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Unravelling the gut-brain connection: a systematic review of migraine and the gut microbiome

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Abstract

Background There is substantial evidence linking migraines to gastrointestinal (GI) issues. Conditions such as irritable bowel syndrome and colitis often co-occur with migraines and GI symptoms are common among migraine patients. However, the evidence supporting the efficacy of gut microbiome-targeted therapies for managing migraines is limited. This systematic review aimed to describe the existing evidence of the gut microbiome in patients with migraine compared to healthy individuals. Additionally, it sought to examine how therapies targeting the gut microbiome including prebiotics, probiotics and synbiotics, might influence clinical outcomes.

Methods We performed searches on Embase, PubMed, and the Cochrane Library to identify studies in migraines and the gut microbiome, focusing on those which investigated the gut microbiome composition and gut microbiome-targeted therapies. Key data was extracted and analysed including study details, patient demographics, migraine type, comorbidities, and clinical outcomes. For gut microbiome composition studies, bacterial diversity and abundance was noted. For gut microbiome-targeted therapies studies, treatment types, dosages, and patient outcomes was recorded.

Results A significant difference between various genera of microbes was reported between migraine patients and controls in several studies. *Bacteroidetes (*also named *Bacteroidota)*, *proteobacteria*, and *firmicutes* (also named *Bacillota*) phyla groups were found significantly abundant in migraine, while studies were conflicted in the abundance of *Actinobacteria* and *Clostridia* with regards to increased migraine risk in migraine patients. Patients with migraine had a gut microbiome with reduced species number and relative abundance, as well as a distinct bacterial composition compared to controls. Synbiotic and synbiotic/probiotic combination treatments have been shown in five randomised controlled trials and one open label pilot study to significantly decrease migraine severity, frequency, duration and painkiller consumption.

Conclusions The significant alterations in microbial phyla observed in migraine patients suggest a potential microbial signature that may be associated with migraine risk or chronic progression. However, the mechanistic underpinnings of these associations remain unclear. This systemic review found that probiotic and synbiotic/probiotic combination therapies may be promising interventions for migraine management, offering significant reductions in migraine frequency and painkiller use. Future randomised controlled studies are needed to evaluate the optimal length of treatment and impact on patient related quality of life.

Keywords Migraine, Gut microbiome, Microbiota, Microbial diversity, Microbiome therapies, Probiotic, Symbiotic

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Background

There is increasing evidence linking migraine to gastrointestinal (GI) symptoms, with population studies associating migraine with irritable bowel syndrome (IBS), colitis, constipation, dyspepsia, gastroesophageal reflux disease, *Helicobacter pylori* infection and peptic ulcers [1–3]. Headache frequency has been linked to increased GI complaints [1], with nausea often reported to be the most bothersome among them [4–6]. Moreover, migraine increases the risk of developing IBS, suggesting shared mechanisms or risk factors [7].

The gastrointestinal tract has also been linked to the migraine prodrome, with up to 23.1% reporting nausea [8] and 32.1% describing food cravings [9, 10] during this period. Cheese or chocolate have been described as common triggers (or ingested in relation to food cravings in the prodrome) [11, 12] and Western diets have been associated with increased migraine frequency [13]. GI side effects are also commonly reported with migraine among migraine patients. 60%-95% of migraine patients experience nausea and 50%-62% experience vomiting [14]. A constipation rate of 4.7% to 65% has been reported in patients when treated with calcitonin gene related peptide (CGRP) monoclonal antibodies, with the highest rate (65%) reported for erunemab [15]. Triptans have also been found to possibly aggravate nausea [16]. Identifying therapeutics which target headache and improve GI symptoms, therefore, would be advantageous.

The gut microbiota produces metabolites like tryptophan, tyrosine and glutamine which are utilized in the synthesis of neurotransmitters and neuromodulators such as dopamine, acetylcholine, serotonin and gamma aminobutyric acid (GABA), linking them to diseases of the central nervous system and may therefore be associated in the pathogenesis of migraine [17–19].

Short chain fatty acids, the main metabolic product of colonic bacteria, are suggested to have a neuro-endocrine function [20]. These fatty acids influence brain chemistry neurotransmitter synthesis including serotonin [21], which has been to be reduced interictally and increase during migraine attacks [22]. Bacteroidetes and species within the Firmicutes phylum are the primary bacterial species involved with short chain fatty acid production. Key butyrate producers in the gut include *Eubacterium rectale*, *Roseburia faecis*, *Eubacterium hallii*, and *Faecalibacterium prausnitzii*. Meanwhile, *Veillonella*, *Lactobacillus*, *Bacteroides*, and *Propionibacterium* are prominent contributors to propionate production. Certain bacteria have also been shown to influence brain function including *Faecalibacterium* sp, *Bifidobacterium* sp, and *Lactobacillus* sp and *Clostridium coccoides* [23]. Short chain fatty acids including butyric acid and propionic acid, can cross the blood–brain barrier (BBB) and activate receptors that influence signalling of dopamine and serotonin [24]. These metabolites may therefore link the gut microbiota to central nervous system disorders and migraine [17–19, 21].

An imbalanced gut microbiome indicated by low bacterial diversity, increased pathogenic bacteria and dysbiosis leads to a decrease in the function of the gut barrier. This leads to increased gut permeability and neuroinflammation which can result in apoptosis, necrosis, cytokine mediated immune response directed at the gut [25, 26]. An increase in gut permeability allows toxic bacterial lipopolysaccharides to enter the circulatory system leading to an global immune response [24].

Migraine attacks have been found to correlate with proinflammatory cytokines, with IL-10 elevated during attacks and TNF-α and IL-2 being decreased interictally compared to controls [27]. Pro-inflammatory cytokines may lead to the release of vasoactive neuropeptides such as CGRP involved in migraine nociception. Activation of the hypothalamic–pituitary–adrenal axis can lead to the release of serotonin which also impacts nociception. A compromised gut barrier and altered microbiome may also increase serotonin release from enterochromaffin cells, influencing trigeminovascular system activation via vagal nerve innervation of the gut [24].

Gut microbiome studies are however, influenced by various confounding factors. Microbiota composition is linked to variables such as BMI, sex, age, geographical demographic, diet, alcohol intake, genetic background, medication intake, comorbidities and bowel movement quality [28, 29]. The gut microbiome varies among adults but is more similar among relatives, likely due to shared environment and genetics [30]. Diet also has a major role in shaping the gut microbiome, with fibre sources influencing composition—fruit and vegetable fibre boosting *Clostridia*, while bean-derived fibre being found to increase *Actinobacteria*. [31]. There is evidence that individuals with obesity have a lower proportion of *Bacteroidetes* compared to lean individuals and this proportion increases with weight loss [32]. Medication use and lifestyle change has been shown to influence the gut composition [33]. Non-steroidal anti-inflammatory drugs (NSAIDs) and opioids have been found to affect the gut microbiota [34], with NSAIDs being linked to intestinal injury, changes in gut microbiota and dysbiosis [35].

Measuring the composition of the gut microbiome includes measurements of alpha and beta diversity. Alpha diversity describes the ecological diversity of a single sample, the number of taxa and their relative abundances [36, 37]. Several indices are used to measure alpha diversity. They are broadly classified into indices of richness which estimate the number of different species in a sample, evenness which account for the species relative

abundances without accounting for the total number, and diversity that account for both species relative abundances and total number of species [36]. Beta diversity measures differences in microbial community composition between individuals and categorizes microbial presence/absence data based on species turnover, including continuity and loss, species richness gradients and gain and loss [37, 38]. Beta-diversity sample size calculations require metrics that quantify differences between microbiome profiles. The most common metric is UniFrac distance (weighted and unweighted) which integrates phylogenetic relationships to compare microbial communities across samples. When combined with multivariate techniques such as principal coordinates analysis (PCoA), it helps explain the factors driving differences among these communities. Other frequently used non-phylogenetic metrics include the Jaccard and Bray–Curtis distances [39, 40].

