

## REVIEW

# The efficacy and safety of probiotics for prevention of chemoradiotherapy-induced diarrhea in people with abdominal and pelvic cancer: a systematic review and meta-analysis

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A systematic review and meta-analysis were designed to evaluate the efficacy and safety of probiotics for prevention of chemoradiotherapy-induced diarrhea in people with abdominal and pelvic cancer. We searched the Cochrane Library, PubMed, EMBASE and Web of Science up to November 2015. We also hand searched the citation lists of included studies and previously identified systematic reviews to identify further relevant trials. Odds ratio (OR) was used to compare efficacy, and the pooled OR was estimated using a random effects model; heterogeneity was assessed with Cochran's Q and the Higgins'  $I^2$ -test. Two reviewers assessed trial quality and extracted data independently. Analysis and bias for each included study were performed using Review Manager 5.2. Nine randomized and placebo-controlled studies ( $N=1265$  participants) were included for assessing efficacy, of which seven were about radiotherapy and two about chemotherapy. Probiotic groups were compared with control groups with respect to the the incidence of diarrhea, OR=0.47 (95% confidence interval 0.28–0.76;  $P=0.002$ ). Eleven studies, including 1612 people (873 consuming probiotics and 739 not consuming probiotics), were used for the analysis of safety of probiotics. Of the 11 studies, seven studies had no adverse events (AEs) caused by probiotics, whereas four studies reported varying degrees of AEs in their treatment. Probiotics may have a beneficial effect in prevention of chemoradiotherapy-induced diarrhea generally, especially for Grade  $\geq 2$  diarrhea. Probiotics may rarely cause AEs.

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## INTRODUCTION

Probiotics are defined by Fuller<sup>1</sup> as live microbial feed supplements that beneficially affect the host improving its intestinal microbial balance. Some microorganisms are able to resist the physicochemical conditions prevailing in the digestive tract if they are ingested by the host, and the strains most frequently used as probiotics belong to the genera *Bifidobacterium* and *Lactobacillus*.

Radiotherapy or chemotherapy-induced gastrointestinal (GI) disease including diarrhea has been increasing nowadays, with more abdominal and pelvic cancers being treated by chemoradiotherapy. A total of 17 000 patients per year are treated with pelvic radiotherapy in the United Kingdom.<sup>2</sup> Across the developed world, an estimated 150 000 to 300 000 people are being treated annually.<sup>3,4</sup>

One of the most troublesome AEs of chemotherapy is diarrhea. For example, 5-fluorouracil-, capecitabine- and irinotecan-based regimens commonly induce diarrhea in the chemotherapy of colorectal cancer.<sup>5</sup> About 20–45% of all chemotherapy patients experience severe diarrhea during their treatment.<sup>6,7</sup> Radiotherapy or chemotherapy-induced diarrhea (CID) may worsen patients' quality of life, which can lead to interruptions or discontinuation of their treatment.<sup>8</sup> Radiation can give rise to changes in bacterial flora, vascular permeability of the mucosal cells and intestinal

motility.<sup>9,10</sup> Furthermore, chemotherapy changes the composition of the native intestinal microflora, which is significant for metabolism of various intestinal enzymes and regulation of intestinal angiogenesis and immune functions that maintain integrity of gut barrier.<sup>11</sup> Gut microbiota influences human health through an impact on the gut defense barrier, immune function, nutrient utilization and potentially by direct signaling with the GI epithelium.<sup>12,13</sup>

Several clinical trials have shown the efficiency of probiotics in patients undergoing pelvic radiotherapy and chemotherapy.<sup>5,9,14–21</sup> However, both their dosages, bacterial strains and time of therapy were short of homogeneity. In addition, some of studies have not shown a positive curative effect and improvement of the quality of patients.<sup>15,19</sup> The adverse events (AEs) such as infection and bacteremia for probiotics have not been also demonstrated.<sup>5,21</sup> Furthermore, one of the primary outcomes—diarrhea—as one of the main side effects of chemotherapy or radiotherapy—has not been detailedly collected, analyzed and synthesized.

Previous systematic reviews and meta-analysis have shown that probiotics could reduce the incidence of diarrhea or bowel disease correlated with acute infections, antibiotic, chemotherapy or radiotherapy.<sup>22,23</sup> However, few systematic reviews and meta-analysis were performed for abdominal and pelvic radiotherapy or CID for the cancers.

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A systematic review of nine studies at low risk of bias on the use of probiotics supplement during abdominal or pelvic cancer treatment with radiotherapy or chemotherapy was carried out to determine whether probiotics are effective in reducing incidence of chemoradiotherapy-induced diarrhea.

