

# Effect of Probiotic, Prebiotic, or Synbiotic Supplement on Children, Adolescents, or Infants: A Protocol of an Umbrella Review

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## Protocol

**Keywords:** probiotic, prebiotic, synbiotic, children, adolescents, Infants, umbrella review, AMSTAR-2, GRADE, CCA

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# Abstract

**Background:** Many systematic reviews and meta-analyses have studied the association between probiotics, prebiotics, or synbiotics and children, adolescents, or Infants. With the promotion of probiotics, prebiotics, or synbiotics in our life and medical practice, more and more attention has been paid to them. Therefore, it is necessary to make a systematic summary of them. When the information was obtained in the identified systematic review, it will be compared with a control group that do not use probiotics, prebiotics, or synbiotics. In addition, our aim is to assess the quality of the included systematic reviews.

**Methods:** We will conduct a comprehensive systematic search by summarizing systematic reviews of randomized controlled trials which have studied effect of probiotic, prebiotic, or synbiotic supplement on children, adolescents, or Infants. Four electronic databases (Embase, PubMed, Medline, and Cochrane Database of Systematic Reviews) will be searched. Two reviewers will independently screen the retrieved papers. Two reviewers will independently extract the data by reference to the JBI Data Extraction Form for Review for Systematic Reviews and Research Syntheses. We will also assess methodological quality and assessment of certainty in the findings by A Measurement Tool to Assess Systematic Review version 2 (AMSTAR-2) and the GRADE (Grading of Recommendations Assessment, Development and Evaluation). We will calculate the corrected covered area (CCA). We will recalculate the summary effect and 95% CIs by using fixed-effect or random-effect models.

**Discussion:** Through quantitative and qualitative comparison by conducting an umbrella review, we hope our results will service better for future clinical practice.

**Systematic review registration:** This protocol have finished the registration in the International Prospective Register of Systematic Reviews (PROSPERO) (registration number: CRD42021244923).

## Background

Probiotic refers to live microorganisms that confer a health benefit on the host when administered in adequate amounts. [1] Prebiotic is defined as a substrate that is selectively utilized by host microorganisms conferring a health benefit.[2] The latest definition of a synbiotic is that a mixture of living microorganisms and substrate(s) that is selectively utilized by host microorganisms for the benefit of host health.[3] It is all acknowledged that probiotic, prebiotic, and synbiotic can together modulate gut microbiota and are widely used to prevent or treat diseases on children, adolescents, or Infants.[4]

According to the reporting from the European Society for Paediatric Gastroenterology Hepatology and Nutrition Committee on Nutrition and the European Society for Paediatric Gastroenterology Hepatology, probiotics have a positive effect on promoting the health of premature infants.[5] Probiotic plus prebiotic supplementation or synbiotic supplementation can contribute to reducing necrotizing enterocolitis morbidity in premature infants, and the combination of probiotics and prebiotics or synbiotic supplementation may bring better efficacy in premature infants when compared with single strain. [6] Bi LW [7] also agreed that the mixture of probiotic can better decrease the incidences of necrotizing enterocolitis, gut-associated sepsis, and mortality in preterm infants than single strains. What's more, by conducting an overview, Xiong T[8] found that a combination of probiotics could reduce the risk of necrotizing enterocolitis in preterm Infants and certainty evidence is moderate. The underlying mechanism may be that combination can better balance gut microecology disrupted by antibiotic treatment or defects in the development of congenital gut microbes.

Probiotics and prebiotics can pose successful defense against respiratory virus infection.[9] Based on the gut–lung axis theory, probiotic and prebiotic supplements can decrease the incidence of upper respiratory tract infections and shorten the disease duration. In addition, according to Carty's reporting[10], they thought that synbiotic supplements can better protect human from suffering from respiratory tract infections than single use of probiotics or prebiotics. Anastasia[11] also agreed that by manipulating upper respiratory tract microbiome, Infants may have better outcome after exposed to respiratory tract infection. By conducting a meta-analysis of randomized controlled trials, Minmin Su[12] found that probiotics can significantly reduce the incidence of Ventilator-associated pneumonia, which further prove that probiotic supplements could be useful for treating respiratory tract infection.

