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Consensus statement

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The International Scientific Association for Probiotics and Prebiotics (ISAPP) consensus statement on the definition and scope of gut health

Maria L. Marco[1] ✉, Marla Cunningham[2], Stephan C. Bischoff[3], Gerard Clarke[4], Nathalie Delzenne[5], James D. Lewis[6], Marlies Meisel[7], Daniel Merenstein[8], Paul W. O'Toole[9], Heidi M. Staudacher[10], Hania Szajewska[11], Jerry M. Wells[12] & Eamonn M. M. Quigley[13]

Abstract

The term 'gut health' is increasingly used as a catch-all phrase by many stakeholders, including scientists, health-care professionals, industry and the general public, to describe a wide range of health-related concepts. Despite its widespread use, particularly in relation to studies on diet, fermented foods, biotics and the gut microbiome, it remains unclear what the term gut health means. Therefore, an expert panel was convened by the International Scientific Association for Probiotics and Prebiotics to address the current state of scientific and clinical knowledge on the physiology, manifestation, application and measurement of the concept of gut health. The panel evaluated the term in the context of the central role of the gastrointestinal tract in health and overall well-being and proposed a definition of gut health as "a state of normal gastrointestinal function without active gastrointestinal disease and gut-related symptoms that affect quality of life". The definition was developed mindful of the functional, subjective and extrinsic domains that contribute to gut health. In this Consensus Statement, clinically relevant and accessible metrics to assess these domains are reviewed and a comprehensive approach to gut health is proposed that is relevant to clinical practice as well as to studies of dietary and biotic interventions.

Sections

A full list of affiliations appears at the end of the paper. ✉e-mail: mmarco@ucdavis.edu

Key points

- A meaningful concept of gut health combines the individual's subjective experience of gastrointestinal activity with objective measures of gut function.
- The presence of a gastrointestinal disease does not preclude a state of gut health, which is possible during periods of pathological remission.
- Poor gut health can exist in the absence of symptoms, or in the absence of measurable abnormalities in function.
- Many measures of function currently lack sufficient validation of a normal range or correlate poorly with patient outcomes.
- Transient symptoms of gastrointestinal origin arising from physiological adaptations (for example, loose bowels with stress or constipation when travelling) should be distinguished from those that are more long-lasting and have a substantial effect on quality of life.
- Risk factors for, and determinants of, future gut health are incompletely understood at present; accordingly, and based on available evidence, the presence or absence of risk factors is not incorporated in the definition of gut health.

Introduction

'Gut health' is a term that has become part of the common lexicon to describe health in a broad sense. In marketing campaigns, foods and supplements often claim to support gut health (with or without scientific documentation), a vague concept that could be interpreted as encompassing any number of health-promoting outcomes. The term is also increasingly used in human and veterinary medicine. In the published scientific literature, the phrase 'gut health' was initially used in the late 1990s[1] and was then proposed in 2002 as a useful way to convey health benefits of prebiotics, such as inulin and oligofructose, to the general public[2]. There are now tens of thousands of papers indexed in PubMed that use the term, with the majority published within the past several years, underscoring the recent proliferation of the term. Unsurprisingly, the general public is also increasingly aware of the concept, although people's understanding might be influenced by the medium via which they are informed[3].

Although gut function is clearly integral to human and animal health, there are many unresolved issues relating to gut health; these include, for example: the difference between gut health and digestive health or gastrointestinal health; the overall importance of gut health to individuals who do not have gastrointestinal disease; how gut health should be measured; and whether gut health is modifiable. More specific aspects that remain poorly understood are, first, how current research on the gut microbiome and intestinal physiology, immunology and the gut–brain axis can advance our understanding of gut health, and second, how the development of a clear framework for gut health could inform research on interventions commonly targeted towards the gut in healthy populations, including diet, probiotics, prebiotics and other biotic substances.

