Quantitative Risk-Benefit Analysis of Probiotic Use for Irritable Bowel Syndrome and Inflammatory Bowel Disease

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Key Points
1. Probiotics are widely used in both IBS and IBD, but published evidence is mixed for both safety and efficacy, and studies are very heterogenous. In general, the frequency of ADE and the efficacy are both close to placebo.
2. The risk-benefit plane for both IBS and IBD is broad. In IBS, most of the confidence region on the risk-benefit plane favors avoiding probiotic use. In IBD, most of the confidence region favors using probiotics.

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ABSTRACT

Probiotics have seen widespread use for a variety of gastrointestinal problems, especially in two common disorders: irritable bowel syndrome and inflammatory bowel disease. Since a wide variety of probiotic preparations has been used, and despite a large number of studies performed, a great deal of heterogeneity exists among them. Straightforward evidence-based recommendations for the use of probiotics in irritable bowel syndrome and inflammatory bowel disease have thus been difficult to formulate. In an effort to improve understanding of the risk-benefit balance of probiotics in these conditions, we (1) queried the FAERS database for all reported adverse drug events related to probiotics in 2013, and (2) constructed risk-benefit planes for both irritable bowel syndrome and inflammatory bowel disease using a geometric approximation of the confidence region between risk and benefit. Our results show that adverse events from probiotics vary widely by disease, and when they occur, they are mild and may be difficult to distinguish from the natural history of the underlying disorders they are used to treat. The risk-benefit plane for irritable bowel syndrome straddles the risk-benefit threshold, so patients can expect a balance between a low chance of risk and also a low chance of benefit. The risk benefit-plane for inflammatory bowel disease largely lies above the risk-benefit threshold, so patients may expect more benefit than risk in most cases. More standardized and high quality research is needed to improve our understanding of risk and benefit for these complex biopharmaceuticals.

BACKGROUND

The use of probiotics has substantially increased over the past decade, more than quadrupling from 2007 to 2012.(1) The World Health Organization defines probiotics as "live organisms which when administered in adequate amounts confer a health benefit on the host,"(2), but the term is often used in situations for which no health benefit has been proven. As such, interest has increased in fostering clinical research to add the weight of evidence to this unique biopharmaceutical. If one searches MEDLINE with the term "probiotics", and results are limited to clinical trials, over 1400 clinical studies have been indexed, and more than 1200 of these have been performed in the past ten years. Given the heterogeneous and complex nature of probiotics as a drug, there is a great deal of heterogeneity in study design(3), and while there are many published trials, only a small percentage of them are of high methodological quality. Perhaps most concerning, however, is that probiotics tend to be lumped into a single category, despite representing a diverse group of organisms with wide differences in biological effect.(4) Yet even when they are considered separately, since most probiotics are regulated as supplements by the United States Food and Drug Administration and other governmental agencies worldwide,(5) there is often no guarantee they contain what they say they do.(6)

Naturally, diseases of the gastrointestinal tract are the most commonly studied. Some of the first disorders treated with probiotics have been those thought to be the direct result of an intestinal dysbiosis, or an abnormal and harmful fluctuation of intestinal bacterial populations. Most effectively studied has been the prevention of antibiotic-associated diarrhea(7, 8) shortening duration of acute infectious diarrhea,(9) and preventing recurrent *Clostridium difficile* infection(10). In such cases, probiotics tend to have a high benefit-risk ratio, mostly owing to relatively low risk,(11) but benefit may also often be low as well, especially with larger, more rigorous clinical trials.(7) Given the abovementioned disorders' association with dysregulation of the human microbiome, interest has mounted in the use of probiotics to treat both irritable bowel syndrome (IBS), and inflammatory bowel disease (IBD). While dysbiosis remains a likely,(12-14) but as yet poorly understood mechanism for IBD and IBS, this has not stunted the *a priori* assumption by many clinicians and patients that probiotics may be helpful.

IBS is a functional gastrointestinal disorder (FGID) that is extraordinarily common throughout the world, occurring in roughly 10% of humans from childhood to late adulthood.(15, 16) The FGID clinical guidelines, known as the Rome III criteria(17), define IBS as abdominal pain or discomfort occurring at least 3 days per month over the preceding 3 months with at least two of the following associated symptoms: improvement with defecation, change in frequency of stool, or change in form or character of stool. The cause is unknown, although a complex etiology with both neurological and intestinal inputs is likely.(18) Therapy typically consists of some combination of dietary changes,(19) antispasmodic medications,(20) or other adjunctive pharmacotherapy or psychotherapy.(21) Probiotics are frequently tried for IBS, either at the advice of a clinician, or over-the-counter by the patient.

Inflammatory bowel disease comes in two general clinical phenotypes: ulcerative colitis (UC) and Crohn disease (CD). UC results in mucosal inflammation confined to the colon, usually in a contiguous fashion beginning in the rectum. Alternatively, CD can involve any portion of the gastrointestinal tract and can extend through the entire intestinal wall. While their etiologies are unknown, they are both likely related to a dysregulated interaction between the normal intestinal microbiota and the host immune system.(12, 13)

Probiotics have been difficult to study(3), largely because they defy typical drug classification in many settings: probiotics are complex organisms taken as medications. As such, existing experience with drug safety and efficacy trials may be insufficient to study them. The assessment of risk and benefit for probiotics is also quite complex, since probiotics do not represent a single chemical compound, but a range of diverse live organisms with an even wider range of dynamic biological activities. Pharmacokinetic and pharmacodynamic considerations are also challenging to assess,(22) since each microbial population may constitute thousands of different active biological molecules.