Probiotics supplementation can pose a positive effect on ameliorating the increasing of weight in human.[13-15] Ruth Baron [16] held that infant antibiotic exposure can result in disrupting balance of the gut microbiota, further causing the increasing of overweight or obesity in children. By following the birth cohort of 165 children and their mothers, Stanislawski [17] found that the gut microbiota in the two years before birth can predict the risk of obesity at age 12, potentially offering an opportunity to prevent childhood obesity. By summarizing the effect of probiotics on body weight and other obesity-related anthropometric measures in overweight and obese patients, Simone Perna[13] found that by modulating the gut microbiota, probiotics supplementation may effectively reduce body mass Index (BMI), waist circumference (WC), and hip circumference (HC), further proving that probiotics supplementation can effectively treat respiratory tract infections.

Some researchers have proposed that probiotics may prevent the development of allergic diseases in children. By conducting Meta-analysis, Pelucchi C [18] and Yin DG[19] both agreed that the use of probiotics in pregnancy and infancy can reduce the risk of Atopic Dermatitis. Tan-Lim CSC [20] found that mixture of *Lactobacillus paracasei* ST11, *Bifidobacterium longum* BL999), and LP (*Lactobacillus paracasei* ssp *paracasei* F19), or mixture of *Lactobacillus rhamnosus* GG and *Bifidobacterium animalis* ssp *lactis* Bb-12 could decrease the risk of atopic dermatitis in children. However, their included literature are major low-quality evidence, reducing credibility with their results. Sorensen K[21] believed that compared with the amino acid formula alone, the hospitalization rate and overall drug use (including antimicrobial agents and antibiotics) of infants allergic to milk protein were lower in the amino acid formula containing synbiotics. However, there are some controversies between different researchers. Sestito S [22] didn't recommend pre/probiotic supplements as preventive treatment for allergic disease. Due to the low evidence about probiotic supplents, EAACI guideline[23] objected to the use of prebiotics, probiotics or synbiotics in pregnancy, when breastfeeding or in infancy for preventing food allergy. EAACI guidelines[24] do not address whether the use of probiotics, probiotics or synbiotics in adolescents and young adults with allergies and asthma can be considered an effective transitional treatment.

There are still many other diseases that probiotics, prebiotics or synbiotics can be used to treat on children, adolescents, or Infants, such as infantile colic[25]. However, there are different arguments about the role of probiotics, probiotics or synbiotics to treat the same disease. Allen SJ[26] held probiotics can effectively shorten the duration and reduce stool frequency in acute infectious diarrhoea. In contrast, Collinson S[27] held that probiotics may have little effect on diarrhea lasting 48 hours or more. In addition, probiotics have a broad impact on the treatment of diseases, so it is necessary for us to make a comprehensive summary of the role of probiotics in the human body. More importantly, we are not sure about the quality of the literature, so to use authoritative evaluation tools to examine the quality level of the literature is imperative.

However, there is no comprehensive and systematic umbrella review of the existing literature on the effects of probiotics, probiotics or symbiotic supplements on children, adolescents or infants. Such an umbrella review of existing systematic reviews will not only contribute to make a thorough discussion about the effect of probiotic, prebiotic, or synbiotic supplementation on children, adolescents, or Infants, but will also help assessing the quality of the existing evidence.

## **Objective**

To assimilate the large amount of literature available on effect of probiotic, prebiotic, or synbiotic supplementation on children, adolescents, or Infants, we plan to conduct an umbrella review of meta-analyses of randomized controlled trial. Furthermore, we will evaluate the quality of the included systematic reviews, in hope for providing reliable evidence for clinical practice.

## **Methods**

We will implement this protocol according to PRISMA-P [Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols] guidelines[28] (see Additional file 1). We have completed the registration of this protocol in PROSPERO (International Prospective Register of Systematic Reviews; registration number: CRD42021244923 ). We will update the modification of the protocol at any time in the future.

## **Search strategy**

We will search in Embase, PubMed, Medline, and Cochrane Database of Systematic Reviews from the time between the establishment of the database and the formal start of retrieval. We will manually search for references to eligible papers. We will only include English literature.

