

Fecal microbiota transplantation in *Clostridioides difficile* infection and inflammatory bowel diseases - a meta-meta-analysis

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Abstract

Fecal microbiota transplantation (FMT) is an increasingly indicated therapy for intestinal disorders. This meta-meta-analysis aimed to evaluate the clinical outcomes of FMT in ulcerative colitis, Crohn's disease, and recurrent CDI. We searched the PubMed online database for meta-analyses of intestinal disorders. After accounting for overlap, 11 publications on CDI and 13 on inflammatory intestinal diseases were obtained. Based on a meta-meta-analysis of these patients, this study quantified the impact of FMT on clinical outcomes. We combined the effects under the random-effects model and pooled the estimates as odds ratios (OR). In recurrent CDI, clinical remission was identified in 86% of patients in the FMT group *versus* 49% (n=449) in the control group [OR 1.82, CI95% 1.69-1.96, $P < 0.0001$]. Eleven studies included data from patients with ulcerative colitis in clinical remission, identified in 36% (n=903) of patients in the FMT group *versus* 16% (n=217) in the control group [OR 3.58, CI95% 2.99-4.28, $P < 0.0001$]. FMT in patients with Crohn's disease was not different from that in the controls. FMT is a promising therapy for recurrent CDI and ulcerative colitis; however, more clinical trials are needed, as well as standardization of the FMT technique and preparation.

Keywords: fecal microbiota transplant; colitis; ulcerative colitis; Crohn's disease; *Clostridioides difficile*

Trasplante de microbiota fecal en la infección por *Clostridioides difficile* y enfermedades inflamatorias intestinales – un meta-meta-análisis

Resumen

El trasplante de microbiota fecal (TMF) es una terapia cada vez más indicada para los trastornos intestinales. El objetivo de este meta-meta-análisis es evaluar los resultados clínicos del TMF en la colitis ulcerosa, la enfermedad de Crohn y la infección recurrente por *Clostridioides difficile* (CDI). Se realizó una búsqueda en la base de datos PubMed de estudios de metaanálisis sobre trastornos intestinales. Tras considerar la superposición de estudios, se incluyeron 11 publicaciones sobre CDI y 13 sobre enfermedades inflamatorias intestinales. Con base en este meta-meta-análisis, se cuantificó el impacto del TMF en los resultados clínicos. Se combinaron los efectos mediante un modelo de efectos aleatorios y se agruparon las estimaciones como razón de momios (OR). En casos de CDI recurrente, se observó remisión clínica en el 86% de los pacientes tratados con TMF, frente al 49% (n=449) en el grupo control [OR 1.82, IC95% 1.69-1.96, $P < 0.0001$]. Once estudios incluyeron datos de pacientes con colitis ulcerosa, observándose remisión clínica en el 36% (n=903) de los pacientes tratados con TMF frente al 16% (n=217) en el grupo control [OR 3.58, IC95% 2.99-4.28, $P < 0.0001$]. En pacientes con enfermedad de Crohn, el TMF no mostró diferencias significativas respecto al grupo control. El TMF es una terapia prometedora para la CDI recurrente y la colitis ulcerosa, aunque se necesitan más ensayos clínicos y una estandarización de la técnica y preparación del TMF.

Palabras clave: trasplante de microbiota fecal; colitis; colitis ulcerosa; enfermedad de Crohn; *Clostridium difficile*

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Introduction

Clostridioides difficile colonization may reach up to 20% of patients admitted to healthcare institutions (35202793). However, it is estimated that 25% of these patients present with *C. difficile* infection (CDI)¹. Additionally, it is estimated that 1% of hospitalized patients may present with *C. difficile*-related diarrhea during admission².

According to the Infectious Diseases Society of America Guidelines for *C. difficile* treatment, fecal microbiota transplantation (FMT) is recommended for second or subsequent recurrences³. Recurrence may occur in up to 35% of patients, and vancomycin efficacy on CDI is approximately 60%. The indications for FMT have increased, but gastrointestinal disorders remain the most important area of concentrated research. There are some concerns about the ideal time for FMT, but some studies have included early indications of ulcerative colitis (UC)⁴. However, there is controversy regarding the indications for FMT and Crohn's disease (CD)^{5,6}.

