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Can $^{18}$F-FDG PET/CT predict EGFR status in patients with non-small cell lung cancer? A systematic review and meta-analysis

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ABSTRACT

Objectives This study aimed to explore the diagnostic significance of $^{18}$F-fluorodeoxyglucose ($^{18}$F-FDG) positron emission tomography (PET)/CT for predicting the presence of epidermal growth factor receptor (EGFR) mutations in patients with non-small cell lung cancer (NSCLC).

Design A systematic review and meta-analysis.

Data sources The PubMed, EMBASE and Cochrane library databases were searched from the earliest available date to December 2020.

Eligibility criteria for selecting studies The review included primary studies that compared the mean maximum of standard uptake value (SUV$_{\text{max}}$) between wild-type and mutant EGFR, and evaluated the diagnostic value of $^{18}$F-FDG PET/CT using SUV$_{\text{max}}$ for prediction of EGFR status in patients with NSCLC.

Data extraction and synthesis The main analysis was to assess the sensitivity and specificity, the positive diagnostic likelihood ratio (DLR+) and DLR−, as well as the diagnostic OR (DOR) of SUV$_{\text{max}}$ in prediction of EGFR mutations. Each data point of the summary receiver operator characteristic (SROC) graph was derived from a separate study. A random effects model was used for statistical analysis of the data, and then diagnostic performance for prediction was further assessed.

Results Across 15 studies (3574 patients), the pooled sensitivity for $^{18}$F-FDG PET/CT was 0.70 (95% CI 0.60 to 0.79) with a pooled specificity of 0.59 (95% CI 0.52 to 0.66). The overall DLR+ was 1.74 (95% CI 1.49 to 2.03) and DLR− was 0.50 (95% CI 0.38 to 0.65). The pooled DOR was 3.50 (95% CI 2.37 to 5.17). The area under the SROC curve was 0.68 (95% CI 0.64 to 0.72). The likelihood ratio scatter plot based on average sensitivity and specificity was in the lower right quadrant.

Conclusion Meta-analysis results showed $^{18}$F-FDG PET/CT had low pooled sensitivity and specificity. The low DOR and the likelihood ratio scatter plot indicated that $^{18}$F-FDG PET/CT should be used with caution when predicting EGFR mutations in patients with NSCLC.

INTRODUCTION

Lung cancer is a common malignant tumour that is associated with considerable social and economic burden. Global statistics show that among malignan tumours, morbidity and mortality from lung cancer ranks first in males, while in females lung cancer is second only to breast cancer. Non-small cell lung cancer (NSCLC) accounts for 85%-90% of lung cancers, with lung adenocarcinomas (LUAD) being the most diagnosed histological subtype of NSCLC. In Asia, up to 50% of patients with LUAD have activating mutations of the tyrosine kinase domain of epidermal growth factor receptor (EGFR). Tyrosine-kinase inhibitor (TKI), which targets EGFR kinase domain mutations, seems to trigger a form of oncogenic shock, resulting in a favourable response in NSCLC. The clinical outcome of the patients with NSCLC harbouring EGFR alteration was significantly improved by three different generations of EGFR TKIs. Therefore, EGFR mutations are considered to have a predictive role in the success of TKI treatment in NSCLC. The standard approach to detecting EGFR status is genetic testing, which is based on tumour specimens captured by resection, fine needle aspiration or biopsy. However, this method does not reflect the status of the entire tumour, and usually results in failure or poor reproducibility due to insufficient samples. Liquid biopsy can identify mutant target gene in circulating cell-free tumour DNA, which is sometimes inconsistent with specimens biopsy, limiting it clinical application. Moreover, neither biopsies nor plasma samples...
can provide accurate anatomical information such as position, size, boundary and relationship with adjacent structures of the tumours, which is critical for clinical treatment planning and response assessment.

