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From diet to function: using synthetic microbial communities to map gut microbial interactions

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Diet shapes gut microbial ecology and function, but causal mechanisms are hard to resolve in native communities. Synthetic microbial communities provide defined systems to test how dietary substrates alter community structure, metabolism, and host responses. This review summarises SynCom design, experimental platforms, and dietary applications, highlights multi-omics and modelling approaches, proposes reporting standards, and considers challenges and future directions, including multi-kingdom and AI-enabled function-first SynComs.

The human gut microbiota comprises a diverse community of microorganisms that live symbiotically with their host. This microbial ecosystem supports health through digestion of complex carbohydrates, biosynthesis of vitamins, immune modulation, Short Chain Fatty Acids (SCFAs) production, neurodevelopment, and colonisation resistance against pathogens^{1–3}.

Its composition varies markedly across age, ethnicity, sex, and lifestyle^{4–7}. In infants, gestational age (preterm/full term), delivery mode (vaginally/caesarean), feeding (human milk/formula), and antibiotics shape early assembly^{7–10}. In adults, diet, geography, host genetics/physiology, and medications are key drivers^{11–14}. Among these factors, diet is a principal modulator: macronutrient availability, fermentable fibre, and bioactive compounds can rapidly and persistently remodel microbial ecology^{15–18}.

Disentangling causality in such a complex ecosystem is challenging. Synthetic microbial communities (SynComs); defined cultivable consortia of gut microorganisms, offer a controlled and reproducible approach to test how specific substrates and nutritional patterns reshape community structure and function and, in host associated models, impact physiology^{19–21}. Advances in culturomics - high-throughput bacterial recovery approaches that employ multiple growth media and varied culture conditions combined with rapid identification to maximise the recovery and characterisation of diverse microorganisms from complex samples, anaerobic culturing, in vitro fermentation systems, gnotobiotic models, and multi-omics now enable the construction and mechanistic interrogation of SynComs at increasing ecological depth^{22–26}.

This review outlines core principles for designing and building SynComs to study diet-microbiota interactions. We summarise experimental models used to investigate nutritional effects and microbial cross-feeding and discuss how specific dietary components shape SynCom ecology and

metabolism. We also highlight analytical approaches, key applications, and practical challenges for reproducible SynCom research. Although we focus primarily on gut-associated SynComs, the design principles are broadly applicable across diverse ecological niches.

SynComs: rationale, types, and design principles

Why SynComs? SynComs offer unique mechanistic insight into microbiome function by enabling controlled, reproducible experiments that are rarely achievable in traditional studies of complex natural communities. SynComs provide a reductionist, controllable framework that overcomes key limitations of observational designs, namely high community complexity, host and ecological variability, and limited causal inference^{27–29}. By precisely specifying community composition, environmental inputs, and dietary variables, SynComs support stepwise addition or removal of taxa, controlled dietary perturbations, and replication under identical conditions, allowing direct attribution of metabolic and functional outputs to defined members or interactions. When combined with host-associated models, they also disentangle microbial from host contributions, strengthening causal interpretation^{19,27,30,31}.

Overall, SynComs reduce native complexity while preserving representative taxa and metabolic capabilities, enabling: (i) causal tests of diet-microbiota (and depending on the model also host) relationships; (ii) identification of functions (e.g. SCFA production, mucin/HMO degradation, pathogen inhibition) to specific members; and (iii) evaluation of dietary, prebiotic/probiotic, and pharmacological interventions in a defined microbial background^{19,21,32}.

Types of SynComs. SynComs can differ widely in both structural complexity (the number and types of species/strains included) and in the

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Table 1 | Classifications of SynComs: descriptions, advantages and limitations

Type	Sub-Type	Description	Advantages	Limitations	References
Simple SynComs	Fully-defined	Low complexity community typically made up of 2–10 cultured and genomically characterised species/strains to test specific mechanistic hypotheses	Easy to setup; Reproducible; Mechanistic clarity. Ease of standardisation. Lower cost	Limited ecological realism; May miss functional redundancy; strong bias towards cultivable organisms	175,176
Complex SynComs	Fully-defined	High- complexity communities (> 10–100 species/strains) composed exclusively of cultured and genomically profiled strains simulating native structure/function	Higher ecological relevance; Captures cross-feeding and competition; High reproducibility relative to semi-defined systems.	Costly; Strong bias towards culturable organisms; May still incompletely mimic native microbiota.	29,177
Complex SynComs	Semi-defined	Microbial communities consisting of a defined core of cultured species/strains supplemented with undefined or partially characterised inocula (e.g. faecal matter)	Improved ecological realism; Includes difficult to culture taxa;	Lower reproducibility; compositional uncertainty	31,178

resolution of characterisation, ranging from broadly defined taxa to fully genome sequenced, strain-resolved members²¹ (see Table 1). Simple SynComs typically include 2–10 organisms and are designed to test specific interactions, responses, or metabolic pathways³². More complex SynComs incorporate a wider range of taxa to better approximate gut community structure while maintaining full control over membership composition^{21,32}. SynComs also vary by how completely members are characterised. Fully defined SynComs consist only of genomically characterised strains, enabling direct links between genotype and community function, whereas semi-defined SynComs combine well characterised isolates with partially characterised members to balance experimental control with ecological realism^{21,33}. Ultimately, SynCom choice depends on the research question: simpler communities may suit in-depth mechanistic studies, while more complex SynComs are potentially better for modelling community-level behaviour and interactions^{21,34,35}.

Selecting strains

Selecting microbial strains is a critical step in building SynComs because it determines both ecological validity and functional relevance. Strains are typically chosen for their ecological importance, metabolic capabilities (needed for diet-microbe SynComs), and how well they represent the gut microbiota of the relevant life stage or physiological condition³⁶. Together, these criteria ensure SynComs capture key aspects of microbiome diversity and function in a controlled system.

Sources of bacteria isolates. Bacterial isolates used in SynComs are typically sourced from faecal samples or from established culture collections^{37,38}. Isolating strains from faeces collected from individuals at the relevant age or physiological state can yield ecologically adapted strains that better reflect real world host-microbe and microbe-microbe interactions³⁷, or from other gut niches such as the small intestine, which may harbour distinct microbial populations with unique capabilities or host interactions that are relevant to the experimental question³⁹. Selecting strains from a single donor or a naturally stable ecological niche where microorganisms are already known to coexist may enhance ecological compatibility and improve stability in the SynCom. In contrast, culture collections provide strains that are often already genotypically and phenotypically characterised⁴⁰, supporting reproducibility and enabling detailed functional studies, particularly when building fully defined SynComs.

Ecological relevance and functional capacity. The human gut microbiota evolves from early life to adulthood⁴¹, and is shaped largely by diet⁴². Strain selection must therefore reflect both the age and dietary context of the target population.

In early life, the gut microbiota of human-milk fed infants is dominated by *Bifidobacterium* spp., which can utilise complex sugars found in human milk, i.e. Human Milk Oligosaccharides (HMOs)⁴³. SynComs that model

the human milk-fed infant gut should therefore include HMO-adapted strains to capture these core early life metabolic functions, noting that microbial composition and functional capacity may differ in formula-fed infants. As solid foods are introduced, the microbiota diversifies and shifts towards taxa that can degrade complex plant fibres⁴⁴. SynComs representing later life stages should therefore incorporate primary fibre degraders to reflect this dietary transition.

Each strain's metabolic capacity (e.g., CAZymes (Carbohydrate Active enZymes - group of enzymes that build, breakdown or modify complex carbohydrates); butyrogenesis; bile acid transformations; amino-acid fermentation), and interaction potentials (e.g. cross-feeding, acid/bacteriocin production, type VI secretion systems (T6SS), inducible prophages) must also be evaluated. To further strengthen the ecological framework, SynCom design should also consider strategies to enhance community stability and coexistence. This includes metabolic niche partitioning, where strains are selected to occupy complementary resource niches reducing direct competition; the incorporation of ecological redundancy - ensuring multiple taxa in the SynCom can perform similar functions to buffer against perturbations^{19,21,29}.

These are important considerations to ensure SynComs capture not only microbial community composition but also functional activity, while minimising competitive exclusion that can cause loss of members and distort the biochemical outputs typical of the native gut microbiota.

Strain selection therefore must integrate ecological origin, life-stage, dietary context, and functional capacity. A conceptual framework of SynCom design across life course aligned with dietary transitions is illustrated in Fig. 1.

Experimental models for studying SynComs

SynComs research depends on experimental models that capture key features of the gut's ecological and physiological environment, while allowing tight control over experimental conditions²¹. Broadly, these approaches fall into in vitro and host-associated systems^{45,46}.

In vitro models. Batch fermentations are closed, short-term anaerobic cultures that are well suited for rapid, low-cost testing of growth kinetics, basic metabolite outputs, and preliminary microbe-microbe interactions^{26,47–49}. They are widely used for complex inputs (e.g., faecal slurries), but can also be readily adapted for SynComs. Their main limitation is that nutrient depletion and metabolite build-up reduce stability over longer time frames.

