

REGISTERED REPORT PROTOCOL

Surgical treatment for cryptoglandular and Crohn's perianal fistulas: Protocol of an umbrella review

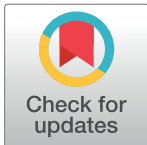
Zubing Mei^{1,2☯‡*}, Qin Feng^{3☯‡}, Peixin Du^{1☯‡}, Bin Li^{4☯‡}, Chenyang Fang¹, Jinghua Gu¹, Yue Li¹, Haikun Zhou¹, Zhuo Shao⁵, Maojun Ge⁶, Yazhou He⁷, Xuejun Yang^{8‡*}, Qingming Wang^{1‡*}

1 Department of Anorectal Surgery, Shuguang Hospital, Shanghai University of Traditional Chinese Medicine, Shanghai, China, **2** Anorectal Disease Institute of Shuguang Hospital, Shanghai, China, **3** Institute of Liver Diseases, Shuguang Hospital, Shanghai University of Traditional Chinese Medicine, Shanghai, China, **4** Department of Neurosurgery, Tongji Hospital, Tongji University School of Medicine, Shanghai, China, **5** Department of General Surgery, Changhai Hospital, The Second Military Medical University, Shanghai, China, **6** Department of General Surgery, Shuguang Hospital, Shanghai University of Traditional Chinese Medicine, Shanghai, China, **7** Usher Institute of Population Health Sciences, The University of Edinburgh, Edinburgh, United Kingdom, **8** Institute of Nephrology, Shuguang Hospital, Shanghai University of Traditional Chinese Medicine, Shanghai, China

☯ These authors contributed equally to this work.

‡ These authors also contributed equally to this work as co-first on this work.

* herrmayor@126.com, herrmayor@shutcm.edu.cn (ZM); yangxuejun@shutcm.edu.cn (XY); davidwqm@163.com (QW)



This is a Registered Report and may have an associated publication; please check the article page on the journal site for any related articles.

OPEN ACCESS

Citation: Mei Z, Feng Q, Du P, Li B, Fang C, Gu J, et al. (2021) Surgical treatment for cryptoglandular and Crohn's perianal fistulas: Protocol of an umbrella review. *PLoS ONE* 16(5): e0251460. <https://doi.org/10.1371/journal.pone.0251460>

Editor: Matteo Rota, Università degli Studi di Brescia, ITALY

Received: November 27, 2020

Accepted: April 23, 2021

Published: May 13, 2021

Copyright: © 2021 Mei et al. This is an open access article distributed under the terms of the [Creative Commons Attribution License](https://creativecommons.org/licenses/by/4.0/), which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

Data Availability Statement: All relevant data are within the paper and its [Supporting information](#) files.

Funding: Dr. Zubing Mei is funded by the National Natural Science Foundation of China (grant no. 81774112), a grant from Siming Scholars from Shuguang Hospital (grant no. SGXZ-201913) and Mrs. Peixin Du is funded by Nursing Research Project of Shuguang Hospital affiliated to Shanghai

Abstract

Introduction

A high prevalence of cryptoglandular and Crohn's perianal fistulas has been reported worldwide, and several surgical options are available for the management of anal fistula, with varying clinical efficacy. However, currently, the available evidence for the effectiveness of these surgical approaches are lacking and of concern in terms of the credibility and strength. The purpose of this study is to evaluate the credibility of the published systematic reviews and meta-analyses that assess the efficacy and safety of the surgical options for cryptoglandular and Crohn's perianal fistulas through an umbrella review.

Methods and analysis

A systematic search in PubMed, Embase and Cochrane library will be performed from inception to December 2020 without any language restriction. We will include systematic reviews and meta-analyses that investigate the efficacy and safety of surgical approaches in the management of cryptoglandular and Crohn's perianal fistulas. Two reviewers will independently screen search results through reading the titles or abstracts. Relevant information will be extracted from each eligible systematic review or meta-analysis. Based on random effects model summary estimates along with their p values, 95% prediction intervals, between-study heterogeneity, small-study effects and excess significance, we will classify the evidence from convincing (class I) to weak (class IV). Findings will be summarized using quantitative synthesis combined with a narrative approach. Cryptoglandular and Crohn's

University of Traditional Chinese Medicine (grant no. 2019SGHL11). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Competing interests: The authors have declared that no competing interests exist.