We will search following terms: (1) Probiotic, Prebiotic, and synbiotics; (2) Child, Adolescent, and infants; (3) metanalysis\*[tw] OR meta-analys\*[tw]; (4) randomized controlled trial. Taking PubMed as an example, the detailed search terms are listed in Table 1 below.

Table 1: the search strategy for PubMed

#1	Probiotic OR Probiotics OR Prebiotic OR Prebiotics OR synbiotics OR Synbiotic
#2	Children OR Child OR PRESCHOOL OR Preschool Child OR Children, Preschool OR Preschool Children OR Adolescent OR Adolescents OR Adolescence OR Teens OR Teen OR Teenagers OR Teenager OR Youth OR Youths OR Adolescents, Female OR Adolescent, Female OR Female Adolescent OR Female Adolescents OR Adolescents, Male OR Adolescent, Male OR Male Adolescent OR Male Adolescents OR Infant OR Infants
#3	metanalysis*[tw] OR meta-analys*[tw]
#4	“randomized controlled trial” OR “clinical trial” OR RCT OR “Clinical Trials” OR “controlled trial” OR “Intervention Study” OR “Intervention Studies” OR randomized OR “randomized controlled trial” or random
#5	#1 AND #2 AND #3 AND #4

### Eligibility criteria

We will only include meta-analysis of randomized controlled trials which explored the effect of probiotic, prebiotic, and synbiotics on children, adolescents, or Infants. We will only consider articles that meet the following criteria:

1. We will consider including populations who are under the age of 18.
2. The difference between the experimental group and the control group is the presence or absence of probiotics, prebiotic, or synbiotic intervention. We will exclude these studies if the effect sizes observed are not related to the effect of probiotics, prebiotic, or synbiotic.
3. We will also exclude meta-analyses that do not report the necessary data, such as the relative risk (RR), effective rate, or odds ratio risk (OR) and 95% confidence intervals (CI).
4. Meta-analyses of randomized controlled trials that are published in full-text format and in English comply with systematic review criteria. We will include other grey literature sources. We will not include network meta-analysis, letter to the editor, abstract, protocols, or conference poster. We will also exclude literature where complete data are unavailable after connecting with the author.

In order to include the relevant literature as comprehensively as possible, we will not set a limit for the publication date. Systematic reviews conducted by different authors are likely to contain partially overlapping literature if the exposures and results of these studies are the same, leading to biased conclusions.[29] In addition, the median updating time of such literature are 5.5 years for the systematic review.[30] Referencing the criteria of the previous umbrella review, [31] we the literature into two categories, namely, outdated (more than 6 years after the beginning of our search) and current (less than 6 years after the beginning of our search). If there are multiple different studies evaluating the same exposures and outcomes, and some of these studies are outdated and some are current, we will exclude the outdated studies during the full-text screening phase. If multiple articles evaluating the same exposures and outcomes are only outdated or not, we will calculate the degree of overlap by the corrected covered area (CCA). [29] The method used to calculate CCA will refer to previously published literature.[29, 31] We will express CCA by percentage, and the specific formula is  $(N - r) / (rc - r)$ , where N means the number of primary literature included in the systematic review, r is the number of rows, and c is the number of columns.[29] See the table 2 for specific examples.

table 2: the example for calculating CCA

	Review 1	Review 2	Review 3	Review 4
Primary literature 1	☐	☐	☐	
Primary literature 2	☐	☐	☐	☐
Primary literature 3	☐	☐	☐	☐
Primary literature 4	☐		☐	☐
Primary literature 5	☐	☐	☐	☐
Primary literature 6	☐	☐	☐	
Primary literature 7	☐	☐		

$CCA = (23-7) / (7*4-7) = 76.19\%$

And we will divide CCA into the following levels: very high (CCA >15%), high (CCA 11-15%), moderate (CCA 6-10%), or slight (CCA 0-5%).[29]

We will generate a graphical crossover table (citation matrix) that overlaps the systematic reviews as columns and the primary literature included in these systematic reviews as rows.[29] The selection criteria for overlapping systematic review after review are as follows: [31]

