**Effect of probiotic supplementation on chemotherapy and radiotherapy-related diarrhea in patients with cancer: An umbrella review of systematic reviews and meta-analyses**

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Online Supplementary Material

Supplementary data, including 6 supplementary Tables &6 supplementary Figures

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| **Supplementary Table 1.** Search strategies including the key terms and the queries for each database |
| **Database****2/2/2022** | **Key terms and the queries** |
| PubMed339 | #1 (((((((((((((((("Neoplasms"[Mesh]) OR "Neoplasm Metastasis"[Mesh]) OR "Neoplasm Invasiveness"[Mesh])) OR "Cancer Survivors"[Mesh]) OR "Cancer-Associated Fibroblasts"[Mesh]) OR "Chemotherapy, Cancer, Regional Perfusion"[Mesh]) OR "Cecal Neoplasms"[Mesh]) OR "Genes, Neoplasm"[Mesh]) OR "Carcinoma"[Mesh]) OR (cancer[Title/Abstract])) OR (tumor[Title/Abstract])) OR (malignan\*[Title/Abstract])) OR (carcinoma\*[Title/Abstract])) OR (oncolog\*[Title/Abstract]))#2 ("Meta-Analysis"[Title/Abstract] OR "meta-analyses"[Title/Abstract] OR "Meta-Analysis"[Title/Abstract] OR "meta-analyze"[Title/Abstract] OR "Systematic Review"[Title/Abstract] OR "Systematic Review"[Publication Type] OR "Systematic Reviews as Topic"[MeSH Terms] OR "Meta-Analysis as Topic"[MeSH Terms] OR "Meta-Analysis"[Publication Type]))#3 (("Probiotics"[Title/Abstract] OR "Synbiotics"[Title/Abstract] OR "Prebiotics"[Title/Abstract] OR "Inulin"[Title/Abstract] OR "resistant dextrin"[Title/Abstract] OR "Microbiota"[Title/Abstract] OR "Microbiotas"[Title/Abstract] OR "Microbiome"[Title/Abstract] OR "Microbiomes"[Title/Abstract] OR "gut microflora"[Title/Abstract] OR "human microbiome"[Title/Abstract] OR "human microbiomes"[Title/Abstract] OR "microbiomes human"[Title/Abstract] OR "microbiome human"[Title/Abstract] OR "Bacteroides"[Title/Abstract] OR "Bacteroidetes"[Title/Abstract] OR "Bifidobacterium"[Title/Abstract] OR "Eubacterium"[Title/Abstract] OR "Clostridium"[Title/Abstract] OR "Lactobacillus"[Title/Abstract] OR "Fusobacterium"[Title/Abstract] OR "Firmicutes"[Title/Abstract] OR ("Probiotics"[MeSH Terms] OR "Synbiotics"[MeSH Terms] OR "Prebiotics"[MeSH Terms] OR "Inulin"[MeSH Terms] OR "Microbiota"[MeSH Terms] OR "Gastrointestinal Microbiome"[MeSH Terms] OR "Bacteroidetes"[MeSH Terms] OR "Bifidobacterium"[MeSH Terms] OR "Eubacterium"[MeSH Terms] OR "Clostridium"[MeSH Terms] OR "Lactobacillus"[MeSH Terms] OR "Fusobacterium"[MeSH Terms] OR "Firmicutes"[MeSH Terms]))#4 #1 AND #2 AND #3 |
| Scopus1181 | #1 ( TITLE-ABS-KEY ( neoplasm ) OR TITLE-ABS-KEY ( carcinoma\* ) OR TITLE-ABS-KEY ( cancer ) OR TITLE-ABS-KEY ( tumor ) OR TITLE-ABS-KEY ( malignan\* ) OR TITLE-ABS-KEY ( oncolog\* ) )#2 ( TITLE-ABS-KEY ( "meta-analyses" ) OR TITLE-ABS-KEY ( "meta-analysis" ) OR TITLE-ABS-KEY ( "meta-analyze" ) OR TITLE-ABS-KEY ( "meta analysis" ) OR TITLE-ABS-KEY ( "systematic review" ) ) #3 ( TITLE-ABS-KEY ( probiotics ) OR TITLE-ABS-KEY ( synbiotics ) OR TITLE-ABS-KEY ( prebiotics ) OR TITLE-ABS-KEY ( inulin ) OR TITLE-ABS-KEY ( resistant AND dextrin ) OR TITLE-ABS-KEY ( microbiota ) OR TITLE-ABS-KEY ( microbiotas ) OR TITLE-ABS-KEY ( microbiome ) OR TITLE-ABS-KEY ( microbiomes ) OR TITLE-ABS-KEY ( "gut microflora" ) OR TITLE-ABS-KEY ( "human microbiome" ) OR TITLE-ABS-KEY ( "human microbiomes" ) OR TITLE-ABS-KEY ( "microbiomes, human" ) OR TITLE-ABS-KEY ( "microbiome, human" ) OR TITLE-ABS-KEY ( bacteroides ) OR TITLE-ABS-KEY ( bacteroidetes ) OR TITLE-ABS-KEY ( bifidobacterium ) OR TITLE-ABS-KEY ( eubacterium ) OR TITLE-ABS-KEY ( clostridium ) OR TITLE-ABS-KEY ( lactobacillus ) OR TITLE-ABS-KEY ( fusobacterium ) OR TITLE-ABS-KEY ( firmicutes ) #4 #1 AND #2 AND #3 |
| Web of Science (ISI)418 | #1:**TOPIC:** (neoplasm\*) *OR* **TOPIC:** (carcinoma\*) *OR* **TOPIC:** (cancer) *OR* **TOPIC:** (tumor) *OR* **TOPIC:** (malignan\*) *OR* **TOPIC:** (oncolog\*) #2:**TOPIC:** ("meta-analyses") *OR* **TOPIC:** ("meta-analysis") *OR* **TOPIC:** (" meta-analyze") *OR* **TOPIC:** (" meta analysis") *OR* **TOPIC:** (" Systematic Review")  #3:**TOPIC:** ("probiotics") *OR* **TOPIC:** ("synbiotics") *OR* **TOPIC:** ("prebiotics") *OR* **TOPIC:** ("Inulin") *OR* **TOPIC:** ("ResistantDextrin") *OR* **TOPIC:** ("Microbiota") *OR* **TOPIC:** ("Microbiotas") *OR* **TOPIC:** ("Microbiome") *OR* **TOPIC:** ("Microbiomes") *OR* **TOPIC:** ("Gut microflora") *OR* **TOPIC:** ("Human Microbiome") *OR* **TOPIC:** ("Human Microbiomes") *OR* **TOPIC:** ("Microbiomes, Human") *OR* **TOPIC:** ("Microbiome,Human") *OR* **TOPIC:** ("Bacteroides") *OR* **TOPIC:** ("Bacteroidetes") *OR* **TOPIC:** ("Bifidobacterium") *OR* **TOPIC:** ("Eubacterium") *OR* **TOPIC:** ("Clostridium") *OR* **TOPIC:** ("Lactobacillus") *OR* **TOPIC:** ("Fusobacterium") *OR* **TOPIC:** ("Firmicutes")#4: #1 AND #2 AND #3 |