Abbreviations: AMSTAR2, Assessment of Multiple Systematic Reviews 2; LIFT, ligation of intersphincteric fistula tract; PRISMA-P, Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols; VAAFT, video-assisted anal fistula treatment.

perianal fistulas will be summarized separately. Two authors will independently perform the literature search, data extraction, and quality assessment of each included systematic review and meta-analysis. Any unresolved conflicts or doubts will be resolved by discussion or by consulting a senior author. The risk of bias of the systematic reviews will be assessed using a 16-item Assessment of Multiple Systematic Reviews 2 (AMSTAR2) checklist. The strength of evidence for the included systematic reviews will be classified as "high", "moderate", "low", or "critically low" quality.

Ethics and dissemination

Ethics approval is not required as we will collect data from the published systematic reviews and meta-analyses without using individual patient data. The results of this umbrella review will be published in a peer-reviewed journal and will be presented at an anorectal disease conference.

PROSPERO registration number

CRD42020200754.

Introduction

Anal fistula, also named fistula-in-ano, is a benign anorectal disease characterized by abnormal inflammatory communication between the anal canal and the perianal skin caused by infection and injury of perianal region [1]. In Europe, the estimated incidence of anal fistula is 1.2–2.8 per 10000 people, with a peak incidence between the ages of 20 and 40 years [2, 3]. In China, epidemiological studies show that anal fistula accounts for 1.67% to 3.60% of the incidence of anorectal diseases, with a ratio of male to female of 5–6: 1 [4]. More than 20% of patients with Crohn's disease will develop anal fistula at least once in their life [5, 6], and a considerable number of patients will have recurrent attacks, so perianal fistulas are considered to be a refractory and recurrent disease, which greatly affects the quality of life of patients and places a significant financial burden to those patients [7, 8].

Cryptoglandular and Crohn's perianal fistulas are two types of fistula with similar pathophysiology but distinct etiologies. Cryptoglandular fistulas are caused by cryptoglandular infections, which contribute to abscess formation, whereas Crohn's perianal fistulas are mainly caused by an abnormally activated immune system, which can result in chronic inflammation and deep infection formation.

Surgery is the primary treatment option for both conditions, and several surgical techniques have been used with varying clinical efficacy in terms of recurrence rate and other postoperative complication rate reported in literatures [9–11]. In particular, the difficulty in the surgical treatment of complex anal fistula is primarily due to: (1) the difficulty of accurately locating and treating the internal openings of some types of anal fistulas; (2) the contradiction between drainage and reduction of wound size; (3) the contradiction between complete wound debridement and protection of anal function; (4) the contradiction between sphincter preservation surgery and long-term effects.

At present, the surgical approaches for patients with anal fistula include fistulotomy, seton, video-assisted anal fistula treatment (VAAFT), autologous adipose-derived stem cells (especially for Crohn's fistula-in-ano), mucosal advancement flap, ligation of intersphincteric fistula

tract (LIFT), fibrin sealant, biologic fistula plugs, synthetic fistula plug and fistula tract laser closure [12–15]. They can cure some types of anal fistula on the premise of maximum protection of anal function, but there is a lack of high-quality evidence supporting an optimal procedure for certain types of anal fistula.

Several randomized controlled trials, clinical controlled trials, comparative studies, and subsequently systematic reviews and meta-analyses, have been conducted to investigate the efficacy of surgical-related interventions on the clinical outcomes in patients with both cryptoglandular and Crohn's perianal fistulas [16–20]. Nevertheless, the current evidence is still debatable, and high-quality evidence is required to objectively assess the clinical efficacy of certain interventions, given the rising prevalence of perianal fistulas in patients with and without Crohn's disease. Umbrella reviews offer a similar metric and methodological framework for evaluating systematic reviews with varying populations, interventions, and outcomes. Furthermore, previously reported evidence of low quality has a significant impact on the credibility of effect estimates. The goal of this umbrella review is to systematically review all available evidence on surgical-related interventions in order to quantify their efficacy for people with cryptoglandular and Crohn's perianal fistulas, as well as to assess the strength and credibility of the findings.