## METHODS

Criteria for considering studies for this review

**Including criteria.** (1) Both randomized and controlled trials (RCTs), and non-RCTs were included; (2) included people with a diagnosis of abdominal or pelvic cancer who had received probiotics; (3) included patients who received radiotherapy, chemotherapy or both; (4) GI symptoms including diarrhea and any AEs such as probiotic-associated infection and bacteremia were reported; (5) the incidence of radiotherapy- or chemotherapy-associated diarrhea was given.

The efficacy of probiotics was assessed with RCTs. Both RCTs and non-RCTs were considered for assessing the safety of probiotics.

**Excluding criteria.** (1) Trials on animals; (2) non-placebo-controlled studies; (3) patients having other primary tumors.

Types of outcome measures

**The primary outcomes.** (1) Incidence of diarrhea (defined by original studies) induced by chemotherapy or radiotherapy; (2) Incidence of the AEs such as infection and bacteremia.

**Secondary outcomes.** Incidence of diarrhea Grade  $\leq 2$ , and Grade  $\geq 2$  and Grade  $\geq 3$  induced by chemotherapy or radiotherapy.

Search strategy

We searched the Cochrane Library, PubMed, EMBASE and Web of Science up to November 2015. We also hand searched the citation lists of included studies and previously identified systematic reviews to identify further relevant trials.

We searched the databases in English, including references of some literatures we read.

Selection of studies

Two assessors independently screened the titles and abstracts of each studies searched through the Cochrane Library, PubMed, EMBASE and Web of Science up to November 2015. When relevant studies became certain, the full texts were obtained for further evaluation.

Data collection

Data for the analysis of the efficacy of probiotics intervention were extracted by a second reviewer. The extracted contents included study demographics, published years, trial design, probiotic regimens outcome(s) and diarrhea grades (according to the National Cancer Institute Common Toxicity Criteria, now called the Common Terminology Criteria for Adverse Events (CTC)),<sup>24</sup> using a standardized form. When the incidence of diarrhea was only presented with percentages, the specific number of people was obtained via converting. In addition, some grades of diarrhea were merged and split to adapt to analyzing the data. Furthermore, incidence of diarrhea Grade  $\leq 2$ , Grade  $\geq 2$ , and Grade  $\geq 3$  was collected, respectively.

The quality of the included studies was scrutinized using the Cochrane Collaboration's 'Risk of bias tool'<sup>25</sup> and assessed according to the Cochrane Collaboration Reviewers' Handbook and in accordance with PRISMA guidelines.<sup>26</sup>

Data collected were input into RevMan 5.2 software for analysis.<sup>27</sup>

Statistical analysis

The data of comparable outcome measures were pooled in meta-analysis, using standard statistical procedures provided in RevMan 5.2,<sup>27</sup> and the odds ratio (OR) was used to compare efficacy. The heterogeneity between studies was evaluated with  $I^2$ .  $I^2 \geq 50\%$  was deemed to represent significant heterogeneity,<sup>25,28</sup> and pooled OR was estimated using a random-effect model. On the contrary, if statistical study heterogeneity was not observed ( $I^2 \leq 50\%$ ), a fixed effects model was used.  $P \leq 0.10$  was considered statistically significant for heterogeneity, whereas  $I^2 = 0\%$  indicates no observed heterogeneity. Subgroup analysis was used in this meta-analysis when the outcomes or intervening measures were significantly different.

Studies analyzed in the meta-analysis were only those that compared placebo or no treatment with probiotics (placebo-controlled studies).

## RESULTS

Included studies

Nine randomized and placebo-controlled studies ( $N=1265$  participants) were included for assessing efficacy, of which seven ( $N=1071$ ) were about radiotherapy and two ( $N=194$ ) about chemotherapy. Of the nine RCTs, seven reported the incidence of diarrhea with grades. Among them, one graded according to the World Health Organization grading<sup>20</sup> and one according to toxicity criteria of the World Health Organization.<sup>15</sup> The others graded according to the Common Toxicity Criteria of the National Cancer Institute.

Eleven studies, including 1612 people (873 consuming probiotics and 739 not consuming probiotics), were used for the analysis of safety of probiotics. Of the 11 studies, seven studies<sup>14-17,19,20,29</sup> had no AEs caused by probiotics, whereas four studies<sup>5,21,30,31</sup> reported varying degrees AEs in their treatment.

