Efficacy and Safety of *Saccharomyces boulardii* for Acute Diarrhea

abstract

BACKGROUND AND OBJECTIVE: The efficacy of *Saccharomyces boulardii* for treatment of childhood diarrhea remains unclear. Our objective was to systematically review data on the effect of *S. boulardii* on acute childhood diarrhea.

METHODS: Our data sources included Medline, Embase, CINAHL, Scopus, and The Cochrane Library up to September 2013 without language restrictions. Randomized controlled trials and non-randomized trials that evaluated effectiveness of *S. boulardii* for treatment of acute diarrhea in children were included. Two reviewers independently evaluated studies for eligibility and quality and extracted the data.

RESULTS: In total, 1248 articles were identified, of which 22 met the inclusion criteria. Pooling data from trials showed that *S. boulardii* significantly reduced the duration of diarrhea (mean difference [MD], −19.7 hours; 95% confidence interval [CI], −26.05 to −13.34), stool frequency on day 2 (MD, −0.74; 95% CI, −1.38 to −0.10) and day 3 (MD, −1.24; 95% CI, −2.13 to −0.35), the risk for diarrhea on day 3 (risk ratio [RR], 0.41; 95% CI, 0.27 to 0.60) and day 4 (RR, 0.38; 95% CI, 0.24 to 0.59) after intervention compared with control. The studies included in this review were varied in the definition of diarrhea, the termination of diarrhea, inclusion and exclusion criteria, and their methodological quality.

CONCLUSIONS: This review and meta-analysis show that *S. boulardii* is safe and has clear beneficial effects in children who have acute diarrhea. However, additional studies using head-to-head comparisons are needed to define the best dosage of *S. boulardii* for diarrhea with different causes. *Pediatrics* 2014;134:e176–e191

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KEY WORDS

acute diarrhea, children, *Saccharomyces boulardi*, safety, efficacy and systematic review

ABBREVIATIONS

CI—confidence interval
MD—mean difference
ORS—oral rehydration solution
RR—risk ratio solution
WHO—World Health Organization

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Diarrhea is defined by the World Health Organization (WHO) as 3 or more passages of loose or watery stool and increments in stool frequency in a 24-hour period. The most common cause of diarrhea is a gut infection (viral, bacterial, and parasitic). Other causes include side effects of medicine (especially antibiotics), infections not associated with the gastrointestinal tract, food poisoning, and allergy.[1] Diarrhea is also categorized into acute (lasts several hours or days) and persistent (continues for 14 days or longer). Diarrhea with any cause and any period of time may lead to dehydration and even may be lethal in infants, children, and the elderly if not corrected immediately.[2] Globally, ~1.7 billion cases of diarrheal disease occur every year, resulting in nearly 760 000 deaths in children younger than age 5 years, especially in developing countries.[3]

The treatment of choice for dehydration caused by diarrhea is the replacement of the lost fluids and electrolytes by oral rehydration solution (ORS). As rehydration therapy does not significantly decrease the frequency/length of diarrhea, scientists are interested in adjunctive treatments.[4] Probiotics as one of the alternative approaches for prevention and treatment of diarrhea are living microorganisms that provide various beneficial health effects in humans. It is proposed that probiotics can modulate the immune response,[5] produce antimicrobial agents,[6] and compete in nutrient uptake and adhesion sites with pathogens.[7] Well-known probiotics with claimed health-improving properties are intestinal lactic acid bacteria like *Lactobacillus rhamnosus, Lactobacillus casei,* and *Lactobacillus johnsonii,* and the yeast *Saccharomyces*.[8]

Saccharomyces boulardii is a beneficial yeast that was first isolated from lychee and mangosteen fruit. In many clinical trials, *S. boulardii* has been shown to be effective in prevention and management of diarrhea, especially antibiotic-associated diarrhea. *S. boulardii* can be administered simultaneously to prevent antibiotic-associated diarrhea owing to its resistance to most antibiotics. However, a recent randomized controlled trial reported *S. boulardii* was not effective in preventing the development of antibiotic-associated diarrhea in elderly hospitalized patients.[9]

According to our knowledge, there is 1 systematic review about the effectiveness of *S. boulardii* in childhood acute diarrhea.[10] To provide an update, Szajewska et al added data from 3 studies to their previous review. They reported a reduction in the duration of the diarrhea (1.08 days) in those treated with *S. boulardii* compared with controls, although there was significant heterogeneity (I^2 = 89%) in results among the studies.[11] However, they proposed to conduct more clinical trials to further specify groups (by etiology of diarrhea or hospitalization) driving better clinical response to *S. boulardii* treatment and to define the most effective dosage.[10] The aim of the current study was to systematically review published studies that assessed the efficacy and safety of *S. boulardii* on the treatment of childhood diarrhea, taking new publications into account. To maximize use of available data, we also included open labeled studies in our review. We further tried to evaluate whether cause, severity of diarrhea, and treatment dose can explain the difference between study results.

METHODS

Protocol and Registration

PRISMA statement was followed for reporting this systematic review and meta-analysis.[12] Search strategy and inclusion criteria were defined and documented in a protocol. The review protocol has been registered in the International Prospective Register of Systematic Reviews (PROSPERO) under registration number CRD42013005869.

Information Sources and Search

We searched Medline, Embase, CINAHL, Scopus, and The Cochrane Library up to September 2013. The exact search terms for each database are shown in Supplemental Table 1. We checked the reference lists of all studies identified by the above methods. We additionally searched the following sources of gray literature (defined here as reports that are produced by all levels of government, academics, business, and industry in print and electronic formats but that are not controlled by commercial publishers): ProQuest Dissertations & Theses Database and ClinicalTrials.gov and Current Controlled Trial Register, which houses the NHS Controlled Trials Register, the National Institutes of Health Register, the National Research Register, and the International Standard Randomized Controlled Trial Number Register. We contacted organizations including the International Scientific Association for Probiotics and Prebiotics and individuals working in the field to help identify unpublished and ongoing trials.

Eligibility Criteria

All randomized controlled trials regardless of language or publication date or state (published, unpublished, in press, and in progress) were included. Participants had to be children (0 to 18 years of age), male or female of any ethnic group with acute diarrhea (≤14 days). We were flexible about definition of diarrhea. Patients in the experimental groups had to receive *S. boulardii* at any dose and in any form (eg, capsule, sachet, yogurt). Trials investigating products that do not label *S. boulardii* dose were not considered. Patients in the control groups had to receive placebo or no treatment control. Primary outcomes were duration of diarrhea, diarrhea lasting ≥4 days, and stool frequency on day 2 after intervention. Secondary outcomes were diarrhea

lasting ≥3 days, stool frequency on day 3 after intervention, and harms.

Study Selection

Title, keywords, and abstract of publications identified according to the above described search strategy were independently screened by 2 reviewers (Dr Akbari and Dr Feizizadeh). Inclusion criteria for title and abstract screening were randomized controlled trials, children who had diarrhea, and studies that compare *S. boulardii* with placebo or no therapy. The same reviewers independently assessed full-texts of relevant studies for final inclusion. Excluded publications and the reasons for their exclusion were presented (Supplemental Table 2). Discrepancies between the reviewers were resolved through discussion by the entire review team (Dr Feizizadeh, Dr Salehi-Abargouei, and Dr Akbari).

Data Collection Process and Data Items

Two reviewers (Dr Akbari and Dr Feizizadeh) independently extracted details of included studies. Information on authors, publication year, study design, study location, source of funding, duration of study, inclusion criteria, exclusion criteria, causes of diarrhea, nutritional status, hydration status, the number of patients who completed the study, interventions, outcomes, adverse effects, and results was extracted from each study. We tried to contact the authors of included studies for missing variable and relevant information.[13–20] Disagreements were resolved by discussion.