We seek to provide guidance to clinicians and others caring for patients with IBS and IBD in regards to the risk-benefit balance for the use of probiotics in these disorders. We have grouped this guidance into three main sections below:

(1) A summary of the literature describing both risk and benefit of probiotics and IBS and IBD,

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(2) A description of the adverse drug events (ADEs) for all probiotics in the FDA's primary reporting service

(3) A quantitative analysis using a combination of systematic literature search of relevant trials, pooling of these existing data and simulation of 5000 patients, and then plotting of these simulated patients on a risk-benefit plane (RBP) to better visualize what we know about the risk-benefit balance for probiotics in these disorders.

SUMMARY OF RISKS

A previous systematic review by Didari and colleagues[23] focused on the risk of probiotics across all settings, and found that probiotics were generally safe, but found increased risk for immunocompromised patients, critically ill patients, and those at the extremes of age. Probiotics have been studied extensively for a broad variety of diseases, including IBS and IBD, yet rigorous assessment of adverse events has only rarely occurred in the many clinical trials performed.

IBS

Multiple recent controlled trials designed to assess efficacy have also assessed risk of adverse events, albeit heterogeneously. [24-38] Most trials had no adverse events reported at all. Most patients who reported ADEs reported mild symptoms, most often related to the gastrointestinal tract. Only three published trials assessed ADEs related to probiotics in IBS in any systematic or standardized way.[27, 29, 34] A recent meta-analysis[39] showed a pooled relative risk (RR) for an adverse event of any type across all published trials of 1.21 (95% CI 1.02–1.44) and number needed to harm was 35. 16.5% of patients in all trials had an ADE on probiotics, compared with 13.8% of controls. There were no deaths reported in any trials, and no serious adverse events such as cardiovascular or respiratory compromise reported.

IBD

As with IBS, multiple recent IBD trials designed to assess efficacy also addressed safety and ADEs as a secondary outcome[40-49]. When these trials were pooled in a recent meta-analysis[50], there was no difference in ADEs in patients on probiotics versus controls, with a relative risk of 0.97 (95% CI 0.77-1.19). No trials reported patient deaths during the study period. Most reported ADEs were gastrointestinal symptoms. However, there was significant heterogeneity among trials, and some trials reported a wide confidence interval

for relative risk of an ADE. As with IBS, there was a large degree of heterogeneity among trials in how they chose to measure ADEs, and only a single trial appears to have approached this measurement in a systematic and comprehensive way.(41)

Special Risk Cases – The Young, the Old, and the Immunosuppressed

Of special concern when introducing a biopharmaceutical containing live bacteria is that patients may develop infection from those bacteria due to impaired host immunity. Three populations are likely to be most affected in this scenario: (1) young children, especially neonates and preterm infants, (2) the elderly, and (3) patients on immunosuppressing medications.

Probiotics have been studied extensively in preterm infants in the context of necrotizing enterocolitis (NEC), a multifactorial necroinflammatory condition thought to have a basis in the interaction between microbiome and host immunity. These infants may be less likely to develop NEC(51-53), and while concern has long existed about probiotic strain-associated sepsis, this risk has not been born out in larger trials. However, studies overall have had mixed results(54, 55). Infants do not develop IBS, and develop IBD only in extremely rare cases, but the apparent safety of probiotics in this group is reassuring that the risk for vulnerable or immunocompromised patients may be relatively low.

The elderly represent a large number of patients with IBS and IBD, but the bulk of disease burden remains in young and mid-adulthood. Most clinical trials for IBS or IBD have included some elderly patients, but this demographic has been largely unstudied in relation to probiotics. No trials selected below for quantitative analysis specifically listed rates of ADEs in patients greater than 65, and none had large numbers of elderly patients enrolled at all. No publications to our knowledge have specifically addressed the risks related to probiotic use in elderly adults for any disease.

Immunocompromised patients are of greatest immediate concern to clinicians prescribing probiotics, since many patients with chronic illnesses have IBS and many patients with IBD take immunosuppressants to manage the disease. Many of the trials included in our analysis have demonstrated no added risk to the

addition of probiotics when patients are taking immunosuppressants such as thiopurines or biologics, but these studies are not designed to effectively determine safety of probiotics in the immunosuppressed host. A MEDLINE search using the terms "lactobacillus," "bifidobacteria," "saccharomyces", "VSL", or "probiotics" combined with "azathioprine," "mercaptopurine," "methotrexate," or "infliximab" did not produce any specific publications addressing the risks of probiotic use concurrently with these medicines. We thus conclude that no clear safety data exist to guide clinicians using both immunosuppressants and probiotics simultaneously.

The risk of sepsis from probiotics in all patients, even the immunocompetent, appears to be low, but non-zero. The prophylactic administration of probiotics has been associated with increased mortality in septic patients(56), so care should be taken before introducing probiotic regimens to severely ill patients. However, sepsis from a probiotic strain such as *Lactobacillus* remains very unlikely(57), even in at-risk patients.

