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Protective efficacy of probiotics on the treatment of acute rotavirus diarrhea in children: an updated meta-analysis

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Abstract. – OBJECTIVE: This meta-analysis aims to uncover the therapeutic efficacy of probiotics on acute rotavirus diarrhea (RVD) in children.

MATERIALS AND METHODS: Randomized controlled studies reporting therapeutic efficacy of probiotics on acute RVD in children published before 1st June 2019 were searched in PubMed, EMBASE, and Cochrane. The citations in all searched literature were manually examined. Data were extracted from eligible literature for calculating STD Mean Difference (SMD) and its corresponding 95% confidence interval (CI). Subsequently, the association between therapeutic efficacy of probiotics and acute RVD in children was evaluated. Moreover, data were weighted by an inverse variance and analyzed by a fixed or random effect model. Heterogeneity test was applied in the enrolled literature. Sensitivity and publication bias was examined. STATA 12.0 was used for meta-analysis.

RESULTS: A total of 19 independent Randomized Controlled Trials (RCTs) involving 1,624 children with acute RVD were enrolled in this study. Three pieces of literature were excluded through sensitivity and publication bias analyses. Data extracted from eligible literatures indicated that probiotics could markedly reduce the occurrence of acute RVD in children (SMD=-0.49, 95% CI=-0.74-0.25). Subgroup analysis conducted based on ethnicity uncovered a poor therapeutic efficacy of probiotics on reducing the occurrence of acute RVD in Asian children (SMD=-0.45, 95% CI=-0.94-0.04), which was markedly significant in Caucasian children (SMD=-0.54, 95% CI=-0.78--0.30). In addition, the subgroup analysis based on the probiotic subtypes found a pronounced efficacy of both *Lactobacillus acidophilus* (SMD=-0.67, 95% CI=-0.92-0.42) and *non-Lactobacillus acidophilus* probiotic (SMD=-0.45, 95% CI=-0.77-0.14) on the occurrence of acute RVD in children.

CONCLUSIONS: Probiotics could reduce the occurrence of acute RVD in children, especially in Caucasian population. Our findings still needed to be further validated in a multi-center institution with larger sample size and more qualified data.

Key Words
Probiotics, Therapeutic efficacy, Acute rotavirus diarrhea in children, Meta-analysis.

Introduction

Diarrheal diseases severely threat children's health worldwide. Rotavirus is the leading cause of diarrhea in infants and young children[1-3]. Globally, about two million people are admitted each year due to rotavirus diarrhea (RVD) infection, with 608,000 deaths in infants[3-5]. The main clinical manifestations of RVD include non-blood watery stools, vomiting, fever, dehydration, nutritional disorders, etc.[5,6]. Rotavirus is mainly transmitted through the fecal-oral route. Even a small amount of virus particles (<100) can induce rotavirus infection[6]. It mainly invades mature epithelial cells and crypt cells of the intestinal villi. Once the virus invades intestinal epithelial cells, it produces NSP4 enterotoxin, further enhancing intracellular calcium ion level through phospholipase C-dependent signaling. Meanwhile, the elevation of cl-secretion leads to secretory diarrhea[6,7]. Besides, viruses replicate in columnar epithelial cells at the top of small intestinal villi. This can cause denaturation and apoptosis of epithelial cells. Insufficient secretion of lactase results in poor absorption of disaccharides in food, incomplete digestion of sugars, as well as increased osmotic pressure in intestinal cavity. As a result, a large amount of fluid accumulates in the intestinal lumen, eventually causing watery and osmotic diarrhea[7]. Current understanding of the potential influence of rotavirus on intestinal mucosal barrier remains unclear. There is still a lack of ideal preventive vaccine and therapeutic drugs for RVD[8-10]. In clinical application, the therapeutic approaches for RVD include fluid infusion, correction of water and electrolyte disorders, and administration

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of intestinal mucosal protective agents, probiotics, and other micro-ecological regulators[10].