1. We will include all non-overlapping systematic review. For overlapping systematic review, we will first include the non-obsolete Cochrane literature.[32] By examining the effects of different inclusion criteria on the comprehensiveness and complexity of medical intervention reviews, some researchers concluded that the data obtained from the Cochrane review was the most comprehensive, and that the quality of Cochrane reviews was higher than that of systematic reviews in other journals. [31, 33]

2. IF there are a high degree of overlap (CCA ≥11%) between two or more reviews, we will select reviews as following grading criteria: the rating is highest or moderate quality by reference to the AMSTAR 2 quality assessment tool; most recent; pooled effect estimates or a meta-analysis is provided; and the number of studies or participants is the highest.[31, 32]

3. For a slight or moderate degree of overlap (CCA ≤10%), we will retain both reviews, and further compare their results.[31]

### Literature screening

Two reviewers will independently select literature by reading the titles and abstracts. After removing articles by reading the titles and abstracts, we will further find the full text for the remained articles. Discrepancy will be solved by discussing with a third reviewer. we will handle the screening of studies in EndNote.

### Data extraction and data synthesis

Two reviewers will extract the corresponding content by reference to the JBI Data Extraction Form for Review for Systematic Reviews and Research Syntheses.[34] (see Additional file 2) We will extract the following data items: first author's name, publication year, name of diseases, the number of studies included in meta-analyses, total sample size, cases and controls, interventions, the dose of intervention, effect sizes and the corresponding 95% confidence interval, publication bias, and heterogeneity. The data will be analyzed by means of Epi Info (V.7.2) after we have entered the information.

We will recalculate the summary effect and 95% CIs using fixed-effect or random-effect models. The  $I^2$  statistic or Cochran's Q test will be used to determine the magnitude of heterogeneity. For Cochran's Q test, the result will be considered as significant heterogeneity when  $p < 0.1$ ; for the  $I^2$  statistic, the result will be classified as significant heterogeneity when  $50\% \leq I^2$ . The 95% prediction interval (95% PI) for the effect size will be assessed. Publication bias and small-study effect will be estimated by Egger's test (a p value < 0.1) or Begg's test (a p value < 0.1). All statistical analyses will be conducted using Review Manager

(RevMan, version 5.3 for Macintosh; The Cochrane Collaboration) and the statistical package PASW 20.0 for Macintosh (SPSS Inc.). If possible, we will conduct sensitivity, subgroup analyses, or meta-regression.

### **Assessment of methodological quality and assessment of certainty in the findings**

Methodological quality will be assessed by checking A Measurement Tool to Assess Systematic Review version 2 (AMSTAR-2), [35] which including 16 items (7 critical domains and 9 non-critical domains). We will categorize the results as high, moderate, low, and critically low after assessing the methodological quality by AMSTAR-2.[35] The specific classification criteria are as follows: No or 1 non-critical weakness will be appraised as high; more than 1 non-critical weakness will be appraised as moderate; 1 critical flaw with or without non-critical weakness will be appraised as low; if more than 1 critical flaw with or without non-critical weakness will be appraised as critically low.

In addition, we will take the GRADE (Grading of Recommendations Assessment, Development and Evaluation)[36] approach to assess the strength of evidence. The strength of evidence will be classified as high, moderate, low or very low.[36, 37]

## **Discussion**

We will summarize the evidence on the probiotic, prebiotic, or synbiotic supplementation for the treatment of diseases on children, adolescents, or Infants by conducting an umbrella review. An umbrella review is a tool which could better compare and contrast the findings of reviews related to a review question, which could make it easier for decision makers to select evidence of higher quality.[34] We will also evaluate the quality of the systematic review by AMSTAR-2 and the GRADE. In addition, we will evaluate the degree of overlap by calculating

CCA. Through quantitative and qualitative comparison, we hope that our results will provide a better basis for future clinical practice.

## **Declarations**

### **Ethics and dissemination**

This is an umbrella review. We do not conduct any experiments on humans or animals, so we will not consider an ethical review. We will open the results of the umbrella review in a peer-reviewed journal.

### **Contributors**

Chen Qiu will be the guarantor of the whole umbrella review. Shunlian Fu will be responsible for designing the structure of the whole umbrella review. This protocol was written after all authors discussed it. All authors agreed to publish this article.