ADVERSE DRUG EVENTS (ADEs)

Probiotics With Reported ADEs

We queried the United States Food and Drug Administration's Adverse Drug Event Reporting System (FAERS)(58) for the entirety of 2013 and a relational database was built linking reported ADEs with drug names. Drug names associated with probiotic preparations were then isolated from this relational database, along with the case's associated adverse event(s). Generic terms and genus names ("probiotic", "lactobacillus", "bifidobacteria", and "saccharomyces") and the trade names (Align, Bio-K, Culturelle, DanActive, Florajen, Florastor, Kefir, Lactinex, ProBacLac, RepHresh, VSL #3, and Yakult) for popular probiotic preparations in the United States were used to find probiotic-related ADEs. Counts of ADEs by probiotic type are shown in Table 1. These drug names only indicate which drug was reported in FAERS, and only show association with an ADE, not causation.

Table 1 – Number of each probiotic (and % of total of 1165 probiotic-associated ADEs) in FAERS in 2013

Probiotic Type	Frequency	%
Probiotic	799	68.6%
Align	132	11.3%
Lactobacillus	87	7.5%

Florastor	65	5.6%
Culturelle	44	3.8%
Bifidobacterium	13	1.1%
Saccharomyces	8	0.7%
Florajen	6	0.5%
Lactinex	6	0.5%
VSL #3	2	0.2%
Bioflor	1	0.1%
Kefir	1	0.1%
Rexell	1	0.1%

Types of ADEs

A total of 2,652,194 ADEs for all drugs were found in the FAERS in 2013. Among these, 1165 (0.04% of all 2013 ADEs) were associated with probiotics according to the above search strategy (Table 2), but most ADEs only occurred once in a single patient, and there were 420 distinct event types enumerated. Among probiotics, the most commonly reported ADEs were abdominal pain (11% of all ADEs), asthenia (3%), and arthralgia (3%). Two episodes of sepsis (0.2% of all ADEs), eight episodes of colitis (0.8%), and a single episode of Crohn disease (0.1% of cases) were reported concurrently with probiotic use. Data on patients' other medications or medical history are not accessible in FAERS. In many cases, patients may have had significant polypharmacy, and adverse events were reported while taking multiple medications. These specific ADEs only indicate the symptom reported in FAERS, and only show association, not causation.

Table 2 – Most common specific adverse drug events in FAERS. All events listed in "Other" have 7 or less total occurrences. Some events could have co-occurred with other medications.

Event	Frequency	%
Abdominal pain	125	10.7%
Drug ineffective	39	3.3%
Arthralgia	34	2.9%
Asthenia	30	2.6%
Fatigue	29	2.5%
Diarrhoea	28	2.4%
Injection site pain	22	1.9%
Injection site bruising	16	1.4%
Anaemia	15	1.3%
Anxiety	14	1.2%
Crohn's disease	14	1.2%

Alopecia	13	1.1%
Cough	13	1.1%
Dizziness	12	1.0%
Back pain	11	0.9%
Clostridium difficile infection	11	0.9%
Flushing	11	0.9%
Headache	10	0.9%
Blood pressure increased	9	0.8%
Dyspnoea	9	0.8%
Colitis	8	0.7%
Constipation	8	0.7%
Contusion	8	0.7%
Death	8	0.7%
Incorrect dose administered	8	0.7%
Injection site erythema	8	0.7%
Other	646	55.5%

Therefore, ADEs are quite rare for probiotics (1165 events reported out of more than 2.6 million reported events in 2013), despite more than 4 million adults per month reporting taking probiotics.(1)

SUMMARY OF BENEFITS

IBS

Overall, current national guidelines are supportive of probiotics,(59) indicating more widespread use by gastroenterologists and primary care doctors to treat IBS. 15 trials met our criteria and were used further in the quantitative analysis below.(24-38) Overall, results were mixed, but the majority of trials showed some benefit. When the results of all published clinical trials were pooled in a recent meta-analysis(39), probiotics were effective at improving IBS symptoms, with an OR of 1.27 (95% CI 1.12 – 1.42). 55.8% of patients on probiotics had persistent IBS symptoms, compared with 73.1% of patients on placebo. The trials with the most power and best design all tended to have higher ORs of a positive effect (see Table 3).(25-27)

IBD

10 trials met our criteria and were used further in the quantitative analysis below.(40-49) Results were also mixed, but a majority of trials showed at least mild benefit of probiotics, more for maintenance of remission

than induction of remission (most trials assessed both). In a recent meta-analysis of all published trials(50),

the pooled odds ratio of induction of remission was 1.28 (95% CI 1.00-1.41), which favored probiotics.   For

maintenance of remission, the pooled odds ratio for relapse was 0.73 (95% CI 0.54-0.99), which favored

probiotics. However, in both cases, the confidence interval is very close to 1.0, so the significance of either

result is marginal.

