present much evidence supporting its use in critically ill COVID-19 patients, we cannot blindly extend it to other

subgroups of COVID-19 or other viral pneumonia. Our meta-analysis further revealed the massive impact of severity of illness on the role of glucocorticoids. It confirmed its efficacy in reducing mortality and the mortality-including composite outcome for COVID-19 patients being critically severe or with severe ARDS but not those being only severe or with mild ARDS. By comparing COVID-19 and SARS, we found differences between these diseases and further determined the optimal treatment regimens regarding sex- and age-specific effects, doses, and treatment timing. These findings appear to indicate that glucocorticoids should be prescribed at a low dose or pulse use but not at early taking (within ten days from illness onset to glucocorticoids therapy) for COVID-19 patients; however, this situation is complementary to that of SARS. Furthermore, sex- or age-specific effect in COVID-19 patients should be noted when considering this treatment. Old age or man was usually related to severe illness and results may be affected by confounding effects of disease severity. However, when stratified according to severity, sex- or age-specific effects still existed across different severity levels. Thus, we infer that sex and age may be severity-of-illness-independent factors for the risk of death. We believe our findings would bring light to the current clinical practice in glucocorticoids treatment of COVID-19.

Conclusion

The findings suggest that glucocorticoids treatment reduced all-cause mortality and mortality-including composite outcome both in COVID-19 and SARS patients of critical severity. However, further benefit subgroups for COVID-19, compared with SARS, should be those who were critical but not only severe, with severe ARDS but not mild ARDS, of critical severity and man but not women, of critical severity and old but not young, taking low-dose or pulse but not medium-high dose, and non-early but not early taking.

Abbreviations

COVID-19, coronavirus disease 2019; SARS, severe acute respiratory syndrome; RCT, randomized controlled trial; MOOSE, meta-analysis of observational studies in epidemiology; PRISMA, preferred reporting items for systematic reviews and meta-analyses; ICU, intensive care unit; NOS, Newcastle-Ottawa-Scale; HRs, hazard ratios; ORs, odds ratios; RRs, risk ratios; CI, confidence interval; PI, prediction interval; ARDS, acute respiratory distress syndrome.

Declarations

Ethics approval and consent to participate

Not applicable

Consent for publication

Not applicable

Availability of data and materials

Additional data available from the corresponding author on reasonable request at kangyan@scu.edu.cn.

Competing interests

All the authors declared no competing interests.

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Authors' contributions

JB.L., ZW.Z., and YK conceived the study and designed the protocol. JB.L. and XL.L. performed the literature search. HY, WZ, YZ, and LP.W. selected the studies, extracted the relevant information, and assessed the risk of bias of included studies. JB.L. synthesized the data and wrote the first draft of the paper. All authors contributed to critically revising successive drafts and approved the final version. JB.L., ZW.Z., and Y.K. are guarantors. The corresponding authors avouch that all listed authors meet authorship criteria and that no other qualified authors have been omitted.

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Supplementary Files

Supplementary Table 1. Definitions of Outcomes, Severity of illness and Administration of Glucocorticoids

Supplementary Table 2. Search Strategy

Supplementary Table 3. Characteristics of 81 Studies Included in the Meta-Analysis of Glucocorticoids Treatment on Mortality for COVID-19 and SARS

Supplementary Table 4. Risk of Bias of Case-control Studies by the Newcastle-Ottawa-Scale (NOS) Assessment

Supplementary Table 5. Risk of Bias of Retrospective Cohort Studies by the Newcastle-Ottawa-Scale (NOS) Assessment

Supplementary Table 6. Sensitivity Analyses

Supplementary Table 7. PRISMA 2009 checklist

Supplementary Figure 1. Risk of Bias Summary for Each Included RCT

Supplementary Figure 2. Risk of Bias Graph for Each Item Risk of Bias Presented as Percentages across All Included RCTs

Supplementary Figure 3. Trial Sequential Analysis for All-Cause Mortality of Trials Evaluating Glucocorticoids for COVID-19

Supplementary Figure 4. Trial Sequential Analysis for All-Cause-Mortality-Including Composite Outcome of Trials Evaluating Glucocorticoids for COVID-19

Supplementary Figure 5. Forest Plot of All-Cause Mortality of Observational Studies Evaluating Glucocorticoids for COVID-19

Supplementary Figure 6. Forest Plot of All-Cause-Mortality-Including Composite Outcome of Observational Studies Evaluating Glucocorticoids for COVID-19

Supplementary Figure 7. Forest Plot of All-Cause Mortality of Observational Studies Evaluating Glucocorticoids for SARS

Supplementary Figure 8. Forest Plot of All-Cause-Mortality-Including Composite Outcome of Observational Studies Evaluating Glucocorticoids for SARS

Supplementary Figure 9. Multimodel Inference for All-Cause Mortality of Observational Studies Evaluating Glucocorticoids for COVID-19

Supplementary Figure 10. Multimodel Inference for All-Cause-Mortality-Including Composite Outcome of Observational Studies Evaluating Glucocorticoids for COVID-19

Supplementary Figure 11. Multimodel Inference for All-Cause Mortality of Observational Studies Evaluating Glucocorticoids for SARS

Supplementary Figure 12. Funnel Plot of All-Cause Mortality of RCTs Evaluating Glucocorticoids for COVID-19

Supplementary Figure 13. Funnel Plot of All-Cause-Mortality-Including Composite Outcome of RCTs Evaluating Glucocorticoids for COVID-19

Supplementary Figure 14. Funnel Plot of All-Cause Mortality of Observational Studies Evaluating Glucocorticoids for COVID-19

Supplementary Figure 15. Funnel Plot of All-Cause-Mortality-Including Composite Outcome of Observational Studies Evaluating Glucocorticoids for COVID-19

Supplementary Figure 16. Funnel Plot of All-Cause Mortality of Observational Studies Evaluating Glucocorticoids for SARS

Supplementary Figure 17. Forest Plot of All-Cause Mortality of Trials or Observational Studies Evaluating Glucocorticoids for COVID-19 Within Subgroups Defined by Characteristics of Patient, Disease Severity and Administration of Glucocorticoids among Studies Reporting Incidence of Events in Control from 0% to 5%

Supplementary Figure 18. Forest Plot of All-Cause Mortality of Trials or Observational Studies Evaluating Glucocorticoids for COVID-19 Within Subgroups Defined by Characteristics of Patient, Disease Severity and Administration of Glucocorticoids among Studies Reporting Incidence of Events in Control from 5% to 10%

Supplementary Figure 19. Forest Plot of All-Cause Mortality of Trials or Observational Studies Evaluating Glucocorticoids for COVID-19 Within Subgroups Defined by Characteristics of Patient, Disease Severity and Administration of Glucocorticoids among Studies Reporting Incidence of Events in Control from 10% to 20%

Supplementary Figure 20. Forest Plot of All-Cause Mortality of Trials or Observational Studies Evaluating Glucocorticoids for COVID-19 Within Subgroups Defined by Characteristics of Patient, Disease Severity and Administration of Glucocorticoids among Studies Reporting Incidence of Events in Control from 20% to 40%

Supplementary Figure 21. Forest Plot of All-Cause Mortality of Trials or Observational Studies Evaluating Glucocorticoids for COVID-19 Within Subgroups Defined by Characteristics of Patient, Disease Severity and Administration of Glucocorticoids among Studies Reporting Incidence of Events in Control from 40% to 80%

Supplementary Figure 22. Forest Plot of All-Cause-Mortality-Including Composite Outcome of Trials or Observational Studies Evaluating Glucocorticoids for COVID-19 Within Subgroups Defined by Characteristics of Patient, Disease Severity and Administration of Glucocorticoids among Studies Reporting Incidence of Events in Control from 20% to 40%

Supplementary Figure 23. Forest Plot of All-Cause-Mortality-Including Composite Outcome of Trials or Observational Studies Evaluating Glucocorticoids for COVID-19 Within Subgroups Defined by Characteristics of Patient, Disease Severity and Administration of Glucocorticoids among Studies Reporting Incidence of Events in Control from 40% to 80%

Supplementary Figure 24. Forest Plot of All-Cause Mortality of Observational Studies Evaluating Glucocorticoids for SARS Within Subgroups Defined by Characteristics of Patient, Disease Severity and Administration of Glucocorticoids among Studies Reporting Incidence of Events in Control from 20% to 40%

Supplementary Figure 25. Forest Plot of All-Cause Mortality of Observational Studies with Low Risk of Bias for Evaluating Glucocorticoids for COVID-19 according to Severity of ARDS

Tables

Due to technical limitations, table 1 is only available as a download in the Supplemental Files section.

Figures

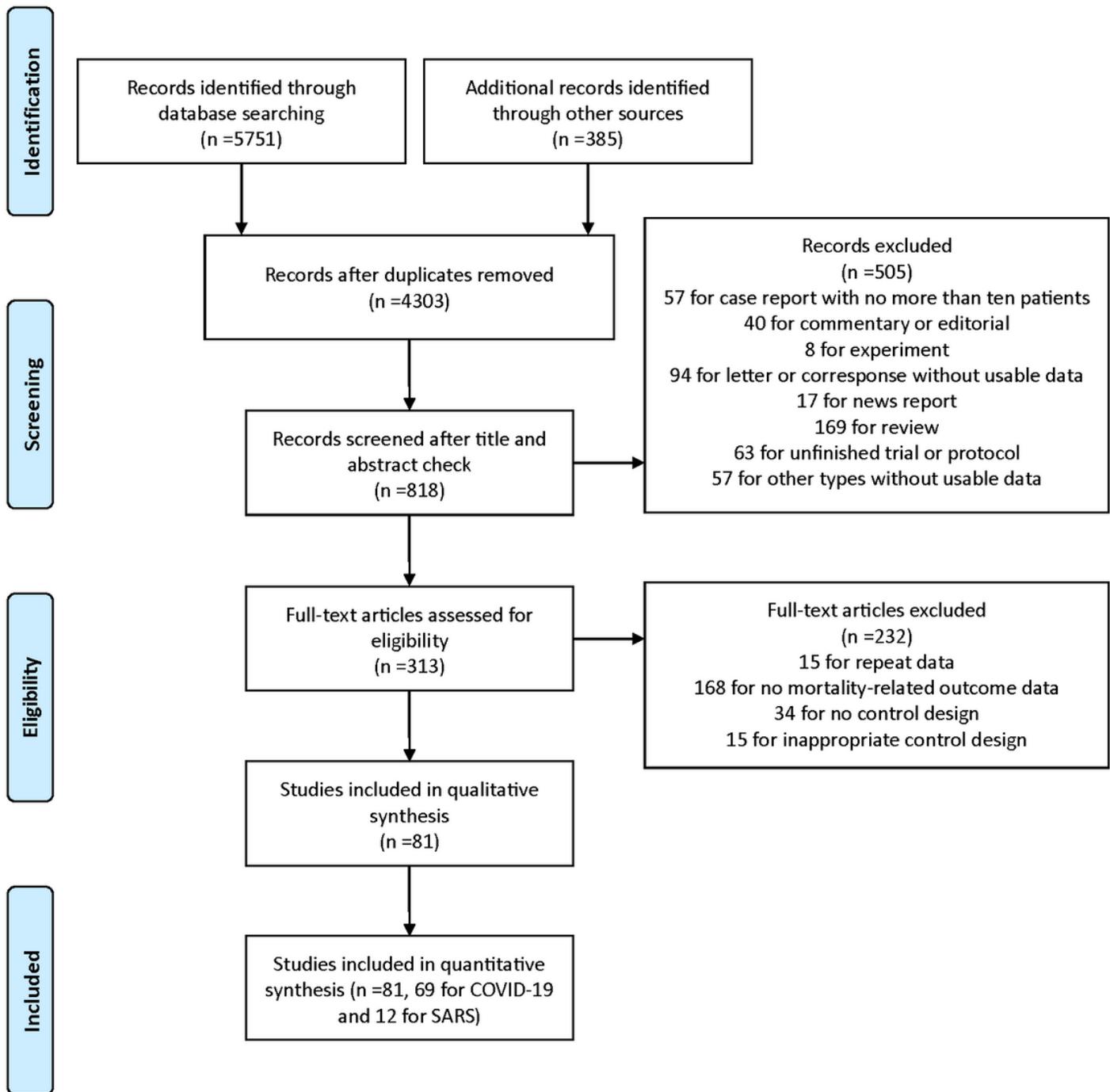


Figure 1

Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) for the Article Selection Process

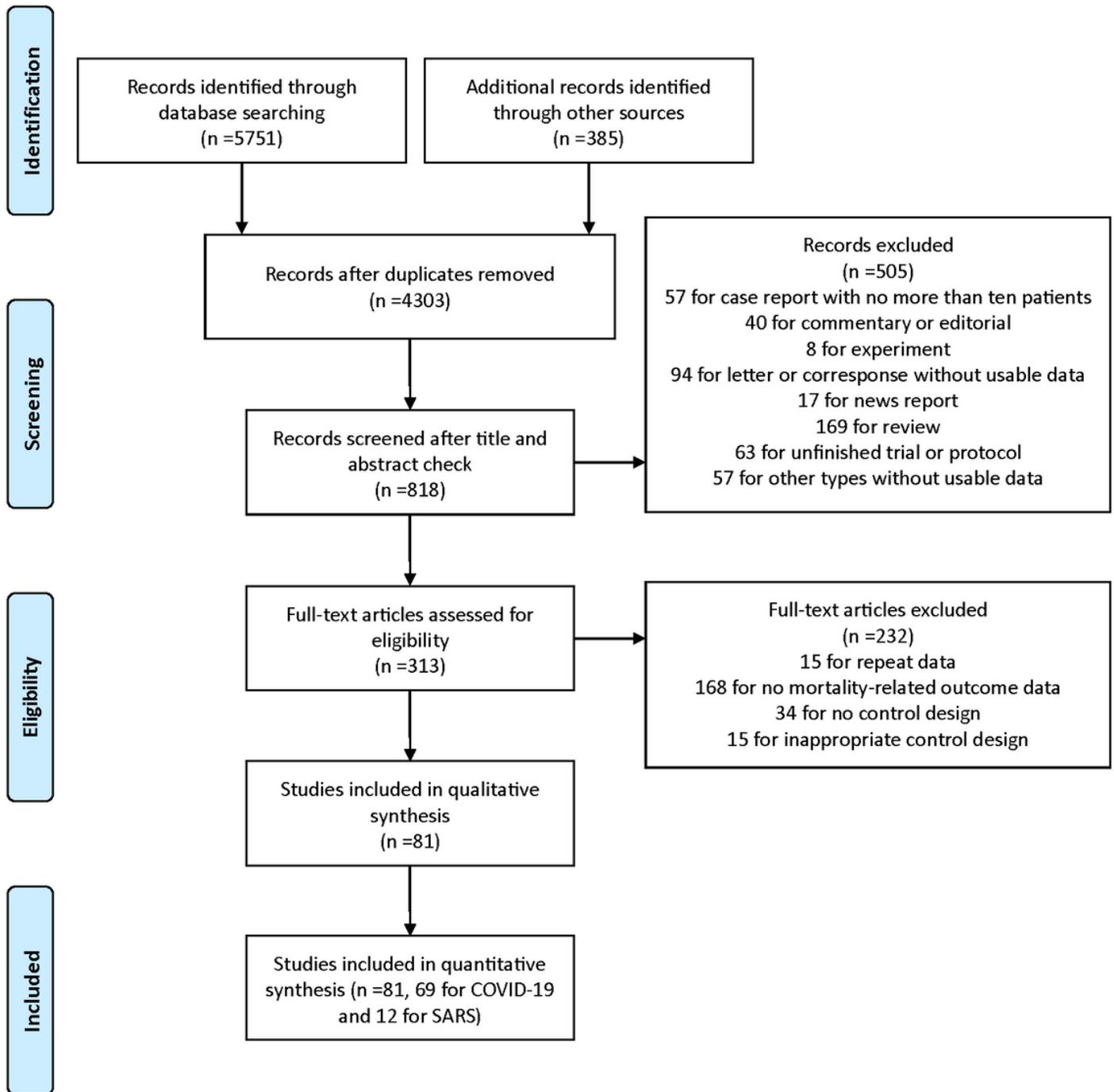


Figure 1

Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) for the Article Selection Process