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### **Competing interests None declared.**

All authors declared no competing interests.

### **Patient consent for publication**

Not required.

## Provenance and peer review

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## References

1. Hill C, Guarner F, Reid G, Gibson GR, Merenstein DJ, Pot B, Morelli L, Canani RB, Flint HJ, Salminen S, et al. Expert consensus document. The International Scientific Association for Probiotics and Prebiotics consensus statement on the scope and appropriate use of the term probiotic. *Nat Rev Gastroenterol Hepatol.* 2014;11(8):506–14. doi:10.1038/nrgastro.2014.66.
2. Gibson GR, Hutkins R, Sanders ME, Prescott SL, Reimer RA, Salminen SJ, Scott K, Stanton C, Swanson KS, Cani PD, et al. Expert consensus document: The International Scientific Association for Probiotics and Prebiotics (ISAPP) consensus statement on the definition and scope of prebiotics. *Nat Rev Gastroenterol Hepatol.* 2017;14(8):491–502. doi:10.1038/nrgastro.2017.75.
3. Swanson KS, Gibson GR, Hutkins R, Reimer RA, Reid G, Verbeke K, Scott KP, Holscher HD, Azad MB, Delzenne NM, et al. The International Scientific Association for Probiotics and Prebiotics (ISAPP) consensus statement on the definition and scope of synbiotics. *Nat Rev Gastroenterol Hepatol.* 2020;17(11):687–701. doi:10.1038/s41575-020-0344-2.
4. Dhar D, Mohanty A. Gut microbiota and Covid-19- possible link and implications. *Virus Res.* 2020;285:198018. doi:10.1016/j.virusres.2020.198018.
5. van den Akker CHP, van Goudoever JB, Shamir R, Domellöf M, Embleton ND, Hojsak I, Lapillonne A, Mihatsch WA, Berni Canani R, Bronsky J, et al. Probiotics and Preterm Infants: A Position Paper by the European Society for Paediatric Gastroenterology Hepatology and Nutrition Committee on Nutrition and the European Society for Paediatric Gastroenterology Hepatology and Nutrition Working Group for Probiotics and Prebiotics. *J Pediatr Gastroenterol Nutr.* 2020;70(5):664–80. doi:10.1097/mpg.0000000000002655.