Image-based phenotyping, which provides a non-invasive method to visualise tumour phenotypic characteristics, is a promising tool for precision medicine. X-ray CT imaging have been systematically analysed to discover anatomical risk factors for EGF mutations prediction in NSCLC. Molecular imaging is an attractive option for evaluating patients with NSCLC receiving targeted treatment because it can non-invasively capture the molecular and genomic characteristics of the tumour. The use of positron emission tomography (PET)/CT as a molecular imaging modality for precision medicine is unique. 18F-fluorodeoxyglucose (18F-FDG) PET/CT can provide information on glucose metabolism and is widely used for cancer diagnosis and image-guided therapy. Semi-quantitative parameters can be used for PET image analysis, with the mean maximum of standard uptake value (SUV<sub>max</sub>) being the most effective and commonly used parameter. It has been reported that 18F-FDG PET/CT can predict EGRF status in patients with NSCLC, but this remains controversial. Some studies have confirmed that higher uptake of 18F-FDG is predictive of mutant EGF in patients with NSCLC, while several other studies have shown the opposite result. A systematic review is needed to clarify this point.

Although 18F-FDG PET/CT was used to predict many biological features or other genetic mutations of certain malignancies through meta-analysis, as far as we know, no meta-analysis has summarised the association between 18F-FDG PET/CT and EGF mutation status in NSCLC. The purpose of our study was to conduct a meta-analysis of the diagnostic performance of 18F-FDG PET/CT in predicting EGF mutations, thereby providing more evidence for precise treatment of patients with NSCLC.

### Inclusion of studies and data extraction

Only original articles focusing on 18F-FDG PET/CT and EGF status in patients with NSCLC were eligible for inclusion. To compare the differences in 18F-FDG uptake between EGF mutant and wild-type patients, the publications that reported SUV<sub>max</sub> and SD of EGF mutant and wild-type groups were first selected. Next, articles using 18F-FDG PET/CT to predict EGF status in patients with NSCLC were included based on whether they provided sufficient data to re-evaluate the sensitivity and specificity, or provided absolute data including true-positive, true-negative, false-positive and false-negative without data overlap. Duplicate publications and publications that do not contain original data, such as case reports, conference papers, review articles and letters, were excluded. Non-relevant studies and basic research were also excluded. Only English articles were evaluated. Two researchers independently reviewed the abstracts of the selected articles using the above inclusion criteria. When there were disagreements between authors, a consensus was reached through a third author who was consulted. The same researchers independently evaluated the full text to determine whether they were eligible for final inclusion.

### Quality assessment and publication bias

For pooled weighted mean difference (WMD) analysis, risk of bias, including random sequence generation, allocation concealment, blinding, incomplete outcome data and selective reporting were assessed. Publication bias was assessed using a funnel plot, and plot asymmetry was considered to be suggestive of publication bias. For diagnostic performance analysis, the Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) tool was employed to assess the risk of bias in diagnostic accuracy

### METHODS

#### Screening of publications

A systematic review of publications relevant to PET and EGF mutations in NSCLC was undertaken using the electronic databases of PubMed, Embase and the Cochrane library from the earliest available date of indexing up to 31 December 2020. A search algorithm based on combined terms was used: (1) “FDG” OR “Fluorodeoxyglucose” OR “2-Fluoro-2-deoxyglucose” OR “2-Fluoro-2-deoxy-D-glucose” and (2) “PET” OR “positron emission tomography” and (3) “Epidermal Growth Factor Receptor” OR “EGFR” OR “c-erbB-1” OR “erbB-1” OR “v-erbB” and (4) “pulmonary cancer” OR “pulmonary cancer” OR “lung neoplasm” OR “lung cancer” and (5) “mutation” (see online supplemental file for further details on search strategy). In order to expand the scope of our search, we also screened the references of the included studies for other studies to include.

![Figure 1](image-url)
studies. The tool consisted of four domains of risk of bias, including patient selection, index test, reference standard and flow and timing. Publication bias was evaluated using a funnel plot and Egger’s regression test.

Data synthesis and analysis
A WMD was calculated through SUV max extracted from the retrieved articles. A random effects model was used for statistical analysis of the data. Pooled data were displayed using forest plots and presented with 95% CIs. An I² test was performed to analyse the heterogeneity between studies (I² value >50% was considered significant). Diagnostic performance for prediction was further assessed. The main purpose was to assess the sensitivity and specificity, the positive and negative diagnostic likelihood ratios (DLR+ and DLR−, respectively), as well as the diagnostic OR (DOR). Publication bias was evaluated using a Deeks’ funnel plot of the effective sample size. The bivariate model allowed us to incorporate the correlation that might exist between the logit-transformed values of paired sensitivity and specificity across studies. Each data point of the summary receiver operator characteristic (SROC) graph was derived from a separate study. Based on these points, the smooth SROC curve was derived from the accuracy of the pooled measures. The likelihood ratio scatter plots graphically showed summary spots of likelihood ratios obtained from the average sensitivity and specificity. Statistical analyses were performed using STATA V.15.1 (StataCorp LP) and RevMan V.5.3 (Cochrane Collaboration, Copenhagen, Denmark). P≤0.05 was considered statistically significant.