Risk for Bias in Individual Studies

Risk for bias of each study was assessed by 2 reviewers (Dr Akbari and Dr Feizizadeh) based on the Cochrane Collaboration's risk for bias tool[21] using generation of allocation sequence, allocation concealment, blinding, and loss to follow-up. We classified these elements as Yes (low risk for bias), No (high risk for bias), or Unclear.

Statistical Analysis

Mean ± SD of diarrhea duration and number of stools on 2 and 3 days after intervention was used to calculate the mean difference (MD) and its SE as effect size to be used in meta-analysis. We also used relative risk (RR) of treatment on days 3 and 4 after the start of probiotic use to calculate log RR and its corresponding SE for meta-analysis.[22] Overall effect for each meta-analysis was derived by using a random effects model, which takes between-study variation into account.[22] Statistical heterogeneity between studies was evaluated by using Cochran's Q test and I-squared.[23] Sensitivity analysis was used to explore the extent to which inferences might depend on a particular study or a number of publications. Subgroup analysis based on cause of diarrhea, severity of diarrhea, and dosage of probiotic was also performed to find possible sources of heterogeneity. Publication bias was evaluated by looking over Begg's funnel plots.[24] Formal statistical assessment of funnel plot asymmetry was also done using Egger's regression asymmetry test and Begg's adjusted rank correlation test.[24] All statistical analyses were conducted by using Stata version 11.2 (Stata Corp, College Station, TX). *P* values $< .05$ were considered statistically significant.

RESULTS

Study Characteristics

The study selection process is depicted in Fig 1. Our search strategy resulted in 1248 studies; of them 304 were duplicates. After reading titles/abstracts, 36 potentially relevant studies were identified. Fourteen studies were excluded after full-text assessment for the following reasons: 3 studies evaluated the preventive effect of probiotic on diarrhea,[25–27] 3 studies had no control group,[28–30] 2 were evaluated in patients who had persistent diarrhea,[31,32] 2 were secondary publication of a study done by Cetina-Sauri et al,[33,34] 1 included patients who had *Blastocystis hominis* infection without diarrhea,[35] 1 used a mixed probiotic preparation for intervention,[36] data from 1 study were not reported,[15] and full-text of 1 study was not available.[20] Characteristics of excluded studies are presented in Supplemental Table 2.

In total, 22 studies were included in our systematic review. Characteristics of included studies are summarized in Table 1. Trials were performed in France, Mexico, Turkey, Pakistan, Italy, Argentina, Myanmar, Bolivia, Brazil, Azerbaijan, Indonesia, and India, and published between 1985 and 2013. All studies were published in English except 1 study that was written in Azarbayejani.[18] Twenty of the included studies were published as an original article, 1 as a letter,[37] and 1 as a meeting abstract.[38] Twenty-two included studies had a total of 2440 patients in their intervention or control groups (1225 interventions, 1215 controls). Patients were aged from 1 month to 15 years. Twelve studies enrolled inpatients,[13,16–19,39–45] 5 enrolled outpatients,[14,37,46–48] and 2 enrolled both inpatients and outpatients.[49,50] There was no information about the hospitalization state of participants in 3 studies.[38,51,52] For most of the studies the daily dosage of *S. boulardii* was 250 to 750 mg (10^9 to 10^{10} colony-forming units). One study used 4×10^{10} lyophilized cells of *S. boulardii*[44] and 1 used 5×10^6 living microorganisms per day.[52] Duration of intervention was 5 to 10 days. In 2 studies duration of treatment was not stated.[42,51]

Risk of Bias Within Included Studies

The methodological quality of included studies is shown in Supplemental Table 3. Briefly, only 1 study was adequate

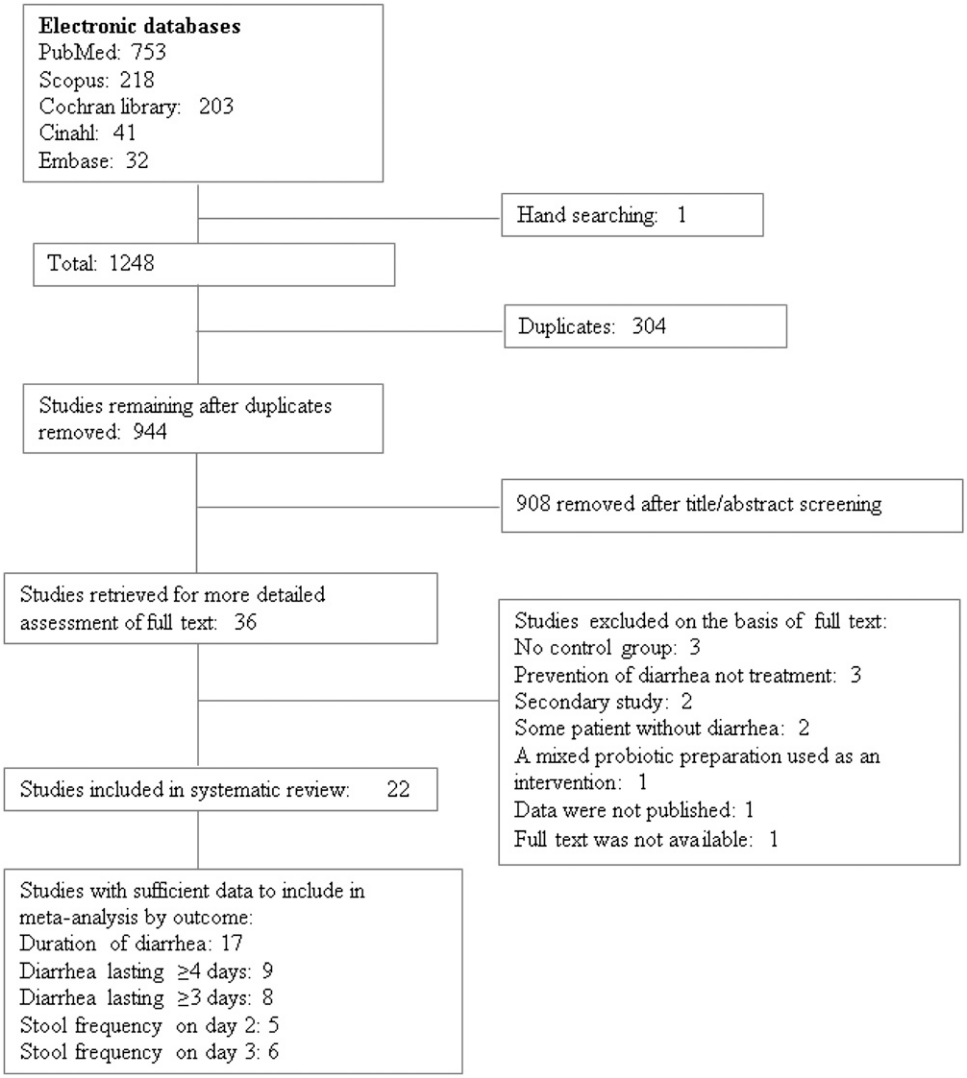

FIGURE 1
Flow diagram of the study selection process.

for all of the 4 methodological quality assessment parameters[43] and 1 was inadequate for all 4 parameters.[46]

Eight studies were rated as adequate[14,16,19,37,43,45,48,51] and 4 were inadequate for generation of the allocation sequence,[17,39,46,47] and the method used for allocation sequence was unclear in 10 studies.[13,18,38,40–42,44,49,50,52] Four studies were adequate,[14,43,45,48] 14 studies were unclear,[13,16,18,19,37,38,40–42,44,49–52] and 4 studies were inadequate (as they used a method such as alternation.[17,39,46,47]) for allocation concealment. Six studies were adequate,[41,43–45,48,50] 12 studies were inadequate,[13,14,16–19,37,39,46,47,49,52] and 4 studies were unclear for blinding.[38,40,42,51] Loss to follow-up was adequate (≤10%) in 12 studies[13,16,17,19,37–40,43,47,49,50]; 7 studies were considered inadequate[14,41,44–46,48,52] and 3 studies unclear for loss to follow-up.[18,47,51] The overall quality was assessed and 4 studies were rated as "good" (low risk for bias),[43,45,48,50] 13 studies rated as "fair," which were susceptible to some bias,[13,14,16,18,19,37,38,40–42,44,49,51] and 5 studies rated as "poor" (high risk for bias).[17,39,46,47,52]

