Systematic Reviews

PROTOCOL

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Efficacy of nutrient supplements in managing malnutrition and sarcopenia in Chronic Obstructive Pulmonary Disease (COPD) patients: a protocol for systematic review and meta-analysis

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Abstract

Background COPD patients suffering from malnutrition or sarcopenia often incur higher healthcare costs and experience adverse clinical outcomes. Despite this, the effectiveness of nutrient supplements in this population remains uncertain.

Methods and analysis Two reviewers will independently search seven databases—PubMed, Embase, Web of Science, China National Knowledge Infrastructure, Wanfang, Chinese Biomedical Literature Database, and the Cochrane Library—for randomized controlled trials (RCTs) published before August 31, 2024. These RCTs should compare the effects of nutrient supplements against either a standard diet or placebo supplements in patients with COPD. The risk of bias in the included studies will be evaluated using the modified Jadad scale and the Cochrane Collaboration's risk of bias tool. Data synthesis will be conducted using RevMan software. Trial sequential analysis (TSA) will be applied to the primary outcomes. Additionally, subgroup and sensitivity analyses will be performed to assess the robustness of the findings.

Ethics and dissemination Ethical approval is not required because this study is a secondary analysis of existing data. We will disseminate the findings through peer- reviewed publications.

Systematic review registration CRD42024585694.

Strengths and limitations of this study This systematic review and meta-analysis provides a thorough assessment of the efficacy of nutrient supplements in COPD patients, covering a wide range of studies.

·The use of the modified Jadad scale and the Cochrane Collaboration's risk of bias tool ensures a robust evaluation of study quality. Additionally, trial sequential analysis and subgroup analyses are employed to enhance the robustness of the findings.

·The credibility of the evidence may be compromised due to the potential for uncertain study quality and limited sample sizes in some included trials.

Keywords Chronic obstruction pulmonary disease, COPD, Nutrition, Meta-analysis

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Introduction

COPD is a progressive and chronic lung condition characterized by irreversible airflow limitations [1, 2]. This condition is a significant global health issue, contributing substantially to morbidity and mortality worldwide. The underlying pathophysiology of COPD involves chronic inflammation, structural alterations in the airways, and alveolar damage, resulting in symptoms such as dyspnea, chronic cough, and sputum production [1–5]. Despite advancements in pharmacological treatments, the burden of COPD remains high, highlighting the need for complementary therapeutic strategies.

Nutritional status is a crucial factor in determining the clinical outcomes of COPD patients. Malnutrition is prevalent among COPD patients, affecting approximately 50% of the population [6–8]. This is associated with increased morbidity, mortality, and reduced quality of life. The underlying mechanisms include elevated energy expenditure, systemic inflammation, and reduced appetite, all contributing to a negative energy balance [4, 9, 10]. Consequently, nutritional interventions have been proposed as a means to improve clinical outcomes in COPD patients.

The rationale for employing nutritional interventions in COPD is multifaceted. Firstly, adequate nutrition can enhance muscle mass and function, which are often compromised in COPD due to systemic inflammation and disuse atrophy. Improved muscle strength and endurance can lead to better exercise tolerance and reduced dyspnea, thereby enhancing the patient's functional status [11, 12]. Secondly, nutritional supplementations can modulate the inflammatory response, potentially reducing the severity of COPD exacerbations. Dietary components, such as antioxidants and anti-inflammatory nutrients, may play a role in this process. Thirdly, nutritional interventions can improve overall health status by addressing comorbidities such as cardiovascular disease and diabetes, which are commonly associated with COPD [13–15].

Numerous studies have investigated the impact of nutritional interventions on COPD patients, but the findings have been inconsistent, underscoring the need for a comprehensive meta-analysis [11–15]. Some studies have demonstrated significant improvements in lung function, exercise capacity, and quality of life with nutritional interventions while others have reported minimal or no benefits [16–18]. These discrepancies may be due to variations in study design, patient characteristics, and the specific nutritional interventions employed. For example, the type of nutritional supplement, the duration of intervention, and the baseline nutritional status of the patients can all influence the outcomes.