Gut microbiome-targeted therapeutics include probiotics, consisting of live bacteria that which confer benefits to the host including activating host immunity; prebiotics, which stimulate the growth of gut microbiota and activate the immune response; and synbiotics, a combination of both [41–43]. However, the evidence regarding the efficacy of modulatory interventions on the gut microbiome and their resulting effects on migraine is limited.

Thus, this systematic review aimed to characterise the gut microbiome composition including bacteria such as *Faecalibacterium*, *Bifidobacterium*, *Lactobacillus*, and *Clostridium* in people with migraine compared to healthy controls. This may elucidate new therapeutic targets and better understanding of the contribution of the gut-brain-axis to migraine pathophysiology. We additionally aimed to identify gut microbiome altering therapies that may impact clinical outcomes in migraine patients.

Methods

Review registration

The protocol for this systematic review was prospectively registered on PROSPERO in 2024 (Protocol: CRD42024513193) (66).

Study identification

This review was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. A search was conducted on Embase, PubMed and the Cochrane Library to identify all potentially relevant articles using the following search string: ('migraine*' OR 'headache*') AND ('gut microbiome' OR 'gastrointestinal microbiome' OR 'microbiota' OR 'bacteria* flora' OR 'probiotic*' OR 'prebiotic*' OR 'synbiotic*') where the *truncation symbol searches for multiple variants of a word. The search was performed on 29/01/2024. Medical Subject Heading terms were used where appropriate for 'migraine' and 'gut microbiome' to ensure the databases were comprehensively searched for suitable studies.

Study inclusion and exclusion criteria

The inclusion and exclusion criteria (Supplementary Table 1) were determined based on Population, Intervention, Comparison and Outcome (PICOS) criteria and included: patients with migraine with and without aura. Rarer migraine subtypes such as hemiplegic migraine, menstrual migraine, vestibular migraines, abdominal migraine and other headache disorders were excluded due to the possible contributions of underlying pathological mechanisms. Trials of gut microbiome targeted therapeutics which included the use of additional prophylactic and acute migraine medications were included. Intervention studies involving dietary changes were excluded as they do not exclusively target the gut microbiome. A control group in the studies was not required for inclusion to maximize the number of relevant studies included.

The exclusion criteria for this study included animals, in vitro models and secondary migraine or headache disorders. Additionally, conditions such as abdominal migraine, vestibular migraine and those related to the oropharyngeal microbiome are excluded. Any treatments that did not specifically target the microbiota, as well as dietary changes, were also not considered. Reviews, including literature, systematic reviews, and meta-analyses, are excluded, along with clinical trial registrations that did not provide results in the abstract.

Study selection

Studies identified from databases were uploaded onto Covidence software [44]. Duplicate studies were removed prior to the initial screening. Two reviewers independently reviewed all articles by title and abstract and then full texts were screened according to predefined criteria (Supplementary Table 1). Discrepancies between the two investigators were resolved by a third reviewer.

Data extraction

For each study included the following data was extracted: authors, year, country, study type, title, number of patients (total, male, female), number of patients used for data analysis (total, male, female), number of patients who dropped out of the study and the reason, inclusion criteria, exclusion criteria, patient age range, ethnicity, migraine type, documented comorbidities, a description of the control group (if applicable), study limitations, and additional information that may be relevant to the

review. For all studies the following patient demographics were calculated: number of patients (total, dropped out of study, used for data analysis, controls, and migraine patients), total number of males and females included, and patient age range.

Data extracted from the observational gut microbiome studies also included: methods and statistical analysis, number of patients analysed, abundance of each bacterial taxa (phylum, class, order, family, genus, species), alpha diversity, beta diversity within both migraine and healthy patients and between the two groups and whether correlations existed between gut bacteria and risk of migraine, or migraine clinical characteristics. Categories of bacteria taxa were listed as: Phylum, class, order, family, genus, species and the association of the bacteria to a risk of migraine and migraine clinical characteristics. The alpha and beta diversity of bacteria was also reported in migraine and control groups.

In gut microbiome therapeutic treatment studies, the following additional data was extracted: treatment administered, number of patients in each treatment arm, dosage, frequency and length of treatment, time points used for assessment, and outcomes used for data analysis. Total number of studies that used each intervention type (probiotic, prebiotic, synbiotic), total number of bacterial species used per study intervention, number of studies that used each bacterial species and improvement of migraine outcomes and painkiller use were reported.

For studies that did not explicitly state raw data values, values were extracted from figures using WebPlotDigitizer (v4.7) software [45].

Quality assessment and risk of bias

Study quality was assessed using the National Institute of Health (NIH) Quality Assessment Tools. Due to the range of study types included in this review, three tools were used [46]. The tool for 'Observational Cohort and Cross-Sectional Studies' was used to assess gut microbiome studies, and tools for 'Controlled Intervention Studies' and 'Before-After (Pre-Post) Studies with No Control Group' were used to assess gut microbiome targeted therapeutic studies. The studies received a 'Yes', 'No', 'Cannot Determine', or 'Not Applicable' score for each question within the tool. The overall bias rating for each study was determined using a numerical scoring system.

Each quality assessment question was assigned a "Custom Bias Impact Score" based on its impact on bias. Scores were calculated by summing these points and expressed as a percentage of the maximum possible bias. Studies were then categorized into "Good," "Fair," or "Poor" bias ratings based on their scores. This method reduced subjective influence, providing a consistent and objective evaluation of bias across studies.

Results

Search results

The database search identified 244 studies from Embase, 163 from PubMed and 122 from the Cochrane Library (Fig. 1). After removing duplicates, 336 articles were retrieved for title and abstract screening. This screening process identified 24 articles for full-text review, resulting in 16 eligible articles for inclusion in qualitative synthesis.

Patient and study characteristics

Gut microbiome composition

Five studies carried out gut microbiome composition sequencing or mass spectrometry to identify bacterial abundance [47–50], while four studies carried out secondary analysis of the gut microbiome in patients with migraine and controls by analysing pre-existing gut microbiome data available from databases [49–52]. The samples used by two studies were likely identical as both studies included 18,340 samples from the MiBioGen consortium and 375,752 samples from the International Headache GWAS [51, 52]. Another 219,381 samples from the FinnGen were also included [52].

Faecal samples were collected from participants and analysed using various microbiome sequencing techniques, including 16S rRNA sequencing; V3-V4 regions [53]; V4, V3-V4, V1-V2 regions [52]; V4 regions [48]; and unreported regions [51]. Shotgun metagenomics was also used in one study [54]. Functional analysis of microbial communities was conducted by mapping amino acid sequences to KEGG orthologous groups (KOs) using basic local alignment search tool (BLAST) [53]. In addition, mass spectrometry was employed to assess gut microbiota composition, including resident and transient microorganisms, fungi, and viral markers [55].

Two papers assessed clinical migraine measurements in patients. One scored participants' pain severity, psychological status and migraine disability using VAS (Visual Analogue Scale), Hamilton's Anxiety Scale (HARS), Beck's Depression Inventory (BDI), and Migraine Disability Assessment (MIDAS) [55]. In contrast, the second study included migraine patients based on self-reported questionnaires or physician-diagnosed migraines [50]. Across all studies, statistical significance was set at $p < 0.05$, with false discovery rate adjustments applied.