In order to determine the balance between the abovementioned varying degrees of benefit and risk for both

IBS and IBD, and to account for the heterogeneous distribution of both benefit and risk, we next proceeded to

a quantitative risk-benefit analysis.
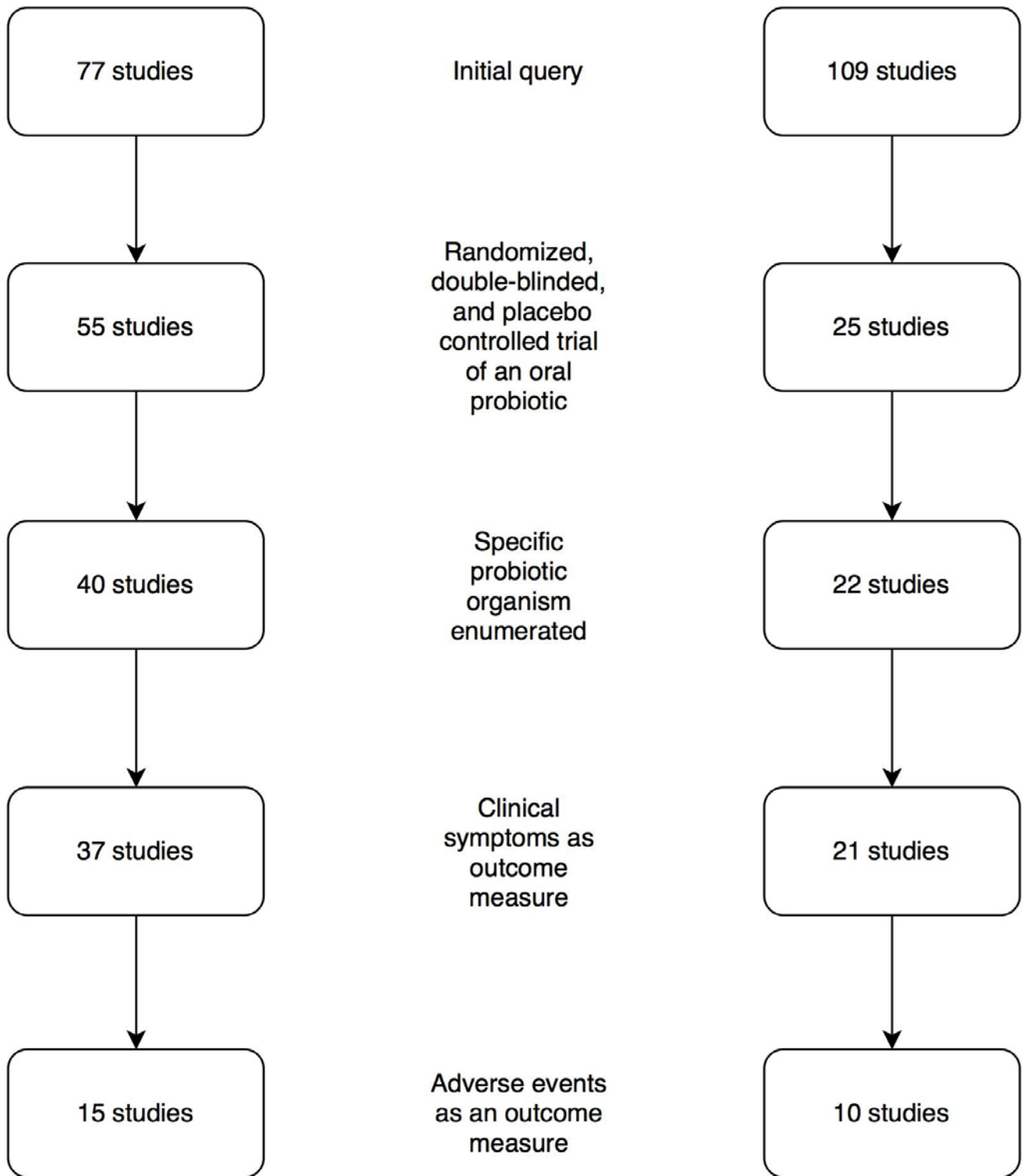
METHODOLOGY OF QUANTITATIVE RISK-BENEFIT ANALYSIS

Search Strategy

We identified studies for quantitative analysis by accessing http://www.pubmed.org. To determine all studies

using probiotics to treat irritable bowel syndrome, the terms ("probiotic," "lactobacillus," "bifidobacteria", "VSL",

or "saccharomyces") and "irritable bowel syndrome" were used. Results were limited to studies performed

through June 30th, 2014, written in English, and entered as clinical trials. To determine all studies using

probiotics to treat inflammatory bowel disease, the terms ("probiotic," "lactobacillus," "bifidobacteria," "VSL," or

"saccharomyces") and ("inflammatory bowel disease" or "Crohn disease" or "Crohn's disease" or "ulcerative

colitis") were used. Results were again limited to studies performed through June 30th, 2014, written in

English with full article text accessible, and entered as clinical trials. The analysis and bibliography of relevant

published meta-analyses were also queried to find additional studies. For initial analysis, 77 studies were

found for IBS and 109 studies for IBD. The details and results of the search strategy are displayed in Figure 1.

Each of the studies selected for further quantitative analysis are listed and described in more detail in Table 3.

In the end, 15 studies were selected for analysis in IBS and 10 studies were selected for IBD.

Figure 1 – Search strategy for studies to include in quantitative analysis.

