

Peer Review File

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Reviewer A

General comment: recommending authors to follow the PRISMA checklist for reporting SRs

Reply: Thanks for your comment. We have completed the entire article according to the PRISMA checklist.

Changes in the text: Paragraph 1 / Results, Figure1

Introduction

Include a brief discussion on the available SRs on the topic and provide rationale for need of a new review

Reply: Thanks for your comment. We have analyzed the controversies in previous research results in the introduction section and added relevant content on the reasons for conducting meta-analysis.

Changes in the text: Paragraph 1,2 / Introduction

Methods

Eligibility criteria: clearly state what outcomes were evaluated in the review

Add section on selection process and describe how it was done

Add section on data items and define outcome domains

Risk of bias: specify which tool was used (Cochrane ROB tool v1)

Add section on effect measures and specify what was used for each outcome

Line 99: suggest to rephrase “If there was statistical homogeneity” to If there was no significant statistical heterogeneity

Line 100: define what is the p-value and I²

Line 102: Describe what type of subgroup analysis was done. Was this preplanned or posthoc? Did you also consider subgroup analysis of whether infants are high risk for allergy or not?

Line 103: Suggest to briefly describe Harbord method

Line 105: Suggest to briefly describe Rabe plots

Add section on certainty assessment

Reply: Thanks for your comment. We have added descriptions of using tools, heterogeneity assessment, and bias assessment in the methods section.

Changes in the text: Paragraph 2,3,4,5,6 / Methods

Results

Line 128-133: Why exclude the follow up studies? In line 70-71, you state that “if multiple reports assessed the same group of patients, we only selected the latest complete report.”

Reply: Thanks for your comment. If multiple reports evaluate the same group of patients, we choose the latest complete report and choose the report with the longest follow-up time and the highest number of AD cases, without including those with shorter follow-up time and fewer cases in the previous period.

Changes in the text: Paragraph 1 / Results

#Quality assessment of the included studies: Provide an overall assessment of risk of bias per study, per outcome.

Reply: Thanks for your comment. We have provided it.

Changes in the text: Paragraph 3/ Results

##Effect of probiotics on AD prevention: Explicitly state that there is significant heterogeneity and explain what are the possible sources

Reply: Thanks for your comment. We have added the value of heterogeneity evaluation I^2 for each result in the results section, and explained the possible sources of heterogeneity in the discussion.

Changes in the text: Paragraph 4-9 / Results

##Subgroup analysis: Include heterogeneity results for each subgroup. Also, your forest plots show odds ratio but your text states risk ratio. This has to be reconciled.

Reply: Thanks for your comment. We have made modifications to the forest map by changing the risk ratio to the ratio.

Changes in the text: figure2,3,4,5,6,7

Line 174: figure 6 is subgroup by trial region, not follow up time

Reply: Thanks for your comment. We have revised it.

Changes in the text: Paragraph 8/ Results

Line 176: Explain in the methods the basis of using 2 years as cut off. Was this preplanned or posthoc?

Reply: Thanks for your comment. I'm very sorry, this is our pen mistake. We have revised it.

Changes in the text: Paragraph 8/ Results

Line 182-186: Rabe diagram “indicating that the heterogeneity was small and the results of the meta-analysis were 186 reliable” but results show there is frank, visual and statistical heterogeneity. This should be reconciled.

Add section on certainty of evidence

Reply: Thanks for your comment. We have revised it.

Changes in the text: Paragraph 9/ Results

Discussion

Heterogeneity is evident in the results, despite subgroup analysis. This should be accounted for as a limitation. I feel that your statements on the usefulness of probiotics are too definitive and needs to take into consideration the certainty of evidence.

Reply: Thanks for your comment. We have revised it.

Changes in the text: Paragraph 6/ Discussion

Conclusion

Conclusion should be modified according to certainty of evidence assessment

Reply: Thanks for your comment. We have revised it.

Changes in the text: Paragraph 1/ Conclusion

Abstract

Results: Add results on heterogeneity, I feel that your statements on the usefulness of probiotics in the results are too definitive and needs to take into consideration the certainty of evidence.

Reply: Thanks for your comment. We have made corresponding modifications to the results in the abstract.

Changes in the text: Paragraph 2/ Abstract

Other information

Add section on REGISTRATION AND PROTOCOL: Was this protocol registered?

Add section on competing interests

Reply: Thanks for your comment. This protocol had not been registered.

Changes in the text: None

Figure 1

Text does not align with values in the figure. In the text, “two articles were excluded as the full text was not found” but in the figure, 31 reports not retrieved.