The baseline demographics varied across the included studies with an age range of < 9–80 years, with more female (62.42%) than male (37.58%) participants (Table 1). Migraine types included migraine with and without aura; chronic and episodic migraine, diagnosed using ICHD (International Classification of Headache Disorders)-3, ICHD-2, ICD (International Classification of Diseases)-10, ICD-8 criteria or self-reported via questionnaires. Most studies did not specify the number of

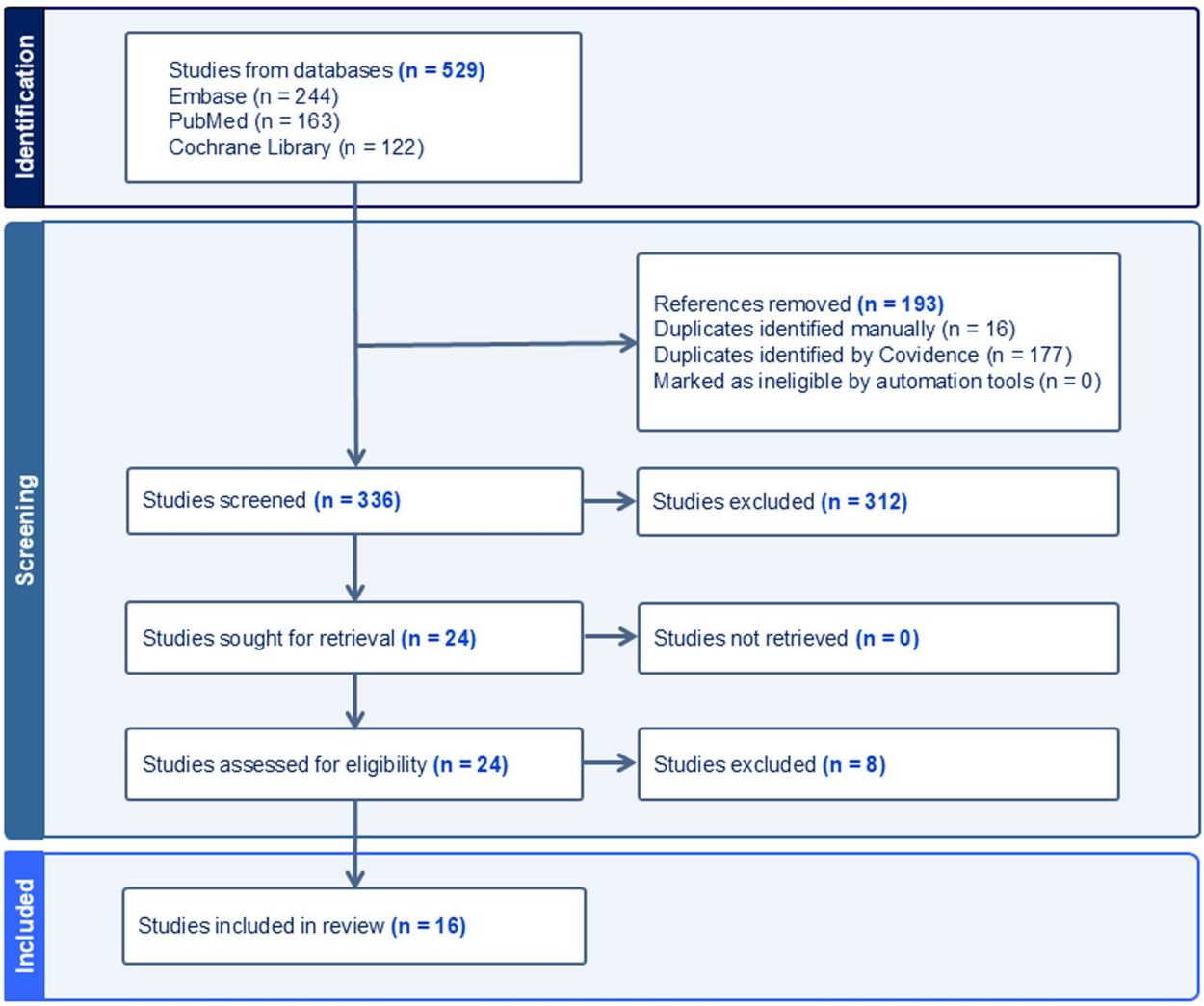

Fig. 1 Flow diagram of the review process and resulting number of studies identified and screened. Created using Covidence software [44]

patients for each type of migraine, except for one study which stated inclusion of 33 episodic migraine and 41 chronic migraine patients [53], and another which included 105 migraine without aura patients [53, 56]. The presence of comorbidities (IBS, hypertension, hyperlipidaemia, diabetes, allergies, asthma, gastric ulcer, anxiety, depression, fibromyalgia) was only reported in two studies [48, 53].

Gut microbiome-targeted interventions included probiotics, synbiotics, with various bacterial combinations

Patients from therapeutic trials had an age range of 6–70 years old with most being female (74.05% female and 25.95% male, Table 2). Patients with all migraine types were included and diagnosed via the ICHD-3, ICHD-2 and unspecified ICHD criteria, with only one study stating the number of patients per migraine type [57]. The only comorbidity included was IBS in one study [58]. Five interventions with a total of 20 species and six genera were used across all the studies (Table 3). Four therapeutic studies used a probiotic [25, 57–59] and three used a synbiotic [60–62], all other outcome measures varied between trials (Table 4).

Outcomes

Gut microbiota profile is different in patients with migraine

The gut microbiome composition was studied at the phylum, class, order, and species level. There were differences in the phylum level across five studies, however findings were not consistent across all studies (Fig. 2) [48–50, 53, 54].

At the class, order, and family levels, the *Tissierellia* class, *Tissierellales* order, *Peptoniphilaceae* family were all significantly increased in adult chronic and episodic migraine patients (*Tissierellia*; approximate fold change (log_{10}) of 3.67 in episodic and 2.9 in chronic migraine,

Table 1 Patient and study characteristics, gut microbiome composition studies

Study Information			Patient Population								
Authors (Year)	Location	Type	Recruited patients (n)			Included in analysis (n)			Age (years)	Migraine Type	Comorbidities
			Total	Male	Female	Total	Male	Female			
Bai, Shen and Liu (2023) [50]	N.S	Secondary data analysis study—analysis of AGP, cross-sectional analysis of gut microbiome data	411	N.S	N.S	381	66.7% (~ 254)	33.3% (~ 127)	7–18	N.S	N.S
Chen et al. (2020) [54]	N.S	Metagenome-wide association study (MWAS)	108	0	108	108	0	108	Median age controls: 65, Median age migraine: 62	N.S	N.S
Kopchak and Hrytsenko (2022) [55]	Ukraine	Observational cohort study	112	~ 18 (16.3%)	~ 94 (83.7%)	N.S	N.S	N.S	18–50	Chronic and episodic	N.S
Yong et al. (2023) [53]	Korea	Cross-sectional case–control study	199 80, EM, 63, CM	N.S	N.S	130: 42 EM 45 CM	21	109: 33 EM 41 CM	19–65	Chronic and episodic	Generalized Anxiety Disorder, Depression Fibromyalgia,
Meng et al. (2024) [52]	N.S	Two-sample Mendelian randomisation analysis study	18340 microbiota participants. 37,500 migraine participants	N.S	N.S	N.S	N.S	N.S	NM	N.S	N.S
(Georgescu et al., 2019) [56]	N.S	Observational, cross-sectional, exploratory, pilot study	105	0	105	105	0	105	< 45	Without aura	N.S
Liu et al. (2024) [49]	China	Cross-sectional observational study	246 (75 gut microbiome analysis, 171 tryptophan metabolites analysis)	138	108	75 children	39 (17 migraine, 22 controls)	36 (16 migraine, 20 controls)	Males < 10 Females < 9 Mean age migraine 7.48 ± 1.95 controls 7.57 ± 2.23	With and without aura	N.S
Liu et al. (2022) [48, 63]	China	Observational, cross-sectional study	29	8	21	29	8	21	23–58	N.S	IBS Hypertension Hyperlipidaemia Diabetes Allergies Asthma Gastric Ulcer