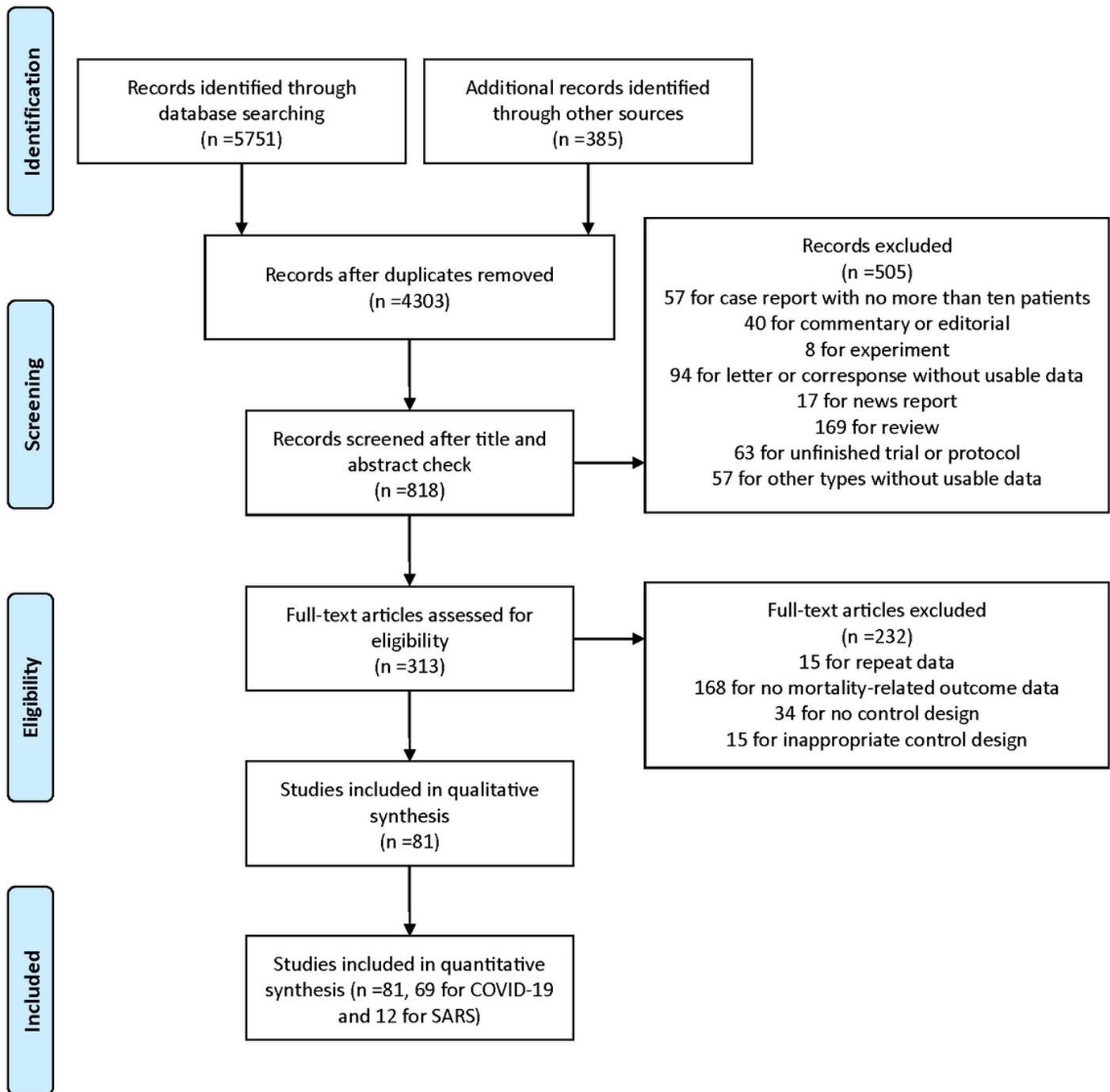


Figure 1

Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) for the Article Selection Process

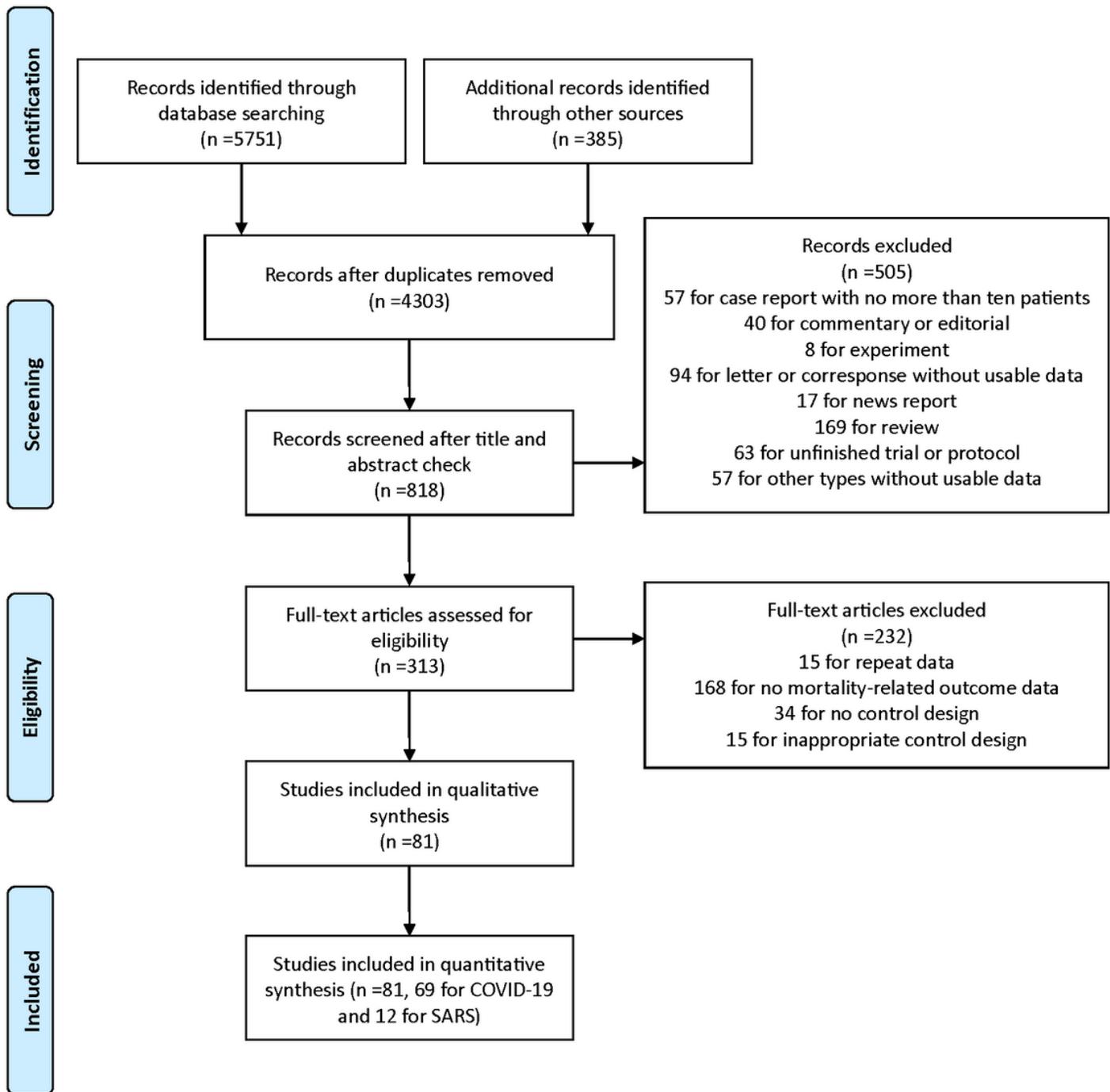


Figure 1

Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) for the Article Selection Process

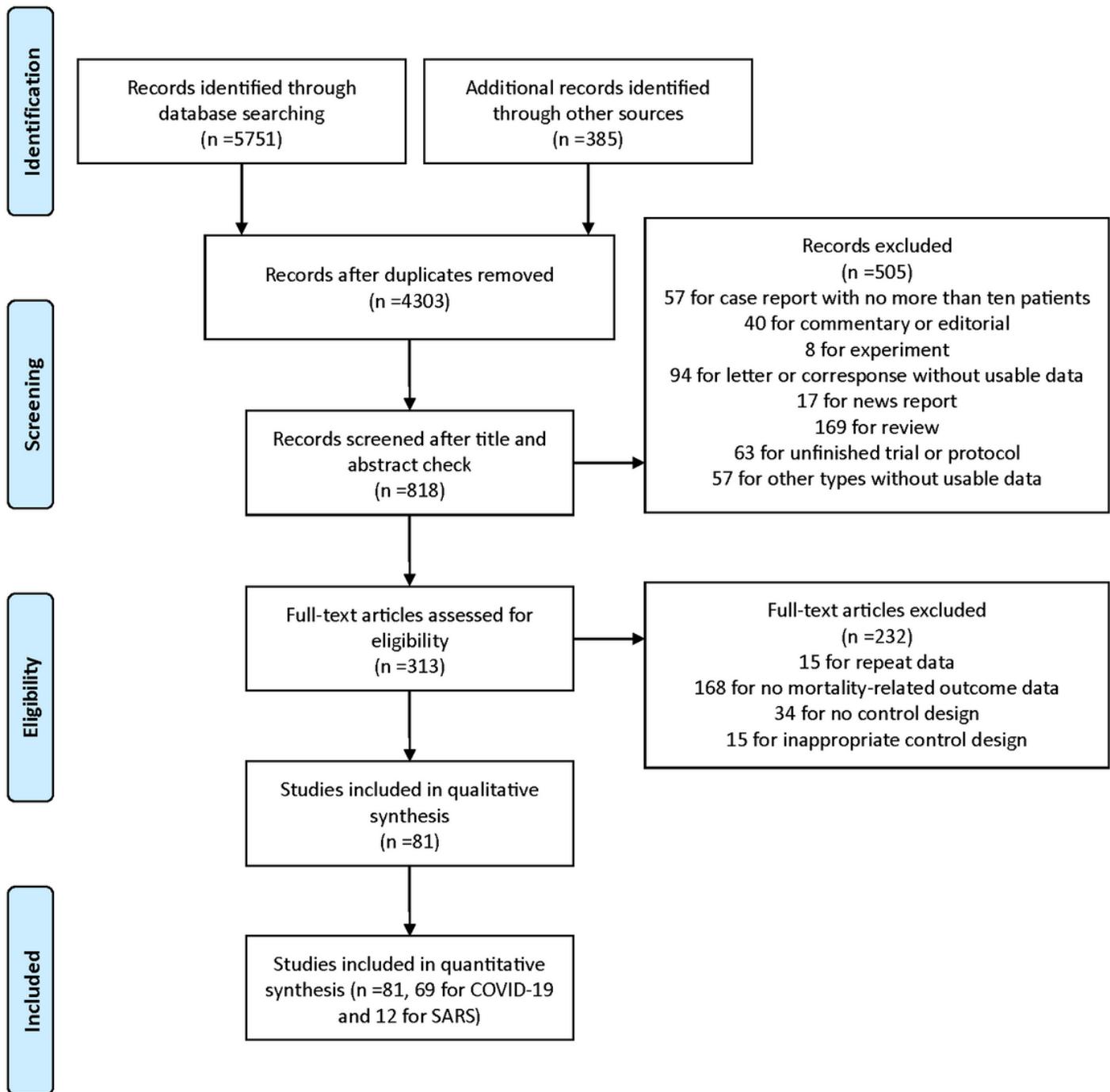


Figure 1

Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) for the Article Selection Process