Irritable bowel syndrome

Inflammatory bowel disease

Irritable bowel syndrome		Inflammatory bowel disease
77 studies	Initial query	109 studies
55 studies	Randomized, double-blinded, and placebo controlled trial of an oral probiotic	25 studies
40 studies	Specific probiotic organism enumerated	22 studies
37 studies	Clinical symptoms as outcome measure	21 studies
15 studies	Adverse events as an outcome measure	10 studies

Table 3 – Description of studies selected for quantitative analysis. Benefit is the clinical endpoint for the study. Risk is the likelihood of any ADE (as defined by the study).

Study (Author, Year)	# Experimental Subjects	95% C.I. (Benefit)	95% C.I. (Risk)
Irritable Bowel Syndrome			
Kim 2003	13	0.51 – 1.67	0.96 – 1.04
Kajander 2005	51	1.12 – 2.44	0.33 – 28.34
Enck 2008	148	1.52 – 2.56	0.47 – 0.97
Hong 2009	34	0.68 – 1.85	0.40 – 2.23
Simren 2010	37	0.85 – 1.61	0.96 – 1.04
Cha 2012	25	1.14 – 2.56	0.24 – 95.90
Nobaek 2000	30	0.89 –1.59	0.96 – 1.04
Niedzielin 2001	20	1.00 – 2.38	0.96 – 1.04
Sinn 2008	20	1.28 – 8.33	0.96 – 1.04
Dapoigny 2012	26	0.57 – 1.23	0.96 – 1.04
Ducrotte 2012	106	1.49 – 2.08	0.12 – 71.49
Guglielmetti 2011	62	1.33 – 2.50	0.96 – 3.06
Enck 2009	150	1.07 – 1.27	0.96 – 1.04
Kruis 2012	60	0.82 – 1.51	0.76 – 1.62
Gade 1989	22	1.01 – 1.89	0.96 – 1.04
Inflammatory Bowel Disease			
Kruis 1997	103	0.53 – 3.79	0.23 – 1.89
Rembacken 1999	83	0.69 – 1.22	0.60 – 3.53
Kruis 2004	327	0.73 – 1.58	0.82 – 1.45
Sood 2009	147	0.90 – 2.13	0.00 – 0.52
Tursi 2010	144	0.58 – 3.36	0.37 – 2.24
Matthes 2010	88	0.58 – 4.42	0.67 – 1.78
Prantera 2002	32	0.79 – 3.65	0.09 – 1.60
Bousvaros 2005	75	0.77 – 4.40	0.33 – 2.00
Marteau 2006	98	0.33 – 5.88	0.36 – 3.01
Van Gossum 2007	70	0.34 – 5.85	0.65 – 1.23

Risk-Benefit Analysis

A wide variety of quantitative methods exist for risk-benefit analysis(60). Since we have little information on

utilities for IBS and IBD in the literature, and most of the existing data on efficacy and risk comes from the

abovementioned large number of clinical trials, we chose to use the risk-benefit plane, a method that plots the

joint distribution of both risk and benefits(61). The primary advantage of this approach is that both risk and

benefit are visualized simultaneously, rather than using a one-dimensional measure such as risk-benefit ratio.

Furthermore, data with a large, heterogeneous distribution across both risk and benefit can be better modeled

as a two-dimensional confidence region than two separate confidence intervals.

First, we constructed a dataset using all existing clinical trials that reported both efficacy and adverse drug events for both IBS(24-38) or IBD(40-49), as described in Figure 1 and Table 1. We sampled across the 95% confidence intervals for each trial weighted by the size of the trial (larger trials had a larger share of sampling). When no adverse events were reported, we estimated the 95% confidence interval as a function of the number of subjects (3/N), as described previously.(62) Once the data set was complete, we simulated 5000 patients by sampling (with replacement) for 5000 iterations. Next, since the distribution of this cross-trial sample could not be assumed to have bivariate normality, we used a recently developed geometry-based method to determine confidence regions in bivariate samples. This method is more robust whether the distribution is normal or non-normal(61), and utilizes the R package "distfree.cr." Finally, the confidence region was plotted using this package on a risk-benefit plane (RBP) to illustrate where the joint distribution of risk and benefit lies.

The end result is a geometric shape that visualizes the joint distribution of risk and benefit. So, when encountering a patient with IBS or IBD who asks about probiotics, there is a 95% chance, based on the dataset employed, that the patient's experience will lie somewhere in that region. The shape of the curve determines where the average patient may fall: if the area of the curve is mostly above the "risk-benefit threshold" line, they have more benefit than risk; if the area of the curve is mostly below this line, they have more risk than benefit. Importantly, this does not quantify the severity of risk – only the presence of risk, nor does it quantify the type of benefit – only the presence or absence of a clinical endpoint of some kind. In the case of probiotics, the severity is often low (worse abdominal pain, for instance), so this must be taken into consideration when interpreting the results.