Table 1 (continued)

Study Information			Patient Population								
Authors (Year)	Location	Type	Recruited patients (n)			Included in analysis (n)			Age (years)	Migraine Type	Comorbidities
			Total	Male	Female	Total	Male	Female			
He et al. (2023) [51]	N.S	Mendelian randomisation study	MiBioGen: 18340 samples, 59674 migraine, 4837 aura 4833 without aura FinnGen: 10536 migraine, (6332 with aura and 8348 without aura)	N.S	N.S	N.S	N.S	N.S	N.S	With and without aura	N.S

AGP American Gut Project, *GWAS* genome-wide association study, *IBS* irritable bowel syndrome, *NS* not specified

Table 2 Patient and study characteristics, gut microbiome targeted therapeutics studies

Study Information			Patient Population								
Authors (Year)c	Location	Type	Recruited patients (n)			Included in analysis (n)			Age (years)	Migraine Type	Comorbidities
			Total	Male	Female	Total	Male	Female			
(Xie et al., 2019) [58]		Double-blind, randomised, controlled cross-over clinical trial	60	N.S	N.S	N.S	N.S	N.S	18–65	Migraine	Uncomplicated IBS
Ghavami et al., 2021) [60]		Double-blind, placebo-controlled, randomised clinical trial	80	0	80	80	0	80	20–50	ICDH-3 diagnosed migraine without aura, chronic, episodic ($n=55$)	No neurologic or endocrine comorbidities
(Abed Ghavami et al., 2021) [62]		Multi-centre, randomised, placebo-controlled, double-blind parallel-group clinical trial	80	0	80	80	0	80	20–50	ICDH-3 diagnosed migraine without aura, chronic ($n=25$), episodic ($n=55$)	No chronic disease or neurological disorders
(Togha et al., 2022) [5]		Double-blind, randomised placebo-controlled trial	50 episodic migraine	15	35	40	12	28	18–60	Chronic and episodic migraine	N.S
(N.M. de Roos et al., 2015) [59]		Open label pilot study	29	2	27	27	1	26	20–64	Episodic migraine with and without aura	N.S
(de Roos et al., 2017) [25]		Randomised, placebo-controlled study	63	N.S	N.S	60	4	56	18–70	Not specified—chronic migraine excluded	Not specified -patients were excluded if they had a comorbidity that could interfere with study
(Bidabadi et al., 2023) [61]		Double-blind, randomised controlled clinical trial	80	45	35	80	45	35	Age 6–15	Not specified—migraine with and without aura	N.S

Table 3 Gut Microbiome-based therapies treatments

Authors (Year)	Intervention							
	Control Group(s)				Intervention Group(s)			
	Treatment	Dose	Frequency	Duration	Treatment	Dose	Frequency	Duration
(Xie et al., 2019) [58]	N.A	N.A	N.A	N.A	IgG elimination diet	N.A	N.A	14 weeks
					Probiotics: *Bifidobacterium infantis, Lactobacillus acidophilus, Enterococcus faecalis, Bacillus cereus*	1.5 g of probiotic	3 times/day	14 weeks
					Combined IgG elimination diet and probiotics: *Bifidobacterium infantis, Lactobacillus acidophilus, Enterococcus faecalis, Bacillus cereus*	1.5 g of probiotic	3 times/day	14 weeks
Ghavami et al., 2021) [60]	Starch capsule	~500 mg (equal to synbiotic capsule weight)	2 capsules/day (before lunch and dinner)	12 weeks	Synbiotic capsule containing 10^9 CFU of 12 types of probiotics (*Lactobacillus casei, Lactobacillus acidophilus, Lactobacillus rhamnosus, Lactobacillus helveticus, Lactobacillus bulgaricus, Lactobacillus plantarum, Lactobacillus gasseri, Bifidobacterium breve, Bifidobacterium longum, Bifidobacterium lactis, Bifidobacterium bifidum, Streptococcus thermophilus) and* prebiotic (fructooligosaccharides)	500 mg synbiotic capsule—contained 21 mg fructooligosaccharide	2 capsules/day (before lunch and dinner)	12 weeks
(Abed Ghavami et al., 2021) [62]	Starch placebo capsule	~500 mg	2 capsules/day (30 min before lunch and dinner)	12 weeks	Synbiotic capsule containing 10^9 CFU of 12 types of probiotics (*Lactobacillus casei, Lactobacillus acidophilus, Lactobacillus rhamnosus, Lactobacillus helveticus, Lactobacillus bulgaricus, Lactobacillus plantarum, Lactobacillus gasseri, Bifidobacterium breve, Bifidobacterium longum, Bifidobacterium lactis, Bifidobacterium bifidum, and Streptococcus thermophilus*) and prebiotic fructooligosaccharides	500 mg synbiotic capsule	2 capsules/day (30 min before lunch and dinner)	12 weeks

Table 3 (continued)

Authors (Year)	Intervention							
	Control Group(s)				Intervention Group(s)			
	Treatment	Dose	Frequency	Duration	Treatment	Dose	Frequency	Duration
(Martami et al., 2019) [57]	Placebo capsule—vegetable capsule (hydroxypropyl methylcellulose) filled with microcrystalline cellulose	N.S	2 capsules/day	Episodic migraine: 10 weeks Chronic migraine: 8 weeks	Multispecies probiotic capsule: Bio-Kult-protexin capsule containing 2× 10^9 CFU. 14 bacterial strains: *Bacillus subtilis* PXN 21, *Bifidobacterium bifidum* PXN 23, *Bifidobacterium breve* PXN 25, *Bifidobacterium infantis* PXN 27, *Bifidobacterium longum* PXN 30, *Lactobacillus acidophilus* PXN 35, *Lactob. delbrueckii ssp. bulgaricus* PXN 39, *Lactob. casei* PXN 37, *Lactob. plantarum* PXN 47, *Lactob. rhamnosus* PXN 54, *Lactob. helveticus* PXN 45, *Lactob. salivarius* PXN 57, *Lactococcus lactis ssp. lactis* PXN 63, and *Streptococcus thermophilus* PXN 66	N.S	2 capsules/day	EM: 10 weeks CM: 8 weeks
(N.M. de Roos et al., 2015) [59]	N.A	N.A	N.A	N.A	Multispecies probiotic sachet Ecologic Barrier: contains 2.5× 10^9 CFU/g, 8 bacterial strains: *Bifidobacterium bifidum* W23, *Bifidobacterium lactis* W52, *Lactobacillus acidophilus* W37, *Lactobacillus brevis* W63, *Lactobacillus casei* W56, *Lactobacillus salivarius* W24, *Lactococcus lactis* W19 and *Lactococcus lactis* W58	2 g	1 sachet per day	12 weeks
(de Roos et al., 2017) [25]	Placebo sachet: maize starch and maltodextrin power (carriers of the probiotic product)	2 g	1 sachet per day	12 weeks	Multispecies probiotic Ecologic Barrier sachet: contains 2.5× 10^9 CFU/g, 8 bacterial strains *Bifidobacterium bifidum* W23, *B. lactis* W52, *Lactobacillus acidophilus* W37, *Lactob. brevis* W63, *Lactob. casei* W56, *Lactob. salivarius* W24, *Lactococcus lactis* W19 and *Lactoc. lactis* W58	2 g	1 sachet per day	12 weeks