Although several systematic reviews and meta-analyses have evaluated the efficacy of fecal microbiota transplantation in gastrointestinal disorders, important limitations remain. Many of these reviews include overlapping primary studies, apply heterogeneous eligibility criteria, and report inconsistent outcomes, particularly for ulcerative colitis and Crohn's disease⁷. These methodological differences hinder direct comparisons and may lead to misinterpretation of the true clinical benefits of FMT. A meta-meta-analytic approach allows for the quantitative synthesis of existing meta-analyses, accounting for overlap while providing a higher-level estimate of effect size. By integrating evidence from multiple reviews, this study seeks to clarify the overall efficacy of FMT in recurrent CDI, ulcerative colitis, and Crohn's disease, thereby offering a more robust and comprehensive perspective to guide clinical decision-making.

Considering the current controversies regarding FMT for gastrointestinal diseases, this study aimed to evaluate the overall efficacy of FMT in gastrointestinal disorders, including CDI, UC, IBS, and CD, using meta-analysis.

Materials and methods

Eligibility criteria

This study was designed according to the PRISMA guidelines (Supplementary material S1). Studies were considered eligible if they were published in English between 2012 and June 2022 (last 10 years), classified as systematic reviews or meta-analyses, and evaluated fecal microbiota transplantation (FMT) in patients with CDI, ulcerative colitis, or Crohn's disease. Studies that did not report extractable data were excluded. For each eligible publication, data were collected on the indication for FMT, route and type of administration, follow-up duration, and reported adverse effects. As this investigation represents a meta-analysis, the quality of the included systematic reviews and meta-analyses was not formally graded.

Information sources and search strategy

Two authors (JC and JT) independently screened the titles and abstracts of systematic reviews and meta-analyses identified in PubMed, Scopus, MEDLINE, EMBASE, and LILACS. Discrepancies in the study selection were resolved by consensus with a third reviewer (FT). The full texts of potentially eligible studies were reviewed to confirm inclusion.

Data collection process

Data extraction was performed independently by two authors using standardized forms. The extracted information included study characteristics, disease type, sample size, route and type of FMT, follow-up duration, and clinical outcomes. Any inconsistencies were discussed and resolved by the senior author.

Data items

The following variables were collected: (i) indication for FMT (recurrent CDI, ulcerative colitis, and Crohn's disease); (ii) route and type of FMT administration; (iii) time of follow-up (minimum and maximum reported); (iv) adverse effects, when available; and (v) measures of clinical remission or response.

Study risk of bias assessment

As this was a meta-meta-analysis, the risk of bias in individual systematic reviews and meta-analyses was not formally graded. Instead, we relied on the published data synthesized in each review.

Effect measures

The primary effect measure was the odds ratio (OR) with 95% confidence intervals (CI) for clinical remission or response after FMT compared with the control groups.

Synthesis methods

Data from eligible meta-analyses were combined using a random-effects model to account for between-study variability. Categorical variables were summarized as percentages. Pooled prevalence and ORs were calculated with corresponding 95% confidence intervals (CIs). Heterogeneity was assessed using the I^2 statistic. In cases of high heterogeneity, the results were interpreted with caution, given the absence of sufficient information to perform subgroup analyses or meta-regression.

Reporting bias assessment

Reporting bias was not formally assessed because no standardized method exists for meta-meta-analyses.

Certainty assessment

The certainty of evidence was not graded, consistent with current recommendations for meta-meta-analyses. Therefore, the results should be interpreted considering the heterogeneity of the included systematic reviews and the variability in FMT protocols.

Statistical analysis

A meta-analysis of the studies was performed using RevMan (Cochrane, revman.cochrane.org). We unified all units of variables, and categorized the variables as percentages. The combined prevalence and 95% confidence intervals (CI) were determined using a random-effects model. A meta-analysis of odds ratios (OR) was performed. Studies were pooled using fixed-effects meta-analytic models to combine odds ratios (ORs) and prevalence with 95% confidence intervals (CIs). The heterogeneity of effect size across trials was established based on I^2 . However, as effect sizes were extracted from published meta-analyses, there was insufficient information to deal with heterogeneity through subgroup analysis or meta-regression. Thus, in the case of a high I^2 , the results should be interpreted with caution. Publication bias was not assessed because there is no standard for meta-meta-analysis.