Chemostats and more advanced dynamic gut models, such Simulator of the human Microbial Intestinal Ecosystem (SHIME) or M-SHIME (includes mucin beads to models the mucosal-associated microbiota), Toddler Mucosal Artificial colon (Tm-ARCOL), Polyfermenter Intestinal Model (PolyFermS), Human-Microbial Crosstalk model (HuMiX)/gut-on-a-chip, micro-Matrix bioreactor platforms (OPTIMATRIX v2.0) and the

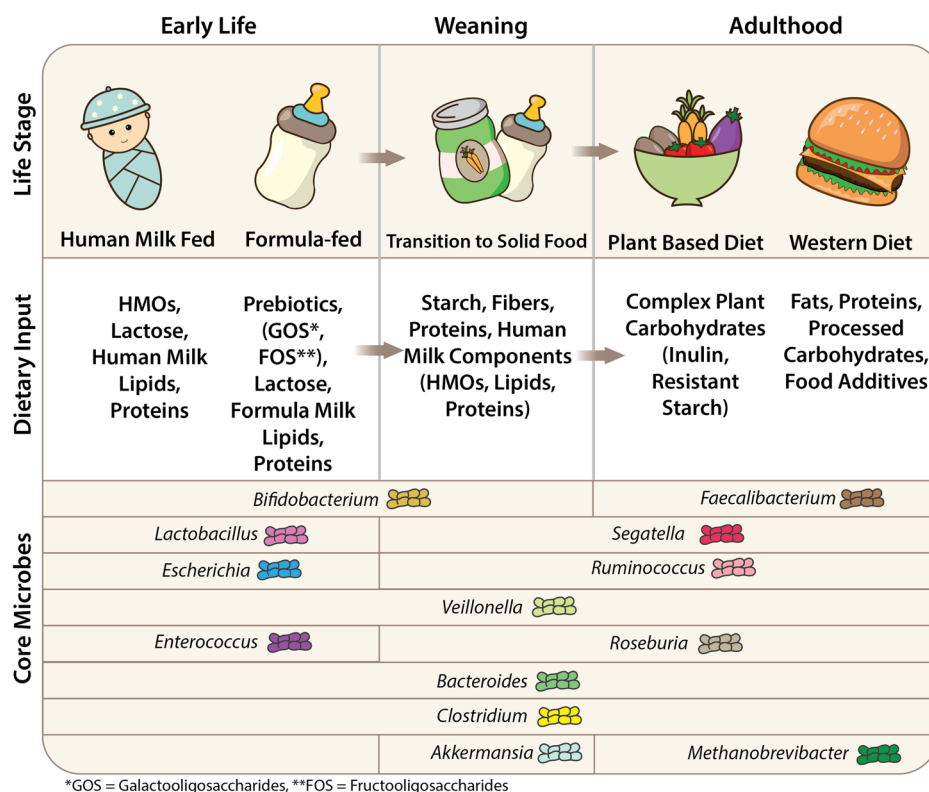


Fig. 1 | SynComs design across life with dietary input^{83,191}.

TNO in vitro model of the colon (TIM-2), address these constraints by providing continuous nutrient supply and waste removal, supporting steady-state growth and more physiologically realistic conditions^{50–56}. These platforms can mimic gut physicochemical parameters, transit, and mucosal surfaces, supporting longer-term studies of microbial cross-feeding, dietary perturbations, and community stability, whether using faecal communities or defined SynComs^{57–59}, and a summarised comparison of batch fermentation vs. continuous fermentation models is presented in Fig. 2.

Host-associated models. Gnotobiotic mice and non-murine models such as pigs, bees, zebrafish, and *Drosophila*, colonised with defined SynComs enable direct assessment of host outputs, including immune, metabolic, and barrier responses^{19,60–66}. The development of minimal defined consortia (e.g., OMM12)^{61,62} and the use of harmonised gnotobiotic protocols such as National Gnotobiotic Rodent Resource Center (NGRRC)⁶⁷ are improving reproducibility and cross-study comparability. These approaches provide deep insights into developmental programming, immune modulation, epithelial barrier regulation and metabolic impacts^{68–71}.

Together, in vitro and host-associated systems provide a practical continuum, from controlled mechanistic testing to integrated host–microbe biology, supporting more robust inference about gut microbial ecology and function.

Dietary modulation of SynComs

Diet is a major driver of gut microbial composition and function⁷². Fibre-rich substrates tend to promote saccharolytic communities and increased SCFA production (acetate, propionate, butyrate)^{73–75}, whereas high-fat inputs can favour bile-tolerant and lipid-utilising taxa^{76,77}. Protein-rich substrates often enrich amino acid fermenters and increase branched-chain fatty acid (BCFA) production^{78–81}. SynComs provide a tractable platform to test these links mechanistically, connecting substrate availability to pathway activation, metabolite outputs, and downstream ecological outcomes. Key diet-target-function relationships are summarised in Fig. 3.

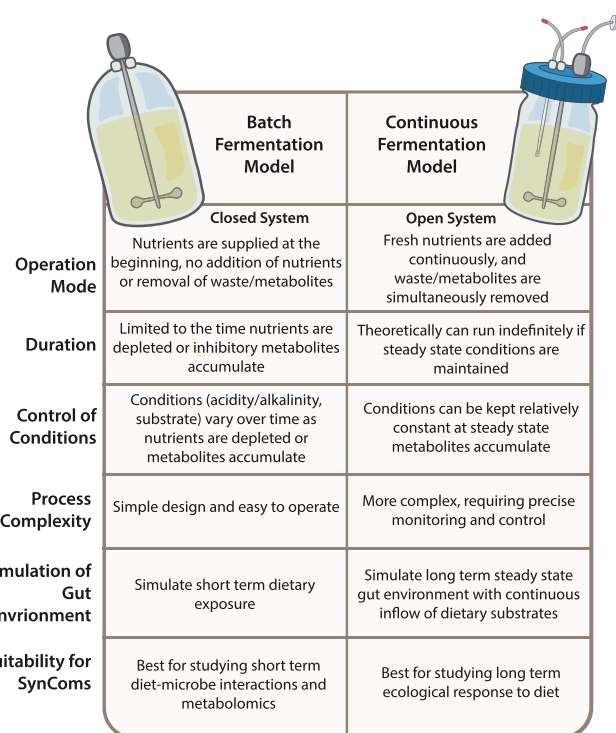
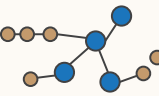
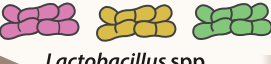
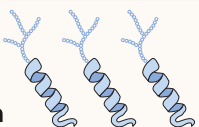
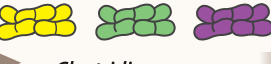


Fig. 2 | Comparison of Batch and Continuous Fermentation modes in SynCom Studies^{82,192–197}.

Functional analysis of SynComs

Functional analysis is central to understanding how diet shapes SynComs. Moving beyond taxonomy, functional approaches reveal how communities metabolise substrates, produce key metabolites, and shift ecological roles.

Dietary Components	Microbial Targets	Functional Outcomes
 HMO's	 <i>Bifidobacterium</i> spp.	Bifidogenic Effect* Acetate and Lactate Cross-Feeding
 Lactose	 <i>Lactobacillus</i> spp. <i>Bifidobacterium</i> spp. <i>Streptococcus</i> spp.	pH Reduction Production of SCFA
 Inulin / FOS	 <i>Lactobacillus</i> spp. <i>Bifidobacterium</i> spp. <i>Bacteroides</i> spp.	Production of SCFA Bifidogenic Effect
Galactooligosaccharides (GOS) 	 <i>Lactobacillus</i> spp. <i>Bifidobacterium</i> spp. <i>Bacteroides</i> spp.	Acetate and Lactate
 Resistant Starch	 <i>Bifidobacterium</i> spp. <i>R. bromili</i> , <i>F. prausnitzii</i> <i>Roseburia</i> spp.	Production of SCFA Cross-Feeding
 Mucin	 <i>Ruminococcus</i> spp. <i>A. muciniphila</i> <i>Bacteroides</i> spp.	Production of SCFA, Fucose, Sialic Acid Cross Feeding
 Fatty Acids	 <i>Bacteroides</i> spp. <i>Clostridium</i> spp. <i>Lactobacillus</i> spp.	Production of SCFA
 Polyphenols	 <i>Lactobacillus</i> spp. <i>Bifidobacterium</i> spp. <i>Bacteroides</i> spp.	Antioxidants Bioactive Compounds
 Proteins/Amino Acids	 <i>Clostridium</i> spp. <i>Bacteroides</i> spp. <i>Enterococcus</i> spp.	BCFA's Ammonia Phenols
 Dietary Fibre	 <i>Segatella</i> spp. <i>Roseburia</i> spp. <i>Ruminococcus</i> spp.	Production of SCFAs Cross-feeding

*Selective stimulation of *Bifidobacterium* growth or activity in the gut

Fig. 3 | Dietary Input, Microbial targets and Functional outcomes^{198–225}.

Nutrient-specific metabolism can directly alter the growth of individual strains and their competitive or cooperative interactions, ultimately influencing community structure, dominance and coexistence in complex SynComs⁸². Integrating multi-omics with targeted biochemical assays and computational tools enables more precise mapping of community function in response to dietary change (Table 2).

Application of SynComs in gut microbiota-diet research

SynComs are powerful tools for dissecting the complex interplay between diet, microbes and host health, because they move beyond largely observational diet-microbiome studies^{83–87}, and allow controlled hypothesis-driven experiments. With defined strains and substrates, SynComs can directly test how specific dietary components are metabolised, how cross-

Table 2 | Omic Approaches and their functional targets

Approach	Purpose	Functional Insight	References
Culturomics	High-throughput isolation and characterisation	Expands strain panels for SynComs	124,179
Metagenomics (Shotgun)	Taxonomic composition, gene content, functional gene potential (CAZymes, SCFA pathways, mucin-degrading enzymes)	Identifies microbial species present and their genetic potential for SCFA production, mucin and HMO degradation etc.	28,180
(Meta)Transcriptomics	Quantify strain level or Community gene wide expression to reveal active pathways at the time of sampling	Reveals which metabolic pathways are actively expressed (e.g., fucosidases, sialidases, SCFA synthesis genes)	32
Proteomics / Metaproteomics	Identify and quantify proteins and enzymes present in a sample	Validates functional expression of CAZymes, transporters, and enzymes for SCFA synthesis and mucin/HMO metabolism	181–183
Metabolomics	Targeted metabolomics quantify predefined metabolites (SCFAs, monosaccharides, organic acids, amino acids, bile acids); Untargeted metabolomics for broad profiling to detect known and novel metabolites.	Measures the products of microbial metabolism; quantifies SCFA profiles, mucin degradation products (fucose, sialic acid)	89,184
Lipidomics	Characterise lipid types and pathways to provide insight into microbe-lipid metabolism	Identification of bioactive lipids, phospholipids, sphingolipids, fatty acids etc.	185,186
Stable Isotope Probing	Incorporation of labelled substrates (e.g., ^{13}C -HMOs) into microbial DNA/RNA/metabolites	Identifies microbes actively consuming specific substrates and tracks metabolic fluxes	187–190

feeding and competition shapes community structure, and how metabolite outputs link to host-relevant outcomes.

SynComs have been especially informative for diet-driven succession. For example, incorporating HMOs has shown how human milk selectively promotes *Bifidobacterium* spp. in early life⁸⁸. Beyond this, SynCom-based models have been widely used to characterise microbial cross-feeding networks, revealing metabolic interdependencies and community assembly patterns in response to specific nutritional substrates^{31,43,89–93}. Similarly, fibre and resistant starch SynComs have revealed how weaning-associated substrates drive diet-dependent ecological shifts, enriching saccharolytic taxa with specialised metabolic capacities and promoting SCFA production, ultimately contributing to microbiome maturation^{43,94–97}.