Table 3 (continued)

Authors (Year)	Intervention							
	Control Group(s)				Intervention Group(s)			
	Treatment	Dose	Frequency	Duration	Treatment	Dose	Frequency	Duration
(Bidabadi et al., 2023) [61]	Sodium valproate	Initial dose 20 mg/kg, maintenance dose 5 mg/kg	Initial dose 20 mg/kg/24 h, maintenance dose 5 mg/kg/24 h	N.S	Sodium valproate	Initial dose 20 mg/kg, maintenance dose 5 mg/kg	Initial dose 20 mg/kg/24 h, maintenance dose 5 mg/kg/24 h	N.S
	Placebo	2 sachets	Daily	4 months	KidiLact probiotic sachet: 10 units of probiotics, contains *Lactobacillus acidophilus* (2.5 × 10^10 CFU), *Lactobacillus rhamnosus* (3.5 × 10^10 CFU), *Lactobacillus bulgaricus* (2 × 10^9 CFU), *Bifidobacterium infantis* (5 × 10^10 CFU), *Lactobacillus casei* (3 × 10^10 CFU), *Bifidobacterium breve* (2.5 × 10^10 CFU), *Streptococcus thermophilus* (2 × 10^9). Also contains fructooligosaccharides, lactose, magnesium stearate, talc, cantaloupe flavor, sucralose, and silicon dioxide	2 sachets (1 sachet = 1 g)	Daily	4 months

Table 4 Overview of population, intervention type, and primary endpoints

Authors (Year)	Study population	Control Group(s) Treatment	Intervention Group(s) Treatment	Primary endpoint
(Xie et al., 2019) [58]	Adult	N.A	IgG elimination diet Probiotics: *Bifidobacterium infantis, Lactobacillus acidophilus, Enterococcus faecalis, Bacillus cereus* Combined IgG elimination diet and probiotics: *Bifidobacterium infantis, Lactobacillus acidophilus, Enterococcus faecalis, Bacillus cereus*	**Probiotic Use** **1.Mean Migraine Days:** No significant decrease in mean migraine days **2.Medication Use:** Reduced over the counter (OTC) analgesic use after 14 weeks, with no change in triptan use **3.MIDAS Score:** Decreased after 14 weeks compared to baseline **Probiotics and IgG Elimination Diet** **1.Medication Use:** Reduced OTC analgesic use after 7 weeks compared to baseline
Ghavami et al., 2021a) [60]	Female adults	Starch capsule	Synbiotic capsule containing 10^9 CFU of 12 types of probiotics (*Lactobacillus casei, Lactobacillus acidophilus, Lactobacillus rhamnosus, Lactobacillus helveticus, Lactobacillus bulgaricus, Lactobacillus plantarum, Lactobacillus gasseri, Bifidobacterium breve, Bifidobacterium longum, Bifidobacterium lactis, Bifidobacterium bifidum, Streptococcus thermophilus) and* prebiotic (fructooligosaccharides)	**1.Migraine index (frequency x severity):** Decrease in 12 weeks **2.Headache diary result (=frequency x duration):** Decrease in 12 weeks **3.Migraine headache index score (=frequency x severity x duration)** Decrease in 12 weeks
(Abed Ghavami et al., 2021b) [62]	Female adults	Starch placebo capsule	Synbiotic capsule containing 10^9 CFU of 12 types of probiotics (*Lactobacillus casei, Lactobacillus acidophilus, Lactobacillus rhamnosus, Lactobacillus helveticus, Lactobacillus bulgaricus, Lactobacillus plantarum, Lactobacillus gasseri, Bifidobacterium breve, Bifidobacterium longum, Bifidobacterium lactis, Bifidobacterium bifidum, and Streptococcus thermophilus*) and prebiotic fructooligosaccharides	1.**Migraine frequency per month** Reduced over a period of 12 weeks **2.Painkiller use** Reduced over a period of 12 weeks

Table 4 (continued)

Authors (Year)	Study population	Control Group(s) Treatment	Intervention Group(s) Treatment	Primary endpoint
(Martami et al., 2019) [57]	Adults	Placebo capsule—vegetable capsule (hydroxypropyl methylcellulose) filled with microcrystalline cellulose	Multispecies probiotic capsule: Bio-Kult-protexin capsule containing 2 × 10^9 CFU. 14 bacterial strains: *Bacillus subtilis* PXN 21, *Bifidobacterium bifidum* PXN 23, *Bifidobacterium breve* PXN 25, *Bifidobacterium infantis* PXN 27, *Bifidobacterium longum* PXN 30, *Lactobacillus acidophilus* PXN 35, *Lactob. delbrueckii ssp. bulgaricus* PXN 39, *Lactob. casei* PXN 37, *Lactob. plantarum* PXN 47, *Lactob. rhamnosus* PXN 54, *Lactob. helveticus* PXN 45, *Lactob. salivarius* PXN 57, *Lactococcus lactis ssp. lactis* PXN 63, and *Streptococcus thermophilus* PXN 66	**1.Migraine frequency** Reduced over a period of 10 weeks in patients with episodic migraines and 8 weeks in chronic migraine patients **2.Migraine severity** Reduced over a period of 10 weeks in patients with episodic migraines and 8 weeks in chronic migraine patients **3.Number of migraine days per month** Reduced over a period of 10 weeks in patients with episodic migraines and 8 weeks in chronic migraine patients **4.Number of painkillers consumed** Reduced over a period of 10 weeks in patients with episodic migraines and 8 weeks in chronic migraine patients
(N.M. de Roos et al., 2015) [59]	Adults	N.A	Multispecies probiotic sachet Ecologic Barrier: contains 2.5 × 10^9 CFU/g, 8 bacterial strains: *Bifidobacterium bifidum* W23, *Bifidobacterium lactis* W52, *Lactobacillus acidophilus* W37, *Lactobacillus brevis* W63, *Lactobacillus casei* W56, *Lactobacillus salivarius* W24, *Lactococcus lactis* W19 and *Lactococcus lactis* W58	**1.Migraine frequency** reduced between weeks 5–12 **2.Migraine intensity/severity** decreased compared to baseline **3.Migraine days** 67% participants reduced number of migraine days below baseline while 15% saw increase to migraine days **4.Medication use** 29% decrease in the total number of dosages of over-the-counter analgesic use The use of prophylaxes and triptans did not change **5.MIDAS score** significant decrease, **6.HDI score** No significant change

Table 4 (continued)