Findings From Meta-analysis

Seventeen studies (2102 participants) reported duration of diarrhea.[13,14,16,17,19,37,38,41,42,44–49,51,52] The reduction in diarrhea duration ranged from −50.4 to 6.0 hours among included studies. Our analysis shows a reduction in duration of diarrhea in the treatment group compared with the control group (MD = −19.7; 95% CI, −26.05 to −13.34; $P < .001$) (Fig 2). The heterogeneity test for diarrhea duration showed a significant heterogeneity between 17 studies (Cochrane Q test, $P < .001$, $I^2 = 64.5\%$). To explore the possible sources of heterogeneity we examined subgroup analysis based on cause of diarrhea, hospitalization status, probiotic dose used for intervention, and blinding. In brief, subgroup

TABLE 1 Characteristics of Studies Included in the Systematic Review

Study, Year/Country	Design	Duration	Participants	Intervention		Outcome Measure	Results
				Probiotic	Control		
Chapoy et al, 1985[39]/ France	Controlled trial	Not stated	38 inpatient children who had acute diarrhea	*S. boulardii* (500 mg/d for 5 d)	ORS	Mean number of stools, mean stool weight, and carmine red transit time on days 1 and 4 Consistency of stools on day 4	Comparison between *S. boulardii* group and control group on days 1 and 4 revealed a significant difference on 4 clinical criteria: number of stools, weight and consistency of stools, and carmine red transit time
Cetina-Sauri et al, 1994[51]/Mexico	Double-blind, placebo-controlled study	11 mo; April 1, 1988 to March 15, 1989	130 children aged 3 mo to 3 y who had acute diarrhea	*S. boulardii* (live *Saccharomyces cerevisiae* Hansen CBS 5926; 600 mg/d; diluted in 5 mL cold water); duration was not stated	Glucose placebo (600 mg diluted in 5 mL cold water)	Number of stools per day First day stools formed	Evaluation of the percentage of clinical cure after 48 and 96 h showed significant differences from the control group.
Hernandez et al, 1998[40]/ Mexico	Randomized controlled trial	Not stated	50 inpatients who had uncomplicated acute diarrhea	*S. boulardii* (600 mg /d for 5 d)	Placebo	Stool frequency Persistence of diarrhea	Persistence of diarrhea was lower in *S. boulardii* group compared with control group
Urganci et al, 2001[42]/Turkey	Double-blind, placebo-controlled study	1 y; June 2000 to May 20, 2001	100 consecutive inpatients aged 2 to 29 mo who had acute, non-bacterial diarrhea (lasting >48 h)	Lyophilized *S. boulardii* (250 mg/d in 5 mL cold liquid)	250 mg glucose daily in 5 mL cold liquid	Stool frequency and consistency at 48 and 96 h Percentage of cases cured after 48 and 96 h	After 48 and 96 h, children treated with *S. boulardii* scored better than controls.
Hafeez et al, 2002[47]/Pakistan	Randomized controlled trial	2 months	109 outpatients aged 6 mo to 5 y who had acute watery diarrhea	Lyophilized *S. boulardii* (500 mg/d for 6 d)	Standard treatment (oral rehydration and feeds)	Frequency and consistency (loose versus formed) of stools Duration of illness (definition of end of diarrhea not stated)	At day 3 the frequency reduced significantly in the *S. boulardii* group compared with the control group. The consistency of stool showed a positive trend in the *S. boulardii* group compared with the control group at days 3 and 6. The average duration of the illness also decreased by a mean of 1.1 days.
Kurugöl et al, 2005[41]/ Turkey	Double-blind, placebo-controlled study	Not stated	200 inpatients aged 3 mo to 7 y who had acute diarrhea	*S. boulardii* (250 mg/d given with water or juice for 5 d)	Placebo (no details given)	Number stools/d and number watery stools/d	The stool frequency after the second day of the treatment was significantly lower in the *S. boulardii* group than in the placebo group.

TABLE 1 Continued

Study, Year/Country	Design	Duration	Participants	Intervention		Outcome Measure	Results
				Probiotic	Control		
						Duration of diarrhea	The duration of diarrhea significantly reduced in the *S. boulardii* group compared with the placebo group.
						Duration of vomiting and fever	The duration of hospital stay was shorter in the *S. boulardii* group than in the placebo group.
						Duration of hospital stay	
Billoo et al, 2006[13]/ Pakistan	Randomized controlled clinical trial	Not stated	100 inpatients aged 2 mo to 12 y who had acute watery diarrhea	*S. boulardii* (500 mg/d for 5 d) Enflor 250 mg 5×10^9	ORS and nutritional support only	Stoppage of diarrhea (not defined)	The duration of diarrhea and stool frequency were lower in the *S. boulardii* group compared with the control group.
						Weight gain	Weight gain was similar in the 2 groups.
						Daily stool frequency and consistency	
Canani et al, 2007[14]/Italy	Prospective, single-blind, randomized, controlled trial	October 1999 to September 2000	600 outpatients aged 3 to 36 mo who had diarrhea (<48 h)	*S. boulardii* (1×10^{10} live microorganisms/d for 5 d)	ORS alone	Mean duration of diarrhea Stool frequency	There was no effect on duration of diarrhea and stool frequency.
Ozkan et al, 2007[50]/Turkey	Randomized, double-blind, placebo-controlled study	October 2004 to March 2005	27 inpatient and outpatient previously healthy children aged 6 mo and 10 y who had acute diarrhea	*S. boulardii* (500 mg/d in 5 mL of water for 7 d)	Placebo	Number, characteristics, and frequency of stools	Stool frequency on day 2 was similar in the 2 groups.
						Blood tests	Stool frequency on day 3 was lower in the *S. boulardii* group compared with the control group.
Vandenplas et al, 2007[38]/ India and Indonesia	Double-blind, randomized, placebo-controlled trial	Not stated	202 children presenting with acute infectious gastroenteritis	ORS with 500 mg/d *S. boulardii* for 5 d	ORS with placebo	Duration of diarrhea Daily stool frequency and consistency Vomiting Weight gain Side effects	Administration of *S. boulardii* as add-on to standard WHO recommendations (ORS and realimentation) results in a social benefit, as more children were cured on day 3.
Villarruel et al, 2007[48]/ Argentina	Double-blind, randomized, placebo-controlled trial	1 y	100 outpatients aged 3 mo to 2 y who had acute diarrhea	*S. boulardii* (250–500 mg/d according to age for 6 d)	Placebo	Duration of diarrhea	Duration of diarrhea was significantly shorter in the *S. boulardii* group.
						Number of stools on days 4 and 7	Number of stools on days 4 and 7 was lower in the *S. boulardii* group.