Probiotics are living microorganisms, which have beneficial effects on the host under a certain amount of administration[11,12]. They are mainly applied for prevention of infection and treatment of allergic disease, diarrhea, and inflammatory diseases, such as inflammatory bowel disease, reproductive tract, and urinary tract infections[13,14]. A great number of articles have reported the pathogenesis of probiotics application in the treatment of RVD, including *Bacillus bifida*, *Streptococcus thermophilus*, *Lactobacillus paracasei*, *Lactobacillus reuteri*, and *Probiotics complex VSL3*[14,15]. Probiotics contribute to stabilize and strengthen the intestinal mucosal barrier, produce antimicrobial active substances, stimulate local immunity, and enhance non-specific immune response[11,16,17]. So far, many studies have been conducted to analyze the therapeutic efficacy of probiotics on acute RVD in children. However, their conclusions are still controversial[18-20]. Therefore, the aim of this meta-analysis was to uncover the precise association between probiotics effect and acute RVD in children.

Materials and Methods

Literature Search

Articles reporting therapeutic efficacy of probiotics on acute RVD in children published before 1st June 2019 were searched in PubMed, EMBASE, and Cochrane. The key words searched were as follows: "probiotic", and "treatment" or "efficacy", and "rotavirus" and "diarrhea". Citations in all searched literature were manually examined. No limitations on publication years and regions were set. Briefly, titles and abstracts were first examined by two investigators independently. Next, the full texts were reviewed to determine whether it could be included. Studies with larger sample size or latest published were selected if data overlapping.

Inclusion and Exclusion Criteria

Completely published articles reporting therapeutic efficacy of probiotics on acute RVD in children were searched. Inclusive criteria were as follows: (1) study design: randomized controlled trials (RCTs) or semi-RCTs, i.e., random assignments either with blinded method or not. Prompt terms were shown in the article, including "randomized control", "randomized grouping", "random number table", "random", etc; (2) subjects: children with clinically diagnosed acute RVD. No limitations were set on age, gender, ethnicity, and nationality; (3) intervention approach: probiotics and placebo were applied in the experimental group and control group, respectively; (4) clinical outcomes: duration of diarrhea after drug intervention in children with acute RVD; (5) precise and adequate data were acquired for analyzing clinical outcomes.

Exclusive criteria: (1) case studies without control group; (2) self-cross-control study; (3) animal or cellular experiments; (4) review, meta-analysis, comments or other non-clinical trials; (5) case report or control studies between disease and non-disease group; (6) repeated articles; (7) non-English published articles; (8) studies with untraceable data.

Data Extraction

Two investigators were responsible for manual review on enrolled articles by examining titles, abstracts, and key words. Non-RCTs, repeated or non-full-text articles were excluded. Subsequently, the full texts were reviewed for further screening. A third investigator was responsible for re-evaluating disagreements.

Baseline data were extracted, including first author, year of research, ethnicity, control resource, probiotics types and doses, clinical outcomes, etc.

Statistical Analysis

STATA 12.1 (London, China) was used for all statistical analysis. Categorical data were expressed as SMD and 95% CI. Heterogeneity in the enrolled studies was tested using χ^2-test, with a test level of $\alpha = 0.10$. The fixed effect model was utilized for analyzing the data of non-heterogeneity; otherwise, a random effect model was applied. The factors with heterogeneity were subjected to subgroup analyses. Sensitivity analysis was conducted by re-calculating pooled SMD using the Z test after removal of one article each time. Begg's test and Egger's test were utilized for evaluating the publication bias.

Results

Characteristics of the Articles

Generally, 19 independent Randomized Controlled Trials (RCTs) involving 1,624 children with acute RVD were enrolled in this study[18-36]. The detailed characteristics of these articles were listed in Table I. Figure 1 depicted article search, selection process, and explanation of reasons.

Table I. Characteristics of studies that investigated the association between Probiotic and acute rotavirus diarrhea.

