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REVIEW PAPER

Probiotics for the prevention of antibiotic-associated diarrhea – an umbrella review of meta-analyses of randomized controlled trials

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ABSTRACT

Introduction and aim. Antibiotic therapies induce diarrhea by disrupting the intestinal microbiota, prompting research into probiotics to prevent antibiotic-associated diarrhea (AAD). The aim of this study was to systematically identify and summarize meta-analyses of randomized controlled trials (RCT) on probiotics for AAD prevention.

Material and methods. Databases including PubMed, EMBASE, Epistemonikos, and the Cochrane Database were searched up to December 11, 2023. Systematic reviews and meta-analyses of RCTs on probiotics for AAD prevention in any age group were included. Meta-analyses were re-performed to calculate pooled risk ratios (RR) with 95% confidence intervals (CI). Evidence quality was assessed using GRADE criteria.

Analysis of the literature. The review included 16 articles with 39 unique meta-analyses. Probiotics reduced AAD risk across various groups: adults (RR 0.47, 95% CI 0.40–0.56), all ages (RR 0.58, 95% CI 0.50–0.68), and outpatients (RR 0.49, 95% CI 0.36–0.66) with a moderate level of evidence. For the use of any probiotics in pediatrics, the initial high-quality evidence (RR 0.48, 95% CI 0.44–0.63) was downgraded to moderate after a sensitivity analysis excluding small studies.

Conclusion. Probiotics are beneficial in preventing AAD, but evidence quality varies from low to moderate. High-quality trials are needed to identify the most effective probiotic species and strains, dosages, and target patient populations.

Keywords. antibiotic-associated diarrhea, *Lactobacillus*, probiotics

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Introduction

Diarrhea is a common adverse effect of antibiotic therapies, primarily attributed to significant disruptions in the intestinal microbiota induced by most antibiotics.[1] The direct adverse effects of antibiotics on the intestines involve disruptions in digestive function stemming from diminished concentrations of gut bacteria or the proliferation of pathogenic microorganisms.[1,2] Antibiotic-associated diarrhea (AAD) is characterized by the occurrence of three or more unformed stools per day, manifesting within hours to up to 8 weeks after initiating antibiotic treatment.[1] Studies indicate that the prevalence of AAD ranges from 5% to 35% among individuals exposed to antimicrobials, with variations based on the antibiotic class, host health, and susceptibility to pathogens.[3] In most cases, AAD is benign and can be resolved with symptomatic treatment. However, when AAD is attributable to a *Clostridium difficile* infection, symptoms tend to be more severe, potentially leading to a fulminant, relapsing, and occasionally fatal pseudomembranous colitis.[3,4] The consequences of AAD extend beyond the immediate health impact, contributing to prolonged hospital stays and increased medical costs, particularly in cases involving *C. difficile* infection.[3,5-7]

Probiotics are defined as 'live microorganisms that, when administered in adequate amounts, confer a health benefit on the host'.[8] Given that AAD primarily arises from an imbalance in the natural intestinal flora, research has concentrated on exploring the advantages of introducing living organisms, such as probiotics, to reinstate the normal flora. Various strains from bacterial species have been tested in clinical studies for the prevention and/or treatment of AAD including those from the *Bacillus, Bifidobacterium, Clostridium, Lactobacillus, Lactococcus, Leuconostoc,* and *Streptococcus* genera. Additionally, the fungi *Saccharomyces boulardii* has been investigated for its potential impact on AAD.[9] Among the probiotics, *Lactobacillus rhamnosus* strain GG and *S. boulardii* strain CNCM I-745 were the most extensively studied.[10,11]

Several systematic reviews and meta-analyses have demonstrated the benefits of probiotics in the prevention of AAD in different populations.[12–16] Umbrella reviews make it feasible to summarize the evidence from multiple meta-analyses on the same topic and enable the grading of evidence.[17–19] To date, there has been little synthesis of the strength and quality of this evidence in aggregate. This umbrella review aims to systematically identify relevant meta-analyses of randomized controlled trials (RCTs) of probiotics for the prevention of AAD, summarize their findings, and assess the strength of evidence.