TABLE 1 Continued

Study, Year/Country	Design	Duration	Participants	Intervention		Outcome Measure	Results
				Probiotic	Control		
						Number of participants who had diarrhea >7 d Number of participants who had liquid stools on days 4 and 7	
Htwe et al, 2008[17]/ Myanmar	Randomized controlled trial	No information	100 inpatients aged 3 mo to 10 y who had acute watery diarrhea	*S. boulardii* (500 mg/d for 5 d)	ORS according to WHO protocol	Mean duration of diarrhea Stool frequency Consistency of stools	*S. boulardii* shortens the duration of diarrhea and normalizes stool consistency and frequency.
Savas-Erdeve et al, 2009[52]/Turkey	Randomized open-prospective study	January 2006 to April 2007	90 children aged 1 to 15 y who presented with *E. histolytica*-associated diarrhea	*S. boulardii* (250 mg [5×10^6 living microorganisms]/d) plus metronidazole 30 to 50 mg/kg/d orally for 10 d (maximum: 500–750 mg)	Metronidazole 30 to 50 mg/kg/d orally for 10 d (maximum, 500–750 mg)	Duration of diarrhea Duration of bloody diarrhea Duration of vomiting Duration of fever Duration of abdominal pain Fever	The duration of diarrhea and duration of bloody diarrhea, fever, abdominal pain, and vomiting were similar in the 2 groups.
Dinleyici et al, 2009[46]/Turkey	Prospective, randomized open-label clinical trial	January 2006 to September 2007	53 outpatient children who had fever and acute bloody diarrhea	*S. boulardii* (500 mg/d) plus metronidazole 60 mg/kg/d for 7 d	Metronidazole (60 mg/kg/d for 7 d)	Duration of diarrhea Duration of bloody diarrhea At day 3, bloody diarrhea and diarrhea At day 5, bloody diarrhea and diarrhea cyst passage	The duration of bloody diarrhea was significantly shorter in the *S. boulardii* group. On day 5, amebic cysts had disappeared in all children in the *S. boulardii* group, whereas in the control group, amebic cysts were still present in 6 children. On day 10, all children were cured and cysts had disappeared in all.
Grandy et al, 2010[44]/Bolivia	Prospective double-blind randomized	July 2007 to February 2008	194 inpatients aged 1 to 23 mo who had acute diarrhea	ORS plus *S. boulardii* (4×10^{10} lyophilized cells for 5 d)	ORS	Duration of diarrhea Duration of hospitalization Fever	The median duration of diarrhea in children who received *S. boulardii* was shorter than in controls. The duration of fever was significantly shorter in the group receiving *S. boulardii* (as compared with controls).

TABLE 1 Continued

Study, Year/Country	Design	Duration	Participants	Intervention		Outcome Measure	Results
				Probiotic	Control		
						Vomiting	There was no effect on duration of hospitalization and duration of vomiting.
Correa et al, 2011[43]/ Brazil	Double-blind, randomized, controlled trial	April 2007 to September 2008	186 inpatients aged 6 to 48 mo who had acute diarrhea	*S. boulardii* (400 mg/d for 5 d)	Placebo (400 mg/d for 5 d)	Frequency of diarrhea 3 d after beginning of intervention	There was a reduction in diarrhea duration when *S. boulardii* was given to children within 72 h after the onset of acute diarrhea.
Dalgic et al, 2011[16]/ Turkey	Prospective, randomized, single-blind, controlled trial	September 2008 to June 2010	480 inpatients aged 1 to 28 mo diagnosed with rotavirus diarrhea (<96 h)	*S. boulardii* (250 mg/d for 5 d)	Oral and/or parenteral rehydration solutions	Duration of diarrhea Time to resolution of vomiting Duration of hospitalization Fever	No statistically significant difference was found between the 2 groups.
Huseynova et al, 2011[18]/Azerbaijan	Trial	No information	43 inpatients aged 1 to 9 y who had diarrhea	Orally *S. boulardii* (500–750 mg/d for 7–10 d) 250 mg	No information	Frequency of diarrhea Pathologic and microbiological status of stool Dehydration status	The frequency of stool in days 5 and 7 was lower in the *S. boulardii* group as compared with the control group.
Erdogan et al, 2012[49]/Turkey	Prospective randomized trial	October 2009 to May 2010	75 outpatients and inpatients aged 5 mo to 5 y who had diarrhea in the last 48 h	Oral rehydration therapy and rapid refeeding with a normal diet with 282.5 mg/d *S. boulardii*	Oral rehydration therapy and rapid refeeding with a normal diet	Duration of diarrhea Vomiting	The duration of diarrhea was significantly shorter in the *S. boulardii* group as compared with the placebo group.
Khan et al, 2012[19]/ Pakistan	Randomized controlled trial	6 mo; June 2009 to November 2009	420 inpatients aged 2 mo to 5 y who had acute watery diarrhea	Orally *S. boulardii* (500 mg/d for 5 d) diluted in water or mixed with semisolid food	Standard treatment (oral rehydration and feeds)	Stool consistency and frequency	Statistically significant differences in terms of stool consistency and frequency were noted in the *S. boulardii* group from day 2 of treatment onward.
						Duration of diarrhea	The *S. boulardii* group also showed reduction in mean duration of diarrhea by 1.1 d compared with the control group.
Riaz et al, 2012[45]/India	Double-blind, randomized, controlled trial	May 2008 through September 2009	108 inpatients aged 3 to 59 mo who had acute-onset diarrhea (<48 h)	*S. boulardii* (500 mg/d for 5 d)	Placebo (puffed rice powder 500 mg/d for 5 d)	Mean duration of diarrhea	Mean post-intervention duration of diarrhea and mean time of appearance of first semi-formed stool were significantly shorter in the *S. boulardii* group as compared with the placebo group.

TABLE 1 Continued

Study, Year/Country	Design	Duration	Participants	Intervention		Outcome Measure	Results
				Probiotic	Control		
						Stool frequency	No statistically significant difference was found in the rest of the parameters.
						Consistency of stools	
						Weight gain	
						Total ORS consumed	
						Total IVF needed	
Burande et al, 2013[37]/India	Prospective, parallel, single-blind, randomized, controlled clinical trial	July 2009 to July 2011	72 outpatient children who had acute diarrhea	*S. boulardii* 500 mg/d for 5 d as lyophilized powder	Standard treatment (oral rehydration and feeds)	Time for recovery from diarrhea	The *S. boulardii* group had significantly early recovery from diarrhea and vomiting.
						Vomiting	
						Side effects	

IVF, intravenous fluids.

analysis according to cause of diarrhea showed the duration of diarrhea reduced in all 3 subgroups, including rotavirus, *Entamoeba histolytica*, and nonspecific cause. Subgroup analysis based on hospitalization indicated that using *S. boulardii* reduced duration of mild diarrhea more than severe diarrhea; although heterogeneity was still significant in outpatients, no evidence of heterogeneity was observed in inpatients. The heterogeneity of the outpatient subgroup may be explained by the ambulatory nature of intervention in these trials. One study reported outcome of inpatient and outpatient children and 3 studies did not report any information about the state of the patient's hospitalization. Our analysis based on intervention dose showed that *S. boulardii* treatment effects might be more in higher doses. We also categorized studies according to blinding. Seven studies were double-blinded and had adequate blinding (MD = −16.37; 95% CI, −21.45 to −11.28; $P < .001$) and 10 studies were single-blinded, open label, or had inadequate blinding (MD = −21.03; 95% CI, −32.19 to −9.88; $P < .001$). No evidence of heterogeneity was found in trials with adequate blinding (Cochrane Q test, $P = .394$, $I^2 = 4.2\%$) and there was a high and significant heterogeneity in the results of inadequate blinded studies (Cochrane Q test, $P < .001$, $I^2 = 76.5\%$). Results of subgroup analysis is presented in Table 2.