RESULTS OF QUANTITATIVE RISK-BENEFIT ANALYSIS

IBS

Figure 2 depicts the RBP for all published trials of probiotics for IBS. The mean risk-benefit (solid black circle) lies along the dotted line representing the risk-benefit threshold. So, the average patient will have an equal balance of risk and benefit. Overall, most of the area within the 95% confidence region (red line) lies below the risk-benefit line, so in a slim majority of patients, risk for any ADE will outweigh benefit. Most simulated risk

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data was modeled along a normal distribution (since most trials did not report any ADEs at all), so the range of risk was much narrower than the range of efficacy, resulting in an ovoid confidence region.

Figure 2 – Risk-Benefit Plane for Irritable Bowel Syndrome. The log transformed relative risk of an ADE is plotted on the horizontal axis. The log transformed relative efficacy (in terms of relative rate of improvement in symptoms) is plotted on the vertical axis. Grey circles are individual sampled points. The black circle is the mean of all sampled points. The red line represents the approximated 95% confidence region. The dotted line represents the threshold between a poor risk-benefit ratio (below line) and an advantageous risk-benefit ratio (above line).
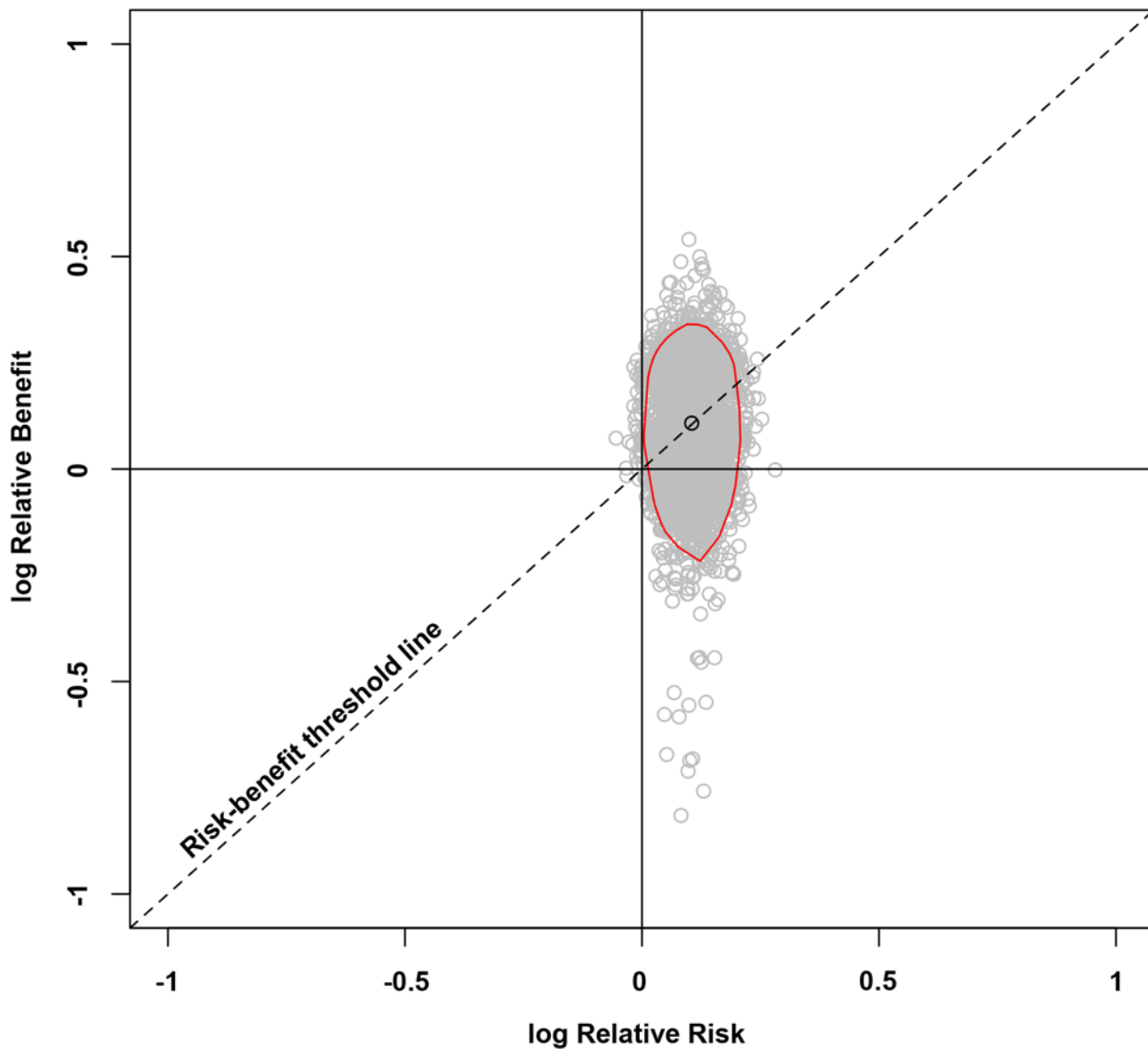

IBD

Figure 3 depicts the RBP for all included trials of probiotics in IBD. The mean risk-benefit (solid black circle) lies well above the dotted line, as does the majority of the 95% confidence region (red line). The confidence region is quite large for IBD, which occurs due to the wide heterogeneity in confidence intervals that formed the primary data source. Thus, in a general sense, probiotics seem to confer more benefit than risk for a majority of hypothetical patients, but with such a large area for the confidence region, the average patient could expect almost any risk-benefit ratio. There is noticeable heterogeneity of the confidence region (for instance, a "cloud" of simulated points in the high-risk, high-benefit range), but this should not be interpreted that any specific sub-population exists. The method employed simply samples from all existing confidence intervals, so if one of the 10 IBD studies had a particular narrow confidence interval, simulated patients may appear to cluster in that region, but the confidence region's shape will take this variation into account. We did not perform sub-group analyses (CD vs. UC or active vs. inactive disease) due to the relative lack of high quality data on which to build a RBP for sub-groups.