Material and methods

The protocol of this review was registered with PROSPERO (CRD42023465792). We report following the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA).[20]

Search strategy and eligibility criteria

We conducted a comprehensive search on PubMed, EMBASE, Epistemonikos, and the Cochrane Database of Systematic Reviews (CDSR) from database inception to December 11, 2023 (S1). We also manually searched the cited references of the retrieved articles and reviews. The process of study selection was independently carried out in EndNote by two reviewers. After removing duplicates, the titles and abstracts of the identified articles were screened for relevance. Full-text articles of potentially eligible studies were retrieved and assessed against the eligibility criteria. Any discrepancies in the selection process were resolved through discussion with a third reviewer.

We included studies that fulfilled the following eligibility criteria: systematic reviews and meta-analyses of RCTs investigating the effects of probiotics for the prevention of AAD in any population of any age. No restriction was applied for comparators. In instances where multiple meta-analyses addressed the same research question, we selected the meta-analysis with the largest dataset, as previously described.[17,21,22] Articles without full-text and meta-analyses that did not provide sufficient or adequate data for quantitative synthesis were excluded.

Data extraction and quality assessment

Data extraction and quality assessment were conducted independently by two reviewers. Discrepancies were resolved through consensus by engaging in discussions with the third reviewer. The quality of the meta-analyses was evaluated using AMSTAR-2 (A Measurement Tool to Assess systematic Reviews), where quality of the meta-analysis is rated into four categories – high, moderate, low, or critically low.[23]

Data synthesis

Effect sizes were categorized based on the population, intervention, comparator, and outcomes to create a list of unique meta-analyses (association). For each association, we extracted effect sizes of individual studies included in each meta-analysis and re-performed the meta-analyses to calculate the pooled effect sizes as risk ratio (RR) with corresponding 95% CIs using the DerSimonian and Laird random-effects model, or the Hartung-Knapp-Sidik-Jonkman approach for meta-analyses with less than five studies.[24,25] $p<0.05$ was considered statistically significant in 2-sided tests. Heterogeneity was evaluated using the I^2 statistic. The evidence for small-study effects was assessed by the Egger regression asymmetry test.[26] $p<0.10$ was taken as statistical evidence of the presence of small-study effects. Statistical analyses were conducted using Stata version 16.0 (StataCorp, Texas, USA).

We assessed the quality of evidence per association by applying the GRADE criteria (Grading of Recommendations, Assessment, Development, and Evaluations) in five domains, including (1) risk of bias in the individual studies, (2) inconsistency, (3) indirectness, (4) imprecision, and (5) publication bias.[27] We graded the strength of evidence (high, moderate, low, and very low) using GRADEpro version 3.6.1 (McMaster University).

Sensitivity analyses

Sensitivity analyses were performed for those meta-analyses graded as high quality in the primary analysis by excluding small-size studies (<25th percentile) and excluding primary studies having a high risk of bias rated by the Cochrane's risk of bias 2 tool (RoB 2) for RCTs from the identified associations.[28,29]

Analysis of the literature

In total, we identified 1617 articles, scrutinized 78 full-text articles, and included 19 eligible articles (1.18%) for preliminary data extraction (Fig. 1). After the selection criteria for the overlapping meta-analyses were applied, 16 articles were ultimately selected for evidence synthesis.[13,15,30-43] Agreement between reviewers for eligibility of articles was excellent (κ statistic=0.8). The list of excluded articles after applying the selection criteria for the overlapping meta-analyses is provided in Table S2.