Methods and analysis

Protocol registration

The umbrella review will be performed according to the predesigned protocol that has been developed based on the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) guidelines [21] (S1 Table). This project has also been registered with the International Prospective Register of Systematic Reviews (PROSPERO) database (www.crd.york.ac.uk/prospero) under the registration number CRD42020200754. The review is scheduled to be conducted between December 2020 and October 2021.

Data sources and search strategies

We will conduct a comprehensive review of all available reviews on the topic using the methodology described in previous reports [22–24]. Umbrella reviews are defined as systematic overviews of systematic reviews and/or meta-analyses, that can be used to provide a picture of broad health-care field and assess the level of evidence for clinical practice [25].

We will conduct a systematic search of five databases, including PubMed, the Cochrane Database of Systematic Reviews, Embase, Web of Science, and Google Scholar, until December 2020. All systematic reviews, meta-analyses, and pooled analyses that investigate the efficacy and safety of surgical approaches in the management of cryptoglandular and Crohn's perianal fistulas will be included.

Our search strategy will be comprised of the three elements listed below: (1) clinical condition (rectal fistula, anal fistula, anorectal fistula, perianal fistula and fistula-in-ano and Crohn disease); (2) interventions (LIFT, fistulectomy, fistulotomy, rectal advancement flap, anal fistula plug, fibrin glue, seton drainage and mesenchymal stromal cells); and (3) study design (systematic reviews, meta-analyses and pooled analyses), with variations for various databases (S2 Table). We will also look through systematic review registries (www.crd.york.ac.uk/prospero and www.inplasy.com). Unpublished grey literature will not be considered. We will not impose any language restrictions. A manual search of reference lists from relevant studies will be conducted.

EndNote X9 software (Thomson Reuters, Toronto, Ontario, Canada) will be used to remove duplicates and screen for literature. Two authors (ZM and QF) will independently

select the potentially relevant systematic reviews by reading through their titles and abstracts. Any disagreements will be discussed with a senior author (XY) until consensus is reached. When titles and abstracts are insufficient to determine whether to include or exclude reviews, we will download full texts to determine eligibility.

Systematic reviews of randomized controlled trials and controlled clinical trials investigating the efficacy of surgery-related interventions for patients with cryptoglandular or Crohn's perianal fistulas will be included. Cryptoglandular and Crohn's perianal fistulas will be summarized separately. Because we only focus on surgical treatment interventions, systematic reviews of non-interventional studies (i.e., observational studies) will be excluded. Finally, only systematic reviews with quantitative data synthesis will be considered. The systematic reviews will be excluded if study-level effect estimates with 95% CIs cannot be obtained. Based on the umbrella review methodology, when multiple systematic reviews provide duplicated datasets for the same comparison, the systematic review with the greatest number of studies providing study-level effect estimates is retained for further analysis [26]. The following are the detailed inclusion criteria:

Participants

Participants are those who have an established diagnosis of cryptoglandular or Crohn's perianal fistulas based on accepted criteria (such as clinical manifestations and magnetic resonance imaging), without limits on age or gender.

Interventions

Surgical interventions (vs. conventional procedures) for the treatment of cryptoglandular or Crohn's perianal fistulas, such as ligation of intersphincteric fistula tract, fistulectomy, fistulotomy, rectal advancement flap, anal fistula plug, fibrin glue, seton drainage and mesenchymal stromal cells, will be included. Our umbrella review will primarily focus on randomized controlled trials and controlled clinical trials of the aforementioned individual interventions in the treatment of anal fistula, and the interventions of the control group involve the commonly used procedures for anal fistula that are not limited to a specific one.

Outcome measures

Systematic reviews and meta-analyses that report one or more of the following types of outcome measures will be considered:

1. Surgical related symptoms or conditions include: surgical time, postoperative pain, postoperative complications or adverse events such as postoperative pain, bleeding, wound swelling, urinary retention, delayed healing, or healing rate.
2. Anal fistula recurrence: recurrence of anal fistula symptoms or clinical manifestations at the end of follow-up.
3. Patient's satisfaction and functional outcomes: patient quality of life, incontinence rate, time needed for return to work or usual activities and duration of hospital stay.