Author	Year	Country	Ethnicity	Age range (months)	Strain	Probiotic treatment		Vehicle	Control group	Concomitant treatment	II
						Dose (CFU)	Duration (day)				
Hong	2018	Vietnam	Asian	11-21	Lactobacillus acidophilus	$5*10^8$	Twice a day for 5 days	Water	Placebo	ORT	
Das	2016	India	Asian	15-34	Saccharomyces boulardii	500 mg	Twice a day for 5 days	Water	Placebo	ORT	
Lee	2015	Korean	Asian	3-73	Bifidobacterium longum, B. lactis, Lactobacillus acidophilus, L. rhamnosus, L. plantarum, and Pediococcus pentosaceus	109	Twice a day for 7 days	–	Placebo	–	
İşlek	2014	Turkey	Caucasian	2-60	B. lactis B94	5*1010	Once a day for 5 days	Water	Placebo	ORT or intravenous fluid therapy	
Aggarwal	2013	India	Asian	7-34	Lactobacillus GG	1010	Once a day for 5 days	Milk	Placebo	ORT	
Abbaskhaniyan	2012	Iran	Asian	6-72	L. acidophilus&Bifidobacteria	107	3 times per day	Yogurt	Placebo	ORS	
Dutta	2011	India	Asian	6-24	Lactobacillus Sporogenes (Bacillus coagulans)	6*107	Twice a day for 5 days	Water	Placebo	ORT	
Dalgic	2011	Turkey	Caucasian	1-28	Saccharomyces boulardii	250 mg	Once a day for 5 days	–	Oral and/or parenteral solutions	ORS	12
Grandy	2010	Bolivia	Caucasian	1-23	Group A. Saccharomyces boulardii, Group B. A compound containing L. acidophilus & L. rhamnosus& B. longum& S. boulardii		Twice a day for 5 days	Water	Placebo	ORT	
Ritchie	2010	Australian	Caucasian	4-24	Lactobacillus casei strain GG	5*109	3 times for 3 days	Capsule contained 5 ml of sterile Nacl 0.9 %	Placebo intravenous	ORS or solution with Ringer's lactate	8

Continued

Table I (continued). Characteristics of studies that investigated the association between Probiotic and acute rotavirus diarrhea.

Author	Year	Country	Ethnicity	Age range (months)	Strain	Probiotic treatment		Vehicle	Control group	Concomitant treatment	II
						Dose (CFU)	Duration (day)				
Narayanappa	2008	India	Asian	3-36	Probiotic (Bifilac)	1 sachet	3 times for 14 days	Sachets	Placebo	ORS	27
Szymanski	2006	Poland	Caucasian	2-72 (Rotavirus infection: 45%)	Lactobacillus rhamnosus GG	1.2*1010	Twice daily for 5 days	Freezed dried	Placebo	–	
Sarker	2005	Bangladesh	Asian	4-24	L. paracasei	5*1010	Twice daily for 5 days	ORS	Placebo	ORS	
Rosenfeldt	2002	Denmark	Caucasian	6-36	L. rhamnosus 19070-2&L.reuteri DSM 12246	4*1010	Twice daily for 5 days	Consisted of lyophilized	Placebo	–	
Guandalini	2000	Mixed	Caucasian	1-36	Lactobacillus GG	At least 1010 CFU/250ml	–	ORS	ORS+ Placebo	ORS	
Simakachorn	2000	Thailand	Asian	3-24	L. acidophilus LB	5*109	Twice daily for 5 days	Sachet	Placebo	ORT	
Shornikova	1997	Russia	Caucasian	1-36	Lactobacillus rhamnosus GG	5*109	Twice daily for 5 days	85	Placebo	ORT	
Shornikova	1997	Russia	Caucasian	6-36	L. reuteri	Small dosage (107 CFU) Large dosage (1010 CFU)	Once a day up to 5 days	Water &mixed	Placebo	–	
Kaila	1995	Finland	Caucasian	7-37	L. casei strain GG	1010-11	125 gr twice daily	Fermented milk product	Placebo	ORT	

ORS: oral rehydration solution; ORT: oral rehydration treatment.