**Supplementary Table 2.** Articles excluded during full text assessment and reasons for exclusion.

|  |  |  |
| --- | --- | --- |
|  | **Author, publication year (ref.)** | **Reason(s) for exclusion** |
| **1** | Abt, 2021 (1) | No eligible outcome |
| **2** | Amitay, 2020 (2) | Not eligible outcome |
| **3** | Cogo, 2021 (3) | Not eligible outcome |
| **4** | Chen, 2020 (4) | No eligible outcome |
| **5** | Colov, 2020 (5) | Not eligible outcome |
| **6** | Calaca, 2017 (6) | Not eligible outcome |
| **7** | Cao, 2017 (7) | Not eligible outcome |
| **8** | Fuccio, 2009 (8) | Duplicate |
| **9** | He, 2013 (9) | Not eligible outcome |
| **10** | Henson, 2013 (10) | Not eligible intervention  |
| **11** | Hamad, 2013 (11) | Duplicate |
| **12** | Kamaluddin, 2020 (12) | Not eligible outcome |
| **13** | Lytvyn, 2016 (13) | Not eligible outcome |
| **14** | Ouyang, 2019 (14) | Not eligible outcome |
| **15** | Rodriguez-Arrastia, 2021 (15) | Systematic review without meta-analysis |
| **16** | Redman, 2014 (16) | Duplicate |
| **17** | Shu, 2020 (17) | Not eligible outcome |
| **18** | Suadoni, 2014 (18) | Systematic review without meta-analysis |
| **19** | Sun, 2012 (19) | Not eligible intervention |
| **20** | Tang, 2021 (20) | Not eligible outcome |
| **21** | Wei, 2018 (21) | Duplicate |
| **22** |  Wu, 2018 (22) | Not eligible outcome |
| **23** | Wedlake, 2013 (23) | Systematic review without meta-analysis |
| **24** | Yang, 2017 (24) | Not eligible outcome |
| **25** | Zeng, 2021 (25) | Not eligible outcome |

ref, reference.