As SynComs offer compositional control, they are also well-suited for mapping cooperative and competitive interactions⁹⁸. This mechanistic resolution is valuable for studying diet-associated disease mechanisms, including malnutrition-related loss of diversity and metabolite production^{99,100} and Western diet-linked disruption of microbial metabolism and inflammation in inflammatory bowel disease (IBD) models^{21,101–103}. Importantly, these controlled systems also direct interrogation of microbial metabolic outputs such as SCFAs, bile acid derivatives, or amino acid metabolites and host immune and metabolic responses^{104–106}. More broadly, SynComs have been used to generate stronger mechanistic evidence connecting dietary perturbations to microbiota-mediated pathways implicated in metabolic and immune-mediated disorders, e.g. type 2 diabetes, obesity^{107,108} colorectal cancer¹⁰⁷, allergy/asthma¹⁰⁹, and in neurodevelopmental and neuropsychiatric outcomes¹¹⁰, helping to address ethical and practical limits of human studies.

SynComs also support personalised nutrition by enabling direct testing of inter-individual functional variation^{111,112}. For instance, *Bifidobacterium* strains differ in their capacity to utilise specific HMOs, suggesting tailored probiotic or dietary approaches in infancy^{43,113}. In adults, Community-Scale Metabolic Modelling (MCMM) and SynComs experiments show that microbial diversity drives distinct metabolite profiles under the same diet, reinforcing the rationale for precision nutrition^{114–117}.

Finally, SynComs can function as intervention testbeds, allowing systematic evaluation of prebiotics, probiotics, and synbiotics, as well as how drugs are transformed by gut microbes and how microbial metabolism influences drug efficacy and toxicity^{118–120}.

Together, these applications position SynComs as versatile, reproducible models that bridge diet, microbial ecology, and therapeutics to uncover mechanisms driving health and disease, including assessment of dietary intervention studies.

A structured overview of how these applications can be operationalised in practice is summarised in Fig. 4. In this framework, experimental development begins with defining the functional objective linked to a dietary substrate, thereby establishing the guiding research question. Candidate strains are then selected based on metabolic capacities relevant to the target substrate and their ability to occupy complementary metabolic niches while maintaining ecological relevance. The selected strains are assembled and evaluated for compatibility, including cooperative and competitive interactions that influence substrate utilisation and metabolite production. The SynCom is then tested in a controlled in vitro system containing the dietary substrate of interest to assess functional activity. Finally, multi-omic analyses are applied to characterise community dynamics and quantify metabolite outputs, supporting optimisation and translation into in vivo or host-relevant models.

Although presented in the context of diet-SynCom studies, the same underlying design principles are broadly applicable to other SynCom applications, including pathogen resistance, ecosystem function, and immune modulation, as the central logic of linking defined inputs to measurable functional outcomes remains consistent across experimental systems.

Minimal reporting checklist for diet-based SynComs studies

Methodological transparency is essential in SynCom research to ensure reproducibility, comparability, and long-term utility¹²¹. Because SynComs experiments involve multiple design layers, from strain provenance, inoculum preparation, culture vessel operation, media composition, substrate characterisation, and multi-omics and analytical workflows, clear reporting is needed to minimise ambiguity. A tailored reporting checklist may help standardise documentation and support alignment with established reporting frameworks such as MIXS and STORMS^{122,123}. We therefore propose a minimal checklist for diet-focused SynCom studies (Table 3) to harmonise reporting across experimental design, implementation, and analysis.

Challenges of using SynComs

SynComs are powerful, reductionist tools for dissecting diet-microbe, microbe-microbe, and host-microbe interactions under controlled conditions. However, wider uptake is still limited by several technical, ecological, and methodological challenges. Overcoming these will require coordinated innovation and greater standardisation to make SynComs more reproducible, scalable, and representative of the gut ecosystem.

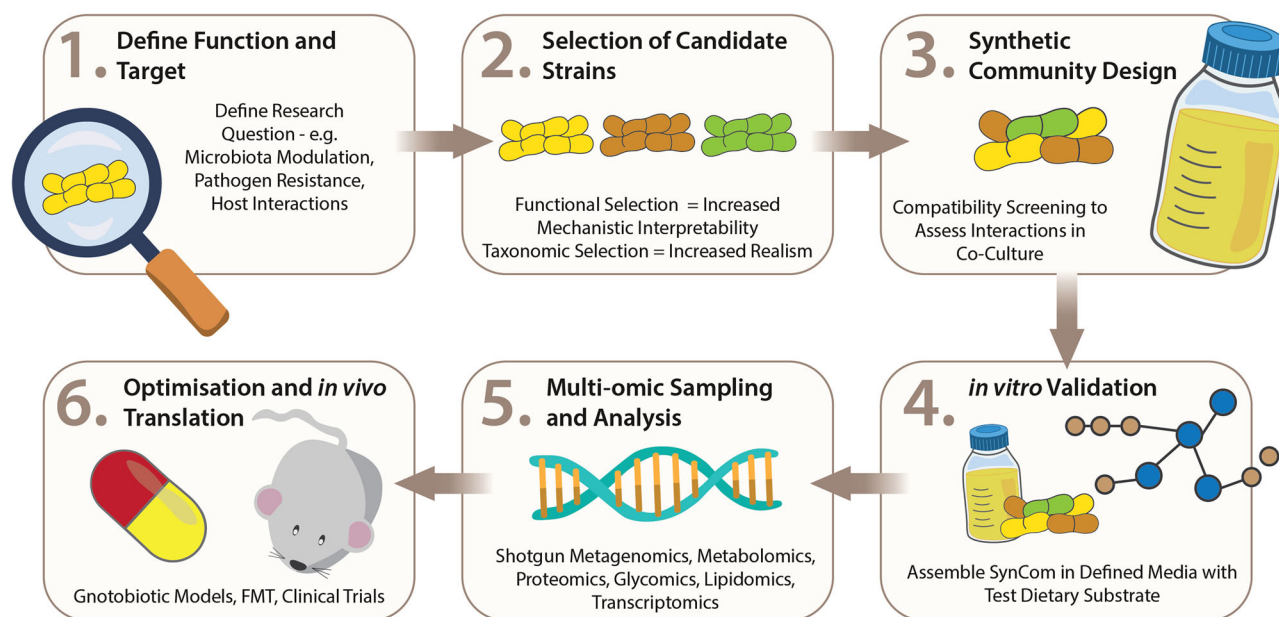


Fig. 4 | Workflow for SynComs-based dietary intervention study.

Table 3 | Proposed Minimal Reporting Checklist for Diet-Based SynComs Studies

Category	Required Reporting Items
Strain Provenance and Identity	Strain names; accession IDs; Donor/Culture-collection source; authentication (Genome/ANI thresholds); antibiotic resistance profile where relevant
Genome characterisation	Assembly identifiers; version numbers; functional annotations (e.g., CAZymes, SCFA pathway genes); and links to public repositories (MIXS-compliant metadata).
Inoculum design	Complete strain list; initial abundances; revival procedures; passage history; viability checks; cryoprotectants, and co-adaptation steps (if any).
Culture Media and Anaerobic conditions	Full media composition (carbon/nitrogen sources; fibres/polymers), redox indicators, gas composition, pH set-points/controls.
Bioreactor parameters	Vessel type; operation mode; feed/wash rates (D); retention times, mucosal compartment (if present), temperature, agitation, sampling scheme; for SHIME/TIM-2 configuration citation.
Dietary Inputs	Substrate type; supplier; lot number; dosing schedule, and analytical verification (e.g., DP distribution, compositional profiling).
Controls and Reference standards	Sterile controls; negative controls; mock communities/standards used (e.g., NIBSC, commercial), spike-ins, and calibration curves
Multi-Omics and Analytics	Extraction kits/protocols; library preparation; sequencing platform; bioinformatics versions/parameters; STORMS/MIXS compliance; deposition of raw data + metadata in public repositories.
Host associated models	Facility SOPs; gnotobiotic monitoring; cage/isolator details; diet; colonisation verification; ethical approvals; references to established protocols or GM consortia where applicable.
Statistical considerations	Power calculations (where feasible); randomisation; batch handling; and pre-registered analyses for translational studies (where applicable).

Culturing and maintaining strict anaerobes. A major practical barrier is the cultivation and long-term maintenance of strict anaerobes, which comprise a large fraction of gut communities, yet are highly oxygen sensitive. Growth requires specialised anaerobic systems, oxygen-free media, and careful handling. Although culturomics has expanded the range of recovered gut anaerobes^{22,124}, sustaining them within mixed communities remains difficult; viability can decline during extended *in vitro* culture, driving community drift and loss of diversity. This is particularly problematic for SynComs built around cross-feeding networks, where the loss of one anaerobe can disrupt dependent taxa and trigger cascading effects across the community, such as accumulation or depletion of critical metabolites and consequently destabilising dependent taxa. Such cascading effects can ultimately compromise the reproducibility, functionality, and ecological relevance of the SynCom, highlighting the need for improved strategies to preserve anaerobe viability and maintain community structure over time.

Selecting species that truly coexist. Designing stable SynComs requires careful selection of community members that can coexist without competitive exclusion. Strain incompatibility, including antagonism, resource competition, or unstable co-existence can arise in multiple ways depending on the isolates and experimental context^{125–128}. Microbial interactions, such as substrate competition, bacteriocin production, and cross-feeding, are highly context dependent, hence difficult to define a universal framework for incompatibility^{129–132}. Overlapping metabolic niches can destabilise communities, while some taxa depend on host-derived factors that are absent *in vitro*²¹. As a result, SynComs are often simplified around “robust growers” rather than ecological representativeness. Because interaction networks are difficult to predict *a priori*, assembly still frequently relies on trial-and-error, reducing reproducibility across studies. Emerging modelling frameworks can reduce this empiricism; tools such as Modelling and Inference of MICrobiomes Project (MIMIC)¹³³ and Microbial COMMunity

modelling (MICOM)¹³⁴, use genome-scale reconstructions and ecological modelling to predict competition, cross-feeding potential and metabolic complementarity, enabling more rational pre-selection of compatible strains, thereby shifting from the trial-and-error assembly towards predictive, mechanism-informed design of SynComs.

Capturing gut complexity and resilience. The human gut microbiome comprises hundreds of interacting species embedded in dense ecological networks^{135–137}. Even “complex” SynComs, typically containing 10–100 strains, cannot fully reproduce this taxonomic and functional breadth¹³⁸. Rare taxa, sometimes important for resilience and redundancy, are frequently missing, limiting the ability of SynComs to reproduce ecological buffering, stability, and adaptability observed *in vivo*¹³¹.