Data collection and verification

We will develop a standardized form for extracting data from each systematic review. Two authors will collect the variables listed below and cross-check the accuracy of the data. Each primary study will yield the following information: first author, year of publication, number of

included studies, population involved (type of anal fistula), type of surgical interventions, outcome reported, sample size, and study-specific standardized mean differences or weighed mean differences with corresponding 95% CIs for continuous outcomes (i.e. surgical time, postoperative pain, patient quality of life, time required to return to work or usual activities and duration of hospital stay), or relative risks/hazard ratios/odd ratios with corresponding 95% CIs for categorical outcomes (i.e. postoperative complications or adverse events and recurrence of anal fistula).

Critical appraisal

Methodological quality of the included systematic reviews will be assessed by two authors using the Assessment of Multiple Systematic Reviews 2 (AMSTAR2, an updated version of AMSTAR) tool, a 16-item checklist used to critically rate the quality of an individual systematic review as high, moderate, low and critically low based on the total score of the AMSTAR2.

Data analysis

Estimation of summary effect. For each intervention and outcome measure, we will re-estimate the summary effect and the 95% CI using random effects model with the DerSimonian-Laird (inverse variance) method by combining effect estimates from previously published meta-analyses after removing duplicates. Furthermore, we will compare the direction, level of statistical significance and overlapping confidence interval for the summary effects of the association for overlapping meta-analyses that investigate the same relationships between surgical interventions and clinical outcomes in the same clinical setting. In general, we will select the most updated one for further evaluation.

Stratified and subgroup analyses. Stratified analyses will also be performed, with estimates summarized by disease type (cryptoglandular anal fistula vs. Crohn's anal fistula), study design (randomized controlled trials vs. non-randomized controlled trials), total sample size (<500 vs. \geq 500), follow-up period (<12 months vs \geq 12 months), and the combined surgical and medical treatment for Crohn's anal fistula (yes vs. no) across studies.

Heterogeneity analysis. The χ^2 -based Cochran's Q test [27] and Higgins I^2 statistic [28] will be used to test between-study heterogeneity. When the I^2 statistic exceeds 25%, 50%, and 75%, the heterogeneity is considered low, substantial and considerable, respectively.

Estimation of prediction intervals. To account for between-study heterogeneity, the prediction intervals (PIs) and 95% CIs, which are used to show the expected range of true effect estimates in future studies, will also be calculated for the summary random effect estimates [29].

Assessment of small study effects. To investigate small study effects, Egger's regression asymmetry test will be used [30]. In generally, smaller studies provide larger effect estimates than larger studies. In random-effects meta-analysis, a P value \leq 0.10 indicates the presence of small-study effects.

Evaluation of excess significance. The Ioannidis' excess significance test will be evaluated by determining whether the results of the observed number of studies (O) included in each meta-analysis (positive studies, $p < 0.05$) differ significantly from the expected number of studies with significant results (E). To estimate the statistical power of each individual study, we will use the effect size of the largest study (smallest SE) in the included meta-analysis [31]. Excess statistical significance will be determined for each individual meta-analysis at two-sided $p < 0.10$ with O greater than E when the statistical significance threshold is considered.

Grading the evidence

We will use the following criteria to evaluate the credibility of the included meta-analyses:

Convincing evidence (class I). > 1000 cases, significant combined associations for random-effects calculation ($p < 10^{-6}$), no evidence of small-study effects, no evidence of excess of significance, 95% prediction intervals excluding the null value and not large between-study heterogeneity ($I^2 < 50\%$);

Highly suggestive evidence (class II). > 1000 cases, significant combined associations for random-effects calculation ($p < 10^{-6}$), and the largest study with 95% CI excluding the null value;

Suggestive evidence (class III). > 1000 cases and significant combined associations for random-effects calculation ($p < 10^{-3}$);

Weak evidence (class IV). Other associations with $p < 0.05$; non-significant associations: Associations with $p > 0.05$ [32–34].

We will conduct all statistical analyses with the STATA V.15.1 software (StataCorp, College Station, Texas, USA).

Discussion

By incorporating evidence from published systematic reviews and meta-analyses, we will provide a comprehensive overview of the summary effects of various surgery-related interventions on the clinical efficacy of patients with cryptoglandular and Crohn's perianal fistulas.