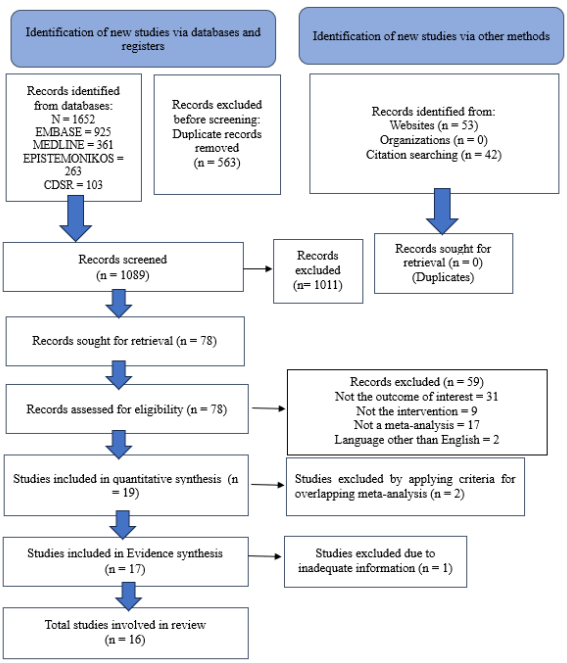

Fig. 1. PRISMA flow diagram

Description and summary of meta-analyses

A total of 39 unique meta-analyses were identified from 16 articles.[13,15,30–43] The included meta-analyses were published between 2002 and 2022. The median number of studies per meta-analysis was 10 (interquartile range [IQR], 6–22) and the median meta-analysis sample size based on 38 meta-analyses was 1847 (IQR: 795–4014). Based on the AMSTAR-2 methodological quality rating, the meta-analyses were classified as follows: six were graded as high quality (15.4%), sixteen as moderate quality (41%), thirteen as low quality (33.3%), and four as critically low quality (10.3%) (Table 1). The descriptive characteristics of meta-analyses were provided in Table 1 and Tables S3 and S4.

Grading of meta-analyses

A summary of evidence of all 39 meta-analyses is presented in Table S4. Ten were supported by a very low level of evidence (25.6%), followed by low (15 meta-analyses (38.5%)), moderate (8 meta-analyses (20.5%)), and high (1 meta-analysis (2.6%)) levels of evidence in the primary analysis. Thirty-two of the 39 meta-analyses (82.05%) were statistically significant at p≤0.05 based on random-effects models and demonstrated the use of probiotics reduce the risk of AAD (Table S4).

Three meta-analyses demonstrated that the use of probiotics as a whole reduced the risk of AAD in adults (RR 0.47, 95% CI 0.40 to 0.56), any age group (RR 0.58, 95% CI 0.50 to 0.68) and outpatients (RR 0.49, 95% CI 0.36 to 0.66) with moderate level of evidence (Figure 2). The associations between risk reduction of AAD and the use of *S. boulardii* (RR 0.50, 95% CI 0.38 to 0.64) in adults, the use of bifidobacteria (RR 0.33, 95% CI 0.29 to 0.39) in pediatrics and the use of *Lactobacillus GG* and *S. boulardii* together (RR 0.40, 95% CI 0.28 to 0.59) in any age group patients[41] were also graded as moderate level of evidence.[13,31,32,43] One meta-analysis finding was supported by high quality evidence (use of probiotics as a whole in the pediatric population (RR 0.48, 95% CI 0.44 to 0.63)) in the primary analysis.[36] However, a sensitivity analysis that excluded studies with small sizes downgraded the evidence to moderate quality (Table S5).

Discussion

This umbrella review systematically identified 39 unique meta-analyses of RCTs investigating the efficacy of probiotics for the prevention of AAD and ascertained the overall strength of evidence using GRADE approach.

Overall, findings from this umbrella review indicated that using probiotics, in general, reduces the risk of AAD. However, there is a caveat – the finding is based on a limited number of high-quality RCTs. The overall strength of evidence from this umbrella review is moderate to low. Despite the promising findings, it is essential to acknowledge that systematic reviews and meta-analyses have consistently reported favorable findings with moderate quality of evidence with regard to the effects of probiotics on the prevention AAD, primarily attributed to concerns related to trial quality, specifically the high risk of bias for some studies, and the notable differences in the spectrum of probiotics and