Lack of standardisation across SynComs design. A key bottleneck is the absence of shared design and reporting frameworks. SynComs studies differ widely in strain sourcing, community composition, and culture conditions, often driven by availability rather than ecological rationale^{21,32,139}. There is no consensus on the minimum number, breadth, or functional coverage required to “represent” a gut ecosystem¹⁴⁰. Variation in media composition, inoculum preparation, and anaerobic handling further undermines comparability between studies. Establishing shared guidelines - analogous to the fields progress with standardised host-associated consortia and facility protocols (e.g., OMM12 and NGRRC), would substantially improve reproducibility and translational impact.

Limited long-term stability *in vitro*. *In vitro* SynComs often lose stability over time due to absence of host-derived ecological regulation. In the host, microbial communities are shaped by constant nutrient flow, mucosal secretions, immune regulation, and spatial structuring¹⁴¹. *In vitro*, even in continuous-flow fermenters, incomplete replication of these dynamics can lead to nutrient depletion, metabolite accumulation, and over-growth of fast-growing taxa¹¹¹. While dynamic and continuous models extend stability, achieving long-term ecological balance and host-mediated feedback remains a key challenge.

Future perspectives and emerging trends

Integrating SynCom experiments with multi-omics; genomics, transcriptomics, metabolomics, and proteomics is rapidly enhancing system-level mechanistic insight into microbial ecology. These approaches enable mapping of cross-feeding networks, functional redundancy, and metabolic fluxes under dietary perturbations¹⁴². Crucially, combined omics can link taxa to specific outputs (e.g., SCFAs or bile acid derivatives), helping explain not just who is present but what the community does and why it remains stable.

In parallel, advances in high-throughput culturomics, microfluidic isolation, and robotic automation are expanding the range of strains available for SynComs construction^{143–146}. This is enabling larger communities with built-in redundancy that better capture native gut diversity and resilience. Coupling these pipelines to curated reference genome collections and defined strain libraries will further improve standardisation and sharing across laboratories.

A major translational step is the rise of hybrid microbe-host platforms, including microfluidic gut-on-a-chip systems and 2D/3D intestinal organoids, which allow SynCom co-culture with epithelial, and increasingly immune components¹⁴⁷. As SynCom experiments can sometimes yield different functional outcomes in simplified *in vitro* systems compared to host-associated environments, where factors such as spatial structure, nutrient fluxes and immune responses shape microbial behaviour^{28,148}, these models introduce physiological relevant gradients and mucosal interfaces, enabling controlled interrogation of diet-driven host-microbe interactions, barrier function, and immune signalling.

An emerging approach to building more realistic SynComs is to incorporate non-bacterial members of the gut ecosystem. Most SynComs

still focus primarily on bacteria, but the gut ecosystem also includes fungi, viruses (predominantly bacteriophages), and archaea, all of which contribute to community assembly, stability, and host-microbe interactions^{149–151}. Fungi can shape bacterial community structure through mechanisms such as nutrient competition and production of bioactive metabolites, and they can also influence host immune responses¹⁵². Similarly, bacteriophages can influence microbiome dynamics by targeting specific bacterial hosts and by lysogeny-associated effects (including gene transfer and altered bacterial phenotypes), thereby influencing bacterial abundance and function at the community level^{151,153}. Archaea, especially methanogens, occupy a distinct metabolic niche and participate in syntrophic interactions (e.g., interspecies hydrogen transfer) that can influence bacterial fermentation and overall ecosystem energetics^{154,155}. Building multi-kingdom SynComs is therefore an important step towards models that better reflect real gut ecology. However, there are substantial practical challenges, including differing growth requirements and replication times across kingdoms, the need to maintain stable multi-partner interactions under controlled conditions¹⁴⁹, and the difficulty of incorporating phages whose host range is often narrow and highly context dependent, complicating reproducibility and predictive design¹⁵⁶. Nevertheless, expanding SynComs beyond bacteria should improve ecological realism and mechanistic insights into community dynamics and intervention effects.

Another emerging direction is the use of ecological modelling and Artificial Intelligence (AI)-enabled design to replace trial-and-error community assembly with rational, predictive pipelines. Network, dynamical, and agent-based models can “forecast” stable configurations and functional complementarity^{135,140,157,158}, while machine learning approaches mine large microbiome datasets to prioritise strain combinations and predict metabolic outputs^{159–162}. Together, these developments promise more reproducible, and scalable SynCom design where communities are engineered to test explicit hypotheses about function, not simply to approximate diversity¹⁵⁹.

Looking ahead, SynCom platforms are well positioned to support translational microbiome research by enabling the rational engineering and testing of microbiome-targeted therapeutics, including next-generation probiotics and biotherapeutics^{163–165}, and by predicting host and microbial responses to dietary interventions, thereby informing personalised nutrition strategies^{61,166,167}. In addition, SynComs enable mechanistic assessment of microbiome-drug interactions (including microbial metabolism of pharmaceuticals) and can serve as controlled preclinical platforms to de-risk interventions, identify functional biomarkers, and support precision nutrition and microbiome therapeutic strategies^{168–174}.

Conclusion

SynComs are powerful tools for untangling the complex interplay between diet and the gut microbiota. By reducing a naturally complex ecosystem into defined, controllable consortia, SynComs enable mechanistic tests of how dietary substrates influence ecology and metabolism, and how these microbial outputs influence host physiology^{19,21}. Evidence from SynComs-based studies reinforces diet as a major driver of gut microbiota composition and function across the life course, from early colonisation through adulthood, with implications for long-term health^{18,43}.

SynComs have generated key insights into nutrient specialisation, cross-feeding, succession, and diet-linked disease mechanisms, and critically, help bridge the gap between observational microbiome studies and causal inference by allowing diet-microbe-host hypotheses to be tested under controlled conditions²⁸.

However, important challenges remain. These include cultivating and maintaining strict anaerobes, predicting stable coexistence, capturing the resilience and buffering capacity of native gut communities, and the lack of widely adopted frameworks for SynComs design and reporting. Many *in vitro* systems also have limited longevity, further limiting studies of long-term dynamics. Addressing these limitations will require continued advances in culturomics, improved continuous-culture platforms, and coordinated standardisation across laboratories.

Looking ahead, integrating SynComs with multi-omics, ecological modelling, multi-kingdom inclusion, and AI-driven design, alongside next-generation host-relevant platforms such as organoids and gut-on-a-chip systems, will enable ecological realism, reproducibility, and translational value. With these developments, SynComs research is well positioned to play a central role in building a more mechanistic, predictive understanding of diet-microbe-host research.

Data availability

No datasets were generated or analysed during the current study.

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References

- Alipour, Z., Duman, H., Lee, J., Karav, S. & Frese, S. Chapter 3 - The microbiome in infant gut health and development. in *Nutrition in the Control of Inflammation* (eds. Ferguson, B. S. & Frese, S.) 29–49 (Academic Press, 2025). <https://doi.org/10.1016/B978-0-443-18979-1.00003-4>.
- Liu, J. et al. Functions of Gut Microbiota Metabolites, Current Status and Future Perspectives. *Aging Dis* **13**, 1106 (2022).
- Ogunrinola, G. A., Oyewale, J. O., Oshamika, O. O. & Olasehinde, G. I. The Human Microbiome and Its Impacts on Health. *Int. J. Microbiol.* **2020**, 8045646 (2020).
- Dwiyanto, J. et al. Ethnicity influences the gut microbiota of individuals sharing a geographical location: a cross-sectional study from a middle-income country. *Sci. Rep.* **11**, 2618 (2021).
- Gupta, V. K., Paul, S. & Dutta, C. Geography, ethnicity or subsistence-specific variations in human microbiome composition and diversity. *Front. Microbiol.* **8**, 1162 (2017).
- Syromyatnikov, M. et al. Characteristics of the Gut Bacterial Composition in People of Different Nationalities and Religions. *Microorganisms* **10**, 1866 (2022).
- Zhernakova, A., Yassour, M., Hall, L. J. & Collado, M. C. Unlocking the power of human milk and infant feeding: Understanding how nutrition and early microbiota interaction shapes health programming. *Cell Host Microbe* **33**, 820–835 (2025).
- Dalby, M. J. & Hall, L. J. Recent advances in understanding the neonatal microbiome. *F1000Research* **9**, F1000 (2020).
- Ma, J. et al. Comparison of the Gut Microbiota in Healthy Infants With Different Delivery Modes and Feeding Types: A Cohort Study. *Front. Microbiol.* **13**, 868227 (2022).
- Roager, H. M., Stanton, C. & Hall, L. J. Microbial metabolites as modulators of the infant gut microbiome and host-microbial interactions in early life. *Gut Microbes* **15**, 2192151 (2023).
- Ecklu-Mensah, G., Gilbert, J. & Devkota, S. Dietary Selection Pressures and Their Impact on the Gut Microbiome. *Cell. Mol. Gastroenterol. Hepatol.* **13**, 7–18 (2022).
- Fishbein, S. R. S., Mahmud, B. & Dantas, G. Antibiotic perturbations to the gut microbiome. *Nat. Rev. Microbiol.* **21**, 772–788 (2023).
- Parizadeh, M. & Arrieta, M.-C. The global human gut microbiome: genes, lifestyles, and diet. *Trends Mol. Med.* **29**, 789–801 (2023).
- Ross, F. C. et al. The interplay between diet and the gut microbiome: implications for health and disease. *Nat. Rev. Microbiol.* **22**, 671–686 (2024).
- Asnicar, F. et al. Gut micro-organisms associated with health, nutrition and dietary interventions. *Nature* **650**, 450–458 (2026).
- Beam, A., Clinger, E. & Hao, L. Effect of Diet and Dietary Components on the Composition of the Gut Microbiota. *Nutrients* **13**, 2795 (2021).
- Carlino, N. et al. Unexplored microbial diversity from 2,500 food metagenomes and links with the human microbiome. *Cell* **187**, 5775–5795.e15 (2024).
- Nova, E., Gómez-Martínez, S. & González-Soltero, R. The influence of dietary factors on the gut microbiota. *Microorganisms* **10**, 1368 (2022).
- Jennings, S. A. V. & Clavel, T. Synthetic communities of gut microbes for basic research and translational approaches in animal health and nutrition. *Annu. Rev. Anim. Biosci.* **12**, 283–300 (2024).
- Mehlferber, E. C. et al. A cross-systems primer for synthetic microbial communities. *Nat. Microbiol.* **9**, 2765–2773 (2024).
- van Leeuwen, P. T., Brul, S., Zhang, J. & Wortel, M. T. Synthetic microbial communities (SynComs) of the human gut: design, assembly, and applications. *FEMS Microbiol. Rev.* **47**, fuad012 (2023).
- Browne, H. P. et al. Culturing of ‘unculturable’ human microbiota reveals novel taxa and extensive sporulation. *Nature* **533**, 543–546 (2016).
- Clavel, T. et al. Enabling next-generation anaerobic cultivation through biotechnology to advance functional microbiome research. *Nat. Biotechnol.* **43**, 878–888 (2025).
- Jans, M. & Vereecke, L. A guide to germ-free and gnotobiotic mouse technology to study health and disease. *FEBS J* **292**, 1228–1251 (2025).
- Lagier, J.-C. et al. The Rebirth of Culture in Microbiology through the Example of Culturomics To Study Human Gut Microbiota. *Clin. Microbiol. Rev.* **28**, 237–264 (2015).
- Pérez-Burillo, S. et al. An in vitro batch fermentation protocol for studying the contribution of food to gut microbiota composition and functionality. *Nat. Protoc.* **16**, 3186–3209 (2021).
- Gonçalves, O. S., Creevey, C. J. & Santana, M. F. Designing a synthetic microbial community through genome metabolic modeling to enhance plant-microbe interaction. *Environ. Microbiome* **18**, 81 (2023).
- Hitch, T. C. A. et al. Function-based selection of synthetic communities enables mechanistic microbiome studies. *ISME J.* **19**, wraf209, <https://doi.org/10.1093/ismejo/wraf209> (2025).
- Wang, Z. et al. Ecological design of high-performance synthetic microbial communities: from theoretical foundations to functional optimization. *ISME Commun.* **5**, ycaf133 (2025).
- Gonzalez-Garcia, J. et al. Synthetic microbial communities as novel models to study gut microbiome-host interactions in metabolic diseases. *Discov. Endocrinol. Metab.* **1**, 12 (2025).
- Tian, S. et al. A designed synthetic microbiota provides insight to community function in *Clostridioides difficile* resistance. *Cell Host Microbe* **33**, 373–387.e9 (2025).
- Berkhout, M., Zoetendal, E., Plugge, C. & Belzer, C. Use of synthetic communities to study microbial ecology of the gut. *Microbiome Res. Rep.* **1**, 4 (2022).
- De Weirtdt, R. et al. Human faecal microbiota display variable patterns of glycerol metabolism. *FEMS Microbiol. Ecol.* **74**, 601–611 (2010).
- Durán, P., Vaillau, F. & Roux, F. Building microbial synthetic communities: get inspired by the design of synthetic plant communities. *N. Phytol.* **246**, 402–405 (2025).
- Vázquez-Castellanos, J. F., Bicló, A., Vrancken, G., Huys, G. R. & Raes, J. Design of synthetic microbial consortia for gut microbiota modulation. *Curr. Opin. Pharmacol.* **49**, 52–59 (2019).
- Elzinga, J., van der Oost, J., de Vos, W. M. & Smidt, H. The Use of Defined Microbial Communities To Model Host-Microbe Interactions in the Human Gut. *Microbiol. Mol. Biol. Rev.* **83**, <https://doi.org/10.1128/mmb.00054-18> (2019).
- Mabwi, H. A. et al. Synthetic gut microbiome: advances and challenges. *Comput. Struct. Biotechnol. J.* **19**, 363–371 (2021).
- Perez, M. et al. A synthetic consortium of 100 gut commensals modulates the composition and function in a colon model of the microbiome of elderly subjects. *Gut Microbes* **13**, 1919464 (2021).