**Supplementary Table 3.** Methodological quality of included systematic reviews and meta-analyses using AMSTAR2

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Author, year (ref.)** | **Q1** | **Q2** | **Q3** | **Q4** | **Q5** | **Q6** | **Q7** | **Q8** | **Q9** | **Q10** | **Q11** | **Q12** | **Q13** | **Q14** | **Q15** | **Q16** | **Level of evidence** |
| Bartsch, 2021 (26) | Yes | Yes | Yes | PY | No | No | No | No | Yes | Yes | Yes | No | No | Yes | Yes | Yes | Critically low |
| Devaraj, 2019 (27) | Yes | Yes | Yes | PY | Yes | Yes | PY | PY | Yes | Yes | Yes | Yes | No | Yes | Yes | Yes | Low |
| Fuccio, 2009 (8) | Yes | PY | Yes | PY | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | No | Yes | Yes | Yes | Low |
| Hassan, 2018 (28) | Yes | Yes | Yes | Yes | Yes | No | PY | No | Yes | No | Yes | Yes | Yes | Yes | Yes | No | Low |
| Hamad, 2013 (11) | Yes | PY | Yes | PY | No | Yes | Yes | Yes | Yes | Yes | Yes | Yes | No | Yes | Yes | Yes | Low |
| Lin, 2020 (29) | Yes | PY | Yes | PY | Yes | Yes | Yes | No | Yes | Yes | Yes | Yes | No | Yes | Yes | Yes | Low |
| Lu, 2019 (30) | Yes | PY | Yes | PY | Yes | Yes | PY | Yes | Yes | Yes | Yes | No | Yes | Yes | Yes | Yes | High |
| Liu, 2017 (31) | Yes | PY | Yes | PY | Yes | Yes | PY | Yes | Yes | Yes | Yes | Yes | No | Yes | Yes | Yes | Low |
| Qiu, 2019 (32) | Yes | PY | Yes | PY | Yes | Yes | PY | Yes | Yes | Yes | Yes | No | No | Yes | Yes | Yes | Low |
| Redman, 2014 (16) | Yes | Yes | Yes | PY | Yes | Yes | PY | No | Yes | No | Yes | Yes | Yes | Yes | No | Yes | Low |
| Wardill, 2018 (33) | Yes | No | Yes | PY | Yes | Yes | PY | No | Yes | Yes | Yes | Yes | No | Yes | Yes | Yes | Critically low |
| Wei, 2018 (21) | Yes | Yes | Yes | PY | Yes | Yes | PY | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | High |
| Wang, 2016 (34) | Yes | PY | Yes | PY | Yes | Yes | PY | Yes | Yes | No | Yes | Yes | Yes | Yes | No | Yes | Low |

**Ref, references. PY,** partially yes**. Q1: Did the research questions and inclusion criteria for the review include the components of PICO?, Q2: 2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?; Q3, Did the review authors explain their selection of the study designs for inclusion in the review?; Q4, Did the review authors use a comprehensive literature search strategy?; Q5, Did the review authors perform study selection in duplicate?; Q6, Did the review authors perform data extraction in duplicate?; Q7, Did the review authors provide a list of excluded studies and justify the exclusions?; Q8, Did the review authors describe the included studies in adequate detail?; Q9, Did the review authors use a satisfactory technique for assessing the risk of bias?; Q10, Did the review authors report on the sources of funding?; Q11, Did the review authors use appropriate methods for statistical combination of results?; Q12, Did the review authors assess the potential impact of RoB in individual studies on the results?; Q13, Did the review authors** **account for RoB in individual studies when interpreting/ discussing the results of the review?; Q14, Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity?; Q15, Did the review authors carry out an adequate investigation of publication bias?; Q16, Did the review authors report any potential sources of conflict of interest?**