Authors (Year)	Study population	Control Group(s) Treatment	Intervention Group(s) Treatment	Primary endpoint
(de Roos et al., 2017) [25]	Adults	Placebo sachet: maize starch and maltodextrin power (carriers of the probiotic product)	Multispecies probiotic Ecologic Barrier sachet: contains 2.5×10^9 CFU/g, 8 bacterial strains *Bifidobacterium bifidum* W23, *B. lactis* W52, *Lactobacillus acidophilus* W37, *Lactob. brevis* W63, *Lactob. casei* W56, *Lactob. salivarius* W24, *Lactococcus lactis* W19 and *Lactoc. lactis* W58	**1.Migraine frequency** Did not reduce migraine frequency more than placebo **2.Migraine intensity/severity** Did not reduce the intensity/severity more than placebo **3.Medication use** Probiotic use did not reduce the use of medication **4.Inflammation markers** Probiotic use did not have a significant effect on inflammation marker levels **5. Impact on quality of life** There was a slight improvement to migraine impact on quality of life in probiotic group
(Bidabadi et al., 2023) [61]	Children	Sodium valproate Placebo	Sodium valproate KidiLact probiotic sachet: 10 units of probiotics, contains *Lactobacillus acidophilus* (2.5×10^10 CFU), *Lactobacillus rhamnosus* (3.5×10^10 CFU), *Lactobacillus bulgaricus* (2×10^9 CFU), *Bifidobacterium infantis* (5×10^10 CFU), *Lactobacillus casei* (3×10^10 CFU), *Bifidobacterium breve* (2.5×10^10 CFU), *Streptococcus thermophilus* (2×10^9). Also contains fructooligosaccharides, lactose, magnesium stearate, talc, cantaloupe flavor, sucralose, and silicon dioxide	**1.Migraine frequency** Probiotic and placebo both caused a significant decrease in migraine frequency compared to baseline. However, probiotic caused a greater significant decrease in the frequency in migraine patients compared to placebo **2.Migraine severity** Probiotic and placebo both caused a significant decrease in migraine severity compared to baseline. However, probiotic caused a greater significant decrease in the severity in migraine patients compared to placebo **3.Daily painkiller consumption** Daily consumption of painkillers significantly decreased in the probiotic group

Fig. 2 Summary of significant changes in relative levels of gut microbiome bacteria in migraine patients. Bacteroides and proteobacteria were increased in two studies [49, 50], and firmicutes were increased in two studies [50, 54]. Both phyla showed no significant differences in both chronic and episodic migraine patients [53]. There were conflicting results for actinobacteria with one study showing a decrease [49] and another showing an increase [50]. The five phyla groups were not studied across all the five studies. Created in BioRender. Hill, L. (2025) https://BioRender.com/undefined

Tissierellales; 3.67 in episodic and 2.9 in chronic migraine, *Peptoniphilaceae;* 3.67 in episodic migraine and 2.9 in chronic migraine). *Eubacteriaceae* family was only significantly increased in episodic migraine patients (approximate fold change (log_{10}) of 1.39) [53].

Veillonella, *Coprobacillus*, and *Sutterella* were consistently found to be significantly increased in both paediatric and adult migraine [49, 50, 53]. Parabacteroides were significantly increased in paediatric migraine [49, 50] and migraine patients with IBS (approximate relative abundance of 0.02 to the whole community of bacteria analysed) [48–50]. *Paraprevotella, Lachnospiraceae* UCG-010*, Lactococus, Collinsella* and *Comamonas* were however, found reduced in migraine patients with IBS (*Paraprevotella;* approximate relative abundance = 0.0152, *Lachnospiraceae* UCG-010 = 0.0012, *Lactococus* = 6.57e-5, *Collinsella* = 1.27e-5, *Comamonas* = 1.27e-5) [53]. *Eggerthella* showed a significant increase in both paediatric migraine [49, 50] and chronic migraine patients (approximate fold change (log_{10}) of 0.9) [53].

Anaerofilum, *Parasutterella*, and *Lachnoclostridium Tyzzerella*, *Desulfovibrio*, *Bilophila* and *Lactobacillus* were found to be significantly reduced in paediatric migraine [49]. *Bacteroides, Veillonella, Coprobacillus, Sutterella, Eggerthella* and *Parabacteroides* were increased in paediatric migraine [49, 50]. Conversely, *Faecalibacterium* showed a significant decrease in both paediatric and adult migraines [49, 50, 53]. There was however, disparity in data reporting an age dependent result for *Lachnospira* and *Dorea,* with an increase in the relative abundance of *Lachnospira (*median abundance value of 993*)* and *Dorea (*median abundance value of 308) in paediatric migraine [50] and a decreased abundance of both genera in adult chronic migraine patients (fold changes of approximately -0.4) [50, 53].

Bacteria such as *Clostridium spp*. showed variable changes across two studies, with species, including *Clostridium bolteae*, *Clostridium ramosum* and *Clostridium hathewayi*, being more abundant in migraine patients [54], and no significant difference noted for

Clostridium ramosum [48]. *Actinobacteria* levels were inconsistent, with one study reporting a decrease [49], and another an increase (higher abundance of *Varibaculum* -median abundance value of 11 and *Eggerthella* – median abundance value of 33) [50] and one observed no significant change [53].

Bacteria from the *Bifidobacteriales* order and *Bifidobacteriaceae* family, *Bifidobacterium*, and Eubacterium *nodatum* were associated with a decreased risk of migraine (both with and without aura). The risk of migraine was increased with the presence of lactobacillus (Inverse Variance Weighted Odds Ratio = 1.10, 95% CI = 1.03–1.18, $p = 0.004$). *Prevotella* genera, however, was reported to cause an increase in risk of migraine with aura in one study (odds ratio of 1.11; 95%CI = 1.01–1.24 [51] and decrease in another (Inverse Variance Weighted Odds Ratio = 0.89, 95% CI = 0.80–0.98, $p = 0.02$) [52].

Alpha diversity was decreased and beta diversity altered in migraine patients compared to healthy individuals

Alpha diversity, describing the ecological diversity of a single sample and beta diversity, measuring differences in microbial community composition, was evaluated across 5 studies (Table 5). Microbial diversity was assessed through alpha (Shannon, Chao1, Simpson, faith's, and Pielou's indices) and beta diversity assessed via PCoA plots (weighted and unweighted UniFrac distance, Bray–Curtis distance).

The Shannon index was the consistent metric used to evaluate alpha diversity across five studies. Alpha diversity was reported as decreased in paediatric migraine [49, 50] and female adult migraine [54]. However, two studies reported no significant change [48, 53]. Beta diversity significantly differed in adult and paediatric migraine compared to control groups [48–50]. Paediatric migraine patients with professionally diagnosed migraines had a different gut microbiome compared to healthy controls ($p = 0.001$ Bray–Curtis distance and weighed UniFrac distance) [50]. There were no reported differences in chronic or episodic migraines at the genus level [53].

Effects of gut microbiome targeted therapeutics on migraine outcomes

Synbiotics and probiotics significantly reduced migraine frequency in both adults and paediatric migraine in five randomised control trials [25, 57, 60–62] and one open pilot study [59]. A probiotic intervention in a randomised control study reduced migraine pain severity in adults and migraine attack duration in adults with chronic migraines [57], while a synbiotic intervention was effective in reducing migraine severity in children in a randomised control trial [61]. Other synbiotic and probiotic interventions however, failed to show this in trials with predominantly female cohorts [25, 60]. Synbiotic and probiotic interventions significantly reduced painkiller consumption in paediatric and adult migraine in three randomised control trials [57, 60, 61], while one randomised control trial reported that probiotic use significantly decreased the consumption of over-the-counter painkillers but not triptans in adults with migraines [58]. In contrast, one randomised control trial found that probiotic use did not significantly change painkiller consumption in predominantly female adults with migraine [25]. There were conflicting results regarding Migraine Disability Assessment Scale (MIDAS) scores in adults or specifically females with migraines [25, 58, 59]. However, in most studies there was no correlation reported between the gut microbiome and migraine clinical characteristics [53, 55, 56, 63].