Among the 19 articles, 9 were conducted in the Asian population and 7 were in the Caucasian population, respectively. Besides, probiotic subtypes were recorded, and 3 articles reported *Lactobacillus acidophilus*.

Quantitative Synthesis Results

Initially, our analysis showed that probiotics could remarkably reduce the incidence of acute RVD in children (STD Mean Difference (SMD)=-1.21, 95% confidence interval (CI)=-1.72-0.70). Due to sensitivity factors and publication bias, three studies were excluded[21-23]. Subsequent analysis demonstrated that probiotics markedly reduced the incidence of acute RVD in children (SMD=-0.49, 95% CI=-0.74-0.25) (Figure 2).

Subgroup analysis uncovered that the therapeutic effect of probiotics on acute RVD in Asian children was poor (SMD=-0.45, 95% CI=-0.94-0.04). However, it was relatively better in Caucasian children (SMD=-0.54, 95% CI=-0.78--0.30) (Figure 3A).

Furthermore, subgroup analysis based on subtypes of probiotic found a pronounced efficacy of both *Lactobacillus acidophilus* (SMD=-0.67, 95% CI=-0.92-0.42) and *non-Lactobacillus acidophilus* probiotic (SMD=-0.45, 95% CI=-0.77-0.14) on reducing the occurrence of acute RVD in children (Figure 3B).

Sensitivity Analysis

Individual influence on SMD was assessed by sensitivity analysis. Pooled SMD in our analysis was not influenced by removal of any single article each time, verifying the robust conclusion (Figure 4).

Publication Bias

In the present study, the publication bias was assessed using the Begg's test and Egger's test. Before the exclusion of three biased articles, the shape of the Begg's funnel plots was asymmetrically distributed, showing a potential publication bias (Figure 5A). After the removal three articles, the shape became symmetrical (Figure 5B).

Discussion

Rotavirus is the most important pathogen of severe diarrhea in infants under 2 years old worldwide[1-3]. In developing countries, rotavirus is the leading cause of fatal diarrhea in infants and young children[3,4]. In China, autumn and winter are the peak seasons for infantile diarrhea. Etiological studies have confirmed that 40-60% of infant diarrhea cases are caused by rotavirus infection[4,5]. Extra-intestinal complications may develop in severe RVD patients. They eventually aggravate due to the infections of the central nervous system, liver, kidney, heart, and pancreas. Currently, there is still a lack of effective anti-rotavirus drugs[5-7]. Meanwhile, the epidemiology of rotavirus is complicated because of its multiple serotypes and subtypes[8-10].

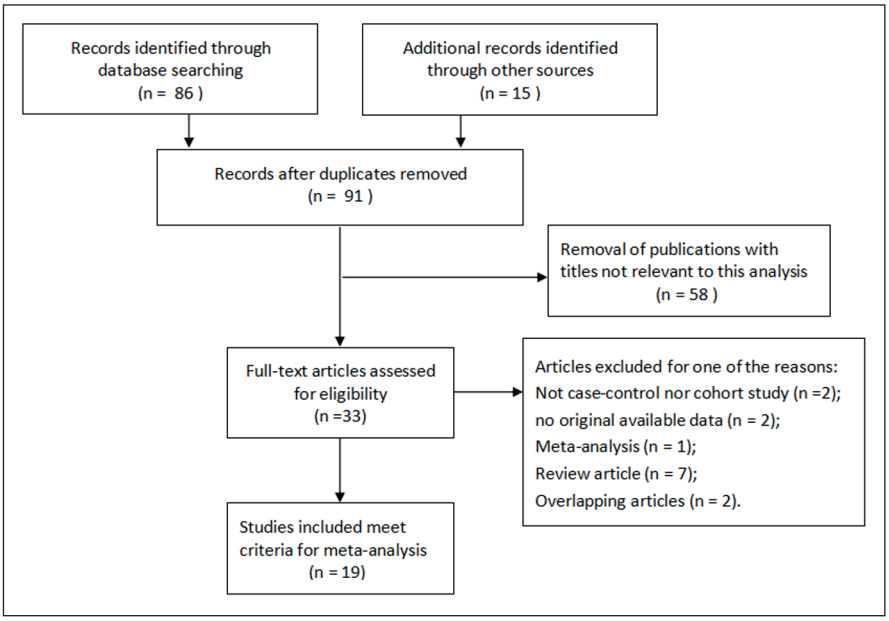

Figure 1. Flow diagram of literature search and selection process.