**Supplementary Table 4.** Methodological quality of the RCTs from the systematic reviews and meta-analyses

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Study, year** | **Random sequence generation** | **Allocation concealment** | **Blinding of participants & personnel** | **Blinding of outcome assessment** | **Incomplete outcome data** | **Selective outcome reporting** | **Other sources of bias** | **Overall quality** |
| **Any grade** |
| Mego, 2015 | L | L | L | L | L | L | L | Good |
| Chitapanarux, 2010 | L | L | L | U | L | L | U | Fair |
| Demers, 2013 | L | L | L | L | H | L | L | Fair |
| Linn, 2018 | L | U | L | L | U | L | L | Fair |
| Delia, 2007 | H | L | H | H | H | H | U | Poor |
| Delia, 2002 | L | U | U | L | L | U | L | Poor |
| Giralt, 2008 | L | L | L | H | U | L | H | Poor |
| Ӧsterlund, 2007 | L | L | H | U | L | L | U | Poor |
| Salminen, 1988 | L | U | H | H | H | L | U | Poor |
| Mansouri-Tehrani, 2015 | U | U | L | U | H | L | L | Poor |
| Fang, 2011 | H | L | L | L | H | L | U | Poor |
| Liu, 2000 | L | L | U | H | H | L | U | Poor |
| Yi, 2018 | L | L | U | H | L | U | L | Poor |
| Wei, 2017 | U | H | L | H | L | L | L | Poor |
| Chen, 2014 | L | U | L | U | U | U | L | Poor |
| Okawa, 1949 | L | U | U | U | L | L | U | Poor |
| **Grade ≥ 2** |
| Mego, 2015 | L | L | L | L | L | L | L | Good |
| Chitapanarux, 2010 | L | L | L | U | L | L | U | Fair |
| Demers, 2013 | L | L | L | L | H | L | L | Fair |
| Delia, 2002 | L | U | U | L | L | U | L | Poor |
| Giralt, 2008 | L | L | L | H | U | L | H | Poor |
| Fang, 2011 | H | L | L | L | H | L | U | Poor |
| Liu, 2000 | L | L | U | H | H | L | U | Poor |
| Mansouri-Tehrani, 2015 | U | U | L | U | H | L | L | Poor |
| **Grade ≥ 3** |
| Mego, 2015 | L | L | L | L | L | L | L | Good |
| Chitapanarux, 2010 | L | L | L | U | L | L | U | Fair |
| Demers, 2013 | L | L | L | L | H | L | L | Fair |
| Linn, 2018 | L | U | L | L | U | L | L | Fair |
| Delia, 2007 | H | L | H | H | H | H | U | Poor |
| Delia, 2002 | L | U | U | L | L | U | L | Poor |
| Fang, 2011 | H | L | L | L | H | L | U | Poor |
| Liu, 2000 | L | L | U | H | H | L | U | Poor |
| Wei, 2017 | U | H | L | H | L | L | L | Poor |
| Giralt, 2008 | L | L | L | H | U | L | H | Poor |
| Ӧsterlund, 2007 | L | L | H | U | L | L | U | Poor |
| **Anti-diarrheal medication use** |
| Chitapanarux, 2010 | L | L | L | U | L | L | U | Fair |
| Demers, 2013 | L | L | L | L | H | L | L | Fair |
| Linn, 2018 | L | U | L | L | U | L | L | Fair |
| Lacouture, 2016 | L | U | L | L | L | L | U | Fair |
| Giralt, 2008 | L | L | L | H | U | L | H | Poor |
| Salminen, 1988 | L | U | H | H | H | L | U | Poor |
| Mansouri-Tehrani, 2015 | U | U | L | U | H | L | L | Poor |
| Urbancsek, 2001 | U | U | U | L | L | H | H | Poor |
| **Soft stool** |
| Chitapanarux, 2010 | L | L | L | U | L | L | U | Fair |
| Demers, 2013 | L | L | L | L | H | L | L | Fair |
| Giralt, 2008 | L | L | L | H | U | L | H | Poor |
| **Watery stool** |
| Chitapanarux, 2010 | L | L | L | U | L | L | U | Fair |
| Demers, 2013 | L | L | L | L | H | L | L | Fair |
| Giralt, 2008 | L | L | L | H | U | L | H | Poor |

U, unclear risk of bias; L, low risk of bias; H, high risk of bias.