Five studies (846 participants) evaluated stool frequency in day 2 after intervention (Fig 3) and 9 studies (1227 participants) reported the risk for diarrhea lasting ≥4 days (Fig 4). Pooling the results of the trials showed that *S. boulardii* reduces the stool frequency on day 2 (MD = −0.74; 95% CI, −1.38 to −0.10; $P = .023$) and the risk ratio (RR) of diarrhea on day 4 after intervention in the *S. boulardii* group compared with the control group was 0.38 (95% CI, 0.24 to 0.59; $P < .001$). The heterogeneity test

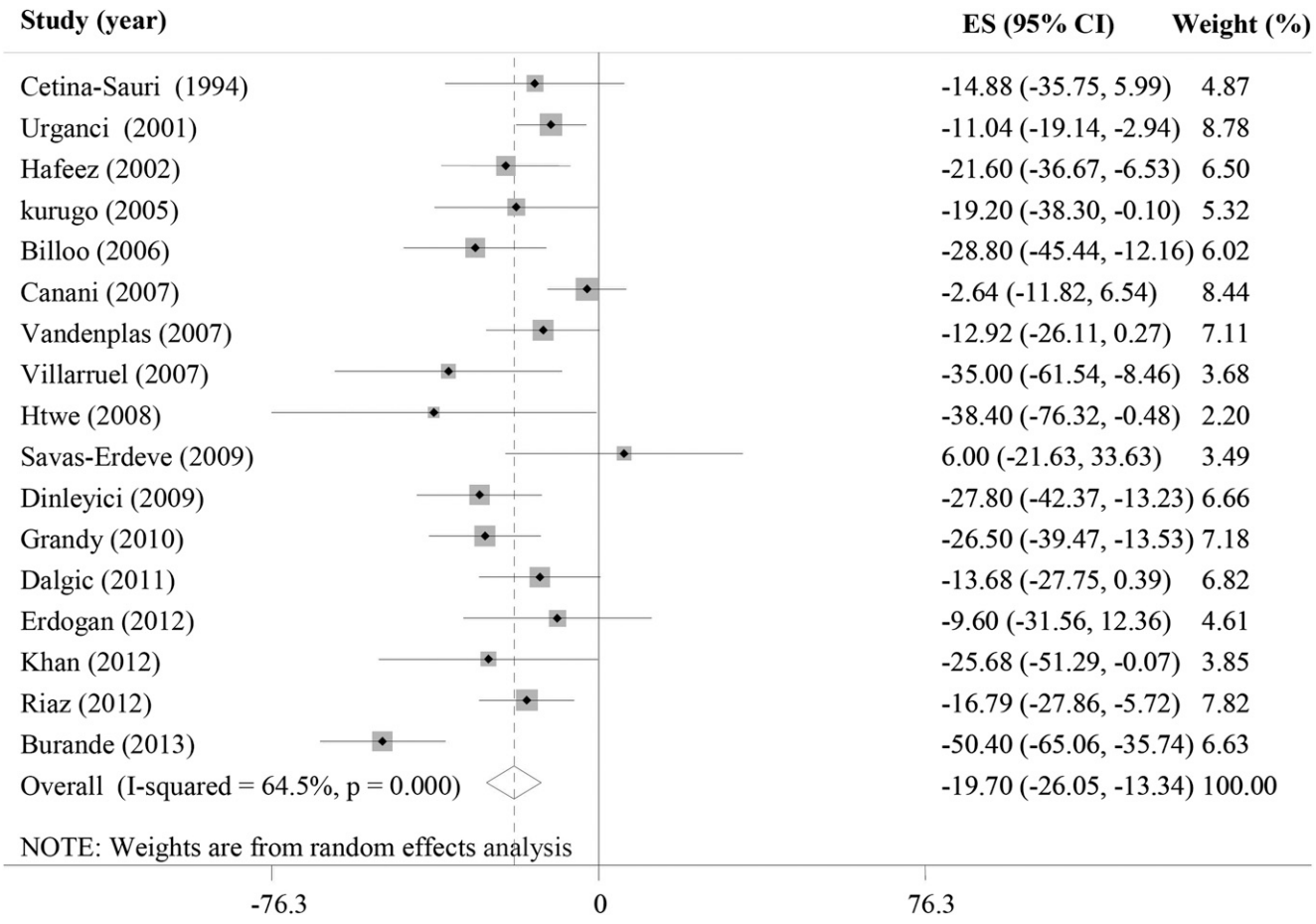

FIGURE 2
Forest plot showing the effect of *S. boulardii* on mean duration of diarrhea.

for the stool frequency on day 2 revealed a significant heterogeneity between 5 studies (Cochrane Q test, $P < .001$, $I^2 = 91.6\%$). The heterogeneity test for RR of diarrhea on day 4 showed a significant heterogeneity between 9 studies (Cochrane Q test, $P = .001$, $I^2 = 71.1\%$). The RR of diarrhea lasting ≥4 days after removing the Khan et al study from meta-analysis was 0.42 (95% CI, 0.28 to 0.63) and heterogeneity decreased (Cochrane Q test, $P = .003$, $I^2 = 67.3\%$).

Six studies (947 participants) reported stool frequency on day 3 (Fig 5) and 8 studies (1227 participants) evaluated diarrhea lasting ≥3 days (Fig 6). Meta-analysis showed that using *S. boulardii* reduced stool frequency on day 3 (MD = −1.24; 95% CI, −2.13 to −0.35; $P = .006$). The heterogeneity test for the stool frequency on day 3 showed a significant heterogeneity between 6 studies (Cochrane Q test, $P < .001$, $I^2 = 93.9\%$). The mean difference of stool frequency on day 3 after removing a study done by Canani et al was −1.62 (95% CI, −1.85 to −1.40); after removing this study, there was no evidence of heterogeneity anymore (Cochrane Q test, $P = .657$, $I^2 = 0.0\%$). In contrast to other studies, Canani et al performed their trial in a developed country, which may explain the difference in results. The overall RR of diarrhea lasting ≥3 days was 0.41 (95% CI, 0.27 to 0.60; $P < .001$). The heterogeneity test for RR of diarrhea on day 3 showed a significant heterogeneity between 8 studies (Cochrane Q test, $P < .001$, $I^2 = 84.7\%$). The RR of diarrhea lasting ≥3 days after removing the Khan et al study from meta-analysis was 0.51 (95% CI, 0.40 to 0.64) and heterogeneity decreased (Cochrane Q test, $P = .050$, $I^2 = 52.4\%$).

Other Outcomes

The effect of using *S. boulardii* for reduction of vomiting duration was evaluated by 6 trials. Five studies reported vomiting was similar in the *S. boulardii* group and the control group.[16,38,41,49,52] Burande et al observed average time of vomiting was shorter in the *S. boulardii* group compared with the control group.[37] Fever duration was evaluated by 3 studies that showed there was no significant difference between the 2 groups.[16,41] Two studies reported duration of hospitalization. Kurugöl et al reported a decrease in the duration of hospitalization in the *S. boulardii* group compared with the placebo group.[41] In

TABLE 2 The Effect of *S. boulardii* Probiotic Supplementation on Diarrhea Duration Among Children Based on Cause of Diarrhea, Hospitalization Status, Probiotic Dose Used for Intervention, and Blinding

Subgroups	Number of Studies/Participants	Meta-analysis		Heterogeneity	
		MD (95% CI)	P	I^2 (%)	*P* value[a]
Cause of diarrhea					
Rotaviruses	4/301	−18.07 (−24.93 to −11.22)	<0.001	0.0	0.454
Parasitic	2/135	−13.02 (−45.88 to 19.84)	<0.437	77.8	0.034
Nonspecific	10/1666	−21.75 (−30.96 to −12.53)	<0.001	74.2	0.000
Hospitalization					
Inpatient	8/1171	−18.16 (−23.51 to −12.80)	<0.001	11.9	0.337
Outpatient	5/478	−26.72 (−45.37 to −8.07)	0.005	87.7	0.000
Inpatient and outpatient	1/50	−9.6 (−31.56 to 12.36)	0.392	—	—
No information	3/403	−10.75 (−21.09 to −0.41)	0.042	0.0	0.435
Dose of probiotic					
≤300 mg	6/605	−14.29 (−21.29 to −7.29)	<0.001	22.0	0.268
500 to 750 mg	10/1456	−22.98 (−33.14 to −12.82)	<0.001	74.3	0.000
>1000 mg	1/41	−26.50 (−39.47 to −13.53)	<0.001	—	—
Blinding					
Adequate	7/837	−16.37 (−21.45 to −11.28)	<0.001	76.5	0.000
Inadequate	10/1265	−21.03 (−32.19 to −9.88)	<0.001	4.2	0.394
Overall	17/2102	−19.70 (−26.05 to −13.34)	<0.001	64.5	0.000