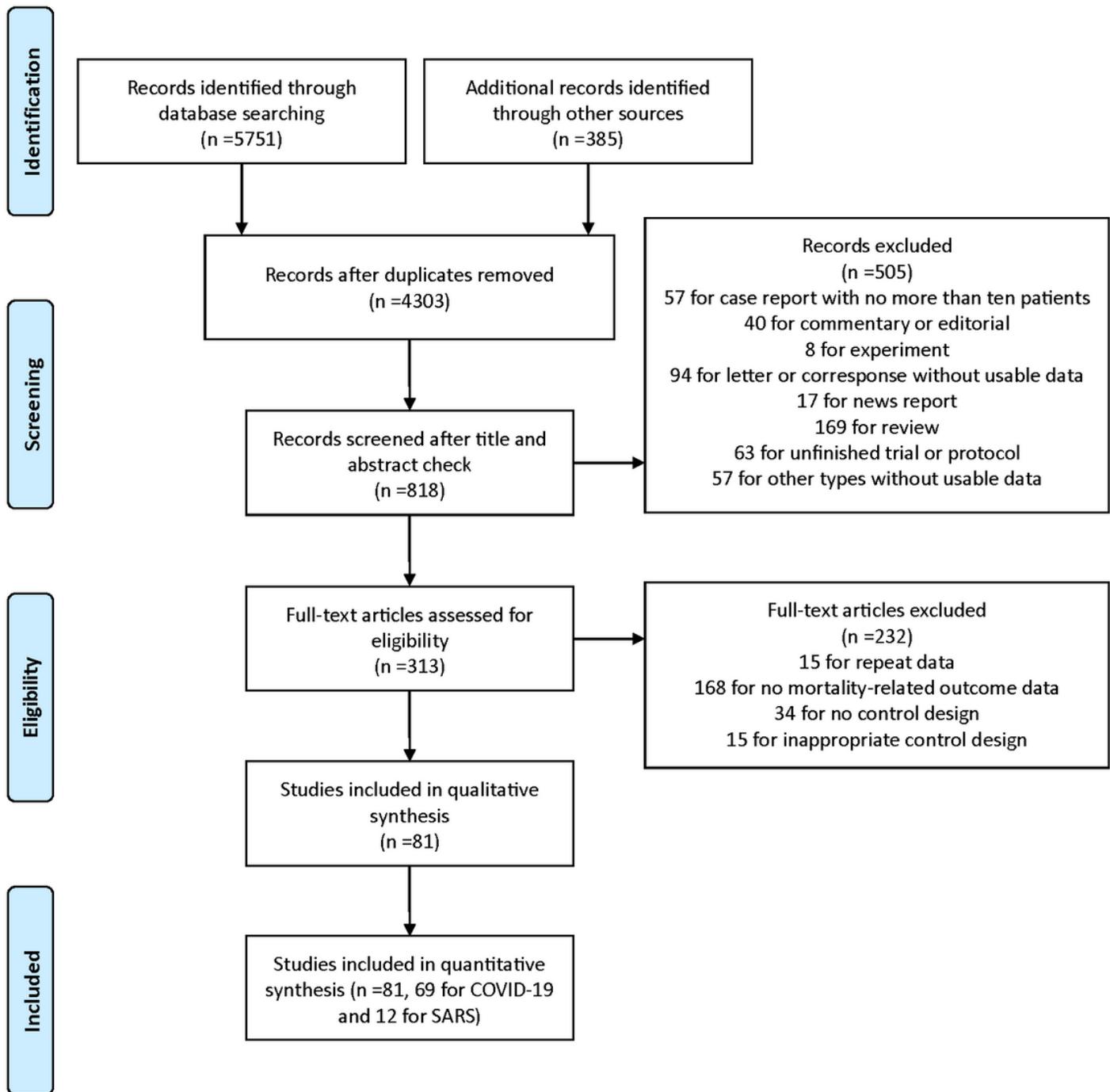


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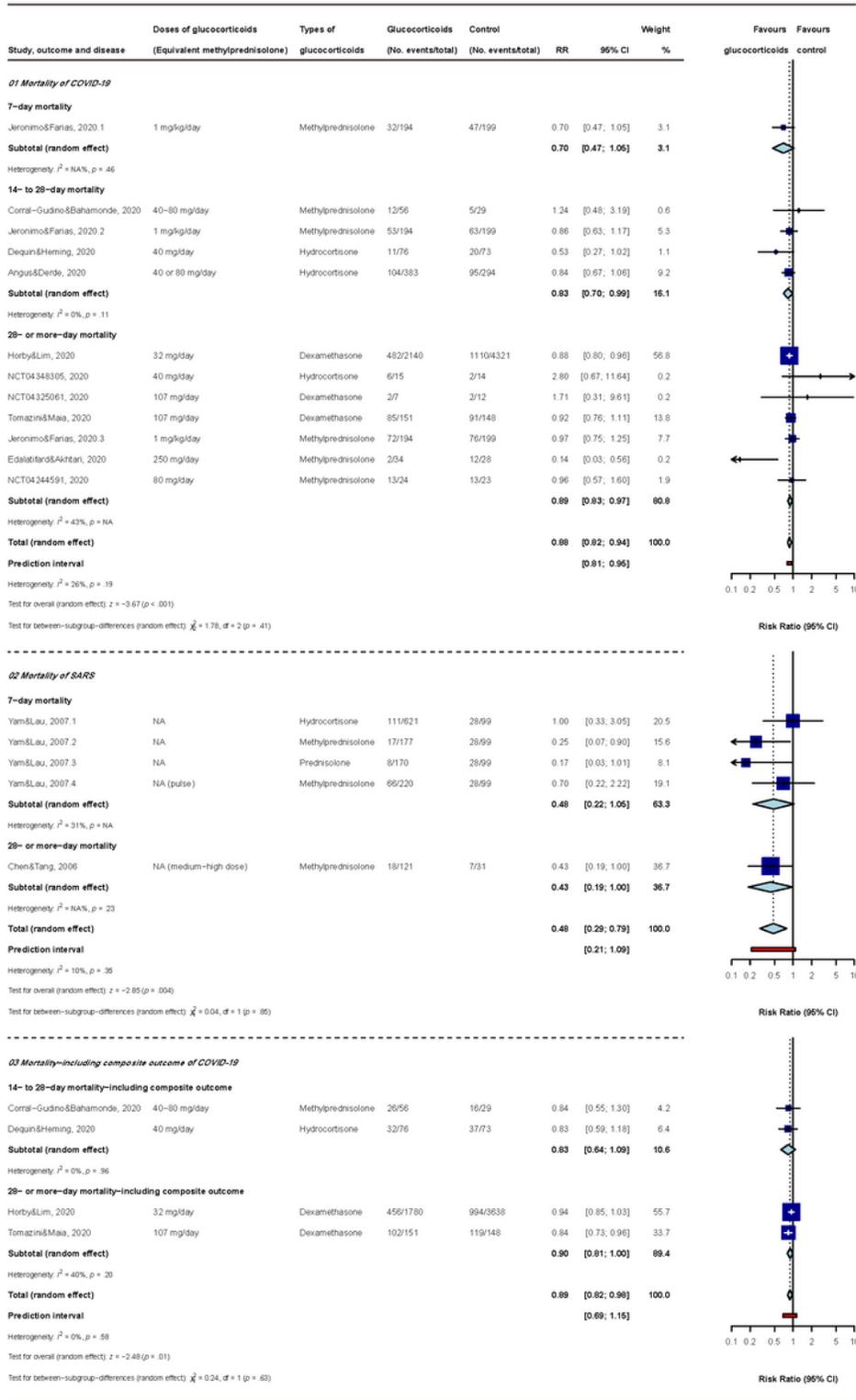


Figure 2

Forest Plot of All-Cause Mortality and Mortality-Including Composite Outcome of RCTs Evaluating Glucocorticoids for COVID-19 and Observational Studies with Low Risk of Bias for SARS

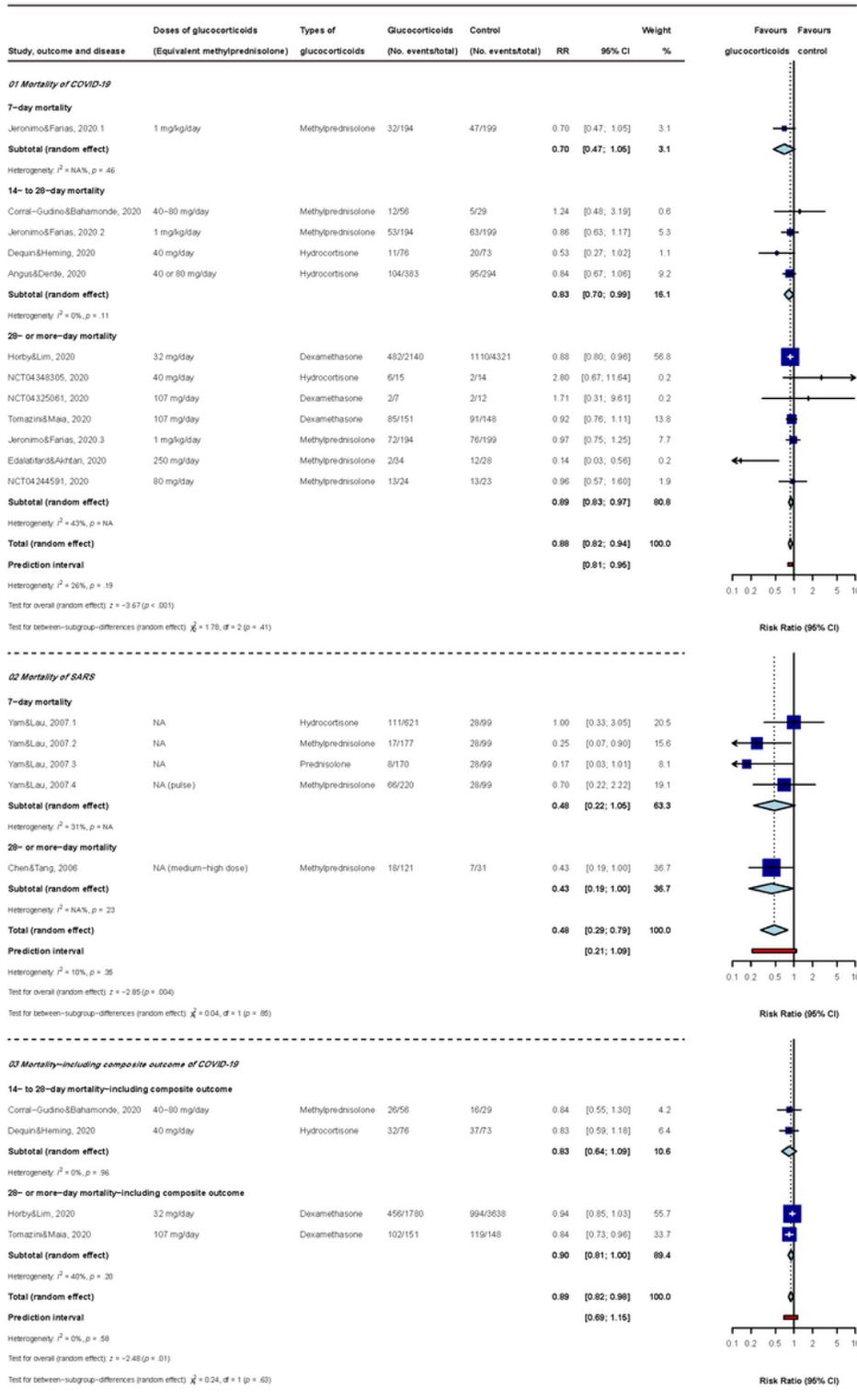


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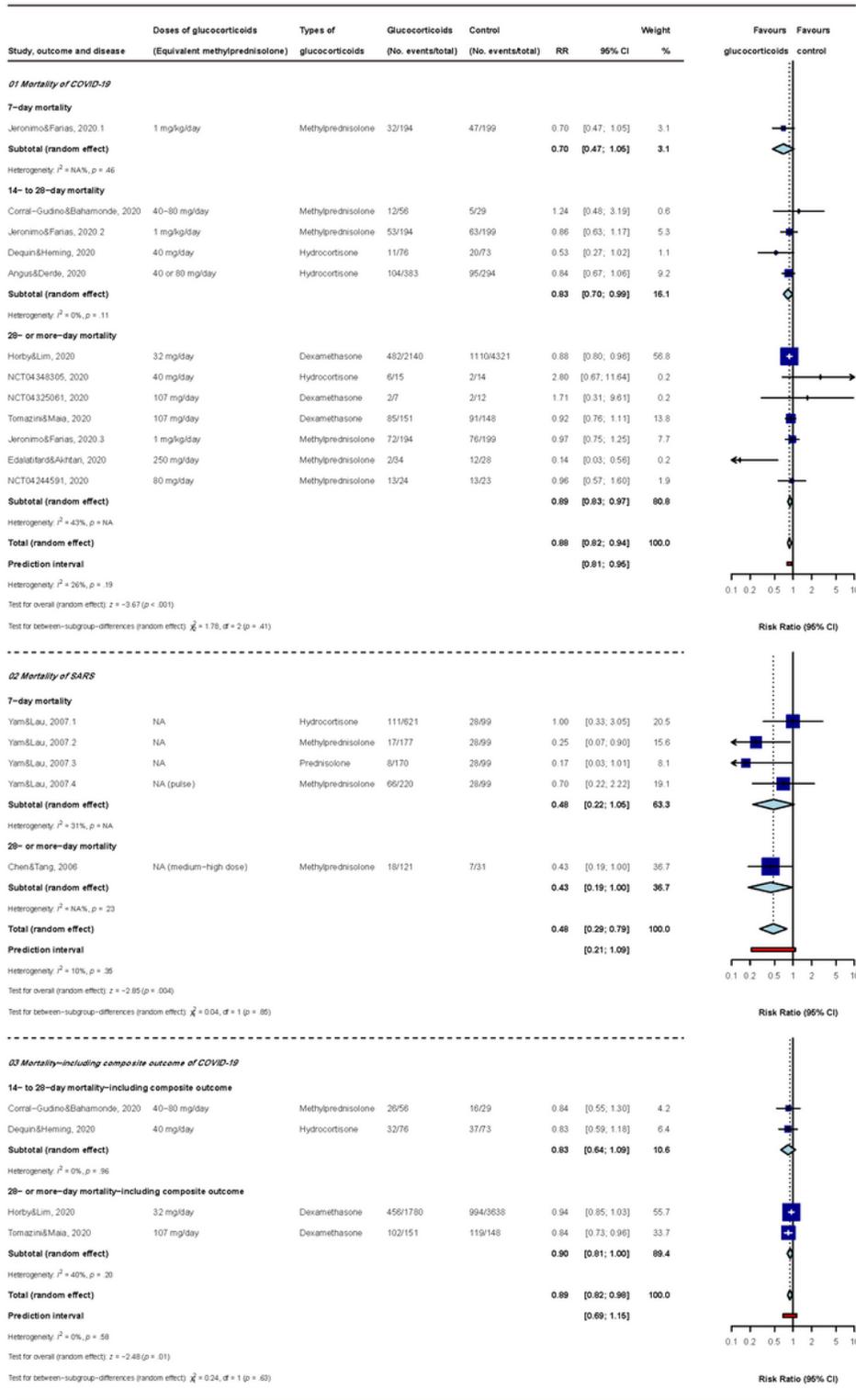


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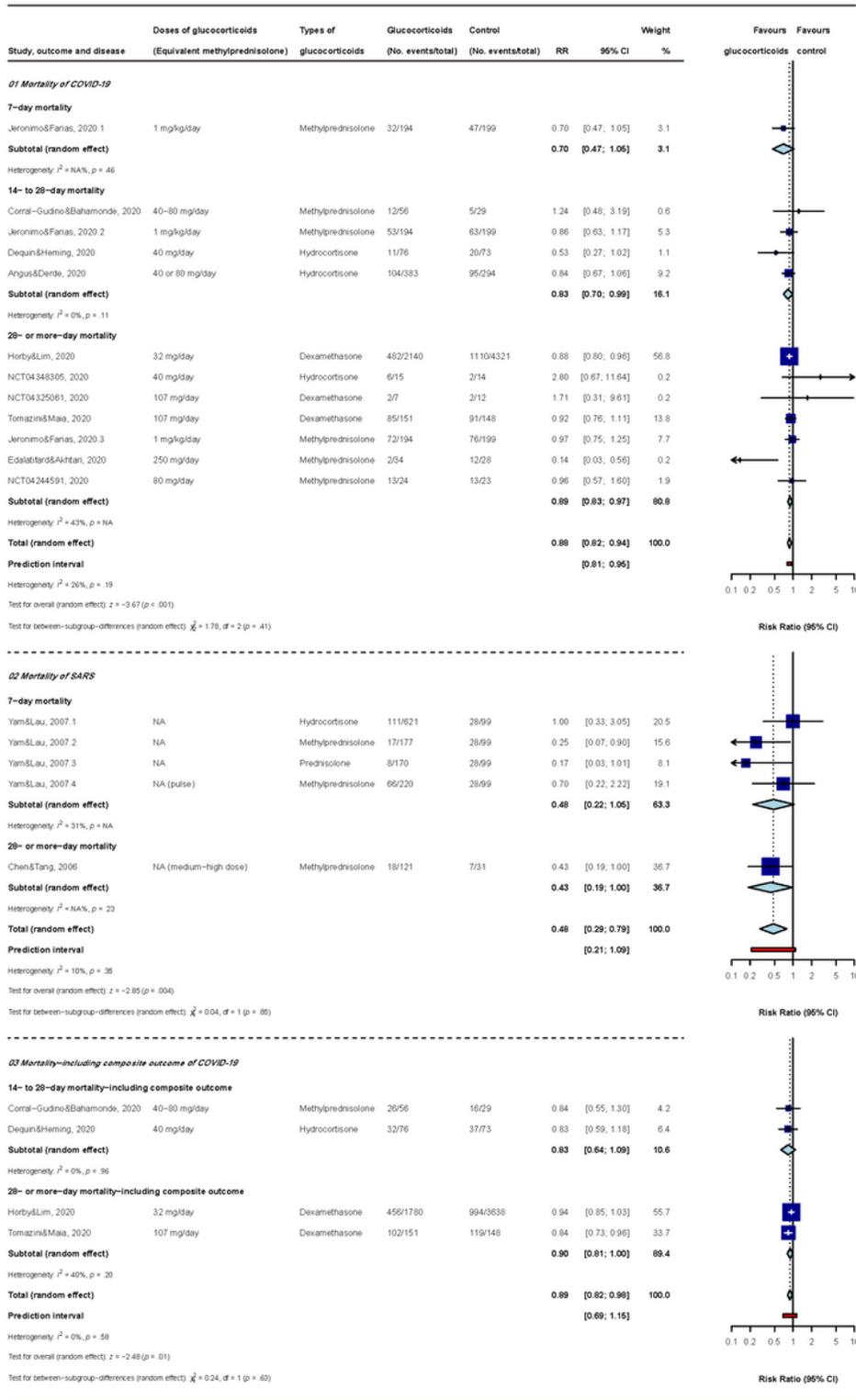