**Supplementary Table 5.** The GRADE quality of evidence for each outcome

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Certainty assessment | No of patients | Effect | Certainty | Importance |
| No of studies | Design | Risk of bias | Inconsistency | Indirectness | Imprecision | Otherconsiderations | Treatment group | Control group | Relative(95% CI) | Absolute(95% CI) |
| **Any grade diarrhea** |
| 16 | randomised trials | seriousa | seriousb | not serious | not seriousc | none | 284/883 (32.2%)  | 482/866 (55.7%)  | **OR 0.35**(0.22 to 0.54) | **199 more per 1,000**(from 312 fewer to 105 fewer) | ⨁⨁◯◯Low | IMPORTANT |
| **Diarrhea ≥ grade 2** |
| 8 | randomised trials | Seriousd | not seriouse | not serious | Seriousf | none | 117/315 (37.1%)  | 185/338 (54.7%)  | **OR 0.43**(0.25 to 0.74) | **250 fewer per 1,000**(from 337 fewer to 152 fewer) | ⨁⨁◯◯Low | IMPORTANT |
| **Diarrhea ≥ grade 3** |
| 11 | randomised trials | Seriousg | Serioush | not serious | Seriousi | none | 73/689 (10.6%)  | 185/662 (27.9%)  | **OR 0.30**(0.15 to 0.59) | **175 fewer per 1,000**(from 224 fewer to 93 fewer) | ⨁◯◯◯Very low | IMPORTANT |
| **Use of antidiarrheal drug** |
| 8 | randomised trials | not serious | Seriousj | not serious | Seriousk | none | 128/355 (36%)  | 182/381 (47.7%)  | **OR 0.49**(0.27 to 0.88) | **120 fewer per 1,000**(from 185 fewer to 25 fewer) | ⨁⨁◯◯Low | IMPORTANT |
| **Soft stool** |
| 3 | randomised trials | not serious | not seriousl | not serious | Seriousm | none | 92/133 (69.1%)  | 94/158 (59.4%) | **OR 1.10**(0.44 to 2.76) | **20 fewer per 1,000**(from 134 fewer to 238 more) | ⨁⨁⨁◯Moderate | IMPORTANT |
| **Watery stool** |
| 3 | randomised trials | not serious | Seriousn | not serious | seriouso | none | 55/133 (41.3%)  | 80/158 (50.6%)  | **OR 0.52**(0.29 to 1.29) | **112 fewer per 1,000**(from 178 fewer to 54 fewer) | ⨁◯◯◯Very low | IMPORTANT |

**CI:** confidence interval; **RR:** risk ratio

Explanations

a. Serious risk of bias since twelve studies were at high risk of bias. Downgraded.

b. Serious inconsistency since I2 = 67.7%, Phet <0.001. Downgraded.

c. Optimal information size met. The 95%CI exclude the null value (OR: 1.00). Not downgraded.

d. Serious risk of bias since five studies were at high risk of bias. Downgraded.

e. Not serious inconsistency since I2 = 48.9%, Phet = 0.048. Not downgraded.

f. Optimal information size did not meet. The 95%CI exclude the null value (OR: 1.00). Downgraded.

g. Serious risk of bias since seven studies were at high risk of bias. Downgraded.

h. Serious inconsistency since I2 = 67.6%, Phet <0.001. Downgraded.

i. Optimal information size did not meet. The 95%CI exclude the null value (OR: 1.00). Downgraded.

j. Serious inconsistency since I2 = 63.4%, Phet =0.008. Downgraded.

k. Optimal information size did not meet. The 95%CI exclude the null value (OR: 1.00). Downgraded.

l. Not serious inconsistency since I2 =49.8 %, Phet =0.113. Downgraded.

m. Optimal information size did not meet. The 95%CI include the null value (OR: 1.00) and the upper bound of the 95%CI >1.2. Downgraded.

n. Not serious inconsistency since I2 = 62%, Phet =0.049. Downgraded.

o. Optimal information size did not meet. he 95%CI include the null value (OR: 1.00) and the upper bound of the 95%CI >1.2. Downgraded.

**Supplementary Table 6**. Assessment of credibility of subgroup difference for the effect of probiotic supplementation on prevention or treatment of chemotherapy and/or radiotherapy related diarrhea based on ICEMAN.