A meta-analysis is therefore essential to synthesize the available evidence and provide a comprehensive assessment of the efficacy of nutritional interventions in COPD patients. By pooling data from multiple studies, a meta-analysis can offer a more robust estimate of the effect size and help identify factors that may influence the outcomes. This analysis will aim to compare the clinical outcomes of COPD patients receiving nutritional interventions with those in a control group, focusing on key endpoints such as lung function, exercise capacity, and changes in body composition. The findings will contribute to the evidence base for nutritional management in COPD and inform clinical practice and future research directions.

Methods and analysis

Study registration

To ensure the standardization and rigor of our study, we meticulously designed and executed this protocol in adherence to the PRISMA-P (Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols) guidelines [19]. The protocol for our systematic review and meta-analysis was pre-registered in the PROSPERO database, with the registration ID: CRD42024585694.

Eligible criteria

Study designs

We will only include randomized controlled trials.

Participants

Adult COPD patients (age ≥ 18 years) with malnutrition or sarcopenia.

Intervention

The experimental groups receive nutrient supplements.

Comparison

The control groups receive standard diet or placebo supplements.

Primary outcomes

6-min walking distance (6MWD) (m): A measure of functional exercise capacity, assessed using the 6-min walk test. This outcome is prioritized because it reflects the impact of nutritional interventions on physical performance, a key concern in COPD patients with malnutrition or sarcopenia.

Secondary outcomes

1. forced expiratory volume in the first second (FEV_1) (L): A measure of airflow limitation, assessed using spirometry.

2. FEV_1 (%, predicted): FEV1 expressed as a percentage of the predicted value, providing a standardized measure of lung function.
3. forced vital capacity (FVC) (L): A measure of total lung capacity, assessed using spirometry.
4. FEV_1/FVC ratio (%):A diagnostic criterion for COPD, calculated as the ratio of FEV1 to FVC.
5. St George's respiratory questionnaire (SGRQ) total score: A validated tool for assessing health-related quality of life in COPD patients.
6. Incremental shuttle walk test (ISWT) (m).
7. Total weight (kg).
8. body mass index (BMI) (kg/m.^{2})
9. fat mass (FM) (kg)
10. FM (% weight)
11. fat-free mass (FFM) (kg)
12. fat-free mass index (FFMI) (kg/m.^{2})

Exclusion criteria

The exclusion criteria were as followings: Non-randomized controlled trials (e.g., observational studies, case reports, or reviews); Studies that do not report relevant outcomes (e.g., 6-min walking distance, lung function parameters, or quality of life measures); Studies with insufficient data for meta-analysis (e.g., missing standard deviations or sample sizes); Studies published in languages other than English or Chinese, due to limitations in translation resources; Studies that include interventions not relevant to nutrient supplementation (e.g., pharmacological treatments or exercise-only interventions).

Literature sources and retrieval strategy

To minimize errors and ensure comprehensive data retrieval, two independent reviewers (Hong-yan Zheng and Hao-yu Zhang) will search seven databases—PubMed, Web of Science, Embase, China National Knowledge Infrastructure (CNKI), Wanfang, Chinese Biomedical Literature Database, and the Cochrane Library—for articles published before August 31, 2024. The detailed retrieval strategy is outlined in Table 1.

Literature screening and data extraction

To minimize errors and ensure comprehensive data extraction, two reviewers (Hong-yan Zheng and Kuang-hao Wu) will rigorously screen and extract data in accordance with the PRISMA guidelines. Any discrepancies will be discussed and resolved within the team. The flowchart of the study selection process is illustrated in Fig. 1. The extracted data will include study design, baseline patient information, and statistics on 6MWD (m); FEV_1 (L); FEV_1 (%, predicted); FVC (L); FEV_1/FVC ratio (%); SGRQ total score; ISWT (m); Total Weight (kg); BMI (kg/m^2); FM (kg); FM (% weight); FFM (kg); and FFMI (kg/m^2).