The search process and strategy (see Figure 1) of all the nine included studies are displayed according to a flow diagram.<sup>32</sup> Further characters of the eligible studies are presented in Table 1 and Supplementary Table S1. One study was excluded as it was about probiotics treatment not about the prevention of probiotics for radiation-induced diarrhea.<sup>30</sup> One ineligible study did not provide the number of people suffering from diarrhea.<sup>16</sup> The third study was excluded because of its follow-up study in Delia *et al.*<sup>20,33</sup>

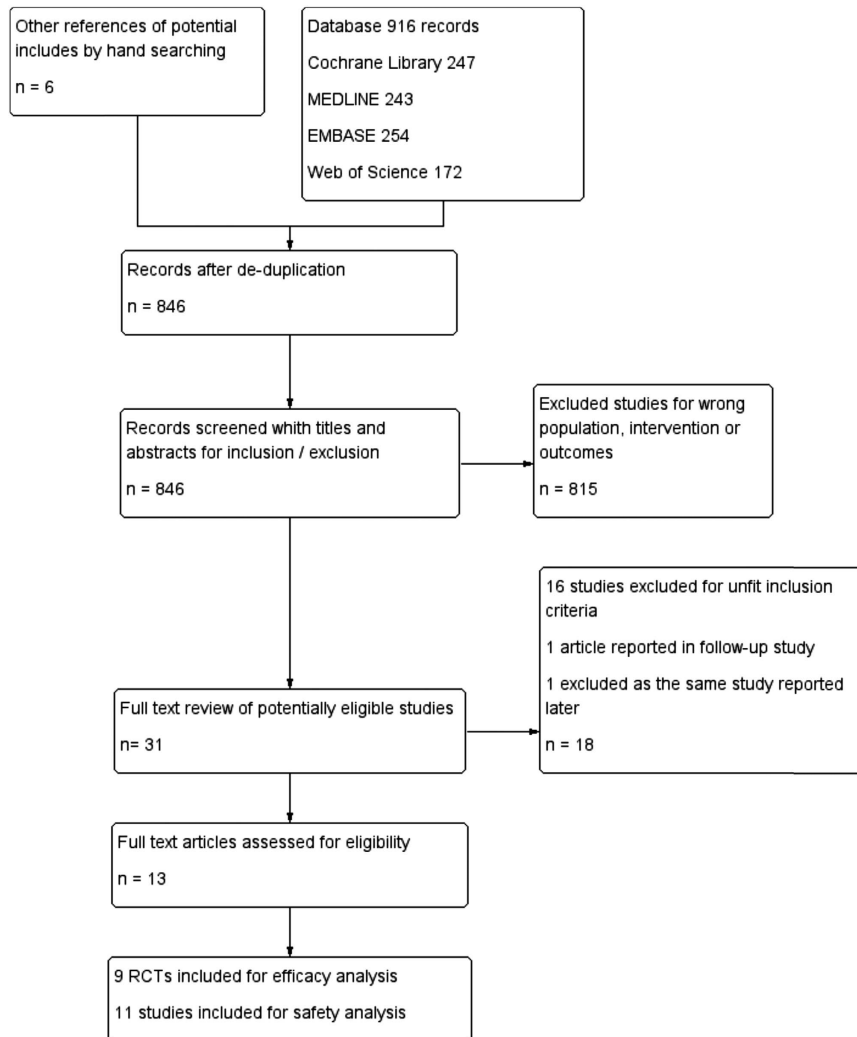
Quality assessment

The risk of bias for each RCT is displayed in Figure 2, and the risk of bias across all RCTs is displayed in Figure 3. These indicated generally good methodological quality. High risk was mainly about blinding issues, which had not been stated in some studies,<sup>5,9</sup> and with one study published only as abstracts.<sup>18</sup> Unclear risks were revealed in quality assessment, because the handling of incomplete outcome data and performance of intention-to-treat analysis were always ambiguous.

The method by Loke *et al.*<sup>34</sup> was used for the quality assessment of studies for the safety analysis. It detected that the definition of AEs in many studies was not clear and reporting bias was evident, which made the measuring of AEs a puzzle.