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Variable | Q1 | Q2 | Q3 | Q4 | Q5 | Q6 | Q7 | Q8 | Overall interpretation |
| **Incidence of any grade diarrhea** |
| Cancer treatment | Completely between | Mostly similar | Rather large | Unclear | Chance a very likely explanation  | Probably no | Definitely yes | Probably yes | Low |
| Duration of intervention | Completely between | Mostly similar | Rather large | Unclear | Chance a very likely explanation  | Probably no | Definitely yes | Probably yes | Low |
| Assessment criteria | Completely between | Mostly similar | Rather large | Unclear | Chance a very likely explanation  | Probably no | Definitely yes | Probably yes | Low |
| Genus of probiotics | Completely between | Mostly similar | Rather small | Unclear | Chance a very likely explanation  | Probably no | Definitely yes | Probably yes | Low |
| Single versus Combined Strains of Probiotics | Completely between | Mostly similar | Rather large | Unclear | Chance a very likely explanation  | Probably no | Definitely yes | Probably yes | Low |
| **Incidence of ≥ grade 2 diarrhea** |
| Cancer treatment | Completely between | Mostly similar | Rather small | Unclear | Chance a very likely explanation | Probably no | Definitely yes | Probably yes | Low |
| Duration of intervention | Completely between | Mostly similar | Rather large | Unclear | Chance a very likely explanation  | Probably no | Definitely yes | Probably yes | Low |
| Assessment criteria | Completely between | Mostly similar | Rather large | Unclear | Chance a very likely explanation  | Probably no | Definitely yes | Probably yes | Low |
| Genus of probiotics | Completely between | Mostly similar | Very small | Unclear | Chance a very likely explanation  | Probably no | Definitely yes | Probably yes | Low |
| Single versus Combined Strains of Probiotics | Completely between | Mostly similar | Very small | Unclear | Chance a very likely explanation  | Probably no | Definitely yes | Probably yes | Low |
| **Incidence of ≥ grade 3 diarrhea** |
| Cancer treatment | Completely between | Mostly similar | Rather large  | Unclear | Chance a very likely explanation  | Probably no | Definitely yes | Probably yes | Low |
| Duration of intervention | Completely between | Mostly similar | Rather large  | Unclear | Chance a very likely explanation  | Probably no | Definitely yes | Probably yes | Low |
| Assessment criteria | Completely between | Mostly similar | Rather small | Unclear | Chance a very likely explanation  | Probably no | Definitely yes | Probably yes | Low |
| Genus of probiotics | Completely between | Mostly similar | Very small | Unclear | Chance a very likely explanation  | Probably no | Definitely yes | Probably yes | Low |
| Single versus Combined Strains of Probiotics | Completely between | Mostly similar | Rather small | Unclear | Chance a very likely explanation  | Probably no | Definitely yes | Probably yes | Low |
| **Use of antidiarrheal drug** |
| Duration of intervention | Completely between | Mostly similar | Very small | Unclear | Chance a very likely explanation  | Probably no | Definitely yes | Probably yes | Low |
| Genus of probiotics | Completely between | Mostly similar | Rather small | Unclear | Chance a very likely explanation  | Probably no | Definitely yes | Probably yes | Low |
| Single versus Combined Strains of Probiotics | Completely between | Mostly similar | Rather small | Unclear | Chance a very likely explanation  | Probably no | Definitely yes | Probably yes | Low |

Q1, Is the analysis of effect modification based on comparison within rather than between trials? Q2, For within-trial comparisons, is the effect modification similar from trial to trial? Q3, For between-trial comparisons, is the number of trials large? Q4, Was the direction of the effect modification correctly hypothesized priori? Q5, Does a test for interaction suggest that chance is an unlikely explanation of the apparent effect modification? Q6, Did the authors test only a small number of effect modifiers? Q7, Did the authors use a random effects model? Q8, If the effect modifier is a continuous variable, were arbitrary cut points avoided?

**Supplementary Figure 1:** Theeffect of probiotics on the incidence of diarrhea (any grade)

**Supplementary Figure 2:** The effect of probiotics on the incidence of grade ≥2 diarrhea

**Supplementary Figure 3:** The effect of probiotics on the incidence of grade ≥3 diarrhea

**Supplementary Figure 4:** The effect of probiotics on the use of antidiarrheal drug

**Supplementary Figure 5:** The effect of probiotics on the incidence of soft stool consistency

**Supplementary Figure 6:** The Effect of probiotics on the incidence of watery stool consistency

**Supplementary References:**

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