[a] Cochrane Q test, *P* value.

another study no statistically significant difference was observed in the hospitalization time between the *S. boulardii* group and the control group.[16] Two studies evaluated weight gain and both of them reported no significant difference of gain between *S. boulardii* and control groups.[13,45]

The studies did not report any serious adverse effects related to using *S. boulardii*. Kurugöl et al reported that 1 child had a complaint meteorism but that does not provide any information of the group allocation.[41]

Sensitivity Analysis and Publication Bias

Findings from sensitivity analysis showed that no particular study significantly affected the mean duration of diarrhea, RR of diarrhea lasting ≥3 days, and diarrhea lasting ≥4 days and mean stool frequency on day 3. Sensitivity analysis revealed that excluding trials done by Khan et al (MD = −0.57; 95% CI, −1.21 to 0.08; *P* = .08), Ozkan et al (MD = −0.47; 95% CI, −1.76 to 0.01; *P* = .058), and Urganci et al (MD = −0.87; 95% CI, −1.76 to 0.01; *P* = .068) can considerably change the mean of

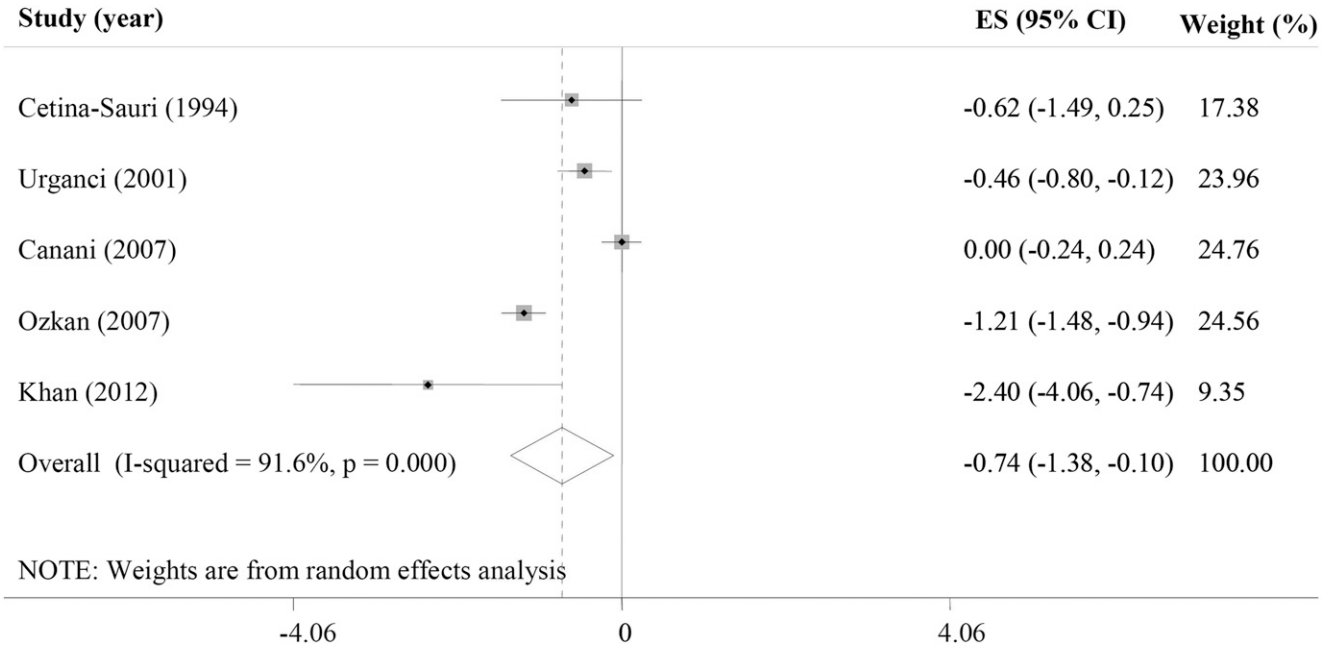

FIGURE 3
Forest plot showing the effect of *S. boulardii* on mean stool frequency on day 2.

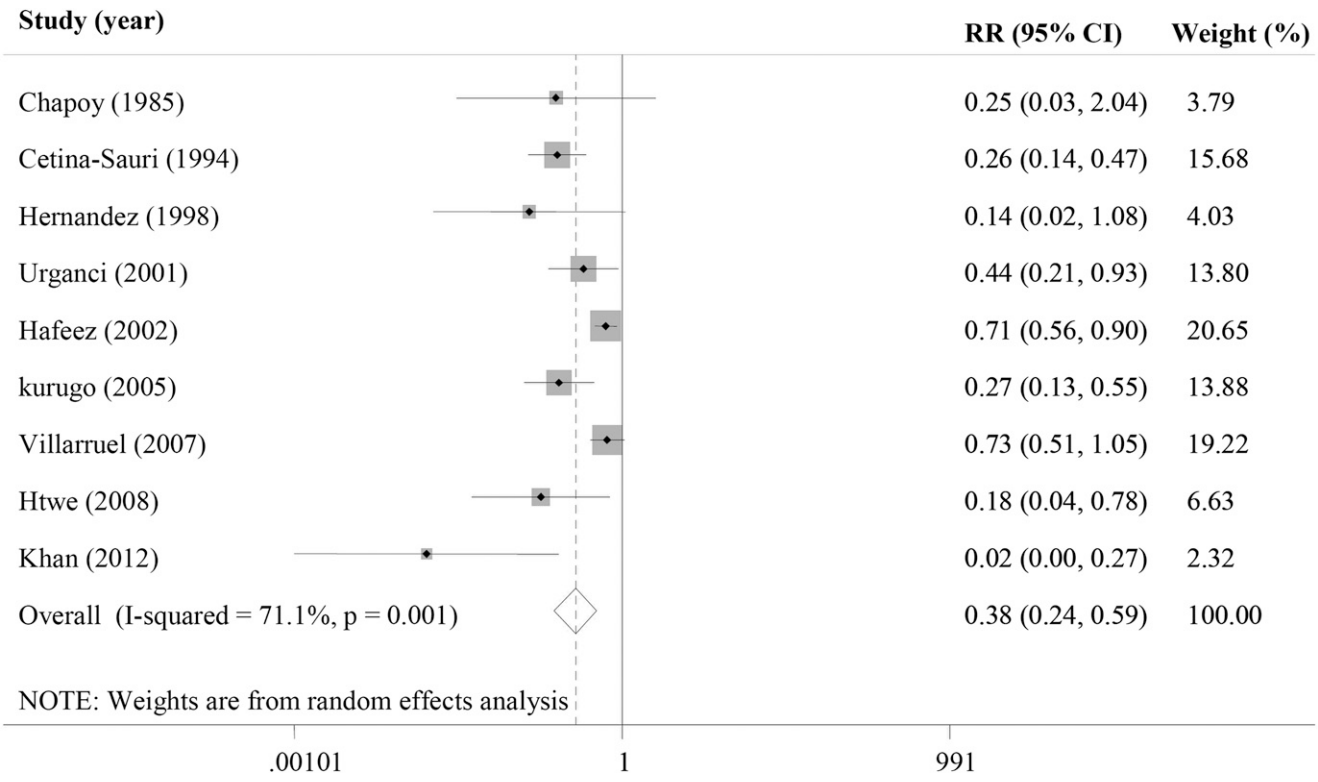

FIGURE 4
Forest plot showing the effect of *S. boulardii* on RR of diarrhea on day 4.

stool frequency on day 2 to nonsignificant results.