39. Tronel, A. et al. Exploring the human small intestinal luminal microbiome via a newly developed ingestible sampling device. *ISME Commun.* **5**, ycaf224 (2025).
40. Smith, D. Chapter 4 - Culture Collections. in *Advances in Applied Microbiology* (eds. Sariaslani, S. & Gadd, G. M.) vol. 79 73–118 (Academic Press, 2012).
41. Mariat, D. et al. The Firmicutes/Bacteroidetes ratio of the human microbiota changes with age. *BMC Microbiol.* **9**, 123 (2009).
42. Rinninella, E. et al. The role of diet in shaping human gut microbiota. *Best. Pract. Res. Clin. Gastroenterol.* **62–63**, 101828 (2023).
43. Lawson, M. A. E. et al. Breast milk-derived human milk oligosaccharides promote Bifidobacterium interactions within a single ecosystem. *ISME J* **14**, 635–648 (2020).
44. Laursen, M. F. Gut Microbiota Development: Influence of Diet from Infancy to Toddlerhood. *Ann. Nutr. Metab.* **77**, 21–34 (2021).
45. Aranda-Díaz, A. et al. Establishment and characterization of stable, diverse, fecal-derived in vitro microbial communities that model the intestinal microbiota. *Cell Host Microbe* **30**, 260–272.e5 (2022).
46. Eng, A. & Borenstein, E. Taxa-function robustness in microbial communities. *Microbiome* **6**, 45 (2018).
47. Ahmadi, S. et al. An In Vitro Batch-culture Model to Estimate the Effects of Interventional Regimens on Human Fecal Microbiota. *J. Vis. Exp. JoVE* **10**, 3791/59524, <https://doi.org/10.3791/59524> (2019).
48. Eastwood, J. et al. The Effect of Probiotic Bacteria on Composition and Metabolite Production of Faecal Microbiota Using In Vitro Batch Cultures. *Nutrients* **15**, 2563 (2023).
49. Evdokimova, S. A. et al. A Study and Modeling of Bifidobacterium and Bacillus Coculture Continuous Fermentation under Distal Intestine Simulated Conditions. *Microorganisms* **10**, 929 (2022).
50. Duysburgh, C., Velumani, D., Garg, V., Cheong, J. W. Y. & Marzorati, M. Combined Supplementation of Inulin and Bacillus coagulans Lactospore Demonstrates Synbiotic Potential in the Mucosal Simulator of the Human Intestinal Microbial Ecosystem (M-SHIME®) Model. *J. Diet. Suppl.* **21**, 737–755 (2024).
51. Wheeler, A. E., Stoeger, V. & Owens, R. Lab-on-chip technologies for exploring the gut-immune axis in metabolic disease. *Lab. Chip* **24**, 1266–1292 (2024).
52. Fournier, E. et al. A child is not an adult: development of a new in vitro model of the toddler colon. *Appl. Microbiol. Biotechnol.* **106**, 7315–7336 (2022).
53. Mukherjee, A. et al. OPTIMATRIX v2.0: Optimised protocol to mitigate microbial blooms in the micro-Matrix bioreactor platform used as an ex vivo human distal colon model. *MethodsX* **14**, 103275 (2025).
54. Rachmühl, C., Lacroix, C., Cabrera, P. M. & Geirnaert, A. Long-term continuous cultivation of Kenyan infant fecal microbiota using the host adapted PolyFermS model. *Sci. Rep.* **13**, 20563 (2023).
55. Wang, S. et al. Effect of Protein Fermentation Products on Gut Health Assessed in an In Vitro Model of Human Colon (TIM-2). *Mol. Nutr. Food Res.* **67**, 2200574 (2023).
56. Zhu, W. et al. Simulator of the Human Intestinal Microbial Ecosystem (SHIME®): current developments, applications, and future prospects. *Pharmaceuticals* **17**, 1639 (2024).
57. Morelli, M., Kurek, D., Ng, C. P. & Queiroz, K. Gut-on-a-chip models: current and future perspectives for host-microbial interactions research. *Biomedicines* **11**, 619 (2023).
58. Rahman, S. et al. The progress of intestinal epithelial models from cell lines to gut-on-chip. *Int. J. Mol. Sci.* **22**, 13472 (2021).
59. Van de Wiele, T. et al. (Springer, Cham (CH), 2015).
60. Aluthge, N. D. et al. Differential longitudinal establishment of human fecal bacterial communities in germ-free porcine and murine models. *Commun. Biol.* **3**, 760 (2020).
61. Brugiroux, S. et al. Genome-guided design of a defined mouse microbiota that confers colonization resistance against Salmonella enterica serovar Typhimurium. *Nat. Microbiol.* **2**, 16215 (2016).
62. Eberl, C. et al. Reproducible Colonization of Germ-Free Mice With the Oligo-Mouse-Microbiota in Different Animal Facilities. *Front. Microbiol.* **10**, 2999 (2020).
63. Kešnerová, L. et al. Disentangling metabolic functions of bacteria in the honey bee gut. *PLOS Biol* **15**, e2003467 (2017).
64. Koyle, M. L. et al. Rearing the Fruit Fly *Drosophila melanogaster* Under Axenic and Gnotobiotic Conditions. *J. Vis. Exp. JoVE* 54219. <https://doi.org/10.3791/54219>. (2016).
65. Rendueles, O. et al. A New Zebrafish Model of Oro-Intestinal Pathogen Colonization Reveals a Key Role for Adhesion in Protection by Probiotic Bacteria. *PLOS Pathog* **8**, e1002815 (2012).
66. Storelli, G. et al. Lactobacillus plantarum Promotes Drosophila Systemic Growth by Modulating Hormonal Signals through TOR-Dependent Nutrient Sensing. *Cell Metab* **14**, 403–414 (2011).
67. The National Gnotobiotic Rodent Resource Center (NGRRC). *National Gnotobiotic Rodent Resource Center* <https://www.med.unc.edu/ngrrc/>.
68. Cheng, A. G. et al. Design, construction, and in vivo augmentation of a complex gut microbiome. *Cell* **185**, 3617 (2022).
69. Lubin, J.-B. et al. Arresting microbiome development limits immune system maturation and resistance to infection in mice. *Cell Host Microbe* **31**, 554 (2023).
70. Lubin, J.-B., Planet, P. J. & Silverman, M. A. Microbial succession at weaning is guided by microbial metabolism of host glycans. *Microbiome* **13**, 218 (2025).
71. Taglialegna, A. A mature microbiome for immune health. *Nat. Rev. Microbiol.* **21**, 344–344 (2023).
72. Guan, L. & Liu, R. The Role of Diet and Gut Microbiota Interactions in Metabolic Homeostasis. *Adv. Biol.* **7**, e2300100 (2023).
73. Bartsch, M. et al. Microbiota-Dependent Fiber Responses: A Proof-of-Concept Study on Short-Chain Fatty Acid Production in Prevotella- and Bacteroides-Dominated Healthy Individuals. *J. Nutr.* **155**, 3809 (2025).
74. Mann, E. R., Lam, Y. K. & Uhlig, H. H. Short-chain fatty acids: linking diet, the microbiome and immunity. *Nat. Rev. Immunol.* **24**, 577–595 (2024).
75. Meiners, F., Ortega-Matienzo, A., Fuellen, G. & Barrantes, I. Gut microbiome-mediated health effects of fiber and polyphenol-rich dietary interventions. *Front. Nutr.* **12**, (2025).
76. Tang, Y. et al. High-fat diet during early life reshapes the gut microbiome and is associated with the disrupted mammary microenvironment in later life in mice. *Nutr. Res. N. Y. N.* **127**, 1–12 (2024).
77. Watanabe, M. et al. Bile acid is a responsible host factor for high-fat diet-induced gut microbiota alterations in rats: proof of the ‘bile acid hypothesis. *Biosci. Microbiota Food Health* **44**, 110–121 (2025).
78. Adejumo, S. A. et al. Dietary Protein Source Shapes Gut Microbial Structure and Predicted Functional Potential: a Systematic Integrative Re-Analysis Using Machine Learning. *Adv. Nutr.* **17**, 100582 (2026).
79. Fu, J., Zheng, Y., Gao, Y. & Xu, W. Dietary fiber intake and gut microbiota in human health. *Microorganisms* **10**, 2507 (2022).
80. Natividad, J. M. et al. *Bilophila wadsworthia* aggravates high fat diet induced metabolic dysfunctions in mice. *Nat. Commun.* **9**, 2802 (2018).
81. Omer, F. et al. High-Protein Diets: Characteristics of Bacterial Fermentation and Its Consequences on Intestinal Health. *Fermentation* **11**, 678 (2025).
82. Venturelli, O. S. et al. Deciphering microbial interactions in synthetic human gut microbiome communities. *Mol. Syst. Biol.* **14**, MSB178157 (2018).
83. Golshany, H. et al. The gut microbiome across the lifespan: how diet modulates our microbial ecosystem from infancy to the elderly. *Int. J. Food Sci. Nutr.* **76**, 95–121 (2025).