Patient and public involvement statement
Neither patients nor the public were involved in the design and planning of the study.

RESULTS
Literature search and selection of studies
The comprehensive search yielded 545 records for analysis. Records with duplicate titles and abstracts (89) were excluded. Additionally, 36 review articles, 144 conference abstracts, 13 basic research articles, 120 case reports, editorials, notes and surveys, 86 non-relevant records and 10 other language studies were excluded. The remaining 47 full-text articles were further assessed for eligibility. For calculating pooled WMD, 24 articles were excluded due to insufficient data and 23 studies were included. For the pooled DOR analysis, 29 articles were excluded due to insufficient data and 3 articles were excluded due to inconsistent results according to pooled WMD results (18F-FDG uptake was significantly lower in EGFR mutant group; the pooled sensitivity, specificity and DOR were also calculated without excluding the three studies). The remaining 15 studies were included in the meta-analysis. The detailed procedure of study selection is shown in figure 1.
Study description and publication bias
All included patients underwent a $^{18}$F-FDG PET/CT examination and EGFR gene test. EGFR mutations analysis was carried out on tissue specimens obtained from resection, aspiration or biopsy. A total of 5220 patients were included in the WMD analysis, and SUV$_{\text{max}}$ between the EGFR mutant and wild-type groups were compared. The patients were enrolled retrospectively in all 23 of the included studies. The pooled comparison of the studies demonstrated that $^{18}$F-FDG uptake was significantly lower in the EGFR mutant group (WMD $-1.73$; 95% CI $-2.34$ to $-1.12$; $p<0.05$; $I^2=78.2\%$, figure 2). The most common domains with reporting deficiencies related to the patient selection, as there was no random sequence generation for retrospective studies (figure 3A). Visual analysis of the funnel plot was not suggestive of publication bias using Egger’s test ($p=0.786$; figure 3B). The principal characteristics of the included 23 studies are shown in table 1. Most of the observational studies demonstrated a low risk of bias as assessed by the QUADAS-2 tool (figure 4A). Deek’s funnel plot asymmetry tests were performed to assess a possible publication bias. No significant bias was found ($p=0.089$; figure 4B).

Diagnostic effectiveness of $^{18}$F-FDG PET/CT
The diagnostic effectiveness of $^{18}$F-FDG PET/CT in predicting EGFR mutation in patients with NSCLC was meta-analysed across 15 studies. The pooled sensitivity was 0.70 (95% CI 0.60 to 0.79) with heterogeneity ($I^2=90.86$, 95% CI 87.38 to 94.34, $p<0.05$). The pooled specificity was 0.59 (95% CI 0.52 to 0.66) with heterogeneity ($I^2=91.43$, 95% CI 88.23 to 94.63, $p<0.05$; figure 5). DLR synthesi...
## Table 1 Characteristics of the included studies