Efficacy of probiotics

Nine RCTs were deemed to be on diarrhea according to the original research, with some including Grade  $\geq 3$  diarrhea and others including Grade  $\geq 2$  diarrhea, according to the Common Terminology Criteria for Adverse Events<sup>24</sup> (CTC). The criteria are as



**Figure 1.** Flow diagram of the search process and strategy for the efficacy and safety of probiotics for prevention of chemoradiotherapy-induced diarrhea in people with abdominal and pelvic cancer.

follows: Grade 1: stools: increase of < 4 per day; mild increase colostomy output; ostomy output: mild increase; Grade 2: stools: increase of 4–6 per day; ostomy output: moderate increase; Grade 3: stools: increase of 7 or more per day; ostomy output: severe increase; other: loss of continence, hospitalization and limiting activities of daily living; Grade 4: life-threatening consequences; Grade 5: death. As Figure 4 shows, probiotic groups were compared with control groups with respect to the incidence of diarrhea (defined as the frequency of Grade  $\geq 3$  or  $\geq 2$  diarrhea according to the original research) and the pooled OR = 0.47 (95% confidence interval (CI) of 0.28–0.76;  $P = 0.002$ ). For subgroup analysis, the pooled OR of radiotherapy induced diarrhea (RID) is 0.48 (95% CI of 0.27–0.85;  $P = 0.01$ ) and for CID, the pooled OR is 0.40 (95% CI of 0.15–1.03;  $P = 0.06$ ).

Six RCTs looked at the frequency of CTC Grade  $\leq 2$  diarrhea. As displayed in Supplementary Figure S1, meta-analysis comparing probiotic group with control groups showed non-significance (OR = 1.33, 95% CI 0.67–2.64,  $P = 0.42$ ). For subgroup analysis, the pooled OR of RID is 0.99 (95% CI of 0.48–2.05;  $P = 0.99$ ) and for CID, the pooled OR is 2.52 (95% CI of 0.97–6.53;  $P = 0.06$ ).

Four RCTs looked at the frequency of CTC Grade  $\geq 2$  diarrhea. As displayed in Figure 5, the pooled OR of incidence of chemoradiotherapy-induced diarrhea is 0.36 (95% CI 0.21–0.59;  $P < 0.0001$ ).

Six RCTs were regarded as the frequency of CTC Grade  $\geq 3$  diarrhea. As displayed in Supplementary Figure S2, meta-analysis comparing probiotic group with control groups showed significance (OR = 0.35, 95% CI 0.13–0.96,  $P = 0.04$ ). For subgroup analysis, the pooled OR of RID is 0.37 (95% CI of 0.09–1.60;  $P = 0.19$ ) and for CID, the pooled OR is 0.40 (95% CI of 0.15–1.03;  $P = 0.06$ ).

#### Safety of probiotics

Eleven studies were used for the analysis of safety of probiotics. As displayed in Supplementary Table S1, of the 11 studies, seven studies had no AEs caused by probiotics in prevention of chemoradiotherapy-induced diarrhea,<sup>14–17,19,20,29</sup> whereas four studies reported AEs with varying degrees in their treatment.<sup>5,21,30,31</sup> The 11 studies included 1612 people (873 consuming probiotics and 739 not consuming probiotics).

The exact number of patients suffering AEs was not clear, because some studies only gave the incidence of AEs without stating the study group or the control group. In both groups, 16 were found with severe AEs, including one death, as discussed later.

In the study from Demers *et al.*,<sup>15</sup> no septicemia was recorded, although a few cases of neutropenia occurred during treatment, but the incidence of neutropenia was not given.