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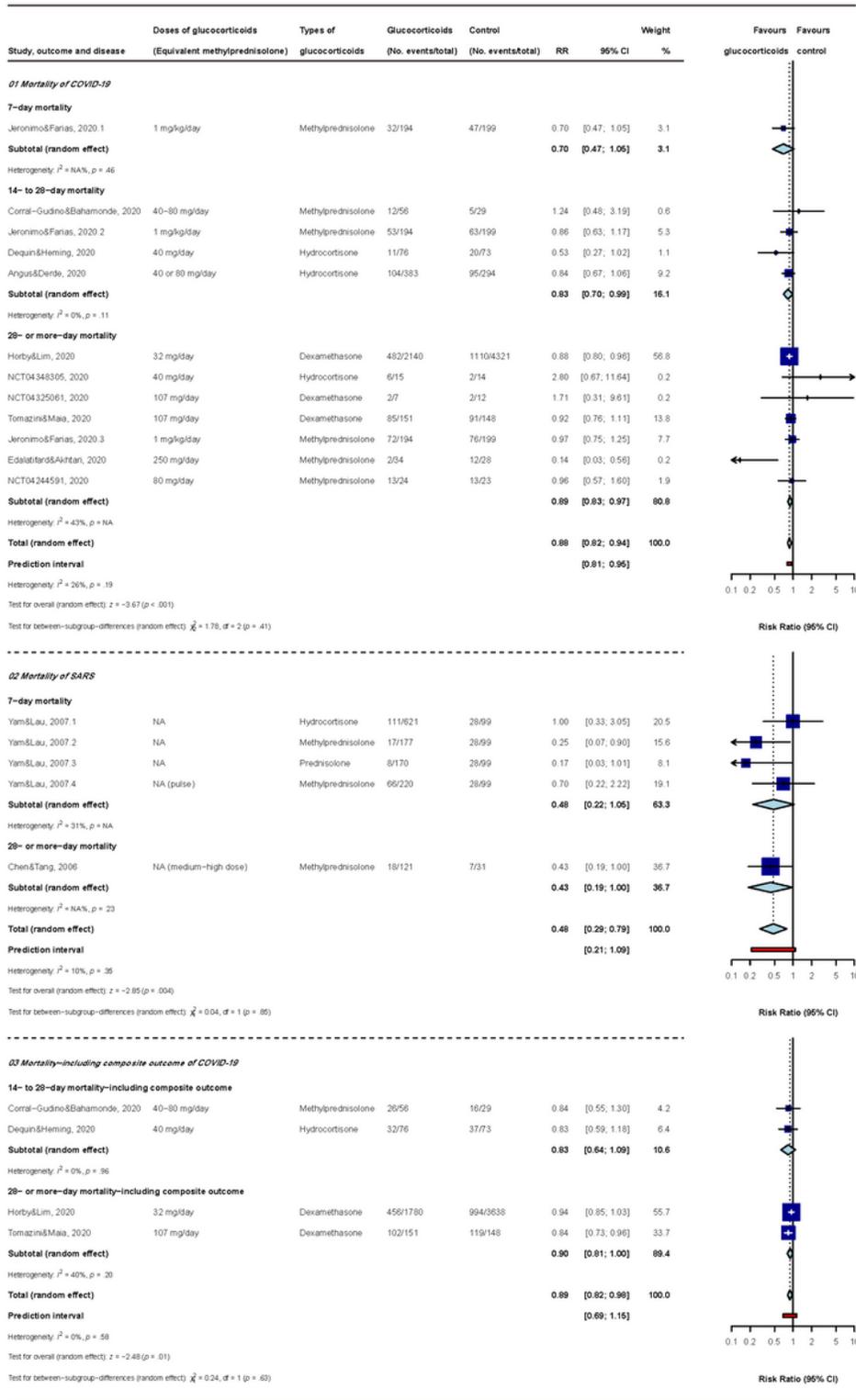


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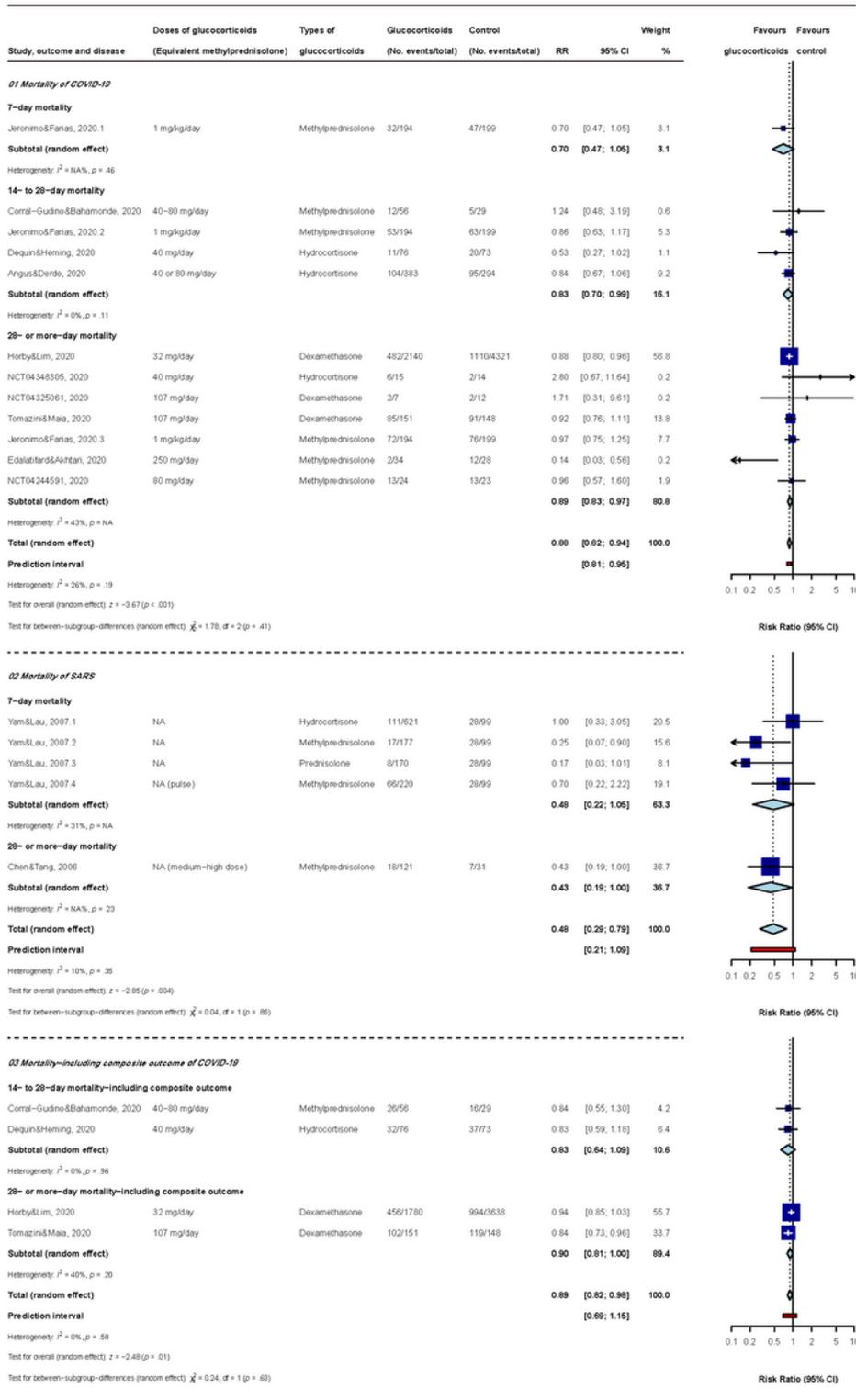


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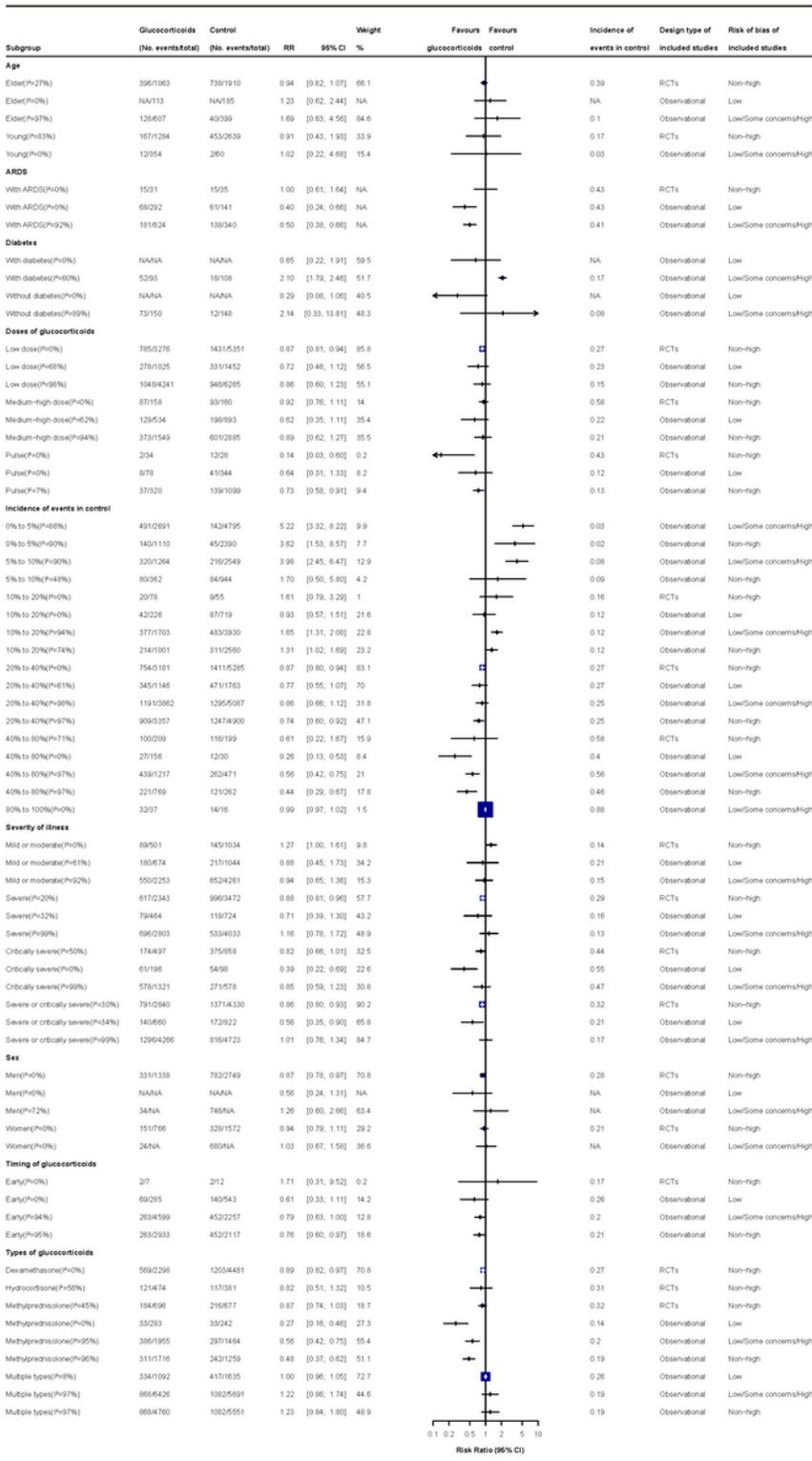


Figure 3

Forest Plot of All-Cause Mortality of Trials or Observational Studies Evaluating Glucocorticoids for COVID-19 Within Subgroups Defined by Characteristics of Patient, Disease Severity and Administration of Glucocorticoids