With the increasing prevalence of perianal fistulas of both cryptoglandular and Crohn's disease origin, the general population bears a significant socioeconomic burden. We will assess the level of evidence for the efficacy of common anal fistula surgical techniques used worldwide, such as ligation of the intersphincteric fistula tract, fistulectomy, fistulotomy, rectal advancement flap, anal fistula plug, fibrin glue, seton drainage, and mesenchymal stromal cells.

To the best of our knowledge, this is the first comprehensive review that summarizes the efficacy of various surgical techniques for cryptoglandular and Crohn's perianal fistulas. When sufficient high-quality data are available, we will stratify our comparisons by type of anal fistula, which will provide surgeons with high-level evidence to help them choose the best surgical technique for these patients. To account for between-study heterogeneity and provide more objective and convincing results in a future study examining the same association, 95% prediction intervals will be estimated. Furthermore, we will only include data from previously published systematic reviews and meta-analyses, which will have a higher level of evidence for this topic.

When we incorporate the high-level evidence of surgery interventions for perianal fistula from our findings, we can provide important information on clinical guidelines and therapeutic selection for those patients, such as the benefits of LIFT procedure and rectal advancement flap on the postoperative functional outcomes. Our umbrella review will have limitations as well. The included systematic reviews vary in their heterogeneity and quality. As a result, random effects meta-reanalyses will be performed for each outcome. In addition, we will use the AMSTAR 2 checklist to assess the quality of each included study.

The findings of this umbrella review will be published in a peer-reviewed journal, and we believe that the result will benefit anorectal surgeons, patients and policy-makers.

Supporting information

S1 Table. PRISMA-P checklist.

(DOC)

S2 Table. Search strategy for Pubmed.
(DOCX)

Acknowledgments

The protocol for this systematic review will be amended when necessary.

Author Contributions

Conceptualization: Zubing Mei, Qingming Wang.

Data curation: Zubing Mei, Qin Feng, Peixin Du, Bin Li, Chenyang Fang, Jinghua Gu, Yue Li, Haikun Zhou, Zhuo Shao, Maojun Ge, Yazhou He, Xuejun Yang, Qingming Wang.

Formal analysis: Zubing Mei, Qin Feng, Peixin Du, Bin Li, Chenyang Fang, Jinghua Gu, Yue Li, Haikun Zhou, Maojun Ge, Yazhou He, Xuejun Yang, Qingming Wang.

Funding acquisition: Zubing Mei, Zhuo Shao.

Investigation: Zubing Mei, Qin Feng, Peixin Du, Bin Li, Yue Li, Haikun Zhou, Maojun Ge, Xuejun Yang.

Methodology: Zubing Mei, Qin Feng, Bin Li, Chenyang Fang, Jinghua Gu, Yue Li, Haikun Zhou, Zhuo Shao, Maojun Ge, Yazhou He, Xuejun Yang, Qingming Wang.

Project administration: Zubing Mei.

Resources: Zubing Mei, Peixin Du.

Software: Zubing Mei, Bin Li.

Supervision: Zubing Mei.

Validation: Zubing Mei, Qin Feng, Peixin Du, Bin Li, Jinghua Gu, Yue Li, Zhuo Shao, Yazhou He, Xuejun Yang, Qingming Wang.

Visualization: Zubing Mei, Yazhou He, Xuejun Yang, Qingming Wang.

Writing – original draft: Zubing Mei, Qingming Wang.

Writing – review & editing: Zubing Mei, Qingming Wang.

References

1. (2007) Benign Anorectal: Abscess and Fistula. In: Wolff BG, Fleshman JW, Beck DE, Pemberton JH, Wexner SD et al., editors. The ASCRS Textbook of Colon and Rectal Surgery. New York, NY: Springer New York. pp. 192–214.
2. García-Olmo D, Van Assche G, Tagarro I, Diez MC, Richard MP, et al. (2019) Prevalence of Anal Fistulas in Europe: Systematic Literature Reviews and Population-Based Database Analysis. *Advances in therapy* 36: 3503–3518. <https://doi.org/10.1007/s12325-019-01117-y> PMID: 31656013
3. Hokkanen SR, Boxall N, Khalid JM, Bennett D, Patel H (2019) Prevalence of anal fistula in the United Kingdom. *World journal of clinical cases* 7: 1795–1804. <https://doi.org/10.12998/wjcc.v7.i14.1795> PMID: 31417925
4. Li J, Yang W, Huang Z, Mei Z, Yang D, et al. (2016) [Clinical characteristics and risk factors for recurrence of anal fistula patients]. *Zhonghua Wei Chang Wai Ke Za Zhi* 19: 1370–1374. PMID: 28000193
5. Marzo M, Felice C, Pugliese D, Andrisani G, Mocci G, et al. (2015) Management of perianal fistulas in Crohn's disease: an up-to-date review. *World journal of gastroenterology* 21: 1394–1403. <https://doi.org/10.3748/wjg.v21.i5.1394> PMID: 25663759
6. Safar B, Sands D (2007) Perianal Crohn's disease. *Clinics in colon and rectal surgery* 20: 282–293. <https://doi.org/10.1055/s-2007-991027> PMID: 20011424