Results

A total of 4,376 publications were identified in PubMed until June 2022. After title and abstract review, 50 systematic reviews and/or meta-analyses were selected for full-text assessment. Only four studies were eligible for inclusion in this review. Of these, 32 articles were included in the meta-meta-analysis. The first article was published in 2013 and the last in 2021 (flowchart is detailed in Supplementary material S2).

C. difficile infection

Eleven systematic reviews and meta-analyses included articles focused on CDI, first published in 2013 and last in 2021 (8-18). Variability was identified in regard to the number of included studies in the systematic reviews (6 to 34), accounting for a total of 167 studies with 9,496 patients (8,585 in FMT and 911 in comparator regimens). Clinical remission was identified in 86% ($n=7387$) of patients in the FMT group versus 49% ($n=449$) in the control group [OR 1.82, CI95% 1.69-1.96, $P < 0.0001$] (Figure 1).

Inflammatory bowel diseases

Thirteen systematic reviews and meta-analyses included articles focused on inflammatory bowel diseases (IBD), first published in 2014 and last in 2021 (19-30). One article included both types of IBD (UC and CD) and was excluded from the data analysis. The article with the lowest number of studies included four, whereas the highest had 56. The 12 studies accounted for 4,220 patients.

Eleven studies included data from patients with UC, accounting for 3,872 patients (2508 in the FMT; 1364 in the comparator group). Clinical remission was identified in 36% ($n=903$) of patients in the FMT group versus 16% ($n=217$) in the control group [OR 3.58, CI95% 2.99-4.28, $P < 0.0001$] (Figure 2).

Five studies included data from patients with CD, accounting for 348 patients (FMT, $n = 330$; comparator regimens, $n = 18$). Clinical remission was identified in 49% ($n=162$) of patients in the FMT group versus 22% ($n=4$) in the control group [OR 1.40, CI95% 0.36-5.50, $P = 0.48$] (Figure 3).

Across the included reviews, pooled analyses confirmed that FMT is effective in improving clinical remission in recurrent CDI and UC but showed no superiority over standard treatment in CD. The findings were consistent across different meta-analyses, although heterogeneity was observed in the sample size, study design, and FMT protocols. Reporting bias was not formally assessed because standardized methods have not been established for meta-meta-analyses. Some reviews may have been subject to selectively reported outcomes. The certainty of the evidence was not graded. Therefore, the results should be interpreted cautiously, particularly because of the heterogeneity among reviews, variable methodological quality, and differences in FMT techniques and follow-up periods.

Discussion

According to our findings, clinical remission is more likely to occur with FMT than with standard treatment for CDI recurrence. Our results showed that clinical remission was observed in 86% (7,387 patients) of the treatment group and 49% (449 patients) of the control group [OR 1.82, CI95% 1.69-1.96, $P < 0.0001$]. These data provide evidence for the solid effectiveness of FMT in the treatment of CDI, as most publications from our meta-meta-analysis have previously reported¹⁷.

IBD comprises a group of chronic diseases that affect the digestive tract, including UC and CD. The severity and prevalence of IBD have increased over the years. Advanced therapies, including biologics and small molecules, can result in loss of response and limitations, making it important to identify effective treatments for these conditions³¹. This group was classified by disease: UC and CD. Clinical remission in the UC group was observed in 36% (903 patients) of the treatment group and 16% (217 patients) of the control group [OR 3.58, CI95% 2.99-4.28, $P < 0.0001$]. These results indicate that FMT was associated with a significantly higher rate of clinical remission than that of the controls. Complete remission at 8 weeks after FMT is uncommon, but the full Mayo score and Mayo clinical score significantly decreased at week 8³². However, we cannot attribute any efficacy of FMT in severe cases.

In the CD group, clinical remission was observed in 49% (162 patients) of the treatment group and 22% (4 patients) of the control group [OR 1.40, CI95% 0.36-5.50, $P = 0.48$]. These results indicate that there was no significant difference in remission between the two groups, as stated by Cheng, 2021³⁰. The Harvey-Bradshaw Index (HBI) is a score used to evaluate the clinical response in patients with CD. Even though FMT improves HBI in CD, the improvement was not superior to that of standard treatment, suggesting that FMT can be an adjuvant therapy in selected patients³³. Currently, in the IBD field, research on FMT is mostly focused on UC, guided by the evidence included in these systematic reviews and meta-analyses.