The publication bias was assessed by using a funnel plot depicting the MD in duration of diarrhea against their SE as a measure of precision (Fig 7). Although a slight asymmetry was seen in Begg's funnel plot, there was no evidence of publication bias using asymmetry tests (Egger's test, $P = .146$; Begg's test, $P = .458$).

DISCUSSION

In this systematic review and meta-analysis we found that supplementing *S. boulardii* in children who have diarrhea has a beneficial effect on different diarrhea outcomes. Meta-analysis of the included studies showed the duration of acute childhood diarrhea (children aged 1 month to 15 years) reduced, with an MD of 19.7 hours, by using *S. boulardii* as adjunct therapy. Our findings also indicate that *S. boulardii* may be effective in treating acute childhood diarrhea regardless of its causes (bacteria, virus, or protozoa) and can significantly decrease RR of diarrhea on days 3 and 4 after intervention and stool frequency on days 2 and 3 compared with controls. We could include 22 trials in the present review, whereas previously published reviews trying to assess the effectiveness of *S. boulardii* for acute childhood diarrhea could include a limited number of studies. For example, a meta-analysis done by Szajewska et al could include only 7 studies and reported that duration of diarrhea reduced by 1.08 days (25.92 hours) in children who received *S. boulardii* compared with controls. They only included randomized controlled trials and did not report MD of frequency of diarrhea on days 2 and 3 and the RR of diarrhea on days 3 and 4. There have been some systematic reviews on the effect of probiotics on acute diarrhea; however, they did not specifically focus on *S. boulardii* alone. A systematic review was performed on the effectiveness of probiotics in the treatment and prevention of acute infectious diarrhea in infants and children. They evaluated the effect of *L. rhamnosus GG* (LGG), *L. reuteri, L. acidophilus LB, S. boulardii, Streptococcus thermophilus lactis, L. acidophilus,* and *L. bulgaricus,* and reported that LGG had the most consistent effect.[53]

Although the precise mechanism of action for *S. boulardii* is not fully described, several explanations have been proposed. *S. boulardii* has antimicrobial activities that could inhibit growth and invasion of pathogens.[54] Geyik et al reported that *S. boulardii* decreases bacterial gut translocation and improves the intestinal barrier function in the animal model.[55] *S. boulardii* could neutralize bacterial virulence factors. Pothoulakis et al reported that viable *S. boulardii* secretes a 54-kDa serine protease able to inhibit binding of *Clostridium*

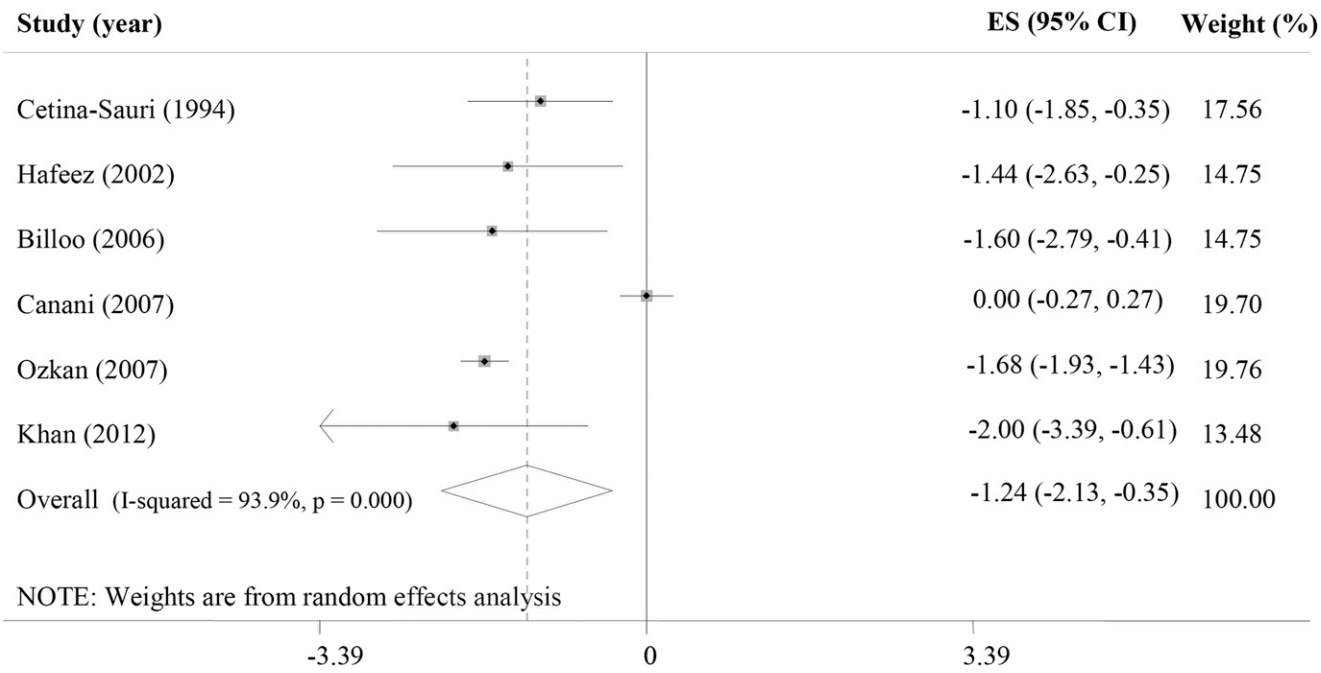

FIGURE 5
Forest plot showing the effect of *S. boulardii* on mean stool frequency on day 3.

difficile toxin A to specific intestinal receptors of ratileum by degradation of toxin and receptor sites of toxin on the enterocyte cell surface.[56] Recent experiments show that *S. boulardii* suppresses the host cell adherence that interferes with bacterial colonization.[57] *S. boulardii* also produces some antiinflammatory factors contributing to regulation of immune responses and antisecretory effects on transepithelial ion transport. Buts et al reported that *S. boulardii* increases the mucosal immune response and secretory IgA intestinal levels in the animal model.[58]

Pooling data of 4 studies performed in children who had rotavirus diarrhea showed a significant reduction in duration of diarrhea (−18.07 hours). There are limited data on the mechanism of action of *S. boulardii* against viral diarrhea (such as *Rotavirus, Adenovirus,* and *Norovirus*).[59] Pooling data of 2 studies performed in children who had diarrhea caused by *E. histolytica* showed that using *S. boulardii* may also reduce duration of diarrhea. Savas-Erdeve et al evaluated the efficacy of 250 mg/day *S. boulardii* in combination with metronidazole and metronidazole alone in treatment of diarrhea caused by amoeba. There was no significant difference in effectiveness between *S. boulardii* in addition to antibiotic and metronidazole alone. Using a lower probiotic dose may help to explain why the addition of *S. boulardii* to antibiotic treatment was not effective. Another study evaluated the efficacy of the addition of 500 mg/day *S. boulardii* to antibiotic for treating childhood diarrhea with the same ethiology. There was a 27.8-hour reduction in duration of diarrhea in the treatment group compared with the control group. This antiamebic effect could be explained by some in vitro studies that showed that *S. boulardii* can reduce the number of red blood cells adhering to amoebae and decrease the number of amoebae bearing red blood cells.[60] More research in this field is required to evaluate the safety and efficacy of *S. boulardii* and to address the best dosage for treatment of children who have amebic diarrhea.

Our subgroup analysis according to dose of *S. boulardii* confirmed there might be a direct relationship between the dosage of probiotic and its therapeutic effect. Most of the studies included in our review did not state the number of viable *S. boulardii* that was administered to participants. Viability of the microorganism is very important for effectiveness of probiotics. Further studies that include reliable microbiological tests to confirm the viability of *S. boulardii* must be conducted to determine the most effective dosing schedule.