Table 1. Characteristics of meta-analyses*

Author, year	Population	Intervention	Comparison	Outcome	No of studies	Total participants	AMSTAR
Agamennone et al., 2018	Any age group	Probiotic dairy products	Placebo	Incidence of AAD	7	488	Critically low
Agamennone et al., 2018	Any age group	Probiotic food supplements (Non-dairy products)	Placebo	Incidence of AAD	25	3232	Critically low
Blaabjerg et al., 2017	Outpatients of any age group	Any probiotics	Placebo	Incidence of AAD	17	3631	Low
Blaabjerg et al., 2017	Outpatients of any age group	*Saccharomyces boulardii*	Placebo	Incidence of AAD	5	1139	Low
Blaabjerg et al., 2017	Outpatients of any age group	*Lactobacillus acidophilus* and *Bifidobacterium lactis*	Placebo	Incidence of AAD	2	455	Low
Blaabjerg et al., 2017	Outpatients of any age group	Any probiotics	Placebo	Incidence of WHO defined diarrhoea	7	1724	Low
Cremonini et al., 2002	Any age group	*Lactobacillus* GG, *Saccharomyces boulardii*	Placebo	Incidence of AAD	7	881	Critically low
Hempel et al., 2012	Any age group	Any probiotics	Placebo	Incidence of AAD	63	11811	Moderate
Hempel et al., 2012	Any age group	Genera blends	Placebo	Incidence of AAD	25	3446	Moderate
Hempel et al., 2012	Any age group	*Genus, Bacillus*	Placebo	Incidence of AAD	2	367	Moderate
Hempel et al., 2012	Any age group	*Genus, Enterococcus*	Placebo	Incidence of AAD	3	1448	Moderate
Hempel et al., 2012	Any age group	*Genus, Lactobacillus*	Placebo	Incidence of AAD	17	2534	Moderate
Hempel et al., 2012	Any age group	*Genus, Saccharomyces*	Placebo	Incidence of AAD	15	3940	Moderate
Jafarnejad et al., 2016	Inpatients	Any probiotics	Placebo	Incidence of AAD	22	6435	Low
Jafarnejad et al., 2016	Elderly	Any probiotics	Placebo	Incidence of AAD	5	3434	Low
Jafarnejad et al., 2016	Adults	*Lactobacillus* sp.	Placebo	Incidence of AAD	22	5828	Low
Jafarnejad et al., 2016	Adults	*Saccharomyces boulardii*	Placebo	Incidence of AAD	11	1832	Low
Jafarnejad et al., 2016	Adults	*Bifidobacteria* sp.	Placebo	Incidence of AAD	13	4511	Low
Kale-Pradhan et al., 2010	Paediatric and adult patients	*Lactobacillus*	Placebo	Risk of AAD	10	1862	Moderate
Ritchie et al., 2012	Any age group	Any probiotics	Placebo	Incidence of CDD	6	NA	High
Szajewska et al., 2005	Adults and children	*Saccharomyces boulardii*	Placebo	Incidence of AAD	5	1076	High
Szajewska et al., 20154	Adults and children	*Lactobacillus rhamnosus* GG	Placebo	Incidence of AAD	12	1499	High
Videlock et al., 2012	Any age group patients treated with antibiotics	Any probiotics	Placebo	Incidence of AAD	34	4138	Moderate
Guo et al., 2019	Paediatric patients treated with antibiotics (any dose)	Any probiotics	Placebo/control	Incidence of AAD	33	6352	High
Guo et al., 2019	Paediatric patients treated with antibiotics (5 billion CFU)	Any probiotics	Placebo/control	Incidence of AAD	20	4038	High
Guo et al., 2019	Pediatric patients treated with antibiotics	*Lactobacillus rhamnosus (strains: GG, ATCC53103 and E/N, Oxy, Pen)*	Placebo/control	Incidence of AAD	6	686	High
Kale-Pradhan et al., 2010	Pediatrics	*Lactobacillus*	Placebo	Risk of AAD	4	585	Moderate
Szajewska et al., 2015	Children	*Lactobacillus rhamnosus* GG	Placebo	Incidence of AAD	4	381	High
Szajewska et al., 2006	Pediatric inpatients or outpatients	Any probiotics	Placebo	Risk of AAD	6	766	High
Videlock et al., 2012	Pediatric patients treated with antibiotics	Any probiotics	Placebo	Incidence of AAD	10	1246	Moderate
Xu et al., 2017	Pediatrics	*Bifidobacterium*	Placebo	Risk and treatment of AAD	30	7225	Critically low
Zhang et al., 2022	Elderly on antibiotics	Any probiotic	Placebo	Incidence of AAD	8	4691	Moderate
Zhang et al., 2022	Elderly inpatients	Any probiotic	Placebo	Incidence of AAD	6	624	Moderate
Zhang et al., 2022	Elderly inpatients	Probiotic given during antibiotic treatment	Placebo	Incidence of AAD	5	420	Moderate
Avadhani et al., 2010	Adult hospitalized population	Any probiotic	Placebo	Incidence of AAD	8	1220	Moderate
Avadhani et al., 2010	Adult hospitalized population	Any probiotic	Placebo	Incidence of CDAD	4	471	Moderate
Liao et al., 2020	Adult inpatients and outpatients	Any probiotic	Placebo	Incidence of AAD	36	9312	Low
Jafarnejad et al., 2016	Adults	Any probiotic	Placebo	Incidence of AAD	25	3826	Low
Videlock et al., 2012	Adult patients treated with antibiotics	Any probiotic	Placebo	Incidence of AAD	24	2921	Moderate