Figure 3 – Risk-Benefit Plane for Inflammatory Bowel Disease. The log transformed relative risk of an ADE is plotted on the horizontal axis. The log transformed relative efficacy (in terms of relative rate of maintenance of remission) is plotted on the vertical axis. Grey circles are individual sampled points. The black circle is the mean of all sampled points. The red line represents the approximated 95% confidence region. The dotted line represents the threshold between a poor risk-benefit ratio (below line) and an advantageous risk-benefit ratio (above line).
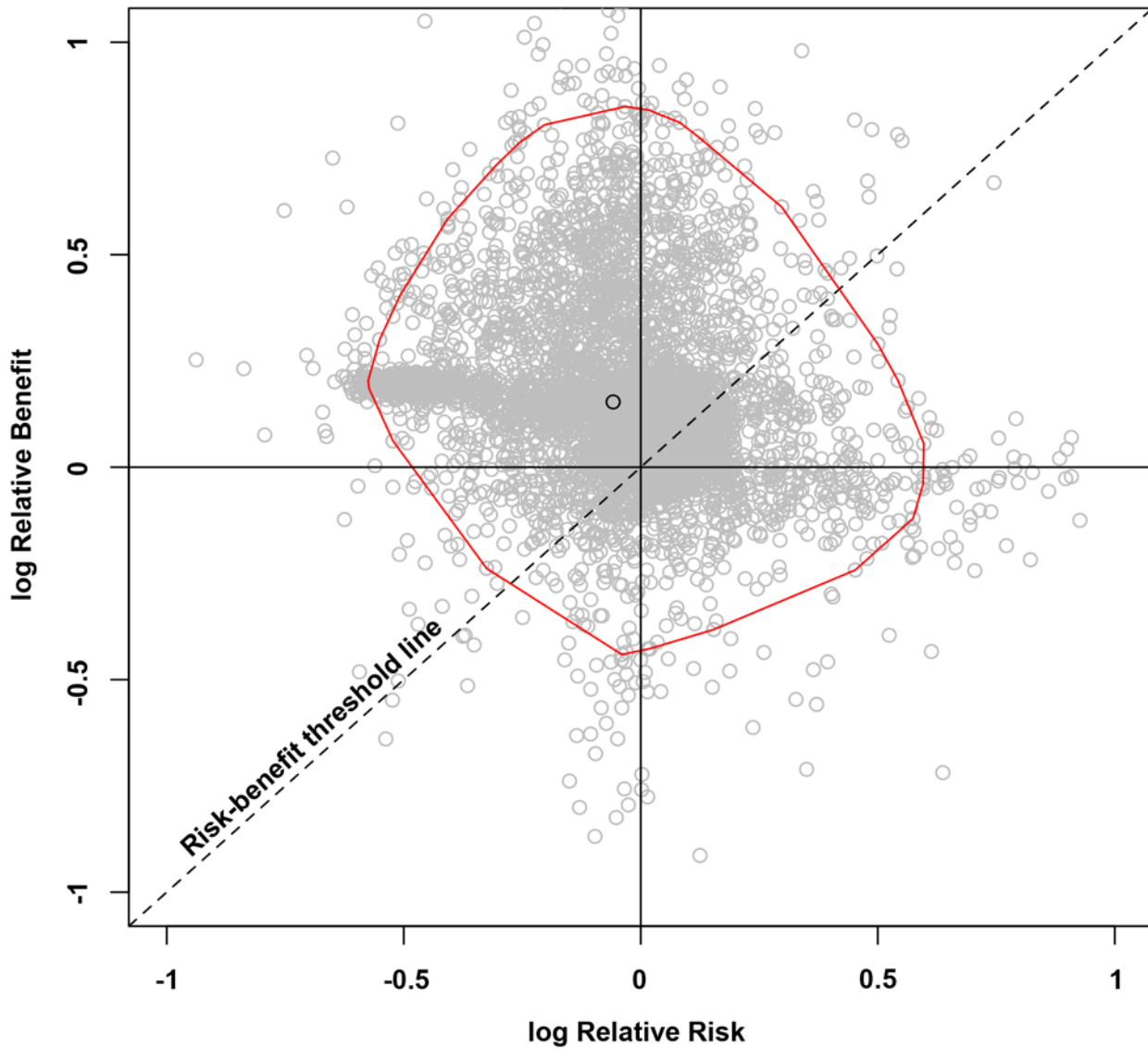
DISCUSSION

Overall, the joint assessment of risk and benefit for probiotic use in either IBS or IBD remain a significant challenge. Risk tends to be low in most patients, but so does efficacy. It is furthermore unknown what risks immunocompromised patients face when taking probiotics. Existing data on ADEs are quite poor, and most trials do not adopt a systematic approach to detecting them.