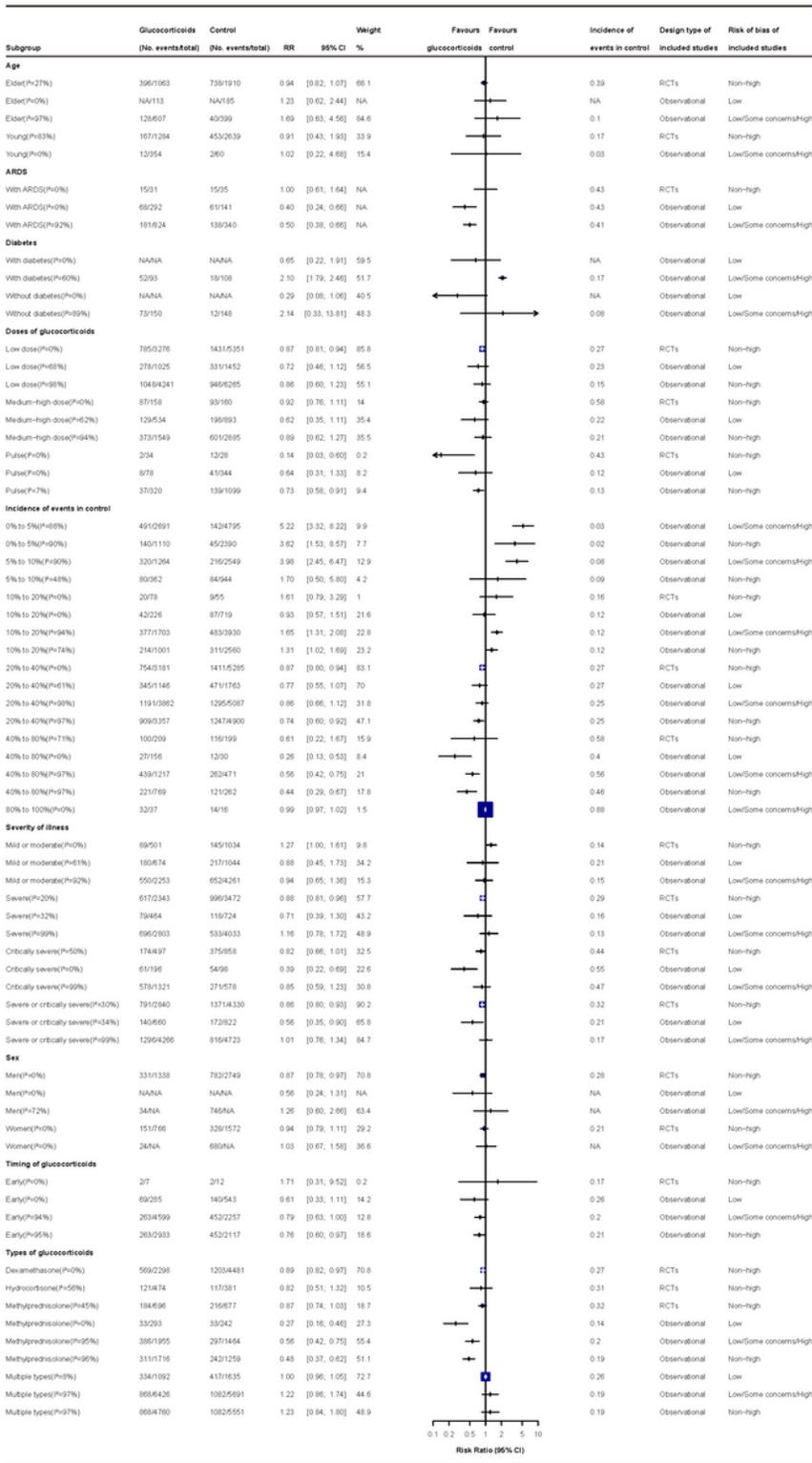


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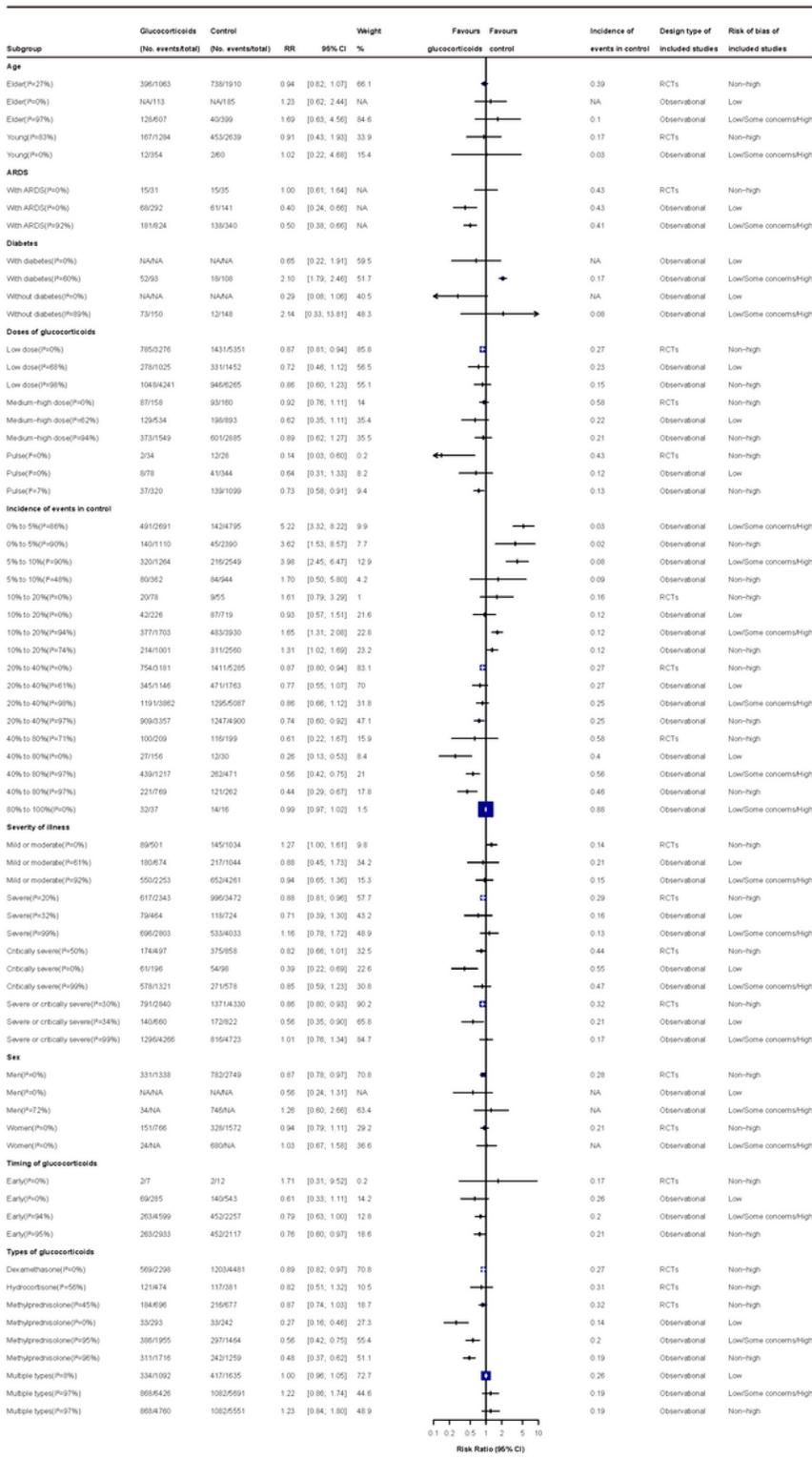


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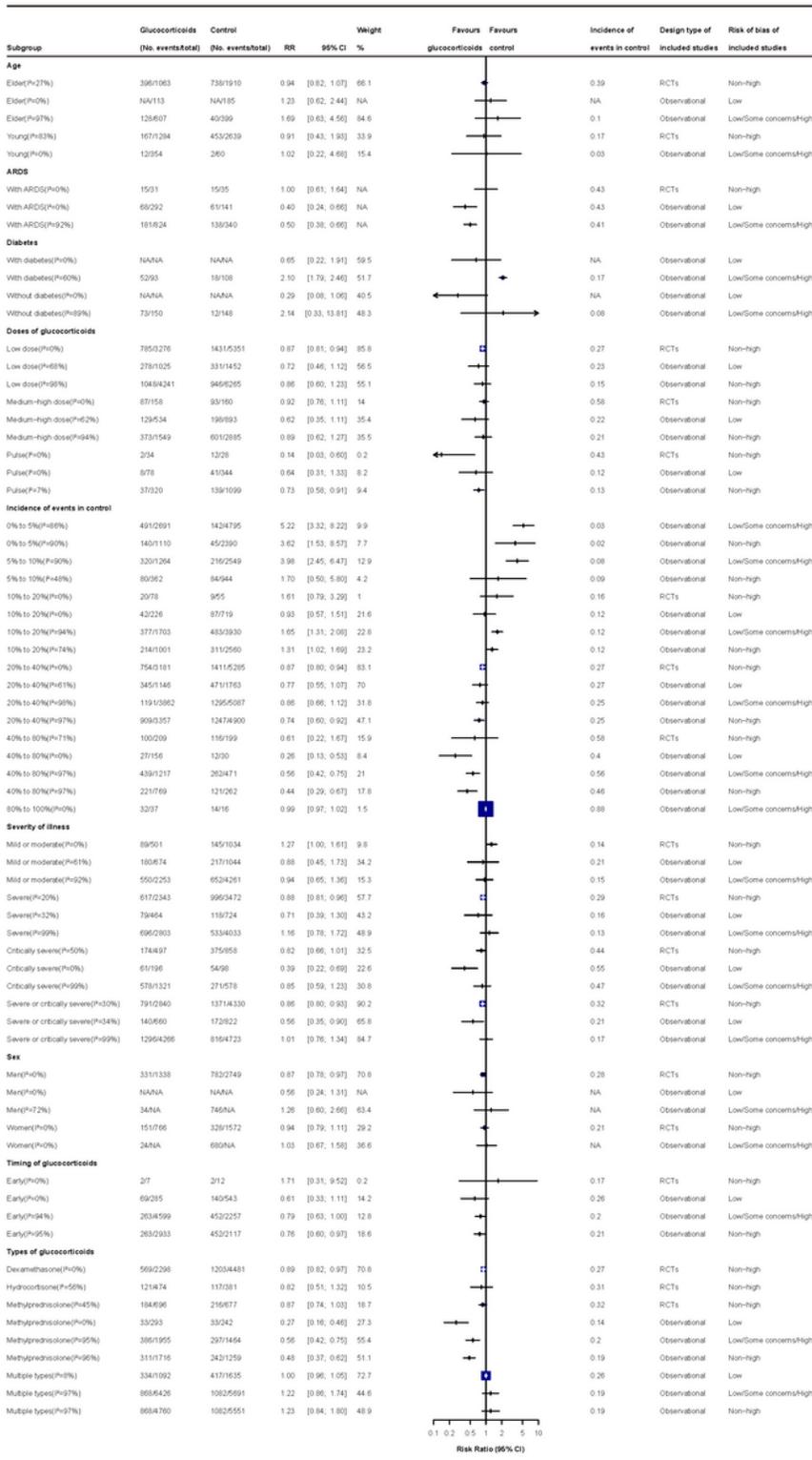


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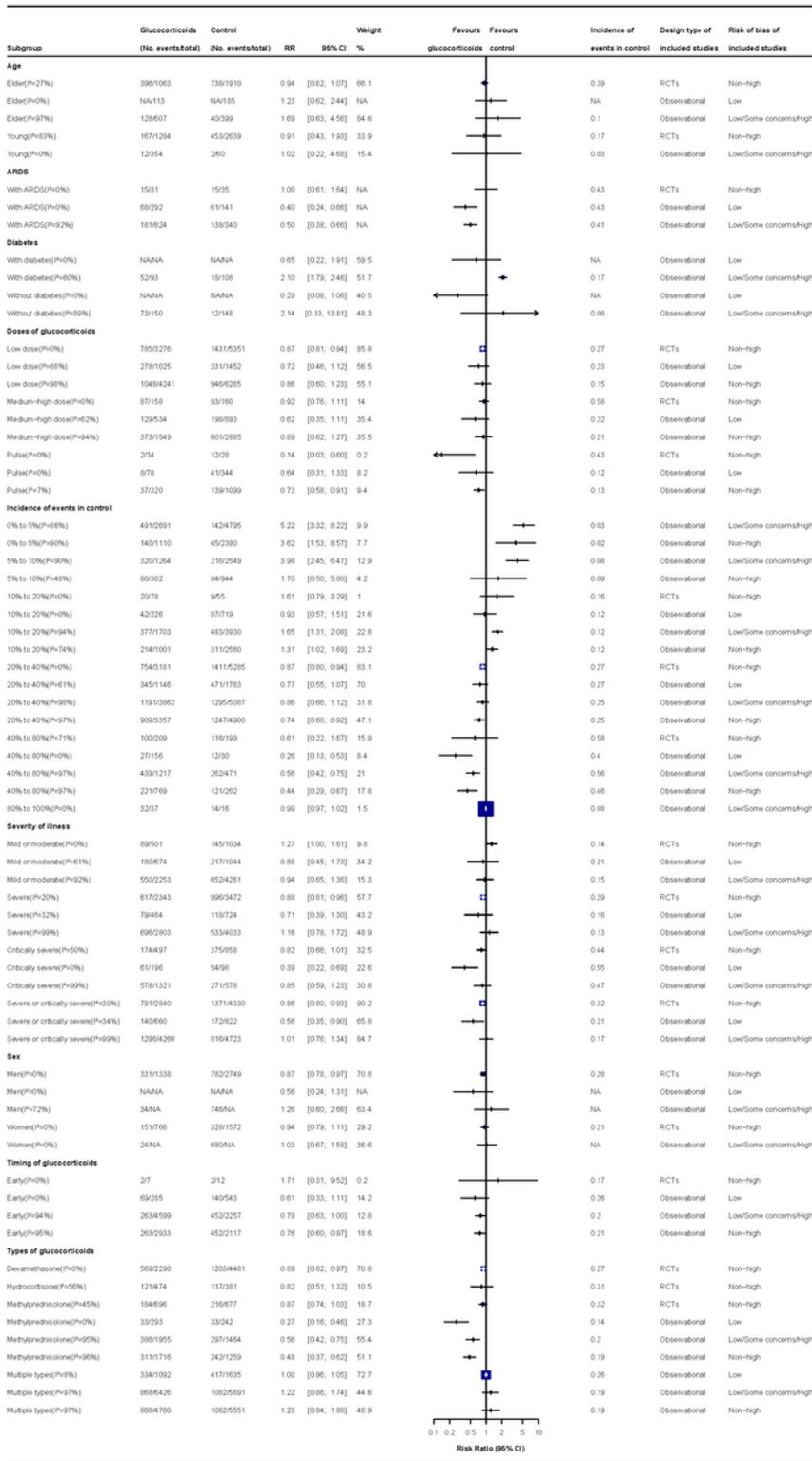


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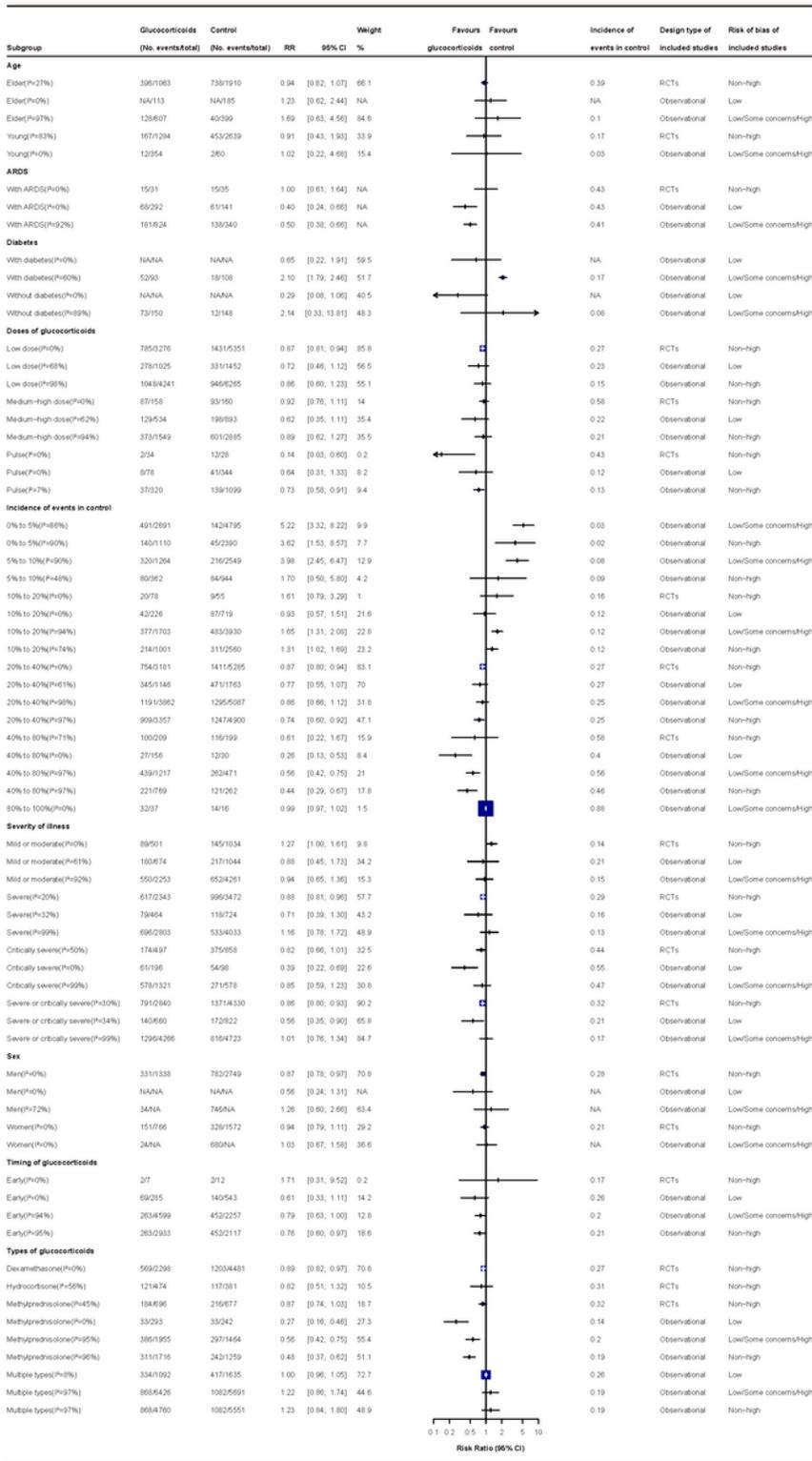