84. Li, C. Understanding interactions among diet, host and gut microbiota for personalized nutrition. *Life Sci* **312**, 121265 (2023).
85. Malan-Muller, S. et al. Exploring the relationship between the gut microbiome and mental health outcomes in a posttraumatic stress disorder cohort relative to trauma-exposed controls. *Eur. Neuropsychopharmacol.* **56**, 24–38 (2022).
86. Martínez, I. et al. Gut microbiome composition is linked to whole grain-induced immunological improvements. *ISME J* **7**, 269–280 (2013).
87. McLeod, A. et al. Comparing the gut microbiome of obese, African American, older adults with and without mild cognitive impairment. *PLOS ONE* **18**, e0280211 (2023).
88. Centanni, M., Ferguson, S. A., Sims, I. M., Biswas, A. & Tannock, G. W. Bifidobacterium bifidum ATCC 15696 and Bifidobacterium breve 24b Metabolic Interaction Based on 2'-O-Fucosyl-Lactose Studied in Steady-State Cultures in a Frater-Style Chemostat. *Appl. Environ. Microbiol.* **85**, e02783–18 (2019).
89. Ioannou, A. et al. Resource sharing of an infant gut microbiota synthetic community in combinations of human milk oligosaccharides. *ISME J.* **18**, wræ209 (2024).
90. Chen, X. et al. A synthetic microbial consortium protects against obesity by regulating vitamin B6 metabolism. *Gut Microbes* **16**, 2304901 (2024).
91. De Vos, W. M. et al. Phytate metabolism is mediated by microbial cross-feeding in the gut microbiota. *Nat. Microbiol.* **9**, 1812–1827 (2024).
92. Gotoh, A. et al. Sharing of human milk oligosaccharides degradants within bifidobacterial communities in faecal cultures supplemented with Bifidobacterium bifidum. *Sci. Rep.* **8**, 13958 (2018).
93. Ross, T. D., Im, H., Keogh, B. G., Klausmeier, C. A. & Venturelli, O. S. Metabolic interplay drives population cycles in a cross-feeding microbial community. *Nat. Commun.* **16**, 8919 (2025).
94. Louis, P., Solvang, M., Duncan, S. H., Walker, A. W. & Mukhopadhyay, I. Dietary fibre complexity and its influence on functional groups of the human gut microbiota. *Proc. Nutr. Soc.* **80**, 386–397 (2021).
95. Armet, A. M. et al. Mechanistic insights into microbiome-dependent and personalized responses to dietary fibre in a randomized controlled trial. *MedRxiv Prepr. Serv. Health Sci.* 2025.11.20.25340625 <https://doi.org/10.1101/2025.11.20.25340625> (2025).
96. Thomson, C., Garcia, A. L. & Edwards, C. A. Interactions between dietary fibre and the gut microbiota. *Proc. Nutr. Soc.* **80**, 398–408 (2021).
97. Zheng, H. et al. The Dose-Dependent Influence of Type 2 Resistant Starch on Gut Microbial Communities and Metabolic Outputs: An In Vitro Simulation. *Foods* **14**, 3255 (2025).
98. Lamas, A., Regal, P., Vázquez, B., Cepeda, A. & Franco, C. M. Short chain fatty acids commonly produced by gut microbiota influence salmonella enterica motility, biofilm formation, and gene expression. *Antibiotics* **8**, 265 (2019).
99. Henson, M. A. & Phalak, P. Suboptimal community growth mediated through metabolite crossfeeding promotes species diversity in the gut microbiota. *PLoS Comput. Biol.* **14**, e1006558 (2018).
100. Huus, K. E. et al. Cross-feeding between intestinal pathobionts promotes their overgrowth during undernutrition. *Nat. Commun.* **12**, 6860 (2021).
101. Agus, A. et al. Western diet induces a shift in microbiota composition enhancing susceptibility to Adherent-Invasive E. coli infection and intestinal inflammation. *Sci. Rep.* **6**, 19032 (2016).
102. Agus, A., Clément, K. & Sokol, H. Gut microbiota-derived metabolites as central regulators in metabolic disorders. *Gut* **70**, 1174–1182 (2021).
103. Desai, M. S. et al. A Dietary fiber-deprived gut microbiota degrades the colonic mucus barrier and enhances pathogen susceptibility. *Cell* **167**, 1339–1353.e21 (2016).
104. Brown, K. et al. Microbiota alters the metabolome in an age- and sex-dependent manner in mice. *Nat. Commun.* **14**, 1348 (2023).
105. Pettersen, V. K., Dufour, A. & Arrieta, M.-C. Metaproteomic profiling of fungal gut colonization in gnotobiotic mice. *Anim. Microbiome* **4**, 14 (2022).
106. Weiss, A. S. et al. Nutritional and host environments determine community ecology and keystone species in a synthetic gut bacterial community. *Nat. Commun.* **14**, 4780 (2023).
107. Bultman, S. J. Interplay between diet, gut microbiota, epigenetic events, and colorectal cancer. *Mol. Nutr. Food Res.* **61**, 1500902 (2017).
108. Wang, L.-Y., He, L.-H., Xu, L.-J. & Li, S.-B. Short-chain fatty acids: bridges between diet, gut microbiota, and health. *J. Gastroenterol. Hepatol.* **39**, 1728–1736 (2024).
109. Trompette, A. et al. Gut microbiota metabolism of dietary fiber influences allergic airway disease and hematopoiesis. *Nat. Med.* **20**, 159–166 (2014).
110. Hsiao, E. Y. et al. Microbiota Modulate Behavioral and Physiological Abnormalities Associated with Neurodevelopmental Disorders. *Cell* **155**, 1451–1463 (2013).
111. Vrancken, G., Gregory, A. C., Huys, G. R. B., Faust, K. & Raes, J. Synthetic ecology of the human gut microbiota. *Nat. Rev. Microbiol.* **17**, 754–763 (2019).
112. Walter, J., Armet, A. M., Finlay, B. B. & Shanahan, F. Establishing or Exaggerating Causality for the Gut Microbiome: Lessons from Human Microbiota-Associated Rodents. *Cell* **180**, 221–232 (2020).
113. Sakanaka, M. et al. Varied pathways of infant gut-associated bifidobacterium to assimilate human milk oligosaccharides: prevalence of the gene set and its correlation with bifidobacteria-rich microbiota formation. *Nutrients* **12**, 71 (2020).
114. Faith, J. J., Ahern, P. P., Ridaura, V. K., Cheng, J. & Gordon, J. I. Identifying gut microbe–host phenotype relationships using combinatorial communities in gnotobiotic mice. *Sci. Transl. Med.* **6**, 220ra11–220ra11 (2014).
115. Kolodziejczyk, A. A., Zheng, D. & Elinav, E. Diet–microbiota interactions and personalized nutrition. *Nat. Rev. Microbiol.* **17**, 742–753 (2019).
116. Quinn-Bohmann, N. et al. Microbial community-scale metabolic modelling predicts personalized short-chain fatty acid production profiles in the human gut. *Nat. Microbiol.* **9**, 1700–1712 (2024).
117. Vandeputte, D. Personalized nutrition through the gut microbiota: current insights and future perspectives. *Nutr. Rev.* **78**, 66–74 (2020).
118. Klünemann, M. et al. Bioaccumulation of therapeutic drugs by human gut bacteria. *Nature* **597**, 533–538 (2021).
119. Maier, L. et al. Extensive impact of non-antibiotic drugs on human gut bacteria. *Nature* **555**, 623–628 (2018).
120. Zimmermann, M., Zimmermann-Kogadeeva, M., Wegmann, R. & Goodman, A. L. Mapping human microbiome drug metabolism by gut bacteria and their genes. *Nature* **570**, 462–467 (2019).
121. Schloss, P. D. Identifying and Overcoming Threats to Reproducibility, Replicability, Robustness, and Generalizability in Microbiome Research. *mBio* **9**, e00525 (2018).
122. Mirzayi, C. et al. Reporting guidelines for human microbiome research: the STORMS checklist. *Nat. Med.* **27**, 1885–1892 (2021).
123. Yilmaz, P. et al. Minimum information about a marker gene sequence (MIMARKS) and minimum information about any (x) sequence (MIXS) specifications. *Nat. Biotechnol.* **29**, 415–420 (2011).
124. Lagier, J.-C. et al. Culturing the human microbiota and culturomics. *Nat. Rev. Microbiol.* **16**, 540–550 (2018).
125. Auchtung, J. M., Hallen-Adams, H. E. & Hutkins, R. Microbial interactions and ecology in fermented food ecosystems. *Nat. Rev. Microbiol.* **23**, 622–634 (2025).
126. Bakkeren, E., Piskovsky, V. & Foster, K. R. Metabolic ecology of microbiomes: Nutrient competition, host benefits, and community engineering. *Cell Host Microbe* **33**, 790–807 (2025).