What do you mean by insufficient calculated data? How was missing data handled in your review? This should be discussed in the methods under data items.

The follow up studies were excluded, and 30 studies were finally included. Suggest to reflect this in the flow diagram

Reply: Thanks for your comment. We have revised it.

Changes in the text: Paragraph 1 / Results, Figure1

Reviewer B

First, the abstract needs substantial revisions. The background did not describe the controversy regarding the preventive effect of probiotics and explain why a meta-analysis is suitable to address this controversy. The methods need to describe the inclusion of studies according to the PICOS principle, the outcome data extracted, and risk of bias assessment of included studies. The results need to report the sample sizes of probiotics and control groups and risk of bias of included studies. Statistics such as P values for the Q test should be reported. The conclusion should be tone down because of the risk of bias f included studies.

Reply: Thanks for your comment. We have added a description of the controversy surrounding the effectiveness of probiotic prevention in current research. We have described the inclusion of the study, the extracted result data, and the risk assessment of bias in the inclusion study based on the PICOS principles in the abstract methods section.

Changes in the text: Paragraph 1-3/ Abstract

Second, the introduction of the main text is poor, which did not provide examples on the controversy regarding the preventive effects of probiotics for AD, did not analyze the potential reasons for the controversy, and did not explain why a meta-analysis is suitable for addressing this research controversy. The authors should be aware of that meta-analysis is used to address controversy so there must be controversy to be reviewed here.

Reply: Thanks for your comment. We have added in the introduction a specific study on the controversial role of probiotics in AD prevention, analyzed its potential reasons, and finally explained that meta-analysis is suitable for resolving this research controversy.

Changes in the text: Paragraph 1,2 / Introduction

Third, in the methodology of the main text, please specify the interventions that controls undergo, placebo and other positive medications are different, as well as the outcome variables extracted. The risk of bias assessment results should be presented by using the figures in the Cochrane Review Manager. In statistics, heterogeneity should be assessed by using statistical tests. The moderators used in the subgroup analyses should also be described. Please describe the P value for statistical significance.

Reply: Thanks for your comment. We have explained in the methods section the intervention measures received by the control group - placebo, and described the outcome variables that need to be extracted. The assessment of bias risk was conducted using the Cochrane system evaluation tool Cochrane ROB v1. In the heterogeneity analysis, the I^2 and P values of each part of the heterogeneity results were supplemented, and the statistical significance of the P values was described: $P < 0.05$ in the statistical analysis indicated the existence of statistical significance.

Changes in the text: Paragraph 2,3,4,5,6 / Methods

Reviewer C

1. Title

Please add “systematic review” in the title as requested by the PRISMA Reporting Checklist.

TITLE		
Title	1	Identify the report as a systematic review.

- Suggested wording: *The effect of probiotics in the prevention of atopic dermatitis in children: a systematic review and meta-analysis*

Reply: Thank you for your comment. We have added it.

2. Abstract

Please double check the full term of AD.

26 **Abstract**

27 **Background:** Probiotics have anti-inflammatory effects and can alleviate clinical
28 symptoms of specific dermatitis (AD). However, the effects of probiotics on atopic
29 dermatitis in children were controversial. This study aimed to evaluate the clinical

Reply: Thank you for your comment. We have revised it.

3. Figure 4 and 5

Please check if the p value is missing.

Before childbirth	Bifidobacterium
Boyle, 2011	Wu, 2010
Subgroup, DL ($I^2 = 0.0\%$, $p = .$)	Subgroup, DL ($I^2 = 0.0\%$, $p = .$)

Reply: The P-value was not missing. In the subgroup analysis, there was only one literature in this group, so the I^2 for heterogeneity testing was 0, and there was no P-value.

4. References/Citations

Please add the citation for these studies at the end of the sentence.

214 included 24 studies in Europe, six studies in Asia, and seven studies in Oceania. The
215 research conducted by Kalliomäki [2003] and Kalliomäki [2007] were follow-up
216 studies of Kalliomäki [2001]; studies by Kuitunen [2009] and Peldan [2017] were
217 follow-up studies of Kukkonen [2007]; studies by Wickens [2012], Wickens [2013],
218 and Wickens [2018] were follow-up studies of Wickens [2008]. Therefore, Kalliomäki
219 [2003], Kalliomäki [2007], Kuitunen [2009], Peldan [2017], Wickens [2012], Wickens
220 [2013], and Wickens [2018] were excluded. Thirty studies were finally included in
221 further analysis.

Reply: Thank you for your comment. We have added it.