Our systematic review and meta-analysis indicate that using *S. boulardii* as adjunct therapy reduces the duration of diarrhea and also may shorten the length of hospital stay, which may provide a social and economic benefit of *S. boulardii* treatment in combination with ORS in acute childhood diarrhea. Considering that most acute diarrhea is self-limiting and requires no specific treatment, it is necessary to conduct cost-effectiveness analysis in both developing and developed countries to identify whether *S. boulardii*

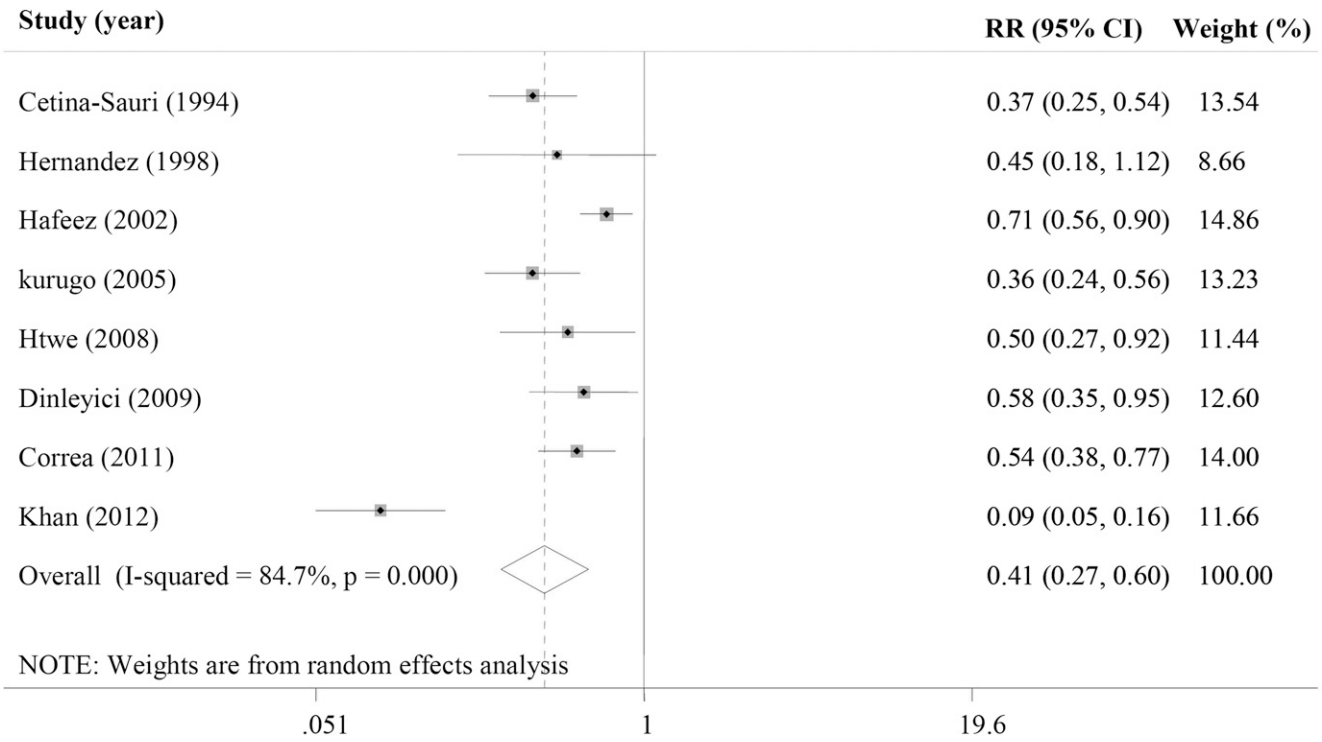

FIGURE 6
Forest plot showing the effect of *S. boulardii* on RR of diarrhea on day 3.

should be used in treating childhood diarrhea.

Although included studies in our review did not mention any serious adverse effects related to administration of *S. boulardii*, these trials were performed in previously healthy children, and susceptible individuals such as children who had malnutrition or immune deficiency were excluded; therefore, the side effects of *S. boulardii* in these children are unknown. In addition, some adverse events were mostly reported in case reports which are not included in our review. For example, there was a case report of fungemia in an 11-month-old infant who received *S. boulardii* to prevent diarrhea associated with chemotherapy.[61] It is necessary to evaluate the safety of *S. boulardii* in these specific populations.

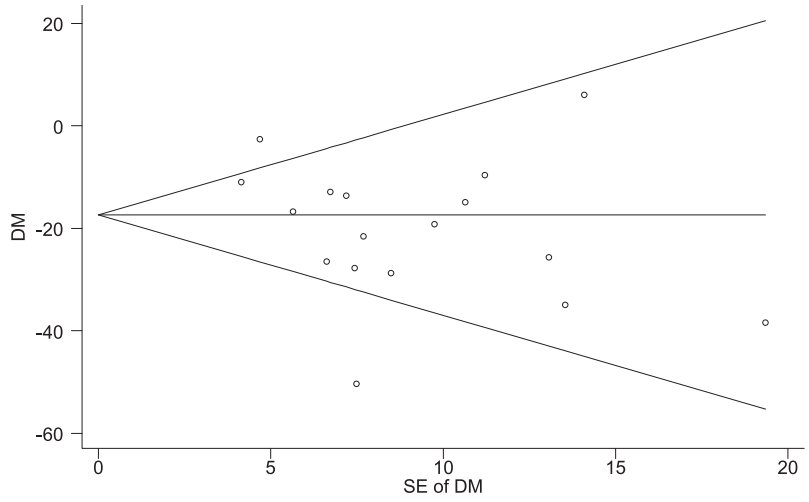

FIGURE 7
Begg's funnel plot in MD versus SE for studies that reported the effect of *S. boulardii* on mean duration of diarrhea.

Our review has some limitations that must be considered while interpreting our results. We used a checklist with 4 features to assess the methodological quality of included trials. The studies included in this review were varied in their methodological quality and some studies did not report sufficient information about sequence generation, allocation concealment, blinding, and incomplete outcome data. The definition of diarrhea, the termination of diarrhea, and inclusion and exclusion criteria were varied among included studies. Most included studies defined diarrhea according to the WHO's definition, whereas others did not state any diarrhea definition. Different exclusion criteria were stated in included studies. In most studies exclusion criteria were underlying conditions, such as severe chronic diseases, cystic fibrosis,

chronic gastrointestinal diseases, short bowel syndrome, food allergy, or any digestive pathology that might interfere with the results, whereas other studies did not consider these criteria. Some studies had a small sample size (eg, n = 27) and other studies did not provide the duration of treatment. There were limited trials among included studies that were conducted in European countries. Canani et al conducted a single blinded trial and reported that *S. boulardii* had no significant effect on treatment of diarrhea in Italian children. Other studies performed in Asian and Latino American countries showed a significant effect of *S. boulardii* in the reduction of duration of diarrhea. Considering the difference in morbidity and cause of acute diarrhea in developed and developing countries, it is important to conduct further trials in developed countries.

CONCLUSIONS

Based on our results, administration of *S. boulardii* in addition to rehydration therapy appears to be effective in the treatment of diarrhea owing to a variety of causes and was not associated with any adverse effects. This systematic review recommends using *S. boulardii* as adjunct therapy in acute childhood diarrhea. However, more clinical trials are needed to inform the development of evidence-based treatment guidelines. It is necessary to conduct more trials to define the best dosage of *S. boulardii* for diarrhea from different causes. Further clinical studies are needed to identify causes of diarrhea for each participant, and specially more studies should be performed in children who have bacterial and parasitic diarrhea.

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