6. Chi C, Li C, Buys N, Wang W, Yin C, Sun J. Effects of Probiotics in Preterm Infants: A Network Meta-analysis. *Pediatrics* 2021, 147(1).doi:10.1542/peds.2020-0706.
7. Bi LW, Yan BL, Yang QY, Li MM, Cui HL. Probiotic strategies to prevent necrotizing enterocolitis in preterm infants: a meta-analysis. *Pediatr Surg Int*. 2019;35(10):1143–62. doi:10.1007/s00383-019-04547-5.
8. Xiong T, Maheshwari A, Neu J, Ei-Saie A, Pammi M. An Overview of Systematic Reviews of Randomized-Controlled Trials for Preventing Necrotizing Enterocolitis in Preterm Infants. *Neonatology*. 2020;117(1):46–56. doi:10.1159/000504371.
9. Wang F, Pan B, Xu S, Xu Z, Zhang T, Zhang Q, Bao Y, Wang Y, Zhang J, Xu C, et al: A meta-analysis reveals the effectiveness of probiotics and prebiotics against respiratory viral infection. *Biosci Rep* 2021, 41(3).doi:10.1042/bsr20203638.
10. Chan CKY, Tao J, Chan OS, Li HB, Pang H. Preventing Respiratory Tract Infections by Synbiotic Interventions: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. *Adv Nutr*. 2020;11(4):979–88. doi:10.1093/advances/nmaa003.
11. Theodosiou AA, Dorey RB, Laver JR, Cleary DW, Read RC, Jones CE. Manipulating the infant respiratory microbiomes to improve clinical outcomes: A review of the literature. *J Infect*. 2021;82(6):247–52. doi:10.1016/j.jinf.2021.03.012.
12. Su M, Jia Y, Li Y, Zhou D, Jia J. Probiotics for the Prevention of Ventilator-Associated Pneumonia: A Meta-Analysis of Randomized Controlled Trials. *Respir Care*. 2020;65(5):673–85. doi:10.4187/respcare.07097.
13. Perna S, Ilyas Z, Giacosa A, Gasparri C, Peroni G, Faliva MA, Rigon C, Naso M, Riva A, Petrangolini G, et al: Is Probiotic Supplementation Useful for the Management of Body Weight and Other Anthropometric Measures in Adults Affected by Overweight and Obesity with Metabolic Related Diseases? A Systematic Review and Meta-Analysis. *Nutrients* 2021, 13(2).doi:10.3390/nu13020666.
14. Shirvani-Rad S, Tabatabaei-Malazy O, Mohseni S, Hasani-Ranjbar S, Soroush AR, Hoseini-Tavassol Z, Ejtahed HS, Larijani B. Probiotics as a Complementary Therapy for Management of Obesity: A Systematic Review. *Evid Based Complement Alternat Med*. 2021;2021:6688450. doi:10.1155/2021/6688450.
15. da Silva Borges D, Fernandes R, Thives Mello A, da Silva Fontoura E, Soares Dos Santos AR, Santos de Moraes Trindade EB. Prebiotics may reduce serum concentrations of C-reactive protein and ghrelin in overweight and obese adults: a systematic review and meta-analysis. *Nutr Rev*. 2020;78(3):235–48. doi:10.1093/nutrit/nuz045.
16. Baron R, Taye M, Besseling-van der Vaart I, Ujčić-Voortman J, Szajewska H, Seidell JC, Verhoeff A. **The relationship of prenatal and infant antibiotic exposure with childhood overweight and obesity: a systematic review.** *J Dev Orig Health Dis* 2019:1–15.doi:10.1017/s2040174419000722.
17. Stanislowski MA, Dabelea D, Wagner BD, Iszatt N, Dahl C, Sontag MK, Knight R, Lozupone CA, Eggesbo M: **Gut Microbiota in the First 2 Years of Life and the Association with Body Mass Index at Age 12 in a Norwegian Birth Cohort.** *mBio* 2018, 9(5).doi:10.1128/mBio.01751-18.
18. Pelucchi C, Chatenoud L, Turati F, Galeone C, Moja L, Bach JF, La Vecchia C. Probiotics supplementation during pregnancy or infancy for the prevention of atopic dermatitis: a meta-analysis. *Epidemiology*. 2012;23(3):402–14. doi:10.1097/EDE.0b013e31824d5da2.
19. Yin DG, He Z, Duan XY, Fan FX, Liao XB, Wang QC. [Effect of probiotic supplementation during pregnancy and infancy in preventing atopic dermatitis in children: a Meta analysis]. *Zhongguo Dang Dai Er Ke Za Zhi*. 2019;21(1):82–8. doi:10.7499/j.issn.1008-8830.2019.01.015.
20. Tan-Lim CSC, Esteban-Ipac NAR, Recto MST, Castor MAR, Casis-Hao RJ, Nano ALM. Comparative effectiveness of probiotic strains on the prevention of pediatric atopic dermatitis: a systematic review and network meta-analysis. *Pediatr Allergy Immunol*. 2021. doi:10.1111/pai.13514.
21. Sorensen K, Cawood AL, Gibson GR, Cooke LH, Stratton RJ. Amino Acid Formula Containing Synbiotics in Infants with Cow's Milk Protein Allergy: A Systematic Review and Meta-Analysis. *Nutrients* 2021, 13(3).doi:10.3390/nu13030935.
22. Sestito S, D'Auria E, Baldassarre ME, Salvatore S, Tallarico V, Stefanelli E, Tarsitano F, Concolino D, Pensabene L. The Role of Prebiotics and Probiotics in Prevention of Allergic Diseases in Infants. *Front Pediatr*. 2020;8:583946. doi:10.3389/fped.2020.583946.