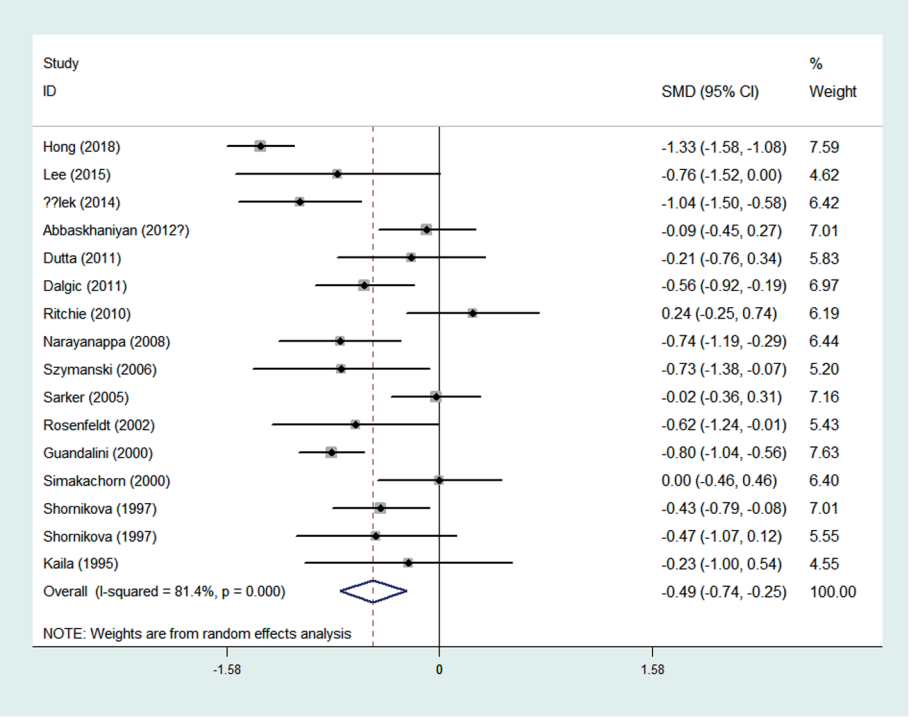

Figure 2. Forest plots of the efficacy of probiotics in treatment of children with acute rotavirus diarrhea in a random-effect model.

Probiotics can improve the defense mechanism of the endogenous hosts. In addition to non-immune regulation of stable micro-ecological environment, probiotics can enhance immune defense function by improving humoral immunity and non-specific immunity of host to pathogen[11,12]. Meanwhile, they can increase the amount of intestinal mucosal cells, infiltrate lymphocytes, histiocytes, macrophages, and plasma cells. Natural killer (NK) cell activity, T cell function, phagocytic activity of monocytes and macrophages, and Secretory immanoglobulinA (SlgA) synthesis are enhanced by probiotics application[11,13-17]. Current studies have indicated that probiotics induce the elevation of local immune function, further resisting infection.