To discuss these questions, develop a greater understanding of the term and ultimately arrive by consensus at a definition of gut health, the International Scientific Association for Probiotics and Prebiotics (ISAPP) convened a panel of clinical and scientific experts in gastroenterology, paediatrics, family medicine, nutrition, microbiology, immunology, neurobiology and physiology who met in September 2024 to explore the concept of gut health and develop a consensus definition. Additional goals were to explore functional and subjective domains of gut health and to provide a framework that can be applied in scientific, medical, industrial and regulatory communities on the appropriate use of the term gut health when studying interventions, including probiotics, prebiotics, fermented foods and related substances.

Methods

The consensus panel was organized under the auspices of ISAPP, which is a non-profit scientific organization governed by a volunteer academic board of directors. Although ISAPP receives annual funding from member companies, the activities of ISAPP are not directed by industry. The mission of ISAPP is to advance research in the field and to provide objective, science-based information on probiotics, prebiotics and related health topics. Necessary areas of scientific and clinical expertise for the panel were identified (gastrointestinal physiology, gut microbiology, intestinal cell biology, immunology, endocrinology and neurobiology) and experts were invited accordingly. To provide additional perspective, clinicians in the fields of primary care, gastroenterology, paediatrics and nutrition were included. An outline addressing each of the topics was developed, and a virtual meeting was held to discuss and confirm the proposed scope and key questions to be addressed. Each panellist was asked to prepare an expertise-specific perspective on gut health, including current research, importance, scope, conceptualization, and putative metrics and determinants. The panel met in London, UK, for a full-day workshop of presentations and discussion, culminating in the development of a definition on gut health. The definition was subsequently debated and refined in two online meetings and finalized in an online vote (all 13 panellists approved). Each panellist wrote relevant sections of the manuscript, and the lead authors assembled the combined draft for further editing, review and approval by all authors.

Existing definitions of gut health

The first definition of gut health was proposed in 2011 as "a state of physical and mental well-being in the absence of GI complaints that require the consultation of a doctor, in the absence of indications of or risks for bowel disease and in the absence of confirmed bowel disease"[4]. This definition aligned with the WHO's broader definition of health as being more than absence of disease[5]. The gut health definition acknowledged gut health as a complex concept, incorporating both the upper and lower gastrointestinal tract, and considering viewpoints of both the individual and the physician[4]. However, it was also acknowledged that the definition was based on exclusion and on mostly subjective standards. Accordingly, five broad features for gut health were proposed (digestion and absorption, gut microbiome, gut barrier, gut immunity and quality of life (QOL)), and available metrics for assessing these features were provided[4].

Over the next 10 years, the term gut health term appeared frequently in the titles of scientific publications. In 2021, gut health was conceptualized as "the absence of gastrointestinal symptoms (eg, abdominal pain, diarrhoea) and disease (eg, inflammatory bowel disease, colon cancer), as well as an absence of other unfavourable local conditions including increased intestinal permeability, mucosal inflammation, or deficiency (or even excess) of short-chain fatty acids"[6].

Among the many factors that might contribute to gut health, diet was singled out as a major driver based on the known effects of diet on metabolism and the gut microbiome. The latter has received considerable interest owing to the many reported associations between an altered microbiome and gastrointestinal and systemic diseases, as well as a recognition of the role of microbial metabolites in regulating epithelial and immune functions[7,8]. Accordingly, the concept of gut health was expanded to include the interface with the gut microbiome[9]. As the various factors and bidirectional relationships that contribute to gastrointestinal homeostasis are considered, the complexity of the term gut health becomes obvious, and is further complicated by the challenges intrinsic to any effort to define where health ends and disease begins.

Gut health consensus definition

To address the current state of the science and the need to provide a concise description, we define gut health as "a state of normal gastrointestinal function without active gastrointestinal disease and gut-related symptoms that affect quality of life". The term is intended to encompass the entirety of the gastrointestinal tract, including processes and functions of the mouth, pharynx, oesophagus, stomach, small intestine, large intestine, rectum and anus. Although the term 'gut health' is the one that is used most frequently, we concluded that it is synonymous with the term 'gastrointestinal health'. In addition, gut health includes the concept of 'digestive health', even though the latter might also be regarded as more limited, referring exclusively to the process of digestion.