* AAD – antibiotic associated diarrhea, CDAD – *Clostridium difficile* associated diarrhea

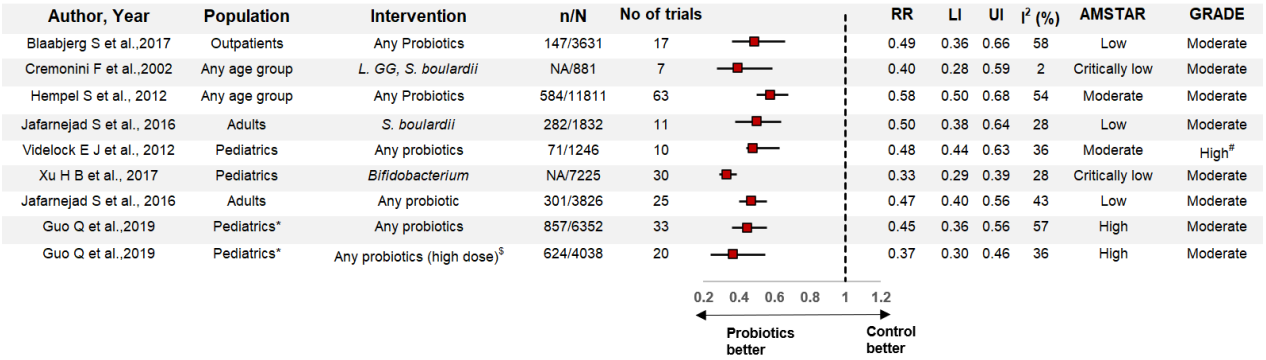

Fig. 2. Meta-analyses graded as moderate to high-quality in primary analysis (*Pediatric patients treated with antibiotics with a follow-up of 5 days to 12 weeks; $high dose (≥ 5 billion CFU/day); #the certainty of evidence of this meta-analysis downgraded to moderate quality after sensitivity analysis (L. GG – *Lactobacillus rhamnosus* GG*; S. boulardii – Saccharomyces boulardii;* NA – not available; RR – risk ratio; LI – lower confidence interval; UL – upper confidence interval; n – number of cases; N – total number of patients))

the conditions of use examined in RCTs.[12–14] As noted in this review, the diversity in probiotics extends to variations in strains and species, including genera blends, as well as differences in potency, dosage, and duration of use. Additionally, variations in study populations, including differences in age groups, types of infections, and patient settings (inpatient vs. outpatient), further complicate the interpretation of results.

Probiotics are increasingly popular globally, with a market expected to reach $52 billion by 2030.[44] They are easily accessible and come in various appealing flavors and dosage forms, including capsules, powders, liquids, and others. These products often contain a mix of microbial strains, primarily from genera like *Lactobacillus*, *Bifidobacterium*, and *Saccharomyces,* rather than single strains.[45] Probiotics exert their health benefits through a range of mechanisms that can be nonspecific, species-specific, or strain-specific.[8,46] Nonspecific effects mechanisms, such as inhibiting the growth of pathogenic microorganisms in the gastrointestinal tract, producing bioactive metabolites, and reducing luminal pH in the colon, vary widely among strains, species, or even genera. Species-specific mechanisms include vitamin synthesis, gut barrier reinforcement, bile salt metabolism, enzymatic activity, and toxin neutralization. Strain-specific mechanisms, which are rare, may involve cytokine production, immunomodulation, and effects on the endocrine and nervous systems. Notably, within the same species, distinct strains can have vastly different activities and biological effects.[46] Additionally, combinations of various strains can result in different activities, as certain microbial activities rely on interactions between different strains.[47] Given these variations, recommendations for probiotic use should be specific to the individual and/or combination of species and strains. In this review, the majority of included studies focused on any ('non-specific') probiotics. Among the meta-analyses graded as moderate to high quality, only three studies examined the use of specific genera or species.[32,41,43] In addition to considering species and strains, probiotics may also exert dose-dependent effects. While commercially available probiotic formulations typically contain at least 10^6 CFUs,[48] the optimal dose, frequency, and duration of probiotic use to achieve clinical effect of preventing AAD is unclear. In this review, the probiotic dosage regimen varied across studies, making cross-comparisons difficult. Therefore, future RCTs exploring effects of specific probiotic species and strains, as well as the optimal dose and duration of treatment are warranted.