7. de Zoeten EF, Pasternak BA, Mattei P, Kramer RE, Kader HA (2013) Diagnosis and treatment of perianal Crohn disease: NASPGHAN clinical report and consensus statement. *J Pediatr Gastroenterol Nutr* 57: 401–412. <https://doi.org/10.1097/MPG.0b013e3182a025ee> PMID: 23974063
8. Gold SL, Cohen-Mekelburg S, Schneider Y, Steinlauf A (2018) Perianal Fistulas in Patients With Crohn's Disease, Part 2: Surgical, Endoscopic, and Future Therapies. *Gastroenterology & hepatology* 14: 521–528.
9. Wang Q, He Y, Shen J (2017) The best surgical strategy for anal fistula based on a network meta-analysis. *Oncotarget* 8: 99075–99084. <https://doi.org/10.18632/oncotarget.21836> PMID: 29228753
10. Tao Y, Han JG, Wang ZJ, Zheng Y, Cui JJ, et al. (2020) [Long-term effect of anal fistula plug treatment on postoperative anal function in patients with trans-sphincteric perianal fistula and risk factors associated with anal function]. *Zhonghua Wei Chang Wai Ke Za Zhi* 23: 774–779. <https://doi.org/10.3760/cma.j.cn.441530-20190424-00184> PMID: 32810949
11. Brabender DE, Moran KL, Brady M, Carmichael JC, Mills S, et al. (2020) Assessing the effectiveness of laser fistulectomy for anal fistula: a retrospective cohort study.
12. Clark SK (2020) Video-assisted anal fistula treatment for complex anal fistula: a long-term follow-up study. *Giarratano et al. Colorectal Dis* 22: 856. <https://doi.org/10.1111/codi.15222> PMID: 32749773
13. Zhou C, Li M, Zhang Y, Ni M, Wang Y, et al. (2020) Autologous adipose-derived stem cells for the treatment of Crohn's fistula-in-ano: an open-label, controlled trial. *Stem Cell Res Ther* 11: 124. <https://doi.org/10.1186/s13287-020-01636-4> PMID: 32183875
14. Samalavicius NE, Klimasauskiene V, Nausiediene V, Cereska V, Dulskas A (2020) The LIFT (ligation of the intersphincteric fistula tract) procedure for a transsphincteric posterior anal fistula—a video vignette.
15. de la Portilla F, Muñoz-Cruzado MVD, Maestre MV, García-Cabrera AM, Reyes ML, et al. (2019) Platelet-rich plasma (PRP) versus fibrin glue in cryptogenic fistula-in-ano: a phase III single-center, randomized, double-blind trial. *Int J Colorectal Dis* 34: 1113–1119. <https://doi.org/10.1007/s00384-019-03290-6> PMID: 31037566
16. Emile SH, Khan SM, Adejumo A, Koroye O (2020) Ligation of intersphincteric fistula tract (LIFT) in treatment of anal fistula: An updated systematic review, meta-analysis, and meta-regression of the predictors of failure. *Surgery* 167: 484–492. <https://doi.org/10.1016/j.surg.2019.09.012> PMID: 31648932
17. Cheng F, Huang Z, Li Z (2019) Mesenchymal stem-cell therapy for perianal fistulas in Crohn's disease: a systematic review and meta-analysis. *Tech Coloproctol* 23: 613–623. <https://doi.org/10.1007/s10151-019-02024-8> PMID: 31286287
18. Stellingwerf ME, van Praag EM, Tozer PJ, Bemelman WA, Buskens CJ (2019) Systematic review and meta-analysis of endorectal advancement flap and ligation of the intersphincteric fistula tract for cryptoglandular and Crohn's high perianal fistulas. *BJS Open* 3: 231–241. <https://doi.org/10.1002/bjs5.50129> PMID: 31183438
19. Choi S, Jeon BG, Chae G, Lee SJ (2019) The clinical efficacy of stem cell therapy for complex perianal fistulas: a meta-analysis. 23: 411–427.
20. Lightner AL, Wang Z, Zubair AC, Dozois EJ (2018) A Systematic Review and Meta-analysis of Mesenchymal Stem Cell Injections for the Treatment of Perianal Crohn's Disease: Progress Made and Future Directions. *Dis Colon Rectum* 61: 629–640. <https://doi.org/10.1097/DCR.0000000000001093> PMID: 29578916
21. Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, et al. (2015) Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Systematic Reviews* 4: 1. <https://doi.org/10.1186/2046-4053-4-1> PMID: 25554246
22. Aromataris E, Fernandez R, Godfrey CM, Holly C, Khalil H, et al. (2015) Summarizing systematic reviews: methodological development, conduct and reporting of an umbrella review approach. *Int J Evid Based Healthc* 13: 132–140. <https://doi.org/10.1097/XEB.0000000000000055> PMID: 26360830
23. Markozannes G, Aretouli E, Rintou E, Dragioti E, Damigos D, et al. (2017) An umbrella review of the literature on the effectiveness of psychological interventions for pain reduction. *BMC psychology* 5: 1–16. <https://doi.org/10.1186/s40359-016-0170-z> PMID: 28081723
24. Khan SU, Khan MU, Riaz H, Valavoor S, Zhao D, et al. (2019) Effects of nutritional supplements and dietary interventions on cardiovascular outcomes: an umbrella review and evidence map. *Annals of internal medicine* 171: 190–198. <https://doi.org/10.7326/M19-0341> PMID: 31284304
25. Biondi-Zoccai G (2016) Umbrella reviews. Evidence synthesis with overviews of reviews and meta-epidemiologic studies Cham, Switzerland: Springer International.
26. Ioannidis JP (2009) Integration of evidence from multiple meta-analyses: a primer on umbrella reviews, treatment networks and multiple treatments meta-analyses. *Cmaj* 181: 488–493. <https://doi.org/10.1503/cmaj.081086> PMID: 19654195