Importantly, the absence of active disease, rather than disease itself, is specified in the definition. While an individual might have a diagnosis of, for example, coeliac disease or inflammatory bowel disease (IBD), this does not preclude the individual from experiencing gut health during periods of complete remission (clinical and pathological). The importance of both gastrointestinal function and gastrointestinal-related symptoms is explicit in the definition. Each of these components is explored in detail below, and core concepts that underpin the definition are summarized in the Key points.

Functional domains of gut health

The complexities of gut functions and their contribution to health can be best understood by their categorization into different domains (Fig. 1). Because these functions operate as an integrated system, attributing primacy to any one of them for a given symptom or disease state is far from simple. Given the centrality of these concepts and their component mechanisms in gut health research, key aspects of each domain are described below along with current metrics for their assessment (Table 1).

Digestive physiology

The various physiological processes that enable digestion of ingested food, assimilation of nutrients and elimination of waste materials are regarded as the primary functions of the gastrointestinal tract. Physiological functions such as secretion, motility, and blood and lymph flow should be viewed primarily as subserving the processes of digestion and absorption. Consequently, key outcomes in gut health, viewed through the prism of digestive physiology, are the maintenance of adequate nutritional status, water and electrolyte homeostasis, and the resulting effects on growth, development and bodily functions throughout all life stages. Among the many components of gastrointestinal physiology, two processes, secretion and motility, are major factors contributing to gut health whose disruption contributes to the development of gastrointestinal symptoms, maldigestion and malabsorption.

Secretion. To facilitate smooth transit of digesta, delivery of digestive enzymes and the assimilation of small molecules, approximately 7 l of fluid are actively secreted into the gut on a daily basis and highly efficient absorptive processes ensure the conservation of all but approximately 100 ml of this fluid[10]. Rates and mechanisms of fluid and electrolyte transport vary along the length of the gut and are influenced by the relative permeability of the gut barrier and transport processes at the different anatomical locations[11]. Secretions entering the gastrointestinal tract convey enzymes and other molecules that have an active role in digestion of the primary nutrients in the diet into metabolites that can be absorbed across the intestinal mucosa[12] (Fig. 1). Other constituents support lubrication, protect against acid-related injury, or exert antibacterial effects. While normal values and ranges for processes of digestion, absorption and secretion have been well documented[13–17], it should be emphasized that all exhibit considerable reserve capacity and there is also some redundancy (such as between salivary and pancreatic lipases). Accordingly, a healthy gut can be sustained despite a relative decline in digestion, absorption or secretion, and for some conditions, such as hypochlorhydria or carbohydrate intolerance, correlations with symptoms can be challenging to define or even absent[17,18]. Similarly, relatively substantial resections of the small bowel or colon can be tolerated without appreciable effects on overall health[18]. Direct measures of intestinal secretions are invasive and, therefore, not applicable to large populations. Indirect insights can be obtained by documenting diarrhoea (see the section 'Patient-reported symptoms: implications for gut health'), dehydration, malnutrition or malabsorption, as determined through diverse measurements including levels of albumin, essential vitamins and minerals in serum, and levels of water, fat or protein loss in stool (Table 1).