| Authors               | Year | Country   | Study design | Patient number | Age (mean) | Gender (M/F) | Smoker | LUAD | Genetic test | EGFR mutant/wild-type | 18F-FDG injection dose | Cut-off value | Meta-analysis |
|-----------------------|------|-----------|--------------|----------------|------------|--------------|--------|------|--------------|-------------------------|-------------------------|---------------|---------------|
| Caicedo et al         | 2014 | Spain     | R            | 102            | 62         | 62/40        | 73     | 90   | PCR          | 22/80                   | NA                      | NA            | WMD           |
| Chen et al            | 2019 | China     | R            | 157            | 66         | 84/73        | 68     | 144  | PCR          | 54/103                  | 481 MBq                 | 9.92          | WMD/DOR       |
| Cho et al             | 2016 | Korea     | R            | 61             | 61         | 33/28        | 29     | 58   | PCR          | 30/31                   | 5.5 MBq/kg             | 9.6           | WMD/DOR       |
| Choi et al            | 2012 | Korea     | R            | 163            | 60         | 99/64        | 73     | 130  | PCR          | 57/106                  | 5.18 MBq/kg             | NA            | WMD           |
| Choi et al            | 2013 | Korea     | R            | 331            | 62         | 158/173      | 145    | 331  | PCR          | 156/175                 | 5.18 MBq/kg             | NA            | WMD           |
| Chung et al           | 2010 | Korea     | R            | 106            | 64         | 63/43        | 60     | 97   | PCR          | 42/64                   | 4.8 MBq/kg             | NA            | WMD           |
| Gao et al             | 2020 | China     | R            | 167            | 58         | 87/80        | 67     | 162  | PCR          | 72/94                   | 370 MBq                | 11.5          | DOR           |
| Gu et al              | 2017 | China     | R            | 210            | 59         | 132/78       | 90     | 161  | PCR          | 70/140                  | 5.18 MBq/kg             | 9             | DOR           |
| Guan et al            | 2016 | China     | R            | 316            | 60         | 216/100      | 162    | 242  | PCR          | 126/190                 | NA                      | 8.1           | WMD/DOR       |
| Hong et al            | 2020 | Korea     | R            | 134            | 69         | 89/45        | 76     | 134  | PCR          | 62/72                   | 52/7 MBq/kg            | 9.6           | WMD/DOR       |
| Huang et al           | 2010 | China     | R            | 77             | 62         | 44/33        | 16     | 77   | PCR          | 49/28                   | 370 MBq                | NA            | WMD           |
| Kanmaz et al          | 2016 | Turkey    | R            | 218            | 62         | 151/67       | 155    | 218  | PCR          | 63/155                  | 3.7–5.2 MBq/kg          | NA            | WMD           |
| Kim et al             | 2016 | Korea     | R            | 198            | 62         | 113/85       | 68     | 183  | PCR          | 101/97                  | 5.18 MBq/kg             | NA            | WMD           |
| Kim et al             | 2018 | Korea     | R            | 232            | 64         | 104/128      | 93     | 232  | PCR          | 132/100                 | 5.18 MBq/kg             | NA            | WMD           |
| Lee et al             | 2015 | Korea     | R            | 206            | 68         | 148/58       | 71     | 135  | PCR          | 47/159                  | 481 MBq                | 11.7          | DOR           |
| Lee et al             | 2015 | China     | R            | 71             | 65         | 33/38        | 19     | 71   | PCR          | 48/23                   | 370 MBq                | NA            | WMD           |
| Liao et al            | 2020 | China     | R            | 191            | 63         | 101/90       | 65     | 191  | PCR          | 63/128                  | 3.7 MBq/kg             | 7.78          | DOR           |
| Lv et al              | 2018 | China     | R            | 808            | 59         | 468/340      | 310    | 731  | PCR          | 371/437                 | 5.5 MBq/kg             | 7             | WMD/DOR       |
| Liu et al             | 2017 | China     | R            | 87             | 60         | 49/38        | 32     | 78   | PCR          | 41/46                   | NA                      | 10.4          | DOR           |
| Mak et al             | 2011 | USA       | R            | 100            | 65         | 39/61        | 73     | 90   | PCR          | 24/76                   | 5.55–7.4 MBq            | NA            | WMD           |
| Minamimoto et al      | 2017 | USA       | R            | 127            | 67         | NA           | NA     | 127  | PCR          | 32/95                   | 12–17 mCi              | NA            | WMD           |
| Mu et al              | 2020 | China, USA| R            | 681            | 63         | 378/303      | 315    | 567  | PCR          | 312/369                 | NA                      | NA            | WMD           |
| Na et al              | 2010 | Korea     | R            | 100            | 64         | 68/32        | 57     | 53   | PCR          | 21/79                   | 370 MBq                | 9.2           | DOR           |
| Qiang et al           | 2016 | China     | R            | 97             | 65         | 50/47        | 51     | 97   | PCR          | 44/53                   | 7.4 MBq/kg             | NA            | WMD           |
| Suárez-Piñera et al   | 2018 | Spain     | R            | 106            | 71         | NA           | NA     | 106  | PCR          | 24/82                   | 5.29 MBq/kg            | NA            | WMD           |
| Takamochi et al       | 2017 | Japan     | R            | 734            | 68         | 367/367      | 363    | 734  | PCR          | 334/400                 | 3.5 MBq/kg             | 2.69          | WMD/DOR       |
| Whi et al             | 2020 | Korea     | R            | 64             | 66         | 34/30        | 25     | 64   | PCR          | 29/35                   | 5.18 MBq/kg            | 9.5           | WMD/DOR       |
| Yang et al            | 2019 | China     | R            | 200            | 61         | 108/92       | 68     | 200  | PCR          | 115/85                  | 3.7–6.66 MBq/kg         | 6.15          | WMD/DOR       |
| Zhu et al             | 2018 | China     | R            | 139            | 62         | 62/77        | 46     | 139  | PCR          | 74/65                   | 4.2 MBq/kg             | 11.19         | WMD/DOR       |