Although our pooled results demonstrate the consistent efficacy of FMT in recurrent CDI and UC, the findings for CD were inconclusive. This discrepancy may, in part, reflect the hete-

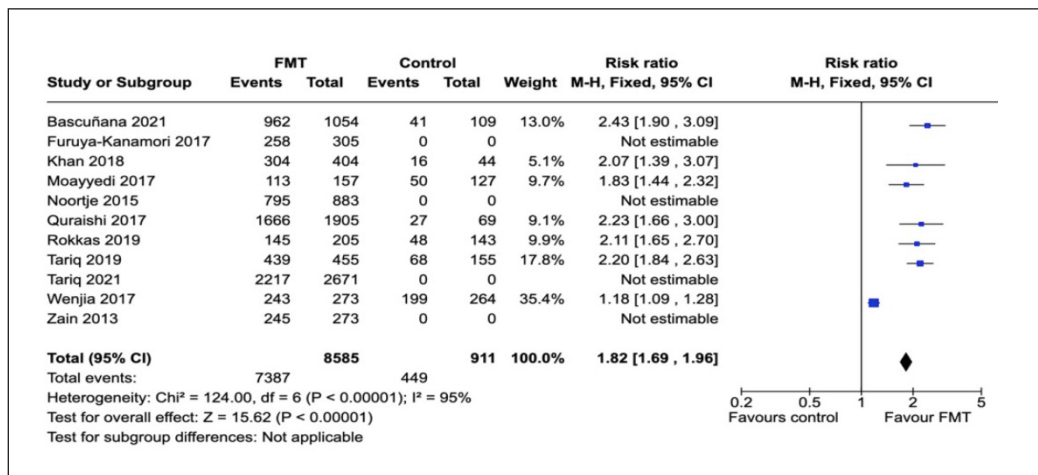


Figure 1. Forest plot of meta-analyses evaluating fecal microbiota transplantation (FMT) for recurrent *Clostridioides difficile* infection (CDI). The figure illustrates the proportion of patients achieving clinical remission in the FMT group compared with those receiving standard antibiotic therapy, with pooled odds ratios and 95% confidence intervals.

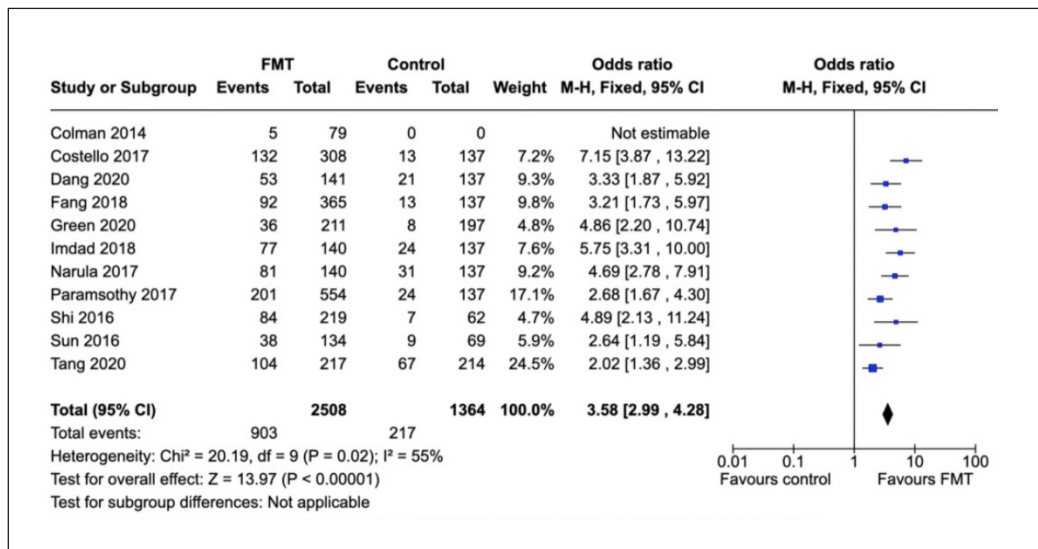


Figure 2. Forest plot of meta-analyses assessing the efficacy of fecal microbiota transplantation in patients with ulcerative colitis (UC). The outcome measured is clinical remission, comparing patients treated with FMT to those receiving standard medical therapy. Pooled estimates are displayed with corresponding odds ratios and 95% confidence intervals.