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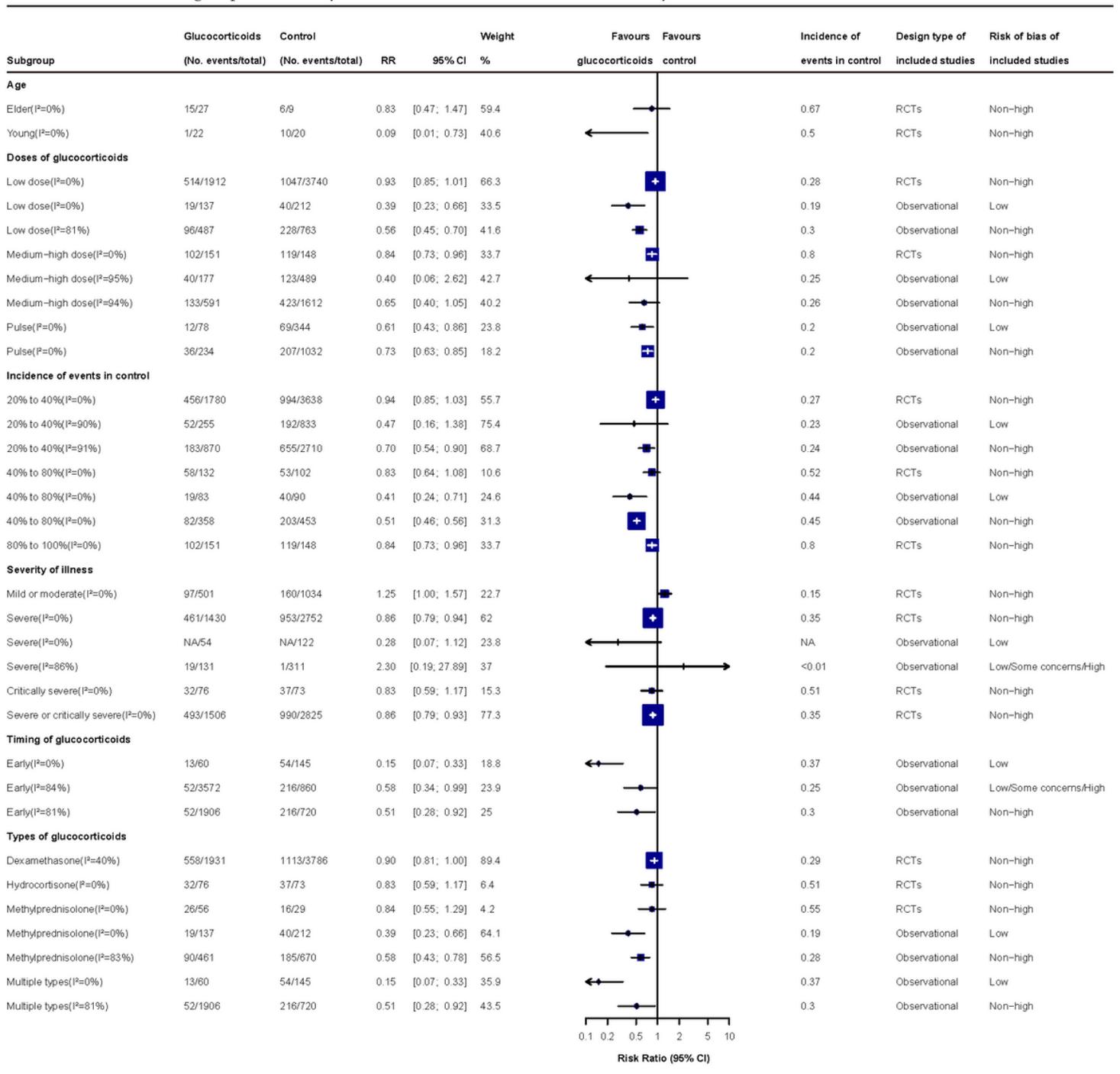


Figure 4

Forest Plot of All-Cause-Mortality-Including Composite Outcome of Trials or Observational Studies Evaluating Glucocorticoids for COVID-19 Within Subgroups Defined by Characteristics of Patient, Disease Severity and Administration of Glucocorticoids

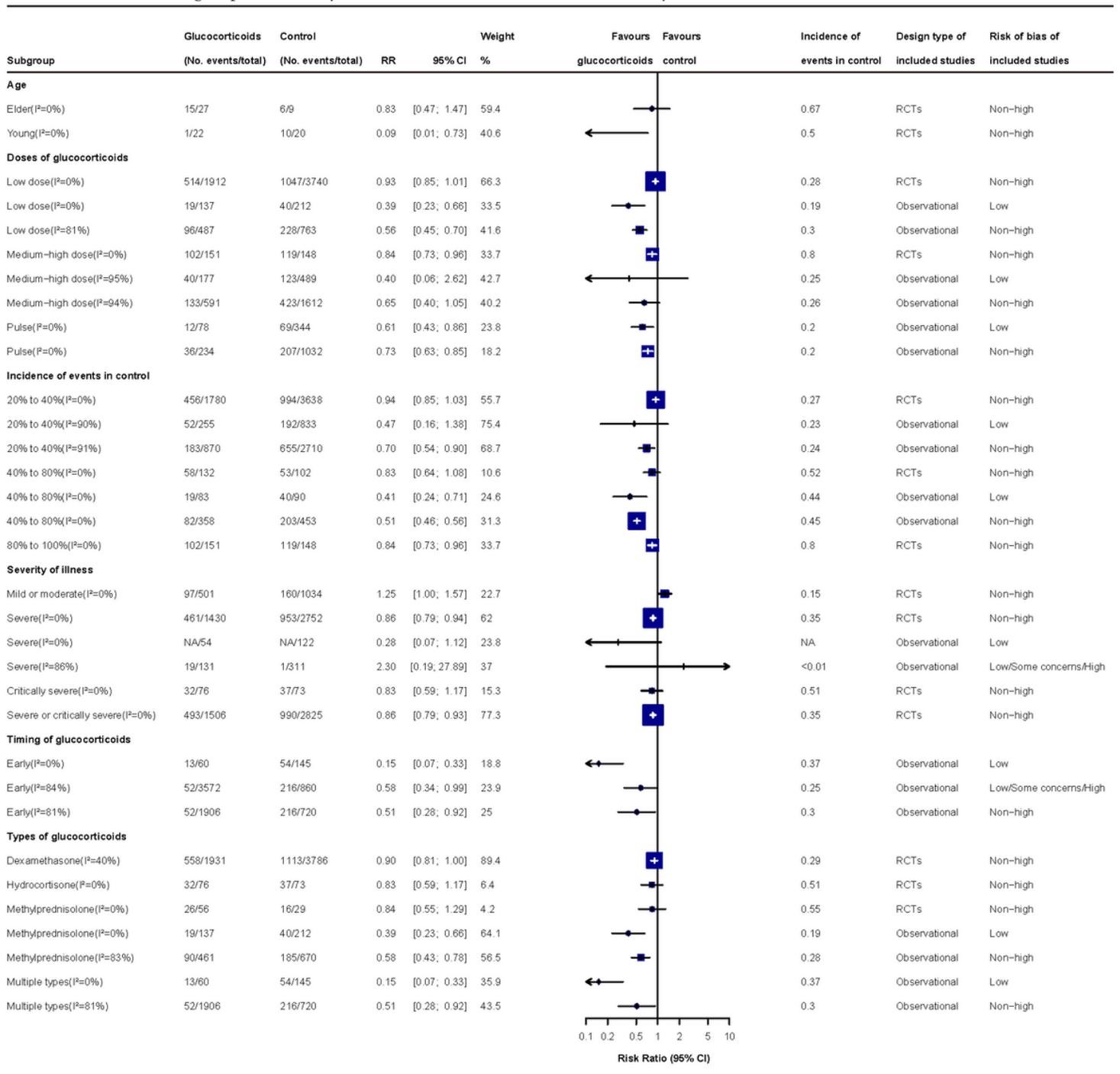


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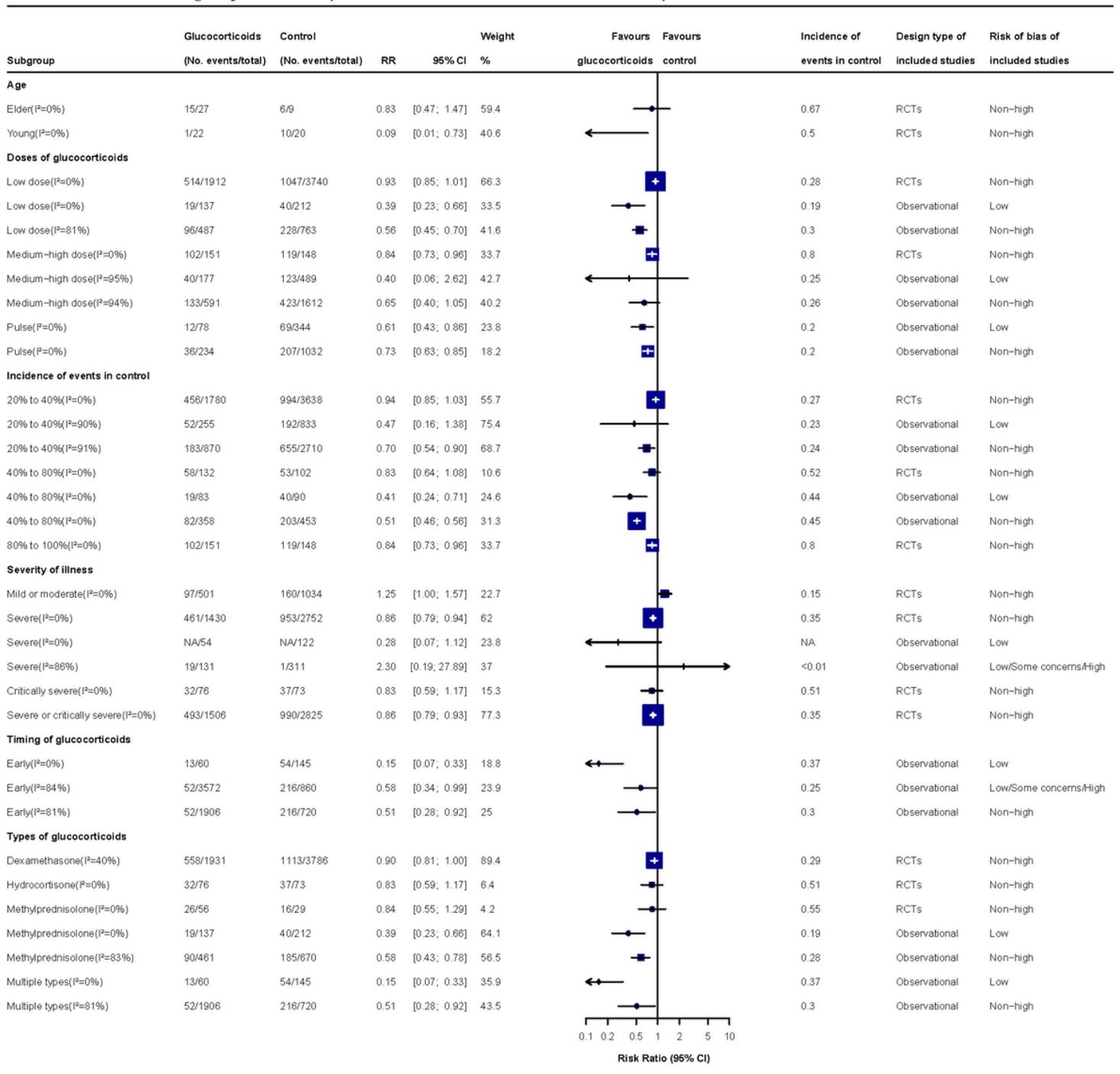


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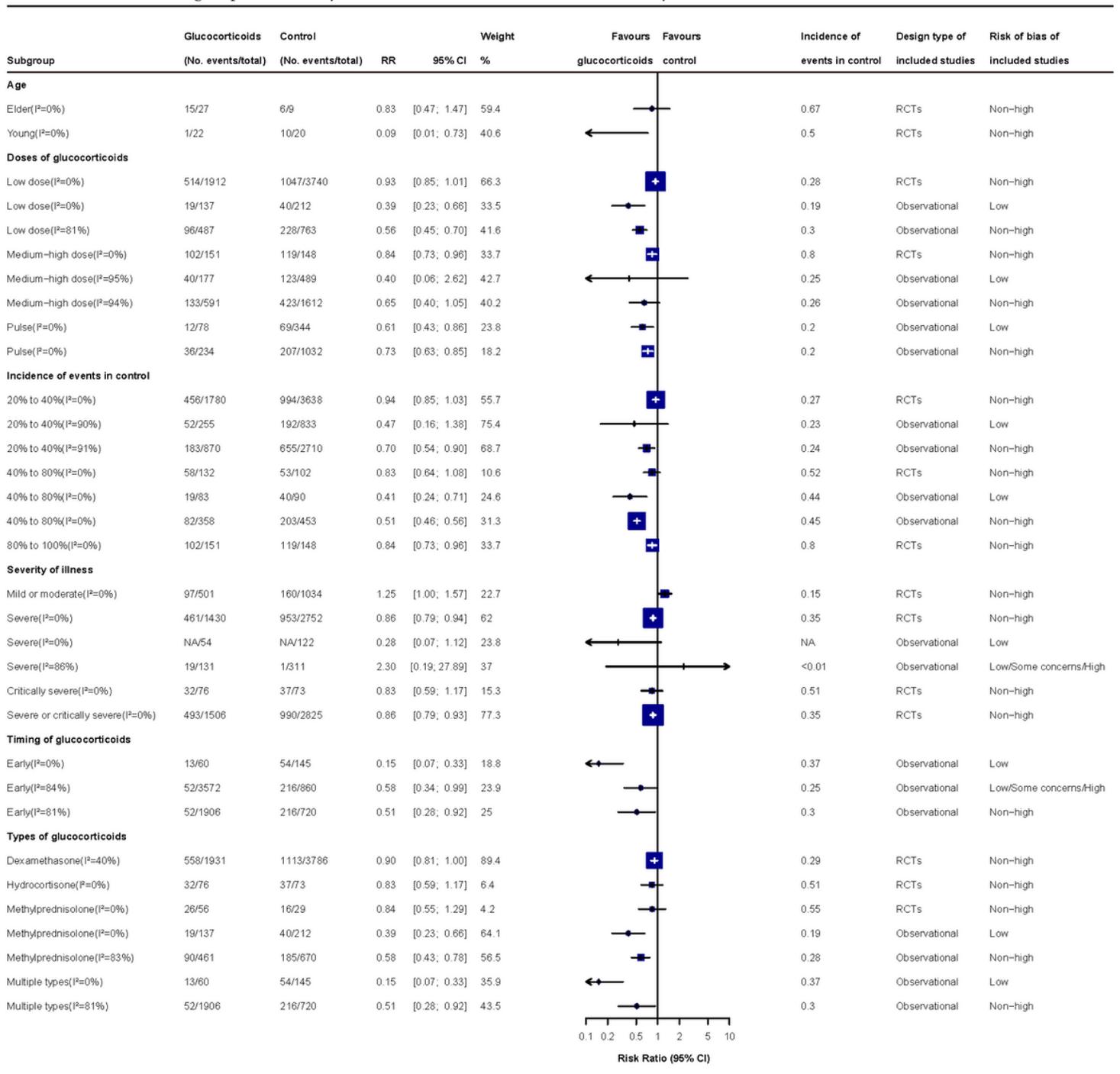