DOR, diagnostic OR; EGFR, epidermal growth factor receptor; 18F-FDG, 18F-fluorodeoxyglucose; LUAD, lung adenocarcinoma; WMD, weighted mean difference.
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Open access gave an overall DLR+ of 1.74 (95% CI 1.49 to 2.03) and DLR− of 0.50 (95% CI 0.38 to 0.65; figure 6). The pooled DOR was 3.50 (95% CI 2.37 to 5.17; figure 6). The area under curve (AUC) obtained from SROC was 0.68 (95% CI 0.64 to 0.72; figure 7A). Lower pooled sensitivity, specificity and DOR were shown with the three studies included in the prediction of EGFR mutations in patients with NSCLC (see online supplementary figure S1).

**Likelihood ratio scatter plot**
The summary value of likelihood ratios obtained from the average sensitivity and specificity shown in the likelihood ratio scatter plot (figure 7B) was located in the lower right quadrant, which indicated that 18F-FDG PET/CT may not be useful for predicting whether there is an EGFR mutation (when positive) or not (when negative).

**DISCUSSION**
In light of the advances in the precise treatment of lung cancer, identifying targetable mutations at the time of diagnosis has become the key to determining the best treatment strategies. The identification of the EGFR mutation led to an important paradigm shift in the treatment and survival of patients with NSCLC. A typical molecular imaging technique, 18F-FDG PET/CT has been used in prediction of EGFR status in patients with NSCLC. However, various studies have published contradictory results. This is the first systematic review and meta-analysis to summarise current evidence for the use of 18F-FDG PET/CT to predict EGFR status in patients with NSCLC. The principal findings of this meta-analysis showed low sensitivity and specificity of 18F-FDG PET/CT in the prediction of EGFR mutations.

Previous studies on the value of 18F-FDG PET in predicting EGFR status have been conflicting. Accumulation of 18F-FDG was reported to be lower in patients with NSCLC, which can be used to predict EGFR status. Na et al first reported that patients with low SUV\textsubscript{max} were more likely to have EGFR mutations than those with high SUV\textsubscript{max}. When using 9.2 as the cut-off value, the specificity and sensitivity reached 72% and 67%, respectively. Lee et al concluded that 18F-FDG avidity had no significant clinical value in predicting EGFR status, while the univariate analysis showed that SUV\textsubscript{max} was significantly correlated with...
EGFR mutation using 11.7 as the cut-off value. Cho et al also found that mutant EGFR had relatively lower glycolysis compared with wild-type EGFR. A cut-off SUV\textsubscript{max} value of 9.6 had the highest sensitivity (79.3 %) in predicting EGFR mutations. Research by Guan et al showed that 18\textsuperscript{F}-FDG uptake values could effectively predict the EGFR mutation status of patients with NSCLC. ROC curve analysis revealed the AUC was 0.65, with an SUV\textsubscript{max} value of 8.1 as the cut-off point. Next, other studies further demonstrated that low SUV\textsubscript{max} was a significant predictor
of $EGFR$ mutations using different cut-off values.\(^8,9,21-23\) Chen et al demonstrated that using 9.92 as the SUV\(_{\text{max}}\) cut-off point can best discriminate the $EGFR$ mutation status with an AUC of 0.75, and they identified that the mechanism responsible for the decreased FDG uptake associated with mutant $EGFR$ was through the NOX4/ROS/GLUT1 axis.\(^10\) However, multiple groups have reported no association between SUV\(_{\text{max}}\) and $EGFR$ status. Mak et al reported that high normalised SUV\(_{\text{max}}\) only correlated with the $EGFR$ wild-type genotype.\(^24\) Moreover, several studies have reported conflicting results. Huang et al found that a higher $^{18}$F-FDG uptake with a SUV\(_{\text{max}}\) cut-off value of 9.5 correlates with the presence of $EGFR$ mutations.\(^31\) While Ko et al showed a trend of higher SUV\(_{\text{max}}\) in patients with an $EGFR$ mutation, with an optimal cut-off was 6.\(^13\) Kannaz et al made a similar conclusion, with an SUV\(_{\text{max}}\) cut-off value of 13.65 as the predictor.\(^12\)