Motility. An intact enteric neuromuscular apparatus and the appropriate regulation of gut motor activity are fundamental servants of digestion, absorption and elimination. Direct and indirect measures of motility are widely available[19–21]. In the more accessible organs (the oesophagus and anorectum), manometry provides direct measures of intraluminal pressure[22,23]. For the stomach, small intestine and colon, less-direct assessments are provided by tests which measure gastric emptying, small-bowel transit and segmental or whole-colon transit, respectively[24] (Table 1). For both direct and indirect approaches, normal values and correlations with discrete clinical consequences are well documented, but there are limitations. For example, oesophageal manometric parameters that fall outside the normal range but do not satisfy criteria for well-defined disorders such as achalasia are relatively common but their clinical implications are largely unknown[25]. Furthermore, measures of transit, including gastric emptying rate and colon transit, are subject to considerable variability related to factors intrinsic to the test performed as well as the individual or population studied, resulting in a wide range of normality and thereby limiting their diagnostic value[26,27]. This should not come as a surprise, as transit reflects the summation of a variety of activities in various parts of the gastrointestinal tract. The shortcomings of these metrics are especially frustrating as many who have common gastrointestinal symptoms such as nausea, bloating, fullness and constipation believe that their symptoms emanate from a lack of movement or stagnation of some part or parts of the gastrointestinal tract[28].

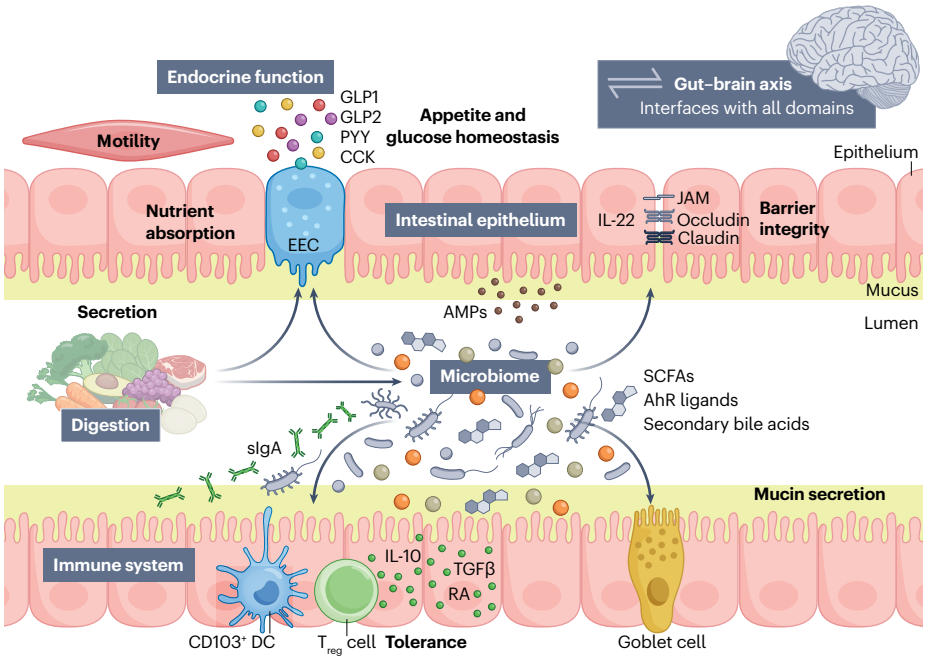

Fig. 1 | Key functional domains of gut health. Selected mechanisms whereby the domains of gut health interact to maintain homeostasis. Digestion: Dietary components are broken down by digestive enzymes and absorbed through the intestinal epithelium via specialized transporters. Microbiome: Microbial metabolites such as short-chain fatty acids (SCFAs), secondary bile acids, ligands for the aryl hydrocarbon receptor (AhR) and microbial macromolecules modulate barrier integrity, immune responses and mucin turnover. Gut barrier: Barrier integrity is maintained by tight junction proteins (for example, occludin, claudins and junctional adhesion molecules (JAMs)), which regulate paracellular permeability. Goblet cells produce mucin that forms a protective mucus layer, while secretion of antimicrobial peptides (AMPs), secretory IgA (sIgA) and the presence of cytokines such as IL-22 support epithelial defence and repair. Immunity: $CD103^+$ dendritic cells (DCs) promote tolerance by producing retinoic acid (RA) and transforming growth factor-β (TGFβ), which induce gut-homing $FOXP3^+$ peripheral regulatory T (T_{reg}) cells and further suppress immune activation by secreting IL-10 and TGFβ that are essential for epithelial barrier integrity and immune balance. Endocrine function: Products of the digestion of food and derived from microbial metabolism modulate gut hormone secretion (glucagon-like peptide 1 (GLP1) and GLP2, cholecystokinin (CCK) and peptide YY (PYY)) from enteroendocrine cells (EECs) and thereby affect gut functions involved in transit, metabolic regulation (glucose homeostasis) and communication with the central nervous system. Gut–brain axis: Two-way communication between the gut and brain involves signals from EECs, as well as the microbiome, immune system, metabolism and gut barrier. These interactions influence both digestive function and brain-related outcomes such as mood, behaviour and stress responses.