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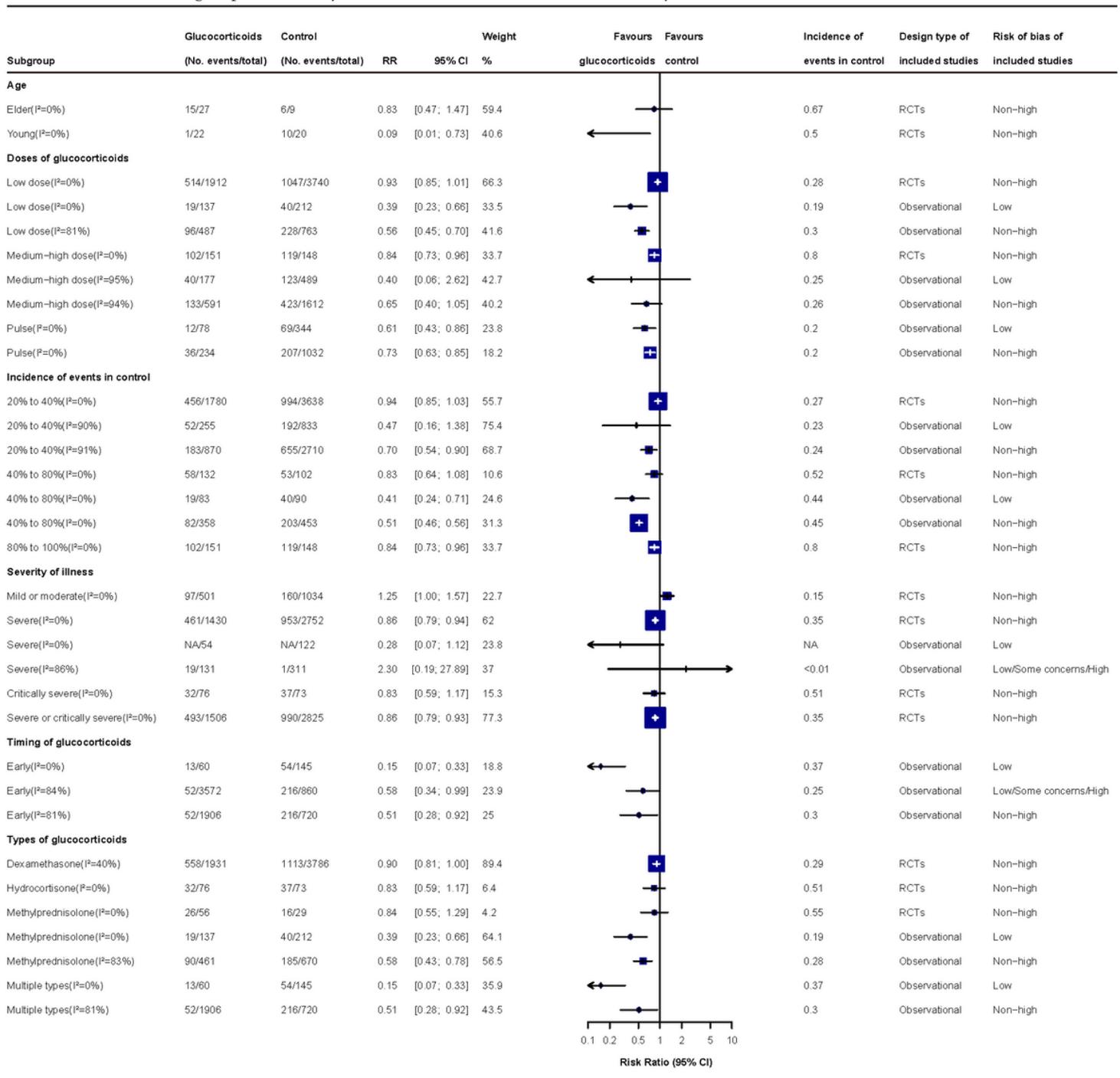


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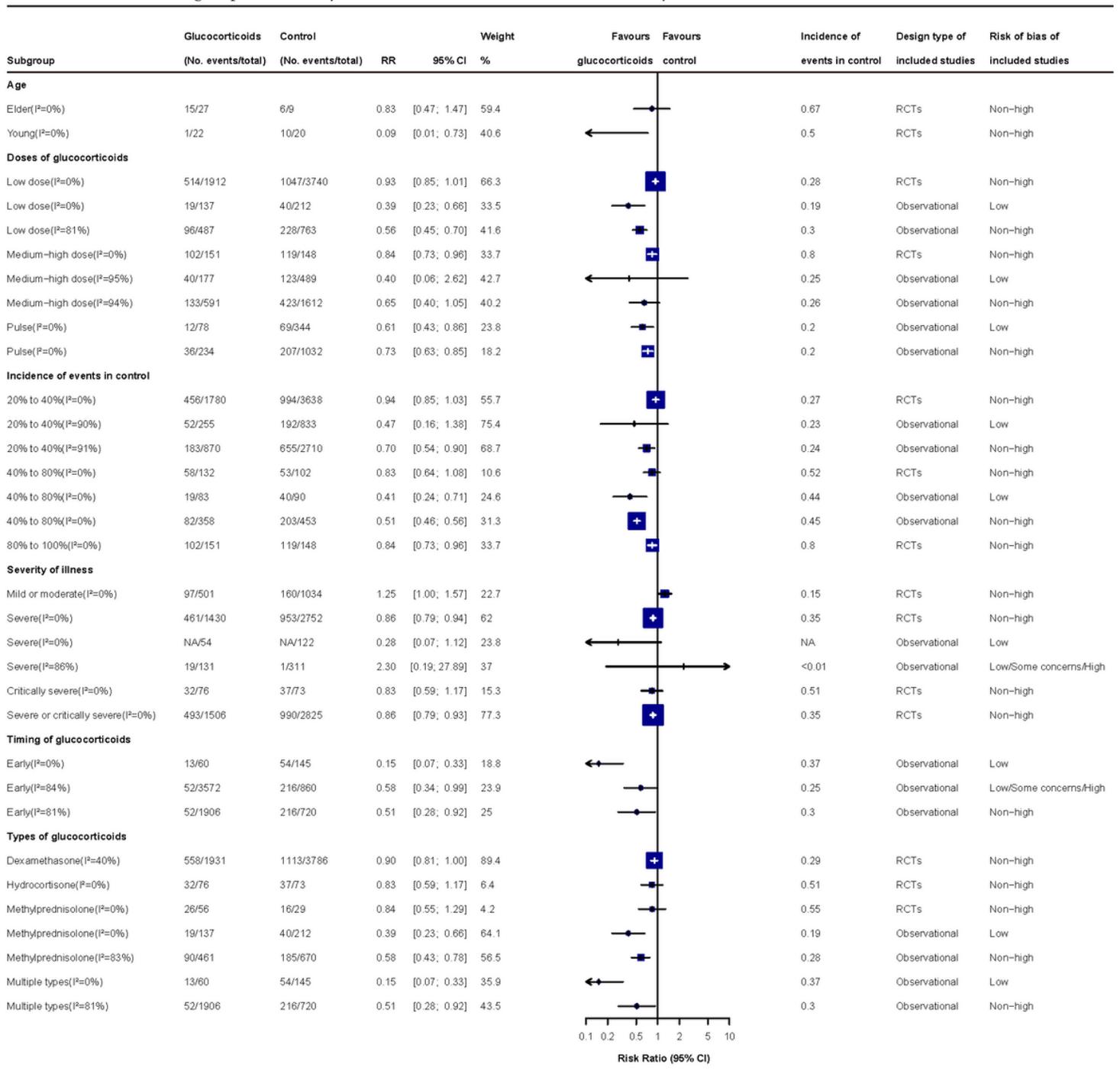


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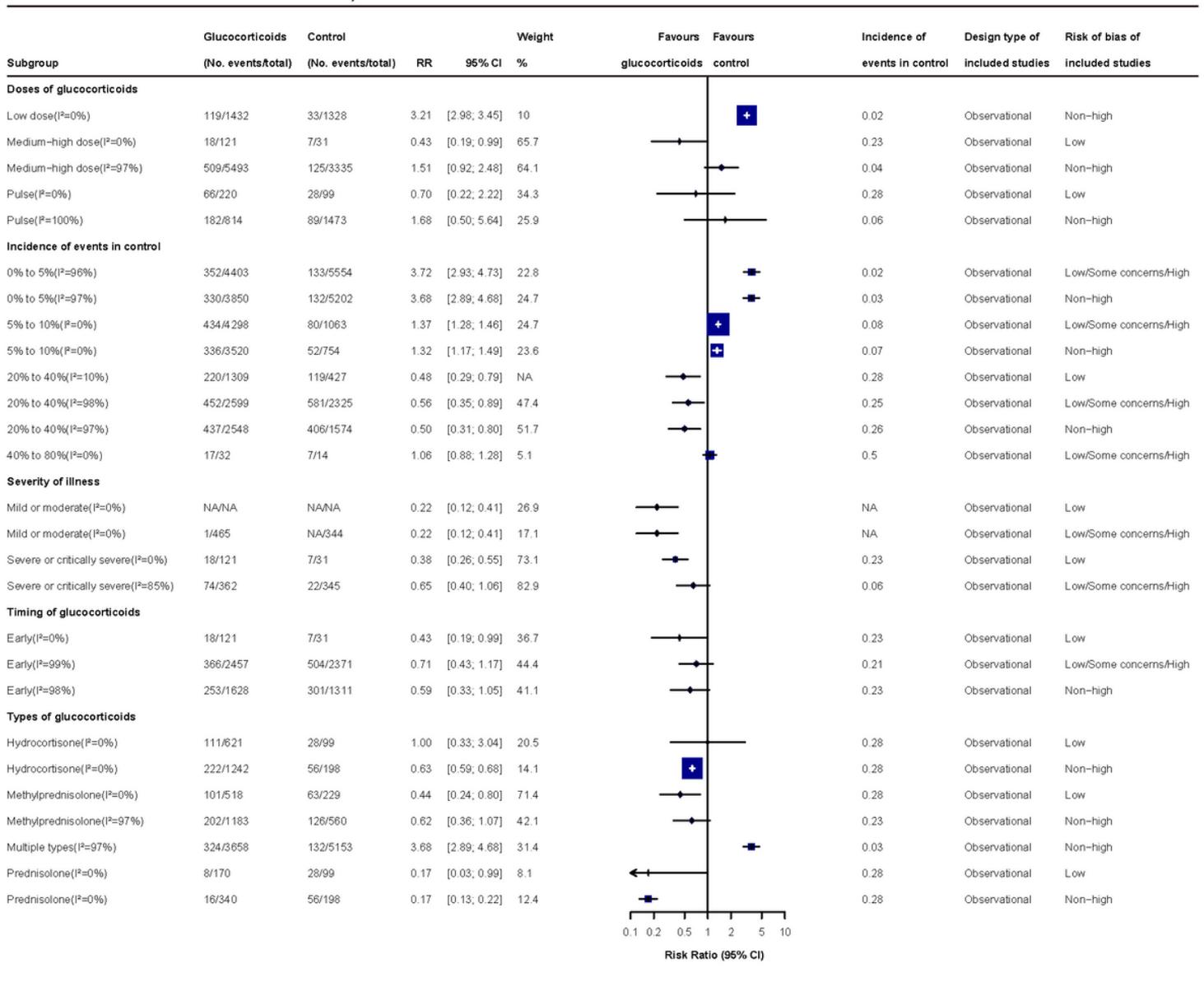


Figure 5

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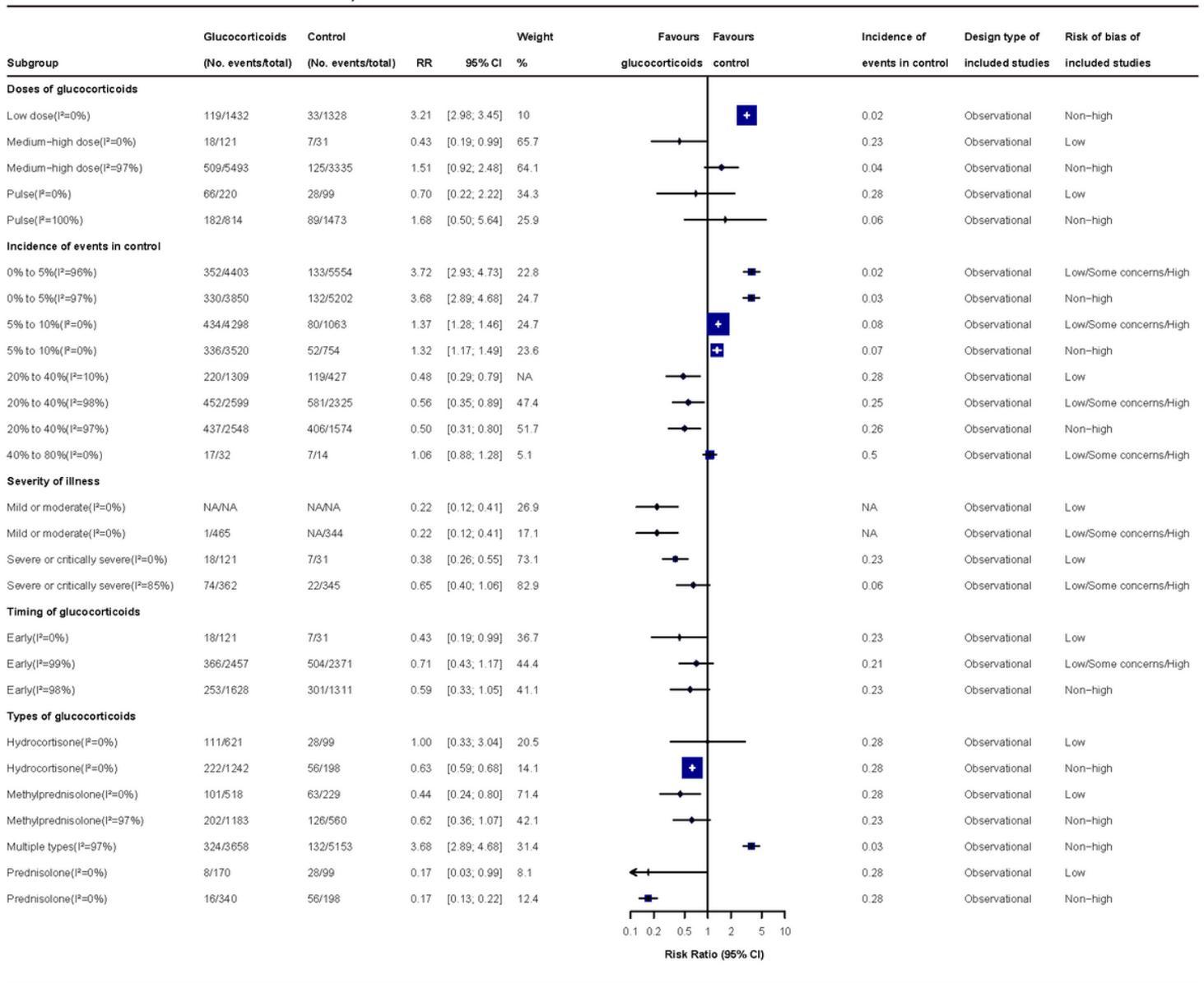