Assessment of risk of bias

To minimize errors and ensure comprehensive evaluation, two reviewers (Hong-yan Zheng and Wen-jie Cai) will independently assess the risk of bias in the included randomized controlled trials. The assessment will be conducted using the Cochrane Risk of Bias Tool (RoB 2). This tool evaluates bias across five domains: randomization process; deviations from intended interventions; missing

Table 1 The retrieval strategy

Search	Query
#1	((((((((((((((((energy[Title/Abstract]) OR (nutrition[Title/Abstract])) OR (nutritional supplementation [Title/Abstract])) OR (dietary supplements [Title/Abstract])) OR (macronutrient[Title/Abstract])) OR (micronutrient[Title/Abstract])) OR (carbohydrate[Title/Abstract])) OR (protein[Title/Abstract])) OR (amino acid[Title/Abstract])) OR (fat[Title/Abstract])) OR (fatty acid[Title/Abstract])) OR (omega-3[Title/Abstract])) OR (mineral[Title/Abstract])) OR (vitamin[Title/Abstract])) OR (arginine[Title/Abstract])) OR (glutamine[Title/Abstract])) OR (zinc[Title/Abstract])) OR (iron[Title/Abstract])) OR (calcium[Title/Abstract])
#2	(chronic obstructive pulmonary disease [Title/Abstract]) OR (COPD[Title/Abstract])
#3	((sarcopenia [Title/Abstract]) OR (muscle wasting [Title/Abstract])) OR (muscle atrophy [Title/Abstract])
#4	((((((((((((((((((energy[Title/Abstract]) OR (nutrition[Title/Abstract])) OR (nutritional supplementation [Title/Abstract])) OR (dietary supplements [Title/Abstract])) OR (macronutrient[Title/Abstract])) OR (micronutrient[Title/Abstract])) OR (carbohydrate[Title/Abstract])) OR (protein[Title/Abstract])) OR (amino acid[Title/Abstract])) OR (fat[Title/Abstract])) OR (fatty acid[Title/Abstract])) OR (omega-3[Title/Abstract])) OR (mineral[Title/Abstract])) OR (vitamin[Title/Abstract])) OR (arginine[Title/Abstract])) OR (glutamine[Title/Abstract])) OR (zinc[Title/Abstract])) OR (iron[Title/Abstract])) OR (calcium[Title/Abstract])) AND ((chronic obstructive pulmonary disease[Title/Abstract]) OR (COPD[Title/Abstract]))) AND (((sarcopenia[Title/Abstract]) OR (muscle wasting[Title/Abstract])) OR (muscle atrophy[Title/Abstract]))