127. Xu, X., Dinesen, C., Pioppi, A., Kovács, Á. T. & Lozano-Andrade, C. N. Composing a microbial symphony: synthetic communities for promoting plant growth. *Trends Microbiol* **33**, 738–751 (2025).
128. Yu, Z., Gan, Z., Tawfik, A. & Meng, F. Exploring interspecific interaction variability in microbiota: A review. *Eng. Microbiol.* **4**, 100178 (2024).
129. Coyte, K. Z. & Rakoff-Nahoum, S. Understanding Competition and Cooperation within the Mammalian Gut Microbiome. *Curr. Biol. CB* **29**, R538–R544 (2019).
130. Culp, E. J. & Goodman, A. L. Cross-feeding in the gut microbiome: Ecology and mechanisms. *Cell Host Microbe* **31**, 485–499 (2023).
131. Poyet, M. et al. A library of human gut bacterial isolates paired with longitudinal multiomics data enables mechanistic microbiome research. *Nat. Med.* **25**, 1442–1452 (2019).
132. Rakoff-Nahoum, S., Foster, K. R. & Comstock, L. E. The evolution of cooperation within the gut microbiota. *Nature* **533**, 255–259 (2016).
133. Fontanarrosa, P., Clare, C., Fedorec, A. J. H. & Barnes, C. P. MIMIC: a Python package for simulating, inferring, and predicting microbial community interactions and dynamics. *Bioinformatics* **41**, btaf174 (2025).
134. Diener, C., Gibbons, S. M. & Resendis-Antonio, O. MICOM: Metagenome-Scale Modeling To Infer Metabolic Interactions in the Gut Microbiota. *mSystems* **5**, <https://doi.org/10.1128/msystems.00606-19> (2020).
135. Coyte, K. Z., Schluter, J. & Foster, K. R. The ecology of the microbiome: Networks, competition, and stability. *Science* **350**, 663–666 (2015).
136. Greenblum, S., Turnbaugh, P. J. & Borenstein, E. Metagenomic systems biology of the human gut microbiome reveals topological shifts associated with obesity and inflammatory bowel disease. *Proc. Natl. Acad. Sci.* **109**, 594–599 (2012).
137. Qin, J. et al. A human gut microbial gene catalogue established by metagenomic sequencing. *Nature* **464**, 59–65 (2010).
138. Faith, J. J. et al. The long-term stability of the human gut microbiota. *Science* **341**, 1237439 (2013).
139. Eng, A. & Borenstein, E. Microbial community design: methods, applications, and opportunities. *Curr. Opin. Biotechnol.* **58**, 117–128 (2019).
140. Friedman, J., Higgins, L. M. & Gore, J. Community structure follows simple assembly rules in microbial microcosms. *Nat. Ecol. Evol.* **1**, 1–7 (2017).
141. Donaldson, G. P., Lee, S. M. & Mazmanian, S. K. Gut biogeography of the bacterial microbiota. *Nat. Rev. Microbiol.* **14**, 20–32 (2016).
142. Raman, A. S. et al. A sparse covarying unit that describes healthy and impaired human gut microbiota development. *Science* **365**, eaau4735 (2019).
143. Huang, Y. et al. High-throughput microbial culturomics using automation and machine learning. *Nat. Biotechnol.* **41**, 1424–1433 (2023).
144. Xu, M.-Q., Pan, F., Peng, L.-H. & Yang, Y.-S. Advances in the isolation, cultivation, and identification of gut microbes. *Mil. Med. Res.* **11**, 34 (2024).
145. Yin, J. et al. A droplet-based microfluidic approach to isolating functional bacteria from gut microbiota. *Front. Cell. Infect. Microbiol.* **12**, 920986 (2022).
146. Zünd, J. N. et al. A flexible high-throughput cultivation protocol to assess the response of individuals' gut microbiota to diet-, drug-, and host-related factors. *ISME Commun.* **4**, ycae035 (2024).
147. Jalili-Firoozinezhad, S. et al. A complex human gut microbiome cultured in an anaerobic intestine-on-a-chip. *Nat. Biomed. Eng.* **3**, 520–531 (2019).
148. Rudzka, A. et al. A Comparison of the Response of the Human Intestinal Microbiota to Probiotic and Nutritional Interventions In Vitro and In Vivo—A Case Study. *Nutrients* **17**(19), 3093 (2025).
149. Hsu, B. B. et al. Dynamic Modulation of the Gut Microbiota and Metabolome by Bacteriophages in a Mouse Model. *Cell Host Microbe* **25**, 803–814.e5 (2019).
150. Nash, A. K. et al. The gut mycobiome of the Human. *Microbiome Project healthy cohort. Microbiome* **5**, 153 (2017).
151. Shkoporov, A. N., Turkington, C. J. & Hill, C. Mutualistic interplay between bacteriophages and bacteria in the human gut. *Nat. Rev. Microbiol.* **20**, 737–749 (2022).
152. Zhang, M. et al. Bacterial–Fungal Interactions: Mutualism, Antagonism, and Competition. *Life* **15**, 1242 (2025).
153. Shkoporov, A. N. & Hill, C. Bacteriophages of the Human Gut: The “Known Unknown” of the Microbiome. *Cell Host Microbe* **25**, 195–209 (2019).
154. Moissl-Eichinger, C. et al. Archaea Are Interactive Components of Complex Microbiomes. *Trends Microbiol* **26**, 70–85 (2018).
155. Weinberger, V. et al. Proteomic and metabolomic profiling of extracellular vesicles produced by human gut archaea. *Nat. Commun.* **16**, 5094 (2025).
156. Alkhalil, S. S. The role of bacteriophages in shaping bacterial composition and diversity in the human gut. *Front. Microbiol.* **14**, 1232413 (2023).
157. Xiao, Y. et al. Mapping the ecological networks of microbial communities. *Nat. Commun.* **8**, 2042 (2017).
158. Zomorodi, A. R. & Segrè, D. Synthetic Ecology of Microbes: Mathematical Models and Applications. *J. Mol. Biol.* **428**, 837–861 (2016).
159. Baimakhanova, B. B. et al. In Silico Modeling of Metabolic Pathways in Probiotic Microorganisms for Functional. *Food Biotechnology. Fermentation* **11**, 458 (2025).
160. Lambert, A., Budinich, M., Mahé, M., Chaffron, S. & Eveillard, D. Community metabolic modeling of host-microbiota interactions through multi-objective optimization. *iScience* **27**, 110092 (2024).
161. Li, P., Luo, H., Ji, B. & Nielsen, J. Machine learning for data integration in human gut microbiome. *Microb. Cell Factories* **21**, 241 (2022).
162. Rozera, T., Pasolli, E., Segata, N. & Ianiro, G. Machine Learning and Artificial Intelligence in the Multi-Omics Approach to Gut Microbiota. *Gastroenterology* **169**, 487–501 (2025).
163. Li, N., Yin, L., Wang, J., Zhang, J. & Tong, Y. Programmable probiotics as next-generation living therapeutics: bridging synthetic biology and precision medicine. *Curr. Opin. Biotechnol.* **96**, 103375 (2025).
164. Murali, S. K. & Mansell, T. J. Next generation probiotics: Engineering live biotherapeutics. *Biotechnol. Adv.* **72**, 108336 (2024).
165. Nazir, A., Hussain, F. H. N. & Raza, A. Advancing microbiota therapeutics: the role of synthetic biology in engineering microbial communities for precision medicine. *Front. Bioeng. Biotechnol.* **12**, 1511149 (2024).
166. Bayer, G. & Philpott, D. J. Defined mouse microbiota: An “evolving” tool. *Cell Host Microbe* **29**, 545–547 (2021).
167. Biggs, M. B. et al. Systems-level metabolism of the altered Schaedler flora, a complete gut microbiota. *ISME J* **11**, 426–438 (2017).
168. Belančić, A. et al. Microbiome-driven PKs: redefining drug metabolism beyond host enzymes. *Expert Opin. Drug Metab. Toxicol.* **22**, 9–28 (2026).
169. Bracken, A. K. & Chang, P. V. Gut microbiota-mediated GPCR drug metabolism affects downstream pharmacological activity. *Nat. Chem.* **17**, 781–783 (2025).
170. Jimonet, P. et al. Gut Microbiome Integration in Drug Discovery and Development of Small Molecules. *Drug Metab. Dispos. Biol. Fate Chem.* **52**, 274–287 (2024).
171. Sousa, T. et al. Unexpected effects of antibiotics on microbiota-mediated drug metabolism in a fistulated dog model. *Eur. J. Pharm. Sci.* **216**, 107360 (2026).