23. Halken S, Muraro A, de Silva D, Khaleva E, Angier E, Arasi S, Arshad H, Bahnson HT, Beyer K, Boyle R, et al. EAACI guideline: Preventing the development of food allergy in infants and young children (2020 update). *Pediatr Allergy Immunol*. 2021. doi:10.1111/pai.13496.
24. Roberts G, Vazquez-Ortiz M, Knibb R, Khaleva E, Alviani C, Angier E, Blumchen K, Comberiati P, Duca B, DunnGalvin A, et al. EAACI Guidelines on the effective transition of adolescents and young adults with allergy and asthma. *Allergy*. 2020;75(11):2734–52. doi:10.1111/all.14459.
25. Ellwood J, Draper-Rodi J, Carnes D. Comparison of common interventions for the treatment of infantile colic: a systematic review of reviews and guidelines. *BMJ Open*. 2020;10(2):e035405. doi:10.1136/bmjopen-2019-035405.
26. Allen SJ, Martinez EG, Gregorio GV, Dans LF. Probiotics for treating acute infectious diarrhoea. *Cochrane Database Syst Rev*. 2010;2010(11):Cd003048. doi: 10.1002/14651858.CD003048.pub3.
27. Collinson S, Deans A, Padua-Zamora A, Gregorio GV, Li C, Dans LF, Allen SJ. Probiotics for treating acute infectious diarrhoea. *Cochrane Database Syst Rev*. 2020;12:Cd003048. doi: 10.1002/14651858.CD003048.pub4.
28. **Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation.** *Bmj* 2016, 354:i4086. doi:10.1136/bmj.i4086.
29. Pieper D, Antoine SL, Mathes T, Neugebauer EA, Eikermann M. Systematic review finds overlapping reviews were not mentioned in every other overview. *J Clin Epidemiol*. 2014;67(4):368–75. doi:10.1016/j.jclinepi.2013.11.007.
30. Shojania KG, Sampson M, Ansari MT, Ji J, Doucette S, Moher D. How quickly do systematic reviews go out of date? A survival analysis. *Ann Intern Med*. 2007;147(4):224–33. doi:10.7326/0003-4819-147-4-200708210-00179.
31. Okoth K, Chandan JS, Marshall T, Thangaratnam S, Thomas GN, Nirantharakumar K, Adderley NJ. Association between the reproductive health of young women and cardiovascular disease in later life: umbrella review. *Bmj*. 2020;371:m3502. doi:10.1136/bmj.m3502.
32. Pollock M, Fernandes RM, Newton AS, Scott SD, Hartling L. A decision tool to help researchers make decisions about including systematic reviews in overviews of reviews of healthcare interventions. *Syst Rev*. 2019;8(1):29. doi:10.1186/s13643-018-0768-8.
33. Pollock M, Fernandes RM, Newton AS, Scott SD, Hartling L. The impact of different inclusion decisions on the comprehensiveness and complexity of overviews of reviews of healthcare interventions. *Syst Rev*. 2019;8(1):18. doi:10.1186/s13643-018-0914-3.
34. Aromataris E, Fernandez R, Godfrey CM, Holly C, Khalil H, Tungpunkom P. Summarizing systematic reviews: methodological development, conduct and reporting of an umbrella review approach. *Int J Evid Based Healthc*. 2015;13(3):132–40. doi:10.1097/xeb.000000000000055.
35. Shea BJ, Reeves BC, Wells G, Thuku M, Hamel C, Moran J, Moher D, Tugwell P, Welch V, Kristjansson E, et al. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. *Bmj*. 2017;358:j4008. doi:10.1136/bmj.j4008.
36. Guyatt G, Oxman AD, Akl EA, Kunz R, Vist G, Brozek J, Norris S, Falck-Ytter Y, Glasziou P, DeBeer H, et al. GRADE guidelines: 1. Introduction-GRADE evidence profiles and summary of findings tables. *J Clin Epidemiol*. 2011;64(4):383–94. doi:10.1016/j.jclinepi.2010.04.026.
37. Balshem H, Helfand M, Schünemann HJ, Oxman AD, Kunz R, Brozek J, Vist GE, Falck-Ytter Y, Meerpohl J, Norris S, et al. GRADE guidelines: 3. Rating the quality of evidence. *J Clin Epidemiol*. 2011;64(4):401–6. doi:10.1016/j.jclinepi.2010.07.015.

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