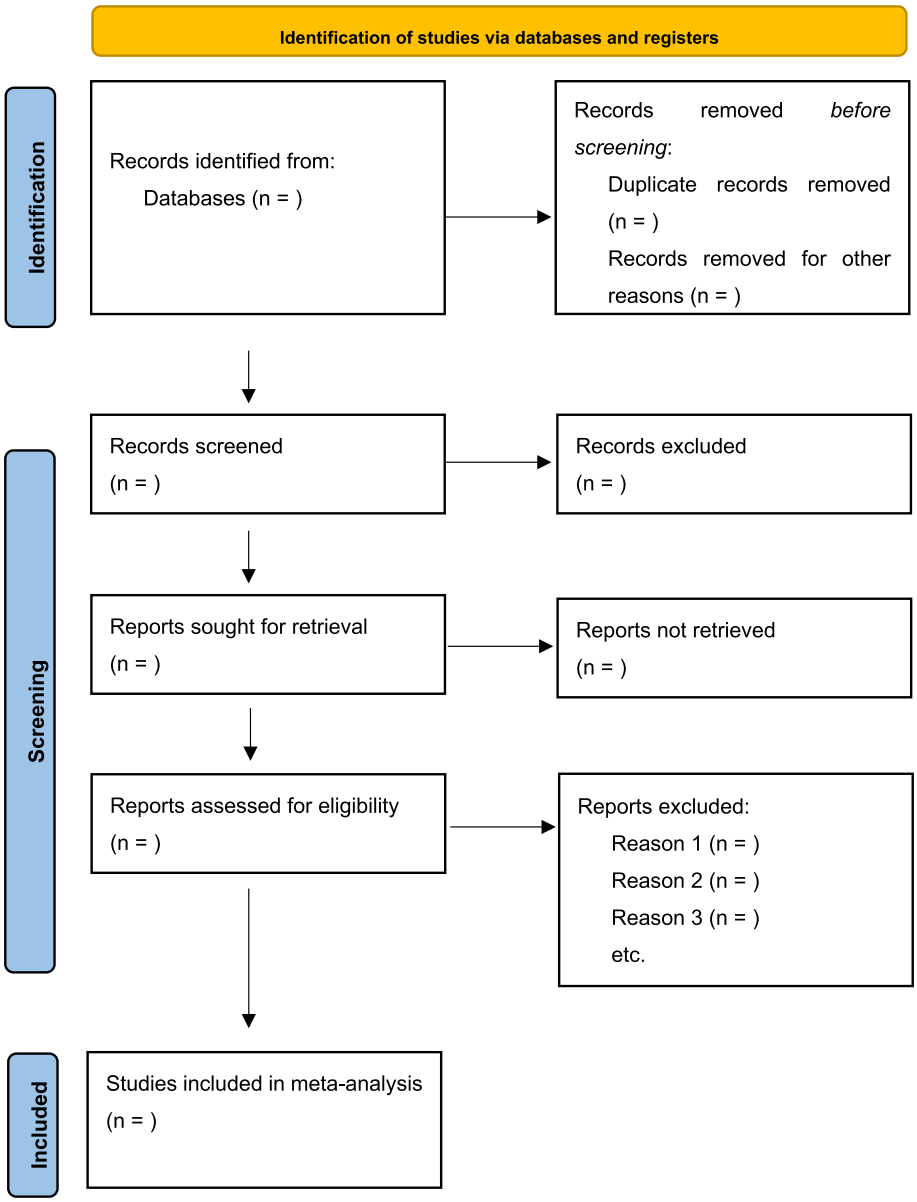

Fig. 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses flowchart of the study inclusion process

outcome data; measurement of the outcome; selection of the reported result.. Each domain will be rated as "low risk of bias," "some concerns," or "high risk of bias." An overall risk of bias judgment will be assigned to each study based on the ratings across all domains. Discrepancies between reviewers will be resolved through discussion or, if necessary, by consulting a third reviewer (Xin-yu Song).

Statistical analyses

Statistical analyses are conducted using Review Manager software (version 5.4). Data will be pooled and forest plots will be generated. For dichotomous variables, risk ratios (RR) with 95% confidence intervals (CI) are calculated using the Mantel–Haenszel method. Continuous variables are analyzed as mean differences (MD) with 95% CI, employing the inverse variance method. The standard α level for statistical tests was set at 0.05. Significant statistical differences are defined as $P < 0.05$. Given the anticipated clinical and methodological heterogeneity across studies, random-effects models will be used by default for all meta-analyses. This approach accounts for variability both within and between studies and provides a more conservative estimate of the effect size. Heterogeneity will be assessed using the I^2 statistic, with values

of 25%, 50%, and 75% indicating low, moderate, and high heterogeneity, respectively. Missing data will be managed using the following approach: contact study authors or use imputation methods to estimate missing values.

Publication bias

Publication bias will be evaluated when the number of included RCTs exceeds 10, as a limited number of studies can compromise the robustness of the assessment. Funnel plots and egger's test will be used to assess publication bias.

Subgroup analysis and sensitivity analysis

Subgroup analyses will be conducted based on the following factors: type of nutrient supplement; severity of COPD; baseline nutritional status; and duration of intervention. Additionally, a sensitivity analysis will be performed to assess the stability and reliability of the findings.

Trial sequential analysis

Random errors can produce misleading results when a meta-analysis is based on a limited number of studies and patients. TSA helps mitigate the risks of random error due to insufficient sample size or repeated testing, and it aids in estimating the required information size (RIS) for the meta-analysis. We will conduct TSA for the primary outcomes using TSA version 0.9.5.10 Beta software, with Type 1 error set at 5% and power at 80%.

Certainty of evidence

The certainty of the evidence will be assessed using GRADEpro, a tool developed by the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) Working Group. The assessment criteria for evidence certainty include the initial study design, risk of bias, imprecision, indirectness, and inconsistency. Following these guidelines, the certainty of the evidence will ultimately be rated as "High," "Moderate," "Low," or "Very low."

Patient and Public Involvement

No patient involved.