172. Verdegaaal, A. A. & Goodman, A. L. Integrating the gut microbiome and pharmacology. *Sci. Transl. Med.* **16**, eadg8357 (2024).
173. Viglioli, M. et al. Investigating drug-gut microbiota interactions: reductive and hydrolytic metabolism of oral glucocorticoids by in vitro artificial gut microbiota. *Int. J. Pharm.* **665**, 124663 (2024).
174. Wang, S., Ju, D. & Zeng, X. Mechanisms and Clinical Implications of Human Gut Microbiota-Drug Interactions in the Precision Medicine Era. *Biomedicines* **12**, 194 (2024).
175. Hromada, S. et al. Negative interactions determine *Clostridioides difficile* growth in synthetic human gut communities. *Mol. Syst. Biol.* **17**, MSB202110355 (2021).
176. Jorin, B. et al. Stable, fluorescent markers for tracking synthetic communities and assembly dynamics. *Microbiome* **12**, 81 (2024).
177. Fonseca-García, C. et al. Defined synthetic microbial communities colonize and benefit field-grown sorghum. *ISME J.* **18**, wrae126 (2024).
178. Singh, V. et al. Cultured fecal microbial community and its impact as fecal microbiota transplantation treatment in mice gut inflammation. *Appl. Microbiol. Biotechnol.* **108**, 463 (2024).
179. Brown, E. M., Clardy, J. & Xavier, R. J. Gut microbiome lipid metabolism and its impact on host physiology. *Cell Host Microbe* **31**, 173–186 (2023).
180. Ravcheev, D. A. & Thiele, I. Comparative genomic analysis of the human gut microbiome reveals a broad distribution of metabolic pathways for the degradation of host-synthesized mucin glycans and utilization of mucin-derived monosaccharides. *Front. Genet.* **8**, 111 (2017).
181. Tanca, A. & Uzzau, S. Contribution of metaproteomics to unveiling the functional role of the gut microbiome in human physiology and metabolism. *Expert Rev. Proteom.* **22**, 389–400 (2025).
182. Valdés-Mas, R. et al. Metagenome-informed metaproteomics of the human gut microbiome, host, and dietary exposome uncovers signatures of health and inflammatory bowel disease. *Cell* **188**, 1062–1083.e36 (2025).
183. Zhang, A. et al. Microbiome-dependent functional responses to structurally distinct oligosaccharides revealed by metaproteomics. *Npj Biofilms Microbiomes* **12**, 15 (2025).
184. Weiss, A. S. et al. In vitro interaction network of a synthetic gut bacterial community. *ISME J.* **16**, 1095–1109 (2022).
185. Mirretta Barone, C. et al. Spatially resolved lipidomics shows conditional transfer of lipids produced by *Bacteroides thetaiotaomicron* into the mouse gut. *Cell Host Microbe* **32**, 1025–1036.e5 (2024).
186. Yasuda, S. et al. Elucidation of Gut Microbiota-Associated Lipids Using LC-MS/MS and 16S rRNA Sequence Analyses. *iScience* **23**, 101841 (2020).
187. Deng, P. et al. Untargeted Stable Isotope Probing of the Gut Microbiota Metabolome Using ¹³C-Labeled Dietary Fibers. *J. Proteome Res.* **20**, 2904–2913 (2021).
188. Tannock, G. W. et al. RNA-stable-isotope probing shows utilization of carbon from inulin by specific bacterial populations in the rat large bowel. *Appl. Environ. Microbiol.* **80**, 2240–2247 (2014).
189. Wong, K. et al. Stable Isotope Carbon-13 Labeling for Identifying Microbial Contributions to the Lower Airway Metabolome. *Am. J. Respir. Crit. Care Med.* **211**, A7911 (2025).
190. Xiao, X. et al. ¹³C-Stable isotope resolved metabolomics uncovers dynamic biochemical landscape of gut microbiome-host organ communications in mice. *Microbiome* **12**, 90 (2024).
191. Geniselli da Silva, V. et al. Dietary patterns influencing the human colonic microbiota from infancy to centenarian age: a narrative review. *Front. Nutr.* **12**, 1591341 (2025).
192. Alessa, H. et al. In Vitro Effects of Twelve Food Additives on Gut Microbiome and Its Fibre Fermentation Capacity in Adults with Crohn's Disease in Remission and Healthy Controls. *Nutrients* **18**, 668 (2026).
193. Gao, Y. et al. In vitro batch fermentation demonstrates variations in the regulation of gut microbiota and metabolic functions by β-glucans of differing structures. *Food Res. Int. Ott. Ont.* **186**, 114287 (2024).
194. Morales, P. S. et al. An in vitro batch culture study to assess the fermentation of human milk oligosaccharides by faecal microbiota from healthy and irritable bowel syndrome stool donors. *Gut Microbiome* **6**, e4 (2025).
195. Cattero, V., Roussel, C., Lessard-Lord, J., Roy, D. & Desjardins, Y. Supplementation with a cranberry extract favors the establishment of butyrogenic guilds in the human fermentation SHIME system. *Microbiome Res. Rep.* **3**, N/A–N/A (2024).
196. Daoust, J. et al. Prebiotic activity of functional whole mushroom powders compared to inulin in SHIME® model colonic simulations. *J. Funct. Foods* **134**, 107030 (2025).
197. Popov, I. V., Koopmans, B. & Venema, K. Modulation of human gut microbiota by linear and branched fructooligosaccharides in an in vitro colon model (TIM-2). *J. Appl. Microbiol.* **135**, lxae170 (2024).
198. Lawson, M. A. et al. Early life milk diets shape infant gut microbiota: evidence of microbial plasticity in response to breast and formula milk. 2024.09.22.614312 Preprint at <https://doi.org/10.1101/2024.09.22.614312> (2024).
199. Marcobal, A. et al. Consumption of Human Milk Oligosaccharides by Gut-Related Microbes. *J. Agric. Food Chem.* **58**, 5334–5340 (2010).
200. Walsh, C., Lane, J. A., van Sinderen, D. & Hickey, R. M. Human milk oligosaccharide-sharing by a consortium of infant derived *Bifidobacterium* species. *Sci. Rep.* **12**, 4143 (2022).
201. Firman, J. et al. An in vitro analysis of how lactose modifies the gut microbiota structure and function of adults in a donor-independent manner. *Front. Nutr.* **9**, 1040744 (2022).
202. JanssenDuijghuijsen, L. et al. Changes in gut microbiota and lactose intolerance symptoms before and after daily lactose supplementation in individuals with the lactase nonpersistent genotype. *Am. J. Clin. Nutr.* **119**, 702–710 (2024).
203. Mäkiyuokko, H. A., Saarinen, M. T., Ouwehand, A. C. & Rautonen, N. E. Effects of lactose on colon microbial community structure and function in a four-stage semi-continuous culture system. *Biosci. Biotechnol. Biochem.* **70**, 2056–2063 (2006).
204. Hughes, R. L., Alvarado, D. A., Swanson, K. S. & Holscher, H. D. The Prebiotic Potential of Inulin-Type Fructans: A Systematic Review. *Adv. Nutr.* **13**, 492 (2021).
205. Jung, T.-H., Jeon, W.-M. & Han, K.-S. In Vitro Effects of Dietary Inulin on Human Fecal Microbiota and Butyrate Production. *J. Microbiol. Biotechnol.* **25**, 1555–1558 (2015).
206. Rubin, I. M. C. et al. Synbiotic Intervention with Lactobacilli, Bifidobacteria, and Inulin in Healthy Volunteers Increases the Abundance of Bifidobacteria but Does Not Alter Microbial Diversity. *Appl. Environ. Microbiol.* **88**, e01087 (2022).
207. Davis, L. M. G., Martínez, I., Walter, J. & Hutkins, R. A dose dependent impact of prebiotic galactooligosaccharides on the intestinal microbiota of healthy adults. *Int. J. Food Microbiol.* **144**, 285–292 (2010).
208. Sims, I. M. & Tannock, G. W. Galacto- and Fructo-oligosaccharides Utilized for Growth by Cocultures of Bifidobacterial Species Characteristic of the Infant Gut. *Appl. Environ. Microbiol.* **86**, e00214–e00220 (2020).
209. Thongaram, T., Hoefflinger, J. L., Chow, J. & Miller, M. J. Prebiotic Galactooligosaccharide Metabolism by Probiotic Lactobacilli and Bifidobacteria. *J. Agric. Food Chem.* **65**, 4184–4192 (2017).
210. DeMartino, P. & Cockburn, D. W. Resistant starch: impact on the gut microbiome and health. *Curr. Opin. Biotechnol.* **61**, 66–71 (2020).
211. Hanes, D. et al. The gastrointestinal and microbiome impact of a resistant starch blend from potato, banana, and apple fibers: A randomized clinical trial using smart caps. *Front. Nutr.* **9**, (2022).

212. Kadyan, S. et al. Resistant starches from dietary pulses modulate the gut metabolome in association with microbiome in a humanized murine model of ageing. *Sci. Rep.* **13**, 10566 (2023).
213. Maier, T. V. et al. Impact of Dietary Resistant Starch on the Human Gut Microbiome, Metaproteome, and Metabolome. *mBio* **8**, <https://doi.org/10.1128/mbio.01343-17> (2017).
214. Egan, M. et al. Cross-feeding by *Bifidobacterium breve* UCC2003 during co-cultivation with *Bifidobacterium bifidum* PRL2010 in a mucin-based medium. *BMC Microbiol.* **14**, 282 (2014).
215. Tailford, L. E., Crost, E. H., Kavanaugh, D. & Juge, N. Mucin glycan foraging in the human gut microbiome. *Front. Genet.* **6**, 81 (2015).
216. Turroni, F. et al. Genome analysis of *Bifidobacterium bifidum* PRL2010 reveals metabolic pathways for host-derived glycan foraging. *Proc. Natl. Acad. Sci.* **107**, 19514–19519 (2010).
217. Turroni, F., Milani, C., Van Sinderen, D. & Ventura, M. Genetic strategies for mucin metabolism in *Bifidobacterium bifidum* PRL2010: An example of possible human-microbe co-evolution. *Gut Microbes* **2**, 183–189 (2011).
218. Amaretti, A. et al. Profiling of Protein Degradation in Cultures of Human Gut Microbiota. *Front. Microbiol.* **10**, 2614 (2019).
219. Diether, N. E. & Willing, B. P. Microbial Fermentation of Dietary Protein: An Important Factor in Diet–Microbe–Host Interaction. *Microorganisms* **7**, 19 (2019).
220. Dodd, D. et al. A gut bacterial pathway metabolizes aromatic amino acids into nine circulating metabolites. *Nature* **551**, 648 (2017).
221. Jiang, J. et al. Strain-Specific Effects of *Bifidobacterium longum* on Hypercholesterolemic Rats and Potential Mechanisms. *Int. J. Mol. Sci.* **22**, 1305 (2021).
222. Wu, T. et al. Probiotics Interact With Lipids Metabolism and Affect Gut Health. *Front. Nutr.* **9**, 917043 (2022).
223. Kuziel, G. A. et al. Functional diversification of dietary plant small molecules by the gut microbiome. *Cell* **188**, 1967–1983.e22 (2025).
224. Rodríguez-Daza, M. C. et al. Polyphenol-Mediated Gut Microbiota Modulation: Toward Prebiotics and Further. *Front. Nutr.* **8**, 689456 (2021).
225. Holmes, Z. C. et al. Microbiota responses to different prebiotics are conserved within individuals and associated with habitual fiber intake. *Microbiome* **10**, 114 (2022).

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Author contributions

L.J.H. conceived the review, developed the conceptual framework, and contributed to early drafting and editing, as well as preparation of the final manuscript. D.K.J.S. prepared the initial draft sections, incorporated revisions, and contributed to the final draft. L.A. created all figures and edited the final draft. All authors approved the final version.

Competing interests

The authors declare no competing interests.

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