**Table 1.** Characteristics of included studies for the analysis of efficacy

Study	Year	Design	Participants and cancers	Interventions and comparisons	Outcomes
<i>Probiotics vs placebo</i> Mego <i>et al.</i> <sup>14,a</sup>	2015	Randomized, double-blind, placebo-controlled study	Between January 2011 and December 2013, 46 patients with colorectal cancer	Probiotics ( <i>Bifidobacterium</i> , <i>Lactobacillus</i> , <i>Streptococcus</i> ) vs placebo (inactive ingredients without probiotic bacteria)	Diarrhea, gastrointestinal and all other toxicity; the number of days when anti-diarrheal drugs were used; number of tablets of anti-diarrheal drugs
Demers <i>et al.</i> <sup>15,b</sup>	2014	Randomized parallel-group, placebo-controlled trial	Patients with rectal, cervical, endometrial or prostatic cancer were treated between 2006 and 2010 ( <i>n</i> = 246)	Standard- and high-dose probiotics ( <i>Lactobacillus acidophilus</i> and <i>Bifidobacterium longum</i> ) vs placebo	Time of appearance and grade of diarrhea; other digestive symptoms
Chitapanarux <i>et al.</i> <sup>17,a</sup>	2010	Randomized, double-blind, placebo-controlled study	Patients undergoing pelvic radiotherapy concurrent with weekly cisplatin ( <i>n</i> = 63); FIGO stage IIB and IIBB squamous cell carcinoma of cervix	Placebo and probiotics ( <i>Lactobacillus acidophilus</i> plus <i>Bifidobacterium bifidum</i> ); ( <i>n</i> = 32); (inflan) vs placebo ( <i>n</i> = 31)	Incidence of diarrhea, anti-diarrhea drug used, stool, WCC in stools, red blood cells in stools, median overall time, median weight change
Castro <i>et al.</i> <sup>18,a</sup>	2009	Randomized, double-blind, placebo-controlled trials	Radiation-induced bowel damage patients with gynecologic cancer ( <i>n</i> = 40)	Probiotics ( <i>Lactobacillus casei</i> Shirota e o <i>Bifidobacterium breve</i> ); ( <i>n</i> = 20) vs placebo ( <i>n</i> = 20)	Daily stool consistency (Bristol scale); incidence of diarrhea, defined by a CTC of two or greater, or the need for loperamide
Giralt <i>et al.</i> <sup>19,a</sup>	2008	Double-blind, placebo-controlled randomized clinical trial in two parallel groups	Female patients with a diagnosis of endometrial adenocarcinoma or advanced cervical squamous cell carcinoma ( <i>n</i> = 85)	Probiotics ( <i>Lactobacillus casei</i> DN-114 001, <i>Streptococcus thermophilus</i> and <i>Lactobacillus delbrueckii</i> , subsp. <i>Bulgarius</i> ) vs placebo	Incidence of diarrhea; incidence of loperamide use; mean time to diarrhea symptoms; stool consistency; median time before loose stools
Osterlund <i>et al.</i> <sup>5,a</sup>	2007	Open-label, prospective, randomized, phase III study	Patients diagnosed with colorectal cancer were treated between November 1997 and August 2001 ( <i>n</i> = 148)	Probiotics ( <i>Lactobacillus rhamnosus</i> GG) ( <i>n</i> = 97) vs placebo (guar gum containing nutritional supplement); ( <i>n</i> = 51)	Incidence of all kinds of stomatitis, diarrhea, neutropenia, neutropenic infection, hand-foot syndrome
Delia <i>et al.</i> <sup>20,c</sup>	2007	Double-blind, randomized, parallel-group, placebo-controlled trial	Patients who underwent adjuvant post-operative radiation therapy after surgery for sigmoid, rectal or cervical cancer ( <i>n</i> = 490)	Probiotics VSL#3 ( <i>Lactobacillus</i> subsp. <i>Bulgarius</i> , <i>Bifidobacterium</i> , <i>Streptococcus salivarius</i> subsp. <i>thermophilus</i> ) vs placebo	Incidence of diarrhea; daily bowel movements; mean time to the use of loperamide
Okawa <i>et al.</i> <sup>21,d</sup>	1993	Randomized, parallel-group, controlled trial	Patients with FIGO stage IIB squamous cell carcinoma of the uterine cervix ( <i>n</i> = 213)	Probiotics LC9018 (yakult, prepared from <i>Lactobacillus casei</i> ); ( <i>n</i> = 102) vs placebo ( <i>n</i> = 111)	Incidence of diarrhea; incidence of abdominal pain
Salminen <i>et al.</i> <sup>9,d</sup>	1988	Randomized parallel-group study (with no treatment group)	Patients with diagnosis of cervix or uterus carcinoma (age: 40–75 years); ( <i>n</i> = 24)	Probiotics ( <i>Lactobacillus acidophilus</i> bacteria) ( <i>n</i> = 11) vs placebo (dietary counseling); ( <i>n</i> = 10)	Incidence of diarrhea, flatulence and loss of appetite

Abbreviations: CTC, common toxicity criteria; FIGO, federation internationale de gynecologie and obstetrique; WCC, white cell counts. <sup>a</sup>Diarrhea was graded according to the Common Toxicity Criteria of the National Cancer Institute. <sup>b</sup>Diarrhea was graded according to toxicity criteria of the World Health Organization (is similar to the CTC of the National Cancer Institute). <sup>c</sup>Diarrhea was graded according to the World Health Organization grading. <sup>d</sup>Diarrhea was not graded and was only reported with the overall incidence. Delia *et al.*<sup>20</sup> did not qualitatively affect the statistical results of CTC Grade  $\leq 2$  and Grade  $\geq 3$  diarrhea, although its diarrhea was not graded according to the Common Toxicity Criteria of the National Cancer Institute.

Osterlund *et al.*<sup>5</sup> reported 2 out of 51 neutropenic infected in the no probiotic group and 9 of 97 in the probiotic group, but no growth of *Lactobacillus* in blood cultures.