When we queried the FAERS database, we found relatively few ADEs. In fact, given the high utilization of probiotics in the general population, the rate of reporting is quite low, and many ADEs have no clear rational association with probiotics (arthralgia, injection site pain from other medications, etc). There may be several reasons for this finding: (1) patients may not report probiotics as a medication since they are often marketed as supplements, (2) our search algorithm did not detect all reported cases, or (3) ADEs for probiotics may be so mild that they are not reported with much consistency. We suspect that patients not primed to report an ADE (as in a clinical trial) probably experience at worst minimal and vague symptoms.

When we performed quantitative risk-benefit plane analysis for both IBS and IBD, we noted a wide range of possible risk-benefit ratios, indicating that our knowledge of risk in probiotics remains poor for both of these disorders. This may be a function of the heterogeneity of organisms used across studies, but also the unique problem inherent to using live organisms as therapy for complex and heterogeneous digestive diseases. In either case, a standardized approach to ADEs in future probiotics trials will be essential to inform future treatment decisions.

In IBS, the majority of the confidence region straddles the risk-benefit threshold, and the mean risk-benefit ratio lies along the threshold. This is likely due to the fact that probiotics have low efficacy, but also low likelihood of an ADE. Since studies used in the analysis are quite broad, it is very difficult to make individual recommendations for specific patients and patient populations. On balance, it is reasonable to advise a trial of probiotics for patients with IBS.

In IBD, the confidence region is larger, owing to wider confidence intervals within and among studies. This could be a result of more varied study design, but also due to the heterogeneity of patients with IBD and the higher percentage of patients reporting ADEs. A majority of the confidence region lies above the risk-benefit threshold, and the mean risk-benefit ratio is well above this threshold as well. On balance, probiotics may be helpful in maintaining (or even inducing) remission, but the overall breadth of the confidence region indicates that uncertainty is high, so further studies are certainly needed to more accurately quantify both risk and benefit. Since we have virtually no understanding of the risk of probiotics in the immunocompromised, very

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careful consideration should be given to this population, which represents most IBD patients. It is simply unknown if there is a sub-population of IBD patients with substantial immunosuppressant-related risk. In situations where efficacy is more convincingly established (pouchitis prophylaxis with VSL#3 in patients with a colectomy, for instance(63, 64)), this unknown risk may be worth it, but in immunosuppressed IBD patients in general, for whom the efficacy confidence interval is broad and marginally significant, the potential severity of risk may not be worth it.

There are several limitations to our quantitative analysis. First, studies were analyzed in bloc, and no sub-analysis was performed based on severity of disease, type of IBD, type of probiotic, outcomes measured, or specific ADEs assessed. Performing a more clear RBP analysis would require a larger number of homogenous studies, especially those assessing risk in a rigorous way. This is a particular challenge in probiotic clinical trials, but which is essential if we wish to expand the evidence base. Second, since several IBS studies did not report any ADEs at all, the risk sampling frequently used the normal distribution. This would tend to narrow the risk axis of the confidence region. Finally, we did not specify what type of ADE patients would have, or the severity of the ADE. Since most ADEs from probiotics are mild and not potentially life threatening, risk may be overestimated when simply specifying the rate of ADEs but not quantifying severity. It is likely that many patients would be willing to tolerate mild gastrointestinal upset and many of the other ADEs listed in Table 2. As noted above, there may also be sub-populations of immunosuppressed patient who have a similar rate of ADEs, but they might be much more severe and concerning.

One very challenging aspect of the assessment of ADEs in probiotics is the difficulty in separating disease course and drug effect. For instance, most suspected ADEs are gastrointestinal side effects, yet probiotics are most often used to treat gastrointestinal diseases, many of which have a relapsing, sporadic course as part of their natural history. Therefore, it can be quite difficult to assess whether a symptom is truly the effect of a drug or simply the effect of the disease being treated.

We believe many of the challenges of risk-benefit analysis in probiotics could be overcome by focusing future research in three ways: (1) standardize methods of assessing ADEs in patients taking probiotics, (2) limiting

the breadth of probiotic species studied, and (3) improving the overall methodological quality of trials involving probiotics by using Guidelines for Good Clinical Practice (published by FDA as well as the World Health Organization) as are used for pharmaceutical trials.

CONCLUSIONS

Overall, the risk of probiotic use is low, but unfortunately so are benefit for both IBS and IBD. Given that many patients (and clinicians) are desperate for effective and safe interventions for these disorders, a trial of a probiotic remains a reasonable, and usually safe, practice for these diseases. Quantitative risk-benefit analysis using a risk-benefit plane indicates a confidence region shifted towards a slightly unfavorable risk-benefit in IBS, and a slightly favorable risk-benefit in IBD.

The use of probiotics in the immunocompromised host (including those on immunosuppressants for IBD) has not been well studied. Given the low likelihood of most probiotic preparations to confer a large clinical benefit to a patient, it may be wise to advise against them in this at-risk population until further safety research has been performed.

The evidence base for probiotics can be dramatically improved by both intensifying basic research into the mechanisms of probiotic efficacy and ADEs and by focusing efforts into higher quality clinical research.

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