27. Cochran WG (1954) The combination of estimates from different experiments. *Biometrics* 10: 101–129.
28. JPT H GS (2018) *Cochrane handbook for systematic reviews of interventions version 5.1.0* [updated March 2011]: The Cochrane Collaboration; 2011. www.handbook.cochrane.org.
29. Riley RD, Higgins JP, Deeks JJ (2011) Interpretation of random effects meta-analyses. *Bmj* 342. <https://doi.org/10.1136/bmj.d549> PMID: 21310794
30. Egger M, Smith GD, Schneider M, Minder C (1997) Bias in meta-analysis detected by a simple, graphical test. *Bmj* 315: 629–634. <https://doi.org/10.1136/bmj.315.7109.629> PMID: 9310563
31. Ioannidis JP, Trikalinos TA (2007) An exploratory test for an excess of significant findings. *Clinical trials* 4: 245–253. <https://doi.org/10.1177/1740774507079441> PMID: 17715249
32. Guyatt G, Oxman AD, Akl EA, Kunz R, Vist G, et al. (2011) GRADE guidelines: 1. Introduction-GRADE evidence profiles and summary of findings tables. *J Clin Epidemiol* 64: 383–394. <https://doi.org/10.1016/j.jclinepi.2010.04.026> PMID: 21195583
33. He Y, Li X, Gasevic D, Brunt E, McLachlan F, et al. (2018) Statins and Multiple Noncardiovascular Outcomes: Umbrella Review of Meta-analyses of Observational Studies and Randomized Controlled Trials. *Ann Intern Med* 169: 543–553. <https://doi.org/10.7326/M18-0808> PMID: 30304368
34. Kavanagh BP (2009) The GRADE system for rating clinical guidelines. *PLoS Med* 6: e1000094. <https://doi.org/10.1371/journal.pmed.1000094> PMID: 19753107