One death during radiation therapy was reported by Okawa *et al.*,<sup>21</sup> which failed to complete treatment, but no evidence proved it was caused by probiotics. Furthermore, fever was reported with 9 of 102 in the study group, but 1 of 111 in the control group; anorexia was reported with 27 of 102 in the study group and 42 of 111 in the control group.

Urbancsek *et al.*<sup>30</sup> reported that severe AEs were not observed in his study. However, three patients reported AEs in both groups. In the Antibiophilus group, three patients reported mild-to-moderate GI problems, whereas in the placebo group, two patients reported moderate-to-severe GI events and one patient observed a mild labial edema.

In the study by Henriksson *et al.*,<sup>31</sup> one patient, taking Verum Halsofil, who was excluded from the evaluation displayed a worse reaction due to lactose intolerance.

The other potential AEs not pointed out above, as shown in Supplementary Table S1, were of similar frequencies comparing probiotic groups with control groups.

## DISCUSSION

This review found nine RCTs of probiotics for prevention of chemoradiotherapy-induced diarrhea and identified eleven studies reporting on AEs. These studies were heterogeneous in terms of the treatment strategies used (strains, doses and therapeutic time of probiotics), the patient ages, comorbidities, tumor types, and therapies given (in the decision to perform surgery) and outcomes assessed, which potentially were the reasons for the between-study heterogeneity of the results.

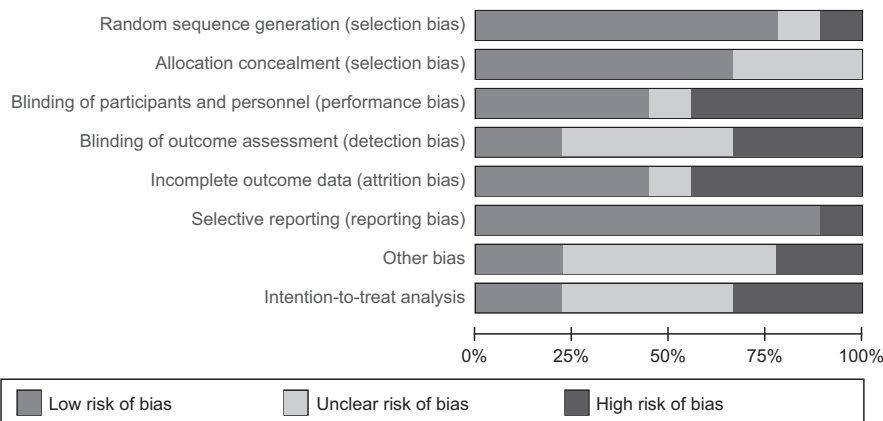
The risk of bias in the efficacy RCTs was mainly in connection with performance bias and attrition bias. The method of Loke *et al.*<sup>34</sup> was used as a qualitative measurement tool for quality assessing the safety of probiotics, which highlighted that many studies were unclear on the definition of an AE and on its measuring method.

We carried out sensitivity analysis by eliminating study *seriatim*. For CTC Grade  $\leq 2$  diarrhea, sensitivity analysis showed a qualitative change in conclusions. When the study by Demers *et al.*<sup>15</sup> was eliminated, the pooled *P*-value of RID changed from 0.99 to 0.04. This may be due to the high incidence of diarrhea in the probiotic group in that study. Likewise, for CTC Grade  $\geq 3$  diarrhea, when the study by Giralt *et al.*<sup>19</sup> was eliminated, the pooled *P*-value of RID significantly changed from 0.19 to 0.04 for the similar reason. However, our sensitivity analysis detected no significant change in conclusions of the incidence of RID (defined by the original researches) and CTC Grade  $\geq 2$  diarrhea.

Diarrhea of Demers *et al.*<sup>15</sup> was graded according to toxicity criteria of the World Health Organization, which was similar to the CTC of the National Cancer Institute, and was classified as the CTC of the National Cancer Institute. Delia *et al.*<sup>20</sup> graded diarrhea according to the World Health Organization grading, but it did not qualitatively affect the statistical results of CTC Grade  $\leq 2$  and Grade  $\geq 3$  diarrhea, although diarrhea was not graded according to the Common Toxicity Criteria of the National Cancer Institute.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias	Intention-to-treat analysis
Castro 2009	?	?	-	-	?	+	-	?
Chitapanarux 2010	+	+	+	?	+	+	?	+
Delia 2007	-	+	-	-	-	-	?	?
Demers 2014	+	+	+	+	-	+	+	-
Giralt 2008	+	+	+	?	-	+	-	?
Mego 2015	+	+	+	+	+	+	+	+
Okawa 1993	+	?	?	?	+	+	?	-
Osterlund 2007	+	+	-	?	+	+	?	?
Salminen 1988	+	?	-	-	-	+	?	-