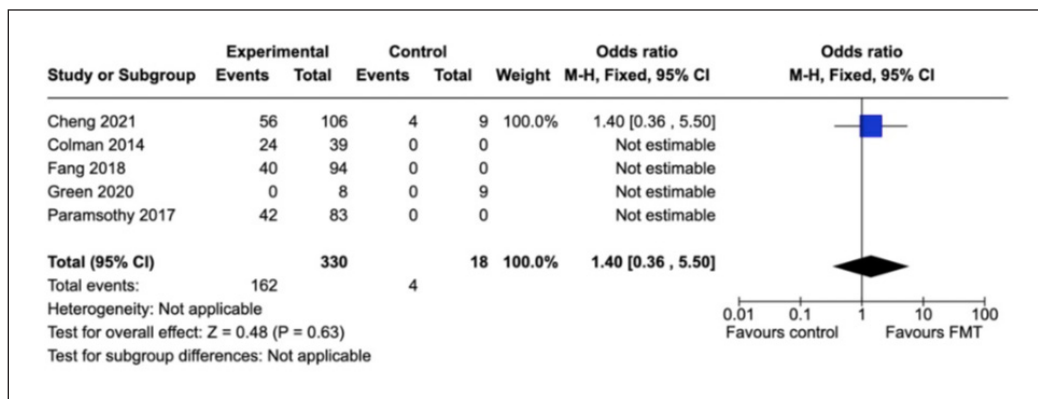


Figure 3. Forest plot summarizing meta-analyses of fecal microbiota transplantation in Crohn's disease (CD). The analysis reports the rates of clinical remission in patients undergoing FMT compared with control groups. Odds ratios and 95% confidence intervals are shown to reflect the overall effect.

ogeneity in treatment protocols and patient characteristics across the included studies. The donor selection criteria, preparation methods (fresh, frozen, or encapsulated stool), and routes of administration (upper vs. lower gastrointestinal delivery) varied considerably, potentially influencing the treatment outcomes. Furthermore, patients with CD typically present with greater clinical heterogeneity than those with UC, including variability in disease location, severity, and history of prior biological or immunosuppressive therapy, which may limit the effectiveness of FMT in this population. In addition, outcome definitions differed across studies, with some assessing clinical remission using patient-reported indices (e.g., Harvey–Bradshaw Index) rather than objective or endoscopic endpoints, thereby complicating cross-study comparisons. Recognizing these sources of heterogeneity is critical for interpreting the apparent differences between UC and CD and underscores the need for standardized FMT protocols and harmonized outcome measures in future trials.

Our study has inherent limitations that need to be interpreted with caution. These limitations include the limited availability of data from meta-analyses and the inability to access certain studies to access certain studies, particularly those published in earlier periods. Limitations regarding the standardization of fecal microbiota protocols should also be considered, such as variability in donor selection criteria, route of infusion, and microbiome standards. In 2023, a commercial fecal microbiota was approved by the *Food and Drug Administration (FDA)* for the treatment of recurrent CDI. However, the cost of this product is very high for some developing countries.

In summary, this meta-meta-analysis demonstrated that FMT leads to increased clinical remission rates in CDI and UC but not in CD and IBS. Several trials testing the efficacy of FMT for different indications are ongoing. Further research can lead to the development and widespread use of fecal microbiota banks, which can help physicians treat challenging and refractory digestive diseases such as CDI and UC.

Ethical considerations

Protection of persons. Not applicable.

Protection of vulnerable populations. Not applicable.

Confidentiality. Not applicable.

Privacy. Not applicable.

Financing. Not applicable.

Conflict of interests. The authors have no conflict of interest to declare.

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Authors' contribution. LHSN: manuscript draft, data review; JFBL: data review; LAFC: data review; JPT, PGK: final review of the manuscript; FFT: statistical analysis and final review. All authors contributed to read and approved the version of the

submitted manuscript.