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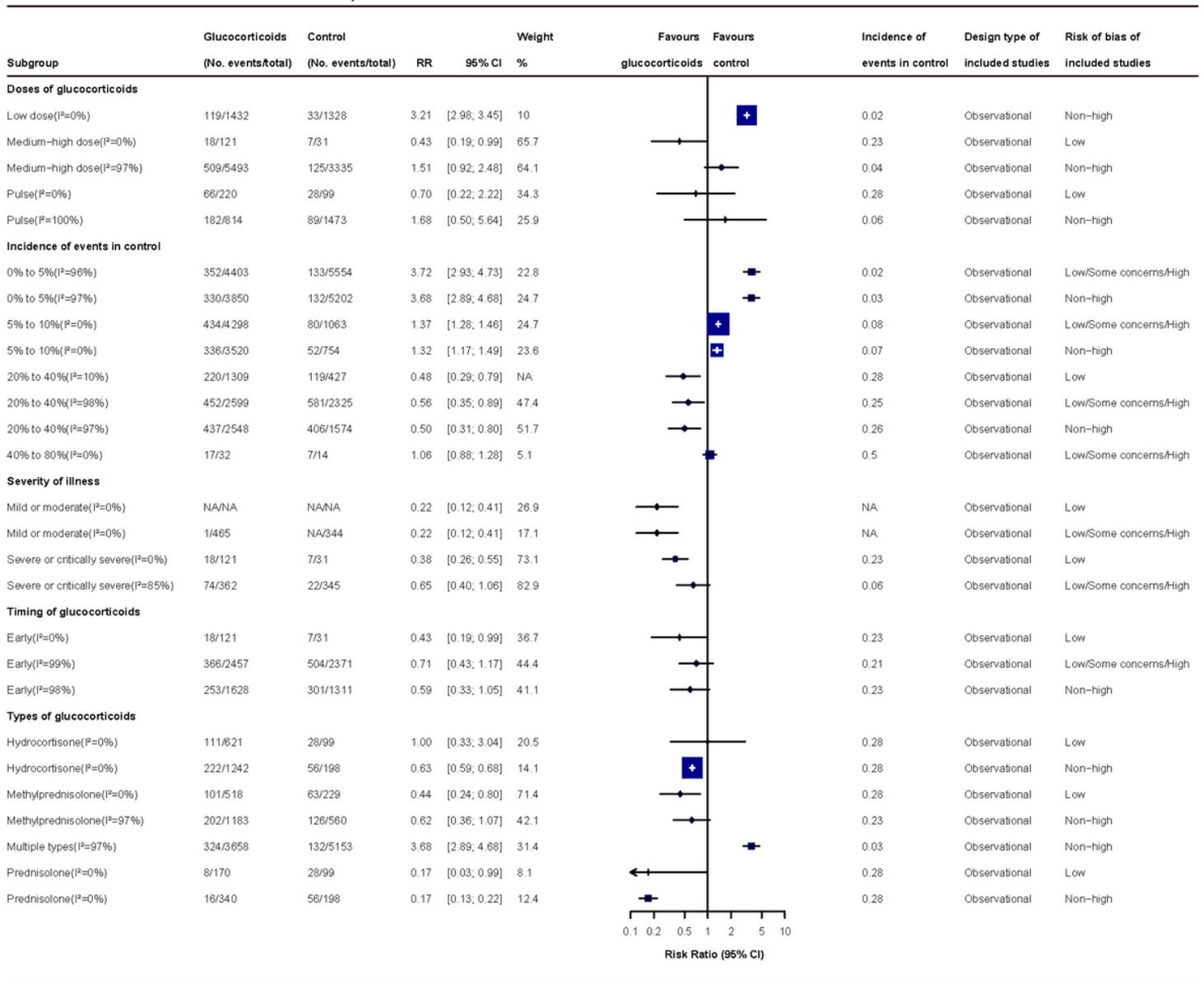


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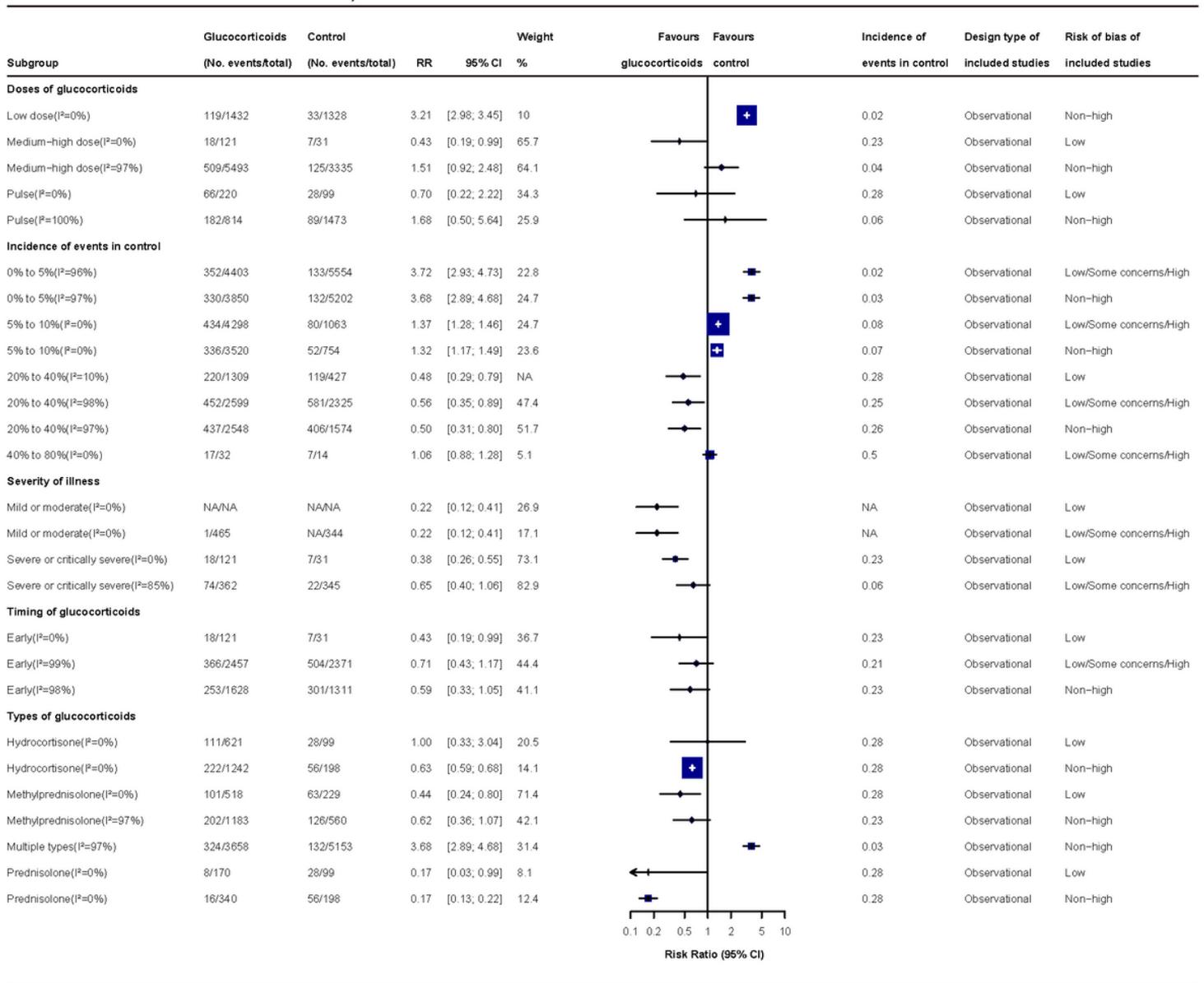


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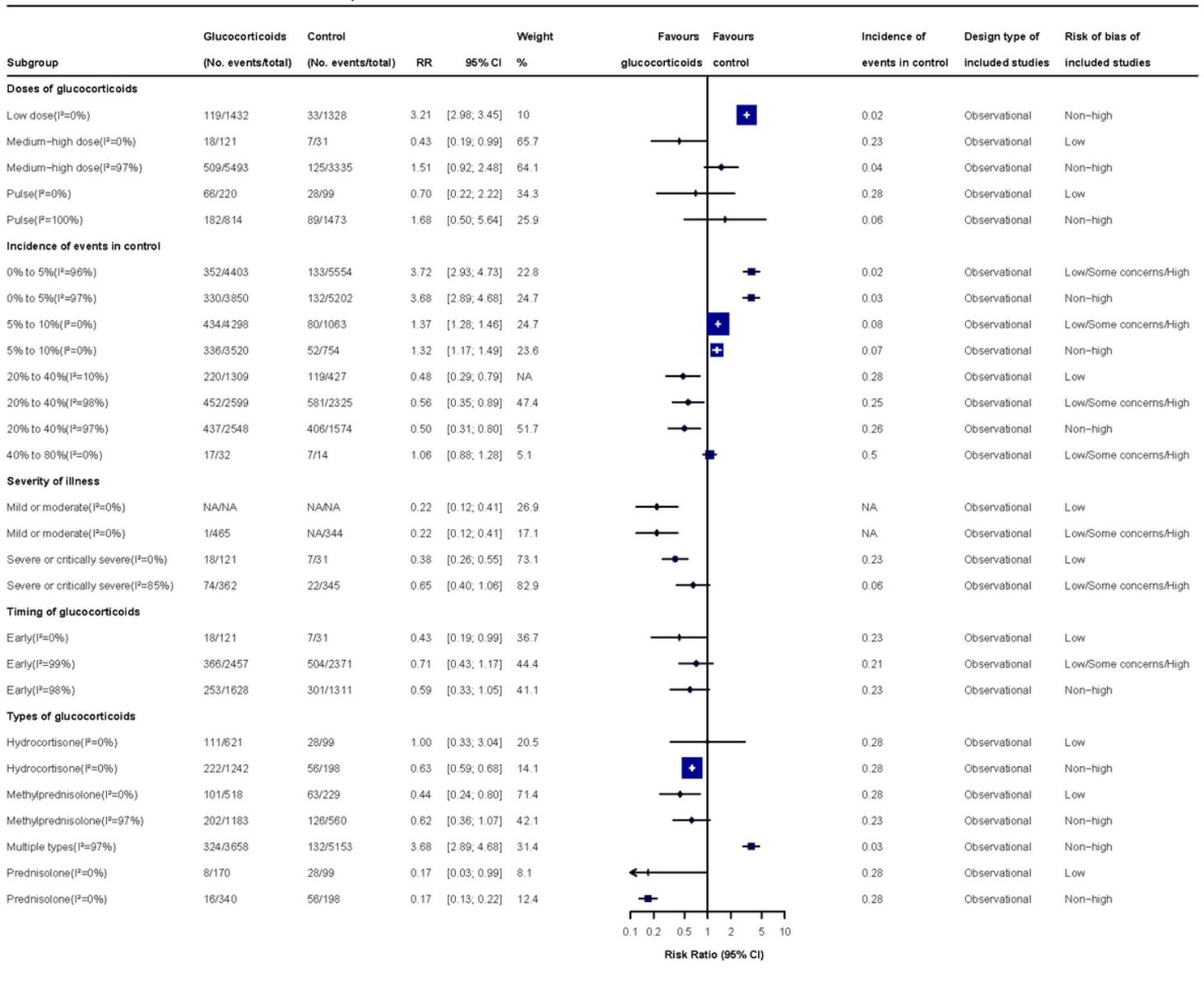


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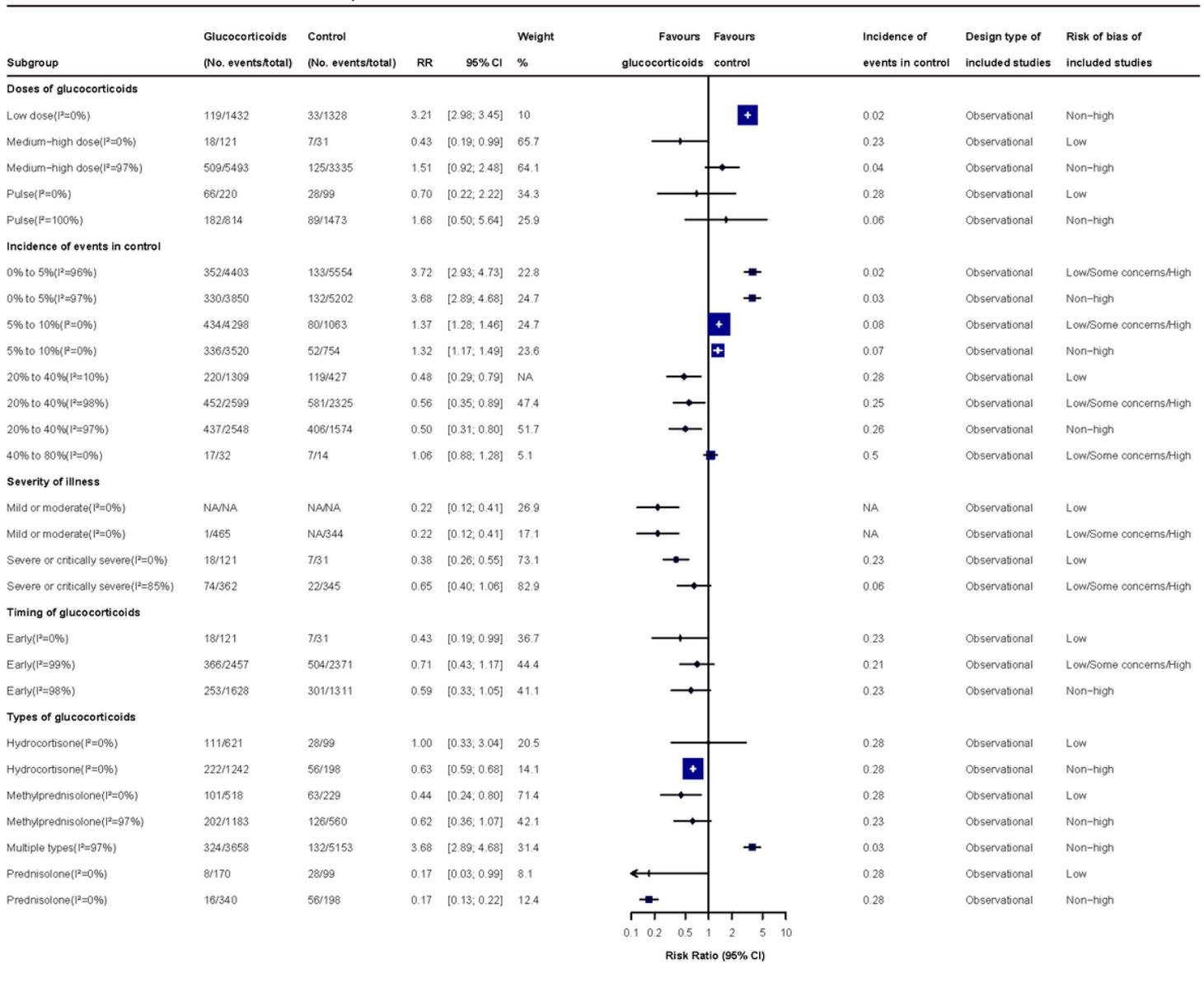


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Supplementary Files

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