**Figure 2.** Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



**Figure 3.** Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

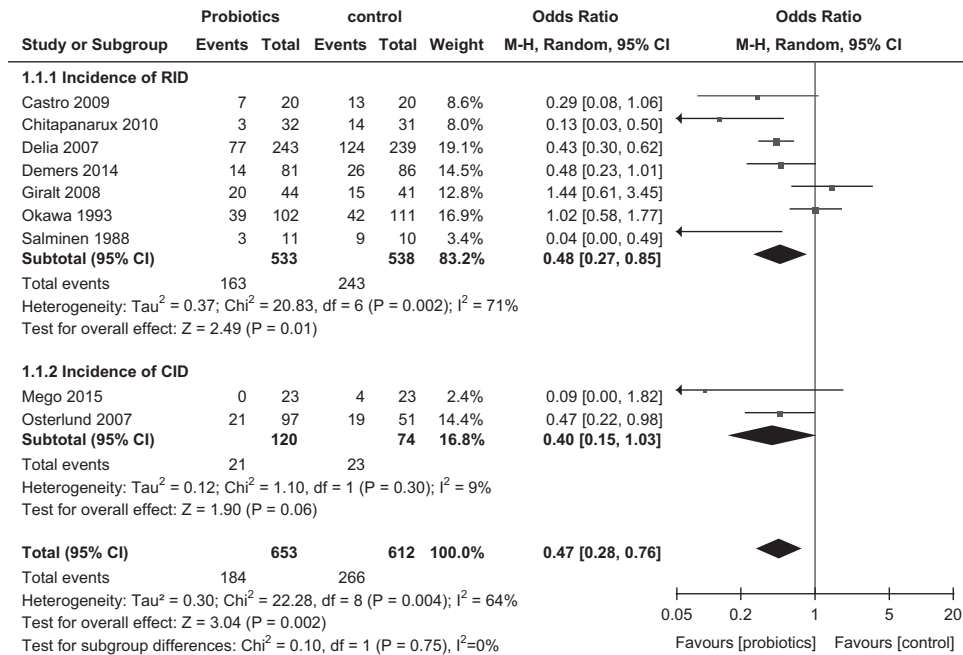


Figure 4. Forest plot comparing probiotics vs placebo with respect to incidence of diarrhea.

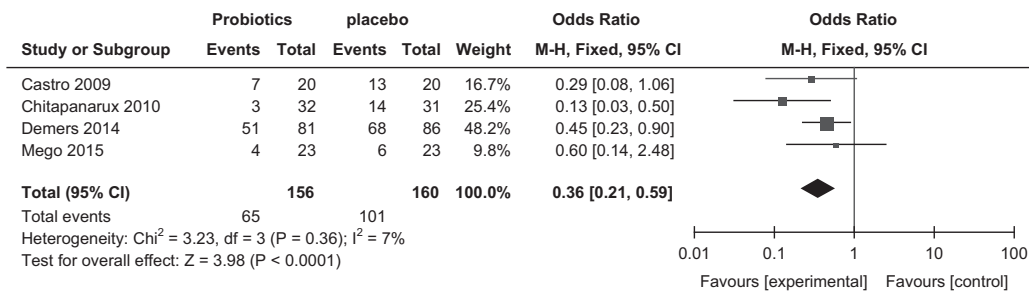


Figure 5. Forest plot comparing probiotics vs placebo with respect to incidence of Grade  $\geq 2$  diarrhea.

### Efficacy

The incidence of diarrhea (defined as the frequency of Grade  $\geq 3$  or  $\geq 2$  diarrhea) according to the original research was used as the primary outcome. CTC Grade  $\leq 2$ ,  $\geq 2$  and  $\geq 3$  diarrhea were valuable indicators for the severity of diarrhea. This meta-analysis found that, for the incidence of diarrhea, the probiotic group had a significant reduction, as the pooled OR = 0.47 (95% CI of 0.28–0.76;  $P = 0.002$ ). For subgroup analysis, the pooled OR of RID is 0.48 (95% CI of 0.27–0.85;  $P = 0.01$ ), consistent with the result of Hamad *et al.*<sup>23</sup> However, for the CID, the probiotic group seemingly had unclear numerical reduction in the incidence of diarrhea, as the pooled OR is 0.40 (95% CI of 0.15–1.03;  $P = 0.06$ ), probably because the small number of studies and patients about chemotherapy were included.