Our results indicated the $^{18}$F-FDG PET/CT has low sensitivity and specificity in predicting $EGFR$ mutations. Comparison of mean SUV\(_{\text{max}}\) between $EGFR$ mutant and wild-type was first pooled with WMD to determine the relationship between $EGFR$ status and FDG uptake. According to result of WMD meta-analysis, $^{18}$F-FDG uptake was significantly lower in the $EGFR$ mutant group. Thus, studies that reported higher $^{18}$F-FDG uptake for prediction of $EGFR$ mutation in patients with NSCLC were excluded in the DOR analysis. The meta-analysis showed low pooled sensitivity of 70% and specificity of 59% for prediction. The low DOR of 0.68 as well as the likelihood ratio scatter plot indicated that $^{18}$F-FDG PET/CT might not be useful—or, at least, should be used with caution—for predicting $EGFR$ mutations in patients with NSCLC. In addition, the obvious heterogeneity, especially for the main parameters, indicated that the differences between studies cannot be ignored and conclusion should be drawn carefully.

Many efforts have been made to improve prediction efficacy, which may be the direction of future research. More $^{18}$F-FDG PET/CT semi-quantitative parameters including metabolic tumour volume and total glucose glycolysis were investigated to potentially predict $EGFR$ mutations.\(^25,26\) Recent studies also focused on $^{18}$F-FDG PET/CT radiotracers.\(^27,28\) Radiomics refers to the extraction of quantitative characteristics from medical images.\(^29\) The PET/CT-based radiomic characteristics showed good performance in the prediction of $EGFR$ mutations in patients with NSCLC.\(^30,31\) Although the prediction efficacy improved, its clinical application requires additional studies to confirm and optimise. Beyond $^{18}$F-FDG, novel radiotracers have also been investigated. $^{18}$F-MPG PET/CT was demonstrated to be a valid strategy for stratifying patients with NSCLC with $EGFR$-activating mutations for $EGFR$-TKI treatment,\(^32\) but this radiotracer is not routinely available. Other promising studies are under way to translate these novel approaches into the clinic to guide effective precision therapy for patients with NSCLC.

**Strengths and limitations**

The strength of this study is that the conflicting results were first analysed using WMD analysis, so that a more reasonable meta-analysis can be performed on the accuracy of the diagnosis. The high level of heterogeneity is the main limitation. However, this can be addressed using a random effects model. The first area of heterogeneity is related to NSCLC subtypes. LUAD is the main pathological type of NSCLC, but even within LUAD, there are different subtypes. For example, alveolar carcinoma demonstrates relatively low $^{18}$F-FDG uptake. Second, SUV\(_{\text{max}}\) is the most stable and commonly used index, but there are many factors that affect SUV\(_{\text{max}}\), including tumour size, glucose level, and image acquisition and reconstruction, especially for different PET/CT
CONCLUSION
Our meta-analysis results showed that 18F-FDG PET/CT had low pooled sensitivity and specificity for EGFR mutation prediction. The low DOR and the likelihood ratio scatter plot indicated that 18F-FDG PET/CT might not be useful—or, at least, that it should be used with caution—for predicting EGFR mutations in patients with NSCLC.

Contributors
BD is the first author. BD and YL obtained funding. BD, XL and YL designed the study. BD, YC, GL and SW collected and analysed the data. BD drafted the manuscript. BD and YL contributed to the interpretation of the results and critical revision of the manuscript for important intellectual content, and approved the final version of the manuscript. All authors have read and approved the final manuscript. BD and YL are the study guarantors.

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Disclaimer
This study was a systematic review and meta-analysis. Ethics committee approval was not necessary because all data were carefully extracted from existing literature.

Competing interests
None declared.

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Supplemental material
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