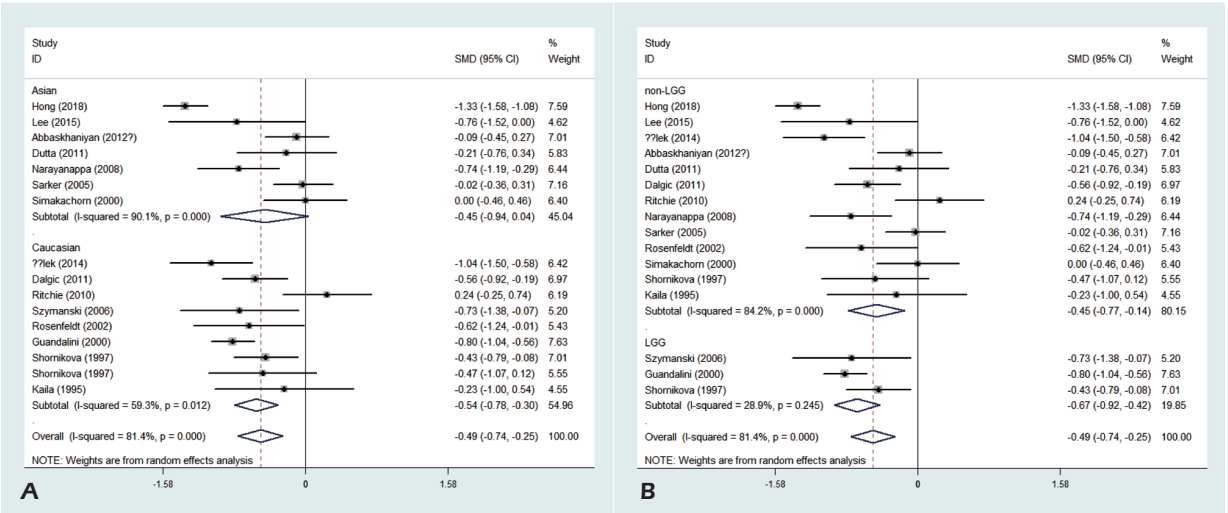

Figure 3. Forest plots of the efficacy of probiotics in treatment of children with acute rotavirus diarrhea in a random-effect model. **A**, Stratified by ethnicity. **B**, Stratified by probiotic subtypes.

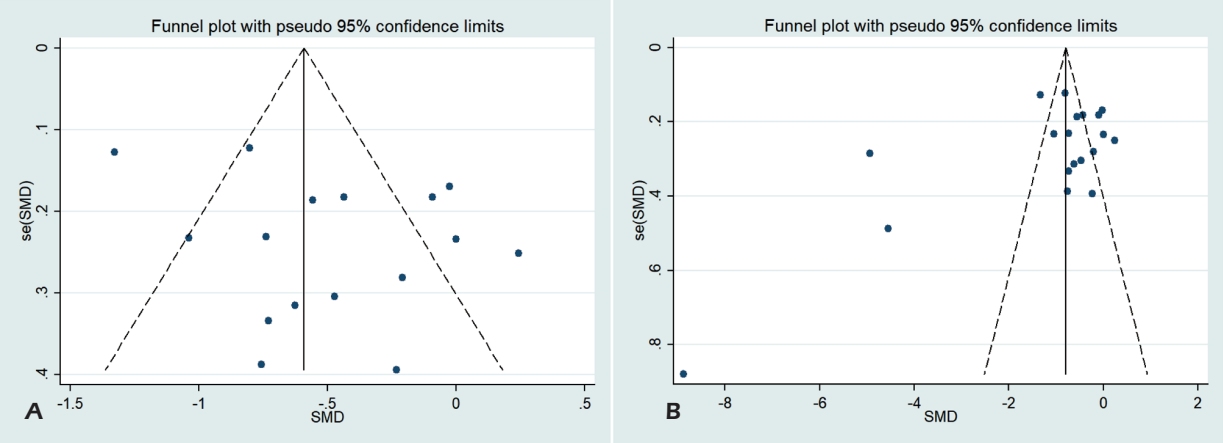

Figure 4. Sensitivity analysis in a random-effect model. **A**, Before removal of three studies. **B**, After the exclusion of these studies.

So far, the therapeutic efficacy of probiotics on acute RVD in children remains inconsistent[18-20]. Hong et al[18] conducted a double-blind, placebo-controlled trial in which probiotics underwent longitudinal quality control. Their findings have suggested that Lactobacillus acidophilus is not always beneficial in the treatment of acute RVD in children. Lee et al[19] have proposed that the selection of a suitable probiotic strain may be helpful in the treatment of acute rotavirus gastroenteritis in children or as an alternative under the circumstance of adverse reactions unhappened.