However, disappointingly, there was nonsignificant reduction in the frequency of CTC Grade  $\leq 2$  diarrhea (OR = 1.33, 95% CI 0.67–2.64,  $P = 0.42$ ). For subgroup analysis, consistent with the overall effect, the pooled OR of RID is 0.99 (95% CI of 0.48–2.05;  $P = 0.99$ ) and for CID, the pooled OR is 2.52 (95% CI of 0.97–6.53;  $P = 0.06$ ).

Amazingly, the probiotic group obviously reduced the incidence of CTC grade  $\geq 2$  diarrhea, (OR = 0.36; 95% CI 0.21–0.59;  $P < 0.0001$ ), also demonstrated in the meta-analysis of Redman *et al.*<sup>22</sup>

However, the effect of probiotics was not so significant for reducing incidence of CTC Grade  $\geq 3$  diarrhea, as the OR is 0.35 (95% CI 0.13–0.96;  $P = 0.04$ ), and that, for subgroup analysis, it is

also unclear for RID (OR = 0.37, 95% CI 0.09–1.60;  $P = 0.19$ ) and for CID (OR = 0.40, 95% CI 0.15–1.03;  $P = 0.06$ ).

There were also some other outcomes in the included studies, such as the use of antidiarrheal (rescue) medication, stool consistency, mean daily number of bowel movements and abdominal pain. However, out of inconsistency and poor homogeneity, these outcomes were not assessed in this meta-analysis. Moreover, for detailedly and systematically assessing and analyzing the efficacy of probiotics to chemoradiotherapy-induced diarrhea, in this meta-analysis, we only strictly selected RCTs that reported incidence of diarrhea with grades.

### Safety

As Redman *et al.*<sup>22</sup> reported in a previous systematic review, there was a wide range of AEs for using probiotics in patients with cancer, 'including: bacteraemia/fungaemia, infection, GI symptoms (diarrhoea, constipation, dysphagia, nausea and vomiting), urinary symptoms (only present in patients with transitional cell carcinomas), sicchasia, raised blood pressure and raised intra-cranial pressure'. Because of the heterogeneity of the different treatment regimes and malignancies, the AEs associated with probiotics could not be distinguished. Another, what Redman *et al.*<sup>22</sup> studied and assessed was all kinds of tumors, including case reports and non-abdominal or pelvic cancers.

The 11 studies assessed in our review included 1612 people (873 consuming probiotics and 739 not consuming probiotics). Seven studies had no AEs caused by probiotics in prevention of chemoradiotherapy-induced diarrhea, whereas four studies reported varying degree AEs in their treatment. The exact number of patients suffering AEs was not clear, for some studies only gave the incidence of AEs without stating the study group or the control group. There were 16 severe AEs found, including one death, in both the probiotic group and the placebo groups. In comparison with the total number of participants, although 16 severe AEs were not a great number, the risk of probiotics needs to be considered because of many cancer patients being immunocompromised.

#### Further work

Our search strategy for this review was comprehensive, broad and systematic, with hand searching some references of included studies and previous systematic reviews.

As different results for different Grades diarrhea previously mentioned in results, further more studies with CTC grading for outcome of diarrhea are needed. With further studies completed and available, more clinically convincing results may be drawn later. In addition, an important question that if the probiotics could lead to infection in people with cancer needs to be answered.

#### CONCLUSION

This systematic review has shown that probiotics may have a role in preventing chemoradiotherapy-induced diarrhea in people with abdominal and pelvic cancer. Our meta-analysis has found that supplement of probiotics could reduce the incidence of radiotherapy-induced diarrhea (defined by the original researches), as well as the incidence of CTC Grade  $\geq 2$  and Grade  $\geq 3$  diarrhea induced by radiotherapy. What deserved to be mentioned is that the incidence of CTC Grade  $\geq 2$  radiotherapy-induced diarrhea can be significantly reduced. However, probiotics may not reduce the frequency of CTC Grade  $\leq 2$  diarrhea induced by both chemotherapy and radiotherapy. For CID, neither incidence of diarrhea (defined by the original researches) nor incidence of CTC Grade  $\geq 3$  diarrhea was reduced. On the basis of our review, there may be a rare risk of probiotics-associated infection, sepsis and bacteremia.

#### CONFLICT OF INTEREST

The authors declare no conflict of interest.

#### AUTHOR CONTRIBUTIONS

K-KW and LJ contributed to the study design, data analysis and quality assessment; Z-XW, Jian-meng Zhao and CXP contributed to the literature search; SH, Jun Wang and NY contributed to the manuscript writing.

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