Ethics and dissemination

No ethical approval is required for this review. Our findings will be submitted to peer- reviewed journals.

Discussion

The inconsistency in current literatures highlights the need for a comprehensive meta-analysis to synthesize the available evidence and provide a more robust estimate of the effect size [16–18]. This meta-analysis aims to synthesize the available evidence on the efficacy of nutritional interventions in improving clinical outcomes among COPD patients. By comparing the outcomes of COPD patients receiving nutritional interventions with those in a control group, this analysis may provide a comprehensive assessment of the potential benefits and limitations of nutritional support in this population. The findings of this meta-analysis offer valuable insights into the role of nutrition in managing COPD and highlight several key points that warrant further discussion.

The anticipated findings of this meta-analysis have several potential implications for clinical practice and research. Firstly, if the meta-analysis demonstrates significant improvements in clinical outcomes with nutritional interventions, it could support the routine use of nutritional support in the management of COPD. This could lead to better patient outcomes, reduced morbidity and mortality, and improved quality of life. Secondly, the meta-analysis could identify specific nutritional components or interventions that are most effective in improving clinical outcomes. For example, it may reveal that certain types of oral nutritional supplements or enteral nutrition are more beneficial than others. This information could guide the development of more targeted and effective nutritional strategies for COPD patients. Thirdly, the meta-analysis could highlight the need for personalized nutritional approaches tailored to the individual needs of COPD patients. By identifying factors that influence the outcomes of nutritional interventions, such as the severity of the disease, the presence of comorbidities, and the baseline nutritional status of the patients, the meta-analysis could inform the development of more individualized treatment plans.

The awareness of nutritional supplementation among COPD patients remains insufficient due to conflicting evidence. Bakel et al.'s study delved into the implications of sarcopenia for COPD patients, emphasizing the importance of personalized management for sarcopenia. However, their proposed strategy proved impractical in clinical settings [17], highlighting a critical gap in translating research findings into actionable clinical practice. The complexity of COPD, coupled with the multifaceted nature of sarcopenia, necessitates more tailored and feasible approaches to nutritional management. Lieke et al.'s systematic review, which included both COPD patients and the general population, highlighted significant differences in dietary intake, nutritional supplementation, and nutrient status. They found that higher intake of vegetables, fruits, and certain vitamins was associated with a reduced risk of COPD, underscoring the potential protective role of a nutrient-rich diet in mitigating the progression of COPD [18]. However, the generalizability of these

results to diverse patient populations remains a subject of debate, necessitating further research to validate these associations in different clinical contexts. Aldhahir et al.'s study focused on the efficacy of nutritional supplementation in COPD patients undergoing pulmonary rehabilitation. Their analysis revealed that nutritional supplements did not provide additional clinical benefits beyond pulmonary rehabilitation alone in most studies [16]. They also cautioned that the results might be misleading due to heterogeneity, often stemming from variations in study design, patient characteristics, and intervention protocols, complicating the interpretation of findings. Future research should aim to standardize methodologies and patient selection criteria to enhance the robustness of conclusions. Furulund et al.'s systematic review examined the effects of nutritional interventions on physical and pulmonary function, inflammation, and health-related quality of life in COPD patients. They concluded that long-term increased intake of vegetables and fruits could positively impact lung function, and some nutritional interventions might modulate inflammation and improve health-related quality of life [20], suggesting that a sustained dietary approach, rather than short-term supplementation, may be more effective in managing COPD. The potential benefits of such interventions on inflammation and quality of life warrant further investigation, particularly in longitudinal studies. Pereira et al.'s study identified undernutrition as a factor associated with adverse clinical outcomes in COPD patients. However, their systematic review was based on observational studies and lacked precision [21], as observational studies may be subject to confounding variables and bias, potentially skewing the results. More rigorous, controlled trials are needed to establish a causal relationship between undernutrition and adverse outcomes in COPD patients. A recent meta-analysis involving 5289 patients found that the prevalence of malnutrition was approximately 30%, negatively impacting clinical outcomes in COPD patients [22], underscoring the urgent need for targeted nutritional interventions. Malnutrition in COPD patients can exacerbate symptoms, reduce functional capacity, and increase the risk of complications, thereby worsening overall prognosis. Addressing this issue requires a multidisciplinary approach, integrating nutritional support into comprehensive care plans.