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Fecal microbiota transplantation in *Clostridioides difficile* infection and inflammatory bowel diseases - a meta-meta-analysis

Trasplante de microbiota fecal en la infección por *Clostridioides difficile* y enfermedades inflamatorias intestinales – un meta-meta-análisis

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The PRISMA guidelines - Supplementary material S1

Table 1. PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	1
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	5
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	5
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	5
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	5-6
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	5-6
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	6

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Section and Topic	Item #	Checklist item	Location where item is reported
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	6
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	6
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	6
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	6
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	6
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	7
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	7
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	7
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	7
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	7
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	7
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	7
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	7
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	7-8
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	7-8
Study characteristics	17	Cite each included study and present its characteristics.	8
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	8
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	8
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	8-9
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	8-9
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	8-9
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	8-9

Section and Topic	Item #	Checklist item	Location where item is reported
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	8-9
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	8-9
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	9
	23b	Discuss any limitations of the evidence included in the review.	10
	23c	Discuss any limitations of the review processes used.	10
	23d	Discuss implications of the results for practice, policy, and future research.	10
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	N/A
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	N/A
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	N/A
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	1
Competing interests	26	Declare any competing interests of review authors.	1
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	1

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ* 2021;372:n71. doi: 10.1136/bmj.n71. This work is licensed under CC BY 4.0. To view a copy of this license, visit <https://creativecommons.org/licenses/by/4.0/>

Flowchart - Supplementary material S2

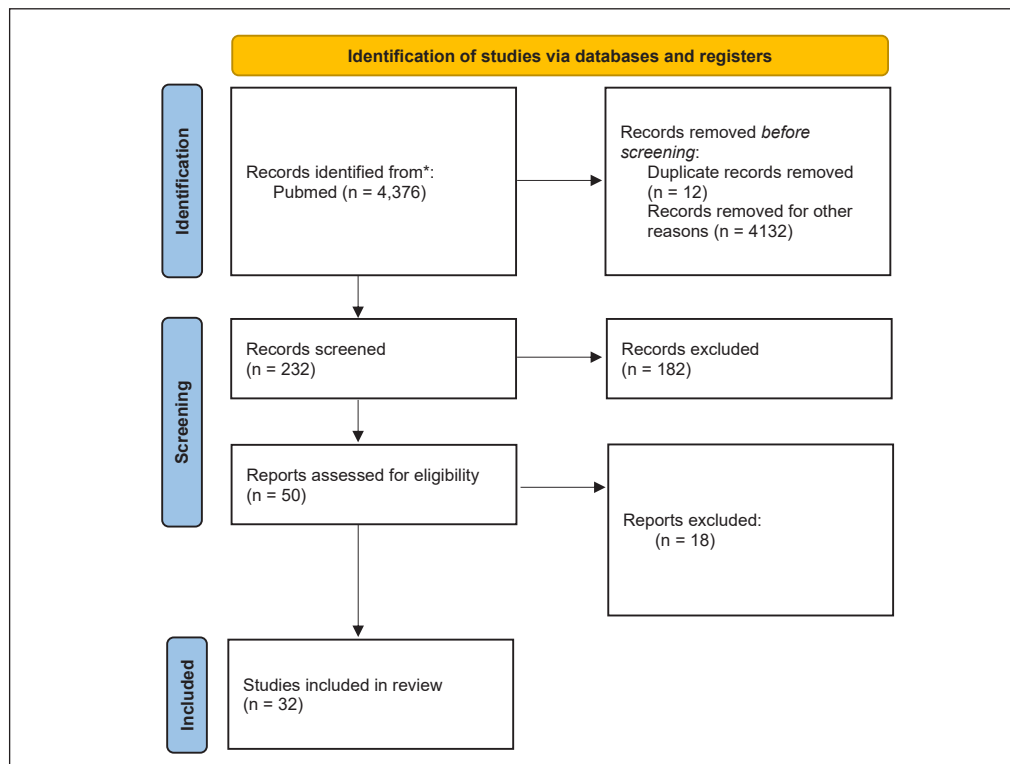


Figure 1. PRISMA 2020 flow diagram for new systematic reviews which included searches of databases and registers only