Meta-analysis is a powerful tool that makes conclusions more credible than individual studies, especially in the analysis of unexplained associations[37]. In this paper, 19 independent RCTs, involving 1,624 children with acute RVD were enrolled. Our findings showed that probiotics could significantly reduce the occurrence of acute RVD in children. Subgroup analysis conducted based on ethnicity uncovered a poor therapeutic efficacy of probiotics on reducing the occurrence of acute RVD in Asian children. However, the therapeutic efficacy was markedly significant in Caucasian children. Though the exact mechanism was unclear, it was likely that different ethnic groups might influence the therapeutic efficacy of probiotics on acute RVD in children. In addition, subgroup analysis based on subtypes of probiotic found a pronounced efficacy of both Lactobacillus acidophilus and non-Lactobacillus acidophilus probiotic on re-

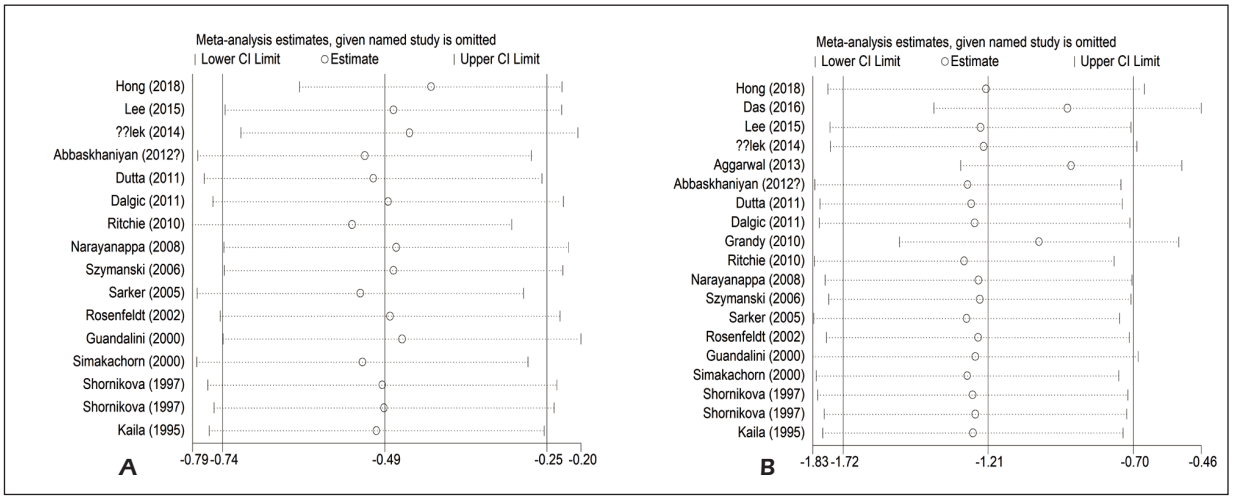

Figure 5. Begg's funnel plots of publication bias test. **A**, Before removal of three studies. **B**, After the exclusion of these studies.

ducing the occurrence of acute RVD in children. All our findings suggested that the therapeutic efficacy of probiotics on RVD was not influenced by different subtypes of probiotics.

A small sample size in each stratified analysis may limit enough statistical power for valid conclusion. Therefore, a larger sample size is required for further studies. Moreover, a comprehensive analysis on subjects with different ages and ethnicities may result in certain deviations. Furthermore, it should be pointed out that the incidence of RVD varies in subjects with different ethnicities and RVD children in African population are lacked. As a result, our conclusion requires for verification in multi-center, large sample size studies.

Conclusions

In summary, probiotics could reduce the occurrence of acute RVD in children, especially in the Caucasian population. Our findings still needed to be further validated in a multi-center institution with larger sample size and more qualified data.

Conflict of Interests

The authors declare that they have no conflict of interest.

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