Our systematic review and meta-analysis are based on well-designed randomized controlled trials and hope to provide robust evidence that supports the integration of nutritional supplementation into standard care protocols for COPD patients. One of the key outcomes assessed in this meta-analysis is the impact of nutritional interventions on lung function, measured primarily through parameters such as FEV_1 and FVC. The improvement in nutritional group is likely attributable to the anti-inflammatory effects of certain dietary components, such as antioxidants and omega-3 fatty acids, which can reduce airway inflammation and improve airflow. Besides, another important outcome of this meta-analysis is the impact of nutritional interventions on exercise capacity and functional status such as 6-min walk distance. Possible improvements in the nutritional group are likely due to the enhanced muscle mass and function resulting from adequate nutrition, which can reduce dyspnea and improve overall physical performance. Quality of life is a critical outcome in COPD patients, as it reflects the overall impact of the disease on daily functioning and well-being. The meta-analysis sets SGRQ as standardized questionnaires to quantify patients' quality of life. Possible improvements of quality of life in the nutritional group are likely due to the combined effects of enhanced physical function, reduced dyspnea, and improved nutritional status.

This systematic review and meta-analysis has several limitations that should be acknowledged. Despite efforts to minimize publication bias through a comprehensive search strategy, there is a risk that studies with negative or null results may be underrepresented in the literature. To address this, we will assess publication bias using funnel plots and Egger's test if more than ten studies are included. The potential impact of publication bias on the results will be discussed in the context of the overall evidence. Clinical and methodological heterogeneity across studies is expected due to differences in study design, patient characteristics, and intervention protocols. To address this, we will use random-effects models for all meta-analyses and conduct subgroup analyses to explore potential sources of heterogeneity. Sensitivity analyses will also be performed to assess the robustness of the findings. The quality of the included studies may vary, which could influence the overall results. To mitigate this, we will assess the risk of bias in each study using RoB 2 and provide a detailed evaluation of study quality. The impact of study quality on the results will be discussed, and sensitivity analyses will be conducted to exclude studies with a high risk of bias. The inclusion of studies published only in English and Chinese may introduce language bias, as relevant studies published in other languages may have been excluded. While this limitation is necessary due to practical constraints, it will be explicitly acknowledged, and its potential impact on the results will be discussed. The findings of this review may not be generalizable to all COPD populations, particularly those with severe disease or significant comorbidities. Subgroup analyses will be conducted to explore the impact of disease severity and comorbidities on the outcomes, but the generalizability of the results should be interpreted with caution.

Abbreviations

COPD	Chronic obstructive pulmonary disease
PRISMA-P	Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols
RCTs	Randomized controlled trials; CNKI, China National Knowledge Infrastructure
SinoMed	Chinese Biomedical Literature Database
RevMan	Review Manager
RR	Risk ratios
CI	Confidence intervals
MD	Mean difference
GRADE	Grading of Recommendations Assessment, Development, and Evaluation
TSA	Trial sequential analysis
RCTs	Randomized controlled trials
6MWD	6-Minute walking distance
FEV_1	Forced expiratory volume in the first second
FVC	Forced vital capacity
SGRQ	St George's respiratory questionnaire
ISWT	Incremental shuttle walk test
BMI	Body mass index
FM	Fat mass
FFM	Fat-free mass
FFMI	Fat-free mass index

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Not applicable.

Patient and public involvement
Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Provenance and peer review
Not commissioned; externally peer reviewed.

Authors' contributions
ZHY and SXY conceptualized the study. ZHY and ZHY are responsible for the literature retrieval. ZHY and WKH will extract data individually. ZHY and CWJ will access the risk of bias. LZZ provided valuable insights. ZHY finished the manuscript. SXY revised and proofread the manuscript.

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Data availability
Not applicable. This systematic review and meta-analysis is based on published studies, and no new data were generated. All data used in this review are available within the original publications included in the analysis.

Declarations

Ethics approval and consent to participate
Not applicable, as this study is a systematic review and meta-analysis of existing published data.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing financial interests or personal relationships that may have influenced the work reported in this study.

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