Four studies examined the correlation between gut microbiota and migraine, yielding inconsistent results [48, 53, 55, 56]. Migraine patients with dysbiotic gut microbiota had higher migraine disability and MIDAS scores in an observational cross sectional exploratory pilot study (105 patients) [56]. A negative correlation was reported between *Clostridium coccoides* and MIDAS scores in an observation cohort study (112 patients) [55]. In a cross-sectional case control (130 patients used for data analysis), an unidentified genus with ID code PAC000195 were negatively correlated with migraine

Table 5 Diversity of bacterium in the gut microbiome composition

Study Reference	Alpha Diversity in Migraine patients	Beta Diversity in Migraine patients
(Liu et al., 2024) [49]	Significantly decreased (Shannon and Simpson index)	Significantly different
(Bai, Shen and Liu, 2023) [50]	Significantly decreased in Professionally diagnosed (Faith's phylogenetic diversity, Shannon index) and self-diagnosed migraine patients (Faith's phylogenetic diversity, Shannon index, Pielou's evenness index)	Significantly different in both professional and self-diagnosed migraines
(Liu et al., 2022) [48, 63]	No significant difference (Chao1, Shannon, Simpson indices, observed species, phylogenetic diversity whole tree)	Significantly different
(Yong et al., 2023) [53]	No significant difference at genus level between adult chronic and episodic migraine patients (Chao1, Shannon, Simpson indices)	No significant difference in chronic and episodic migraine patients at the genus level
(Chen et al., 2019) [54]	Significantly decreased at the genus & species level (Shannon index)	Not specified

frequency but not intensity, while *Agathobacter* genera were negatively correlated with headache intensity but not frequency [53]. An observational cross-sectional study showed that *Alcaligenes* species were negatively correlated with migraine frequency and pain scores, whereas *Eggerthella lenta* showed a positive correlation with pain scores [48].

Risk of bias and quality of evidence

Findings in paediatric migraines had poor study quality based on the risk of bias analysis, while adult studies exhibited better, but mixed, quality ratings in the observational cohort and cross-sectional studies. In both paediatric migraine studies, the sample size was not justified and effect estimates were not provided [49, 50]. There was also the lack of a formal definition for 'self-diagnosed' migraines in a paediatric study [50]. All controlled gut microbiome targeted therapeutics studies were rated as having "Good" bias (Supplementary Table 2). Differences were noted in baseline characteristics and unclear intervention adherence in some studies [25, 57, 60–62]. High drop-out rates and the use of computer analysis in a few studies also increased the risk of bias [25, 57]. Additionally, reliance on patient recall for baseline values in some cases further heightened the risk of unreliable results [60].

The two uncontrolled gut microbiome targeted therapeutic studies were rated as "Fair" and "Poor" (Supplementary Table 3). Bias stemmed from gender imbalance, reliance on subjective recall for baseline values and missed doses [59]. Demographic details were not reported, had a small sample size and did not control background interventions [58]. Both studies did not address masking, multiple outcome measurements, or analysis by intention-to-treat, leading to increased bias and reduced reliability of their findings.

Four gut microbiome studies were rated "Fair" [48, 51–53], and five were rated "Poor" [49, 50, 54–56] (Supplementary Table 4). Limitations included unclear patient populations [55], participation rates [48, 49, 54, 55], and recruitment criteria [51, 52, 54, 55], which could impact selection bias and therefore generalizability. Many studies lacked details on sample size and power, potentially affecting the detection of meaningful results [48–56]. The methods for exposure and outcome measurement [49, 51, 52, 54, 55], also impacted bias scores.

Discussion

There is growing evidence that alterations in the gut microbiome may be implicated in migraine. Using this systematic approach, the literature determined that the gut microbiome was found the be different in patients with migraine compared to controls. In some studies, bacterial species were found to be associated with an increased risk of migraine. Differences in some genera were found to be age dependent. Within the included studies, evidence suggested that both synbiotics and probiotics reduced painkiller consumption. Probiotics and synbiotics were found to improve migraine frequency, synbiotics resulted in reduced migraine pain severity in both adult and paediatric migraine. In migraine patients with IBS, studies showed a reduction in specific genera of the *Firmicutes* phylum compared to IBS controls without migraine. Though this finding is debated due to mixed results in IBS research [64, 65]. These results have identified a potential interplay between migraine and changes in the gut microbiome.

The altered gut bacteria may contribute to the production of metabolites which influence migraine

The low abundance of *Faecalibacterium* in migraine [48–50] might contribute to migraine pathology. These microbes produce large amounts of butyrate [66], a short chain fatty acid in the gut involved in improving intestinal barrier function, anti-inflammatory and antioxidant pathways [67–69]. This suggests reduced butyrate, a key fatty acid in gut health, may indicate lower anti-inflammatory and antioxidative activity may contribute to migraine pathophysiology and highlights this microbial as a potential therapeutic target. Decreased *Faecalibacterium* genera has been found to correlate with IBS, further supporting that dysbiosis identified in migraine may contribute towards GI symptoms [70].

Increased *Bifidobacterium* and *Prevotellaceae* were associated with a decreased risk of migraine, while increased *Lactobacillus* was associated with an increased risk of migraine. Both *Bifidobacteria* and *Lactobacilli* produce acetate and lactate, which contribute to the short-chain fatty acid mediated health benefits of prebiotics [71]. *Prevotellaceae* are also involved in the breakdown of carbohydrates and fibres in the production of short-chain fatty acids [72]. This could suggest that elevated *Lactobacilli* may contribute to increased acetate levels which may directly influence trigeminal sensitivity.

Acetate is thought to have several beneficial properties in the gut, including anti-inflammatory properties [73]. However, in headache, it is the primary metabolite linked to the "hangover headache" phenomenon. This metabolite has been shown to enhance sensitivity in headache pathways through the trigeminal system in rodent models of migraine [74]. Therefore, the benefits of acetate may differ based on its tissue expression. Although both *Bifidobacterium* and *Lactobacillus* both produce acetate, the downstream metabolites produced may interact differently to mediate different effects. Further research

is needed to clarify acetate's systemic correlation with migraine.

Microbial diversity differed between healthy and migraine patients, with the latter having a lower alpha diversity and different beta diversity compared to controls. This suggests that patients with migraine have a gut microbiome with reduced species number and relative abundance, as well as a distinct bacterial composition compared to controls [75]. Lower diversity may suggest an imbalance (dysbiosis) that may lead to reduced gut barrier function making individuals more susceptible to increased gut permeability. An increase in gut permeability allows toxic bacterial lipopolysaccharide to enter the circulatory system leading to an immune response. Migraines have been found to be correlated with proinflammatory cytokines such as IL-1β, IL-6, IL-8 and TNF-α. Migraine patients may have a specific microbial profile that differentiates them from healthy individuals, potentially characterized by an overabundance of pro-inflammatory bacteria or a depletion of protective microbes [24, 76].

Certain phyla were altered in paediatric but not adult migraine

Proteobacteria and *Bacteroidetes* phyla were more abundant in paediatric migraine than adult. It has been shown that the microbiome changes with age. The infant microbiome is initially less diverse than that of an adult, influenced by various factors including delivery method, diet, medication exposure and environment. During childhood, microbial diversity and stability gradually increase and by adolescence, the gut microbiome shows a decrease in aerobes and facultative anaerobes and a rise in anaerobic species [77, 78]. However, the relative abundance of these two phyla in particular remain relatively stable until 70 years of age [79]. *Bacteroides* help preserve a balanced and healthy microbiome [80]. Although *Bacteroides* were increased in paediatric migraine [49, 50], which may seem contradictory to be upregulated in migraine, children have been shown to have a higher relative abundance of this genera than adults which may influence results [81]. *Veillonella, Coprobacillus,* and *Sutterella* were also increased in paediatric migraine [49, 50]. These bacteria have been shown to be correlated with tryptophan metabolism and production of tryptophan catabolites [82, 83]. Alterations in tryptophan metabolic pathways may correlate with the onset, progression, and severity of migraines [84] and may explain why the relative abundance of these bacteria were increased.