Another challenge arises due to a lack of thorough evaluations specifically targeting probiotic-related adverse events. While RCTs generally report low rates of adverse events, it is important to highlight that several case studies have documented serious adverse events, particularly in vulnerable patients. A survey of specific populations examined in clinical trials identified an instance of invasive disease in an immunocompromised patient, and concerns were also raised about the safety of probiotics in children receiving intensive care and adults with severe acute pancreatitis.[49-51] These reports emphasized the necessity for improved documentation regarding the safety of probiotics. Consequently, the current state of evidence underscores the limitation in drawing firm conclusions regarding the safety of probiotics in managing AAD.

Overall, it remains to be answered, specifically which probiotics, what dosage regimen, and in which population the use of probiotics will be safe and beneficial in managing AAD. Currently, there is no global consensus on the clinical use of probiotics for AAD. The American Gastrointestinal Association suggests certain strains and combinations of probiotics in adults and children on antibiotic treatment, but this recommen-

dation is conditional (not strong) due to limited supporting evidence. The recommendation also note that patients who are concerned about financial costs or potential harms (e.g., immunocompromised), and who have a low risk of developing *C. difficile* infection (e.g., outpatients in the community), may opt not to use any probiotics.[47] The World Gastroenterology Organization[52] and Infectious Diseases Society of America[53] offer similar recommendations citing insufficient high quality evidence on the efficacy and safety of probiotics in AAD. In Asia, clinical practice echo a comparable standpoint. For instance, a position statement from the Malaysian Society of Gastroenterology and Hepatology generally affirms the efficacy and safety of specific probiotic strains in AAD, including *C. difficile*-associated diarrhea. However, it also advises careful scrutiny of claimed health benefits and supportive evidence before advocating their clinical use.[54] In the recent European Society for Pediatric Gastroenterology, Hepatology and Nutrition position paper, it is suggested that high doses (≥5 billion CFU per day) of *S. boulardii* or *L. rhamnosus* GG may be considered for preventing AAD in outpatients and hospitalized children with specific risk factors, though the evidence is of moderate certainty.[55] The paper also notes that the strain designation of *S. boulardii* was unclear in many of the trials. Therefore, until high quality evidence becomes available, healthcare professionals and consumers should exercise caution and carefully weigh the potential benefits and risks associated with probiotic use. Addressing the identified gaps through higher quality trials is essential before definitive recommendations can be made regarding the role of probiotics in AAD.

Study limitations

The present umbrella review has several limitations that should be acknowledged. Firstly, the search strategy was confined to English language publications only, which may have led to the exclusion of relevant studies published in other languages. The findings of this review are based on moderate to low-quality evidence. Therefore, the results should be interpreted with caution, and further research is needed to confirm the findings of this review.

Conclusion

The findings of this study support the use of probiotics for the prevention of AAD. However, the quality of the evidence was mostly low to moderate. More high-quality trials are warranted in this area. Future research should focus on identifying the most effective probiotic species and/or strains, optimal dosage regimens, and specific patient populations (e.g., adults/children, inpatient or outpatient) that will benefit from probiotic use.

Supplementary materials

S1: Search Strategy, Table S2: Excluded studies and reason for exclusion, Table S3: Description of probiotics, Table S4: GRADE Meta-analysis, Table S5: Sensitivity analysis

Declarations

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Author contributions

Conceptualization, E.L. and S.V.; Methodology, E.L., S.T.S. and S.V.; Formal Analysis, S.T.S, S.K. and S.V.; Investigation, E.L., M.K.M., P.V.I., S.S., S.K. and S.V.; Resources, E.L.; Data Curation, S.V.; Writing – Original Draft Preparation, E.L., S.T.S. and S.V.; Writing – Review & Editing, E.L., S.T.S., M.K.M., S.S., P.V.I., S.K., S.M.C., Y.Y.L. and S.V..; Visualization, S.V.; Project Administration, E.L.

Conflicts of interest

The authors declare no competing interests.

Data availability

All data generated or analyzed during this study are included in this published article (and its Supplementary Information files).

Ethics approval

Not applicable.

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