Bacterial species showed mixed associations with clinical characteristics

A dysbiosis in the gut microbiome, including *Clostridium coccoides, Alcaligenes* species [55], *Agathobacter* genera [53], *Eggerthella lenta* [48], were reported to be associated with migraine clinical characteristics. *Agathobacter* genera *and Clostridium coccoides* are significant butyrate-producing bacteria. This suggests a potential inverse relationship between the abundance of butyrate-producing bacteria and migraine clinical characteristics [85, 86]. *Eggerthella lenta* may contribute to migraine clinical characteristics by stimulating Th17 cell activation [87]. Although studies found various correlations between gut microbiota and clinical characteristics, the contrasting associations suggest there are no consistent pattern in bacterial species and features of migraine pathophysiology. The studies could have been underpowered as many of them lacked details on sample size and power, potentially affecting the detection of meaningful results. The diversity in findings ranging from positive to negative correlations with different microbial species and migraine characteristics highlights the complexity of the gut-migraine relationship and suggests that further research is needed to clarify these interactions.

Gut targeting therapies consistently improved painkiller consumption

A reduction in painkiller consumption, excluding triptan use, emerged as the most significantly improved outcome of gut microbiome targeting treatments [57–61]. Triptans specifically target serotonin receptors (5-HT1B/1D) to possibly counteract migraine-related vasodilation, block pain signalling and release of pro-inflammatory neuropeptides [88], a mechanism that probiotics may not directly influence. While probiotics may help reduce general inflammation and pain, making other analgesics less necessary, their effects may not be strong or specific enough to prevent the neurological mechanisms involved in migraines targeted by triptans. The reduction of painkiller use was also likely attributable to additional improvements in migraine-related parameters, including the number of migraine days, MIDAS scores, frequency, severity and intensity.

Consequently, the literature suggests that gut microbiome-targeted therapeutics demonstrated overall efficacy in alleviating migraine symptoms. The bacteria included in the gut microbiome targeted therapies were used in combination, limiting the ability to draw conclusions on the benefit of specific strains in migraine therapeutics. The studies showed the benefits of probiotics and synbiotics to migraine patients, however there is a need for mechanistic studies to explain how these therapies target migraine pathophysiology.

Bifidobacterium and *Lactobacillus* are commonly included in synbiotic and probiotic formulations for their known health benefits. *Bifidobacterium* has been shown to regulate immune responses and anti-inflammatory

properties, in addition to production of short chain fatty acids [20, 47]. These may prove beneficial for migraine treatment as immunomodulating agents have been shown to improve headache [57, 89]. *Lactobacillus spp* also produces lactic acid and preserves the integrity of the intestinal lining [90, 91]. This is particularly important as immune factors can move from the gut into the bloodstream if the intestinal lining is permeable [92]. However, since *Lactobacillus* are involved with an increased risk of migraine, it would be important, to determine the threshold for safe dosage in patients.

Bacillus spp, Enterococcus spp, Lactococcus spp, and *Streptococcus thermophilus*, also found widely in probiotic formulations, are lactic acid producing bacteria [93, 94]. These bacteria help to maintain the intestinal barrier junction by promoting the growth of intestinal epithelial cells and mucosal repair [95], thereby preventing gut permeability. *Bacillus subtilis* has been shown to be a producer of GABA [96] which is found dysregulated in migraine, dependent on the presence of aura [97, 98]. The impact of this on treating migraine with aura should be further investigated.

Several studies demonstrated beneficial effects of gut targeted therapies, however the results varied depending on the study population, type of intervention and primary endpoint (Table 4). One pilot study demonstrated a reduction in migraine frequency, severity and MIDAS scores [59]. When scaling to a randomised control trial, however, the same authors did not show any improvements [25]. The increase in the population size between pilot (27 participants) and randomised control trial (60 participants), suggesting the pilot study was under-powered. Frequency of pain-killer use was reported by all 5 studies, however all other outcome measures varied between trials.

Limitations

The studies included in this systematic review have some limitations, including the disparities between migraine diagnosis tools utilised, bias of self-reporting migraine and the lack of a formal definition for "self-diagnosed migraine" (33). There was little consistency in the clinical phenotype of the migraine, including duration of disease and family history. Most studies did not distinguish between episodic and chronic migraine, making it unclear whether gut microbiome composition varies by migraine type or if gut microbiome-targeted therapies have differential effects based on migraine classification. The variety of methods of the included studies may have influenced the pooling of data and overall outcomes. Studies included a mix of shot gun sequencing, 16 s sequencing and Matrix-Assisted Laser Desorption/Ionization Time-of-Flight mass spectrometry introduced method variability which limited generalizability of results. Gut microbiome studies are also heterogeneous due to confounding factors earlier discussed and variations in sequencing methods. To improve reliability and comparability, researchers should adopt standardized methodologies for DNA extraction, sequencing and bioinformatics analysis.

The presence/absence of co-morbidities such as IBS were not uniformly reported across all studies. One of the most important limitations is that migraine medication may interfere with the gut microbiome and data on pharmacotherapy were not routinely reported. This is very likely to have had an impact on the altered gut microbiome composition in migraine patients. The methods used to collect and analyse specimens were neither consistent nor fully reported. This presented a limitation of heterogeneity potentially affecting the comparability of results across studies and introducing variability in microbiome assessments.

The duration of probiotic/synbiotic randomised controlled trials should also account for the time required to observe a meaningful impact on migraines. Given that conventional migraine treatments often take months to show efficacy, probiotic interventions may also require extended treatment periods. This underscores the need for assessing gut microbiome changes at multiple time points to determine the optimal duration for clinical effectiveness. However, we were able to identify patient-centred outcomes with relative consistency across most studies.

Conclusion

This systemic review identified a potential link between the gut microbiome and migraines. Specifically, the gut microbiome composition is altered in individuals with migraine and this alteration may be correlated to an increased risk of migraines, appearing to involve genera commonly found in probiotics. This underscores the importance of optimizing probiotic formulations for those suffering from migraines in future clinical trials to standardise their use. The five randomised control studies identified had a short duration. The evidence assessed here could pave the way for further randomised controlled trials evaluating probiotic formulations for migraine, in both children and adults. Future research should focus on identifying gut bacteria linked to migraine and associated pathophysiological changes to develop targeted therapies, including restoring specific bacterial populations. The gut microbiome presents a promising target for migraine intervention. To strengthen the evidence on gut-targeted therapies for migraine, future research should standardize outcome measures, establish uniform inclusion criteria, differentiate between migraine subtypes and age groups, and account for confounding factors.

Abbreviations

AGP	American Gut Project
CD	Cannot Determine
GABA	Gamma aminobutyric acid
GI	Gastrointestinal
GWAS	Genome-Wide Association Study
MIDAS	Migraine Disability Assessment Scale
IBS	Irritable Bowel Syndrome
ICD	International Classification of Diseases
ICHD	International Classification of Headache Disorders
IL	Interleukin
NA	Not Applicable
NS	Not Specified
PCoA	Principal Coordinate Analysis
PICO	Population, Intervention, Comparison and Outcome
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
TNF	Tumour necrosis factor
NSAIDs	Non-steroidal anti-inflammatory drugs

Supplementary Information

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Supplementary Material 1.

Authors' contributions

CM and EC independently screened the titles and abstracts of identified studies for eligibility. OG served as the third reviewer, resolving any disputes during the screening process. EC and CM performed data extraction and quality assessment of the included studies. EC and CM synthesized the findings and CM and OG drafted the manuscript. LJH, AS, RH, HB, AND SM substantively revised the drafted manuscript.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

Alexandra Sinclair reports has consulted for Novartis, AbbVie, Vertex and Orion Pharma and speaker fees from Teva Uk and Novartis. She was previously a Director and Chief Scientific Officer (CSO) with shares at Invex Therapeutics.

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