As is the case with other functional domains, the physiological processes that control digestion and absorption also interact with the other functional components that sustain homeostasis in the gut and beyond[29].

Gut microbiome

The gut microbiome has been identified in the past two decades as an important modulator of health. Evidence supporting this role was generated mainly by the application of culture-independent methodologies (reviewed previously[30,31]). High-throughput methodologies involving ribosomal RNA gene amplicon sequencing and metagenomic shotgun sequencing enabled the assembly of large databases of taxa and microbial genes associated (in most studies) with disease or with healthy controls[32,33]. Comparisons within and between studies established that many diseases are characterized by an altered gut microbiome composition and/or function. However, other factors, such as the age of the patient, geography and site of sampling, might confound observed associations. The structure and function of the gut microbiome changes radically with age, as exemplified by taxa such as *Bifidobacterium* that are dominant in infancy and youth and become rare in older individuals[34] being replaced by taxa such as *Ruminococcus*, *Coprobacillus*, *Odoribacter* and *Butyricimonas*[35]. Furthermore, these age–microbiome interactions differ by global geography, such that associations between microbiome uniqueness and healthy ageing are different in different continents[36]. Additionally, at present, most microbiome assessments focus on faeces, which predominantly reflect the luminal content of the colon and rectum, rather than the small intestine or the mucosa-adherent microbiome. Accordingly, disentangling causality remains challenging: the microbiome features that confer risk for health loss, to what extent the microbiome mediates that risk and to what degree observed shifts merely reflect disease responses remain unknown. This, in turn, has complicated the search for microbiome-directed therapeutics[37]. Because of the density and complexity of gut microbiome interactions with the host (Fig. 1), any attempt to define gut health necessarily requires consideration of how the gut microbiome is involved and what descriptors or quantitative indices might be usefully applied to it[9].

The biggest challenge in clarifying the role of the gut microbiome in gut health lies in the definition of a ‘healthy gut microbiome’ or, as more correctly expressed, ‘a health-associated gut microbiome’[38]. The microbiomes of healthy controls in both prospective and cross-sectional cohort studies differ widely (that is, there is a

Table 1 | Potential metrics of normal gastrointestinal function across six domains

Metric (sample or technique)	Clinical utility	Comments
Digestive physiology		
Secretions: salivary, gastric, biliary and intestinal	Direct measures too invasive for widespread application	Indirect measures such as stool weight, water content and markers of nutrition and/or absorption (for example, complete blood count, metabolic panel, faecal fat) more applicable (Table 2)
Secretions: pancreatic (faecal elastase)	Readily available marker of pancreatic exocrine sufficiency Normal ranges well established but non-pancreatic causes of abnormal results complicate the interpretation	A normal level (>200 µg/g of stool) is a good indicator of pancreatic exocrine function but diarrhoea regardless of cause can result in low levels and, thus, false-positive results for pancreatic insufficiency[194]
Gastric motor function	Tests of gastric emptying, although generally available, may involve some radiation exposure and need to be performed according to a validated protocol Not indicated for screening purposes	Nutrient drink test provides a measure of gastric accommodation or sensation
Small intestinal and colonic motor function Whole gut or colonic transit time (scintigraphy, capsule technologies, radio-opaque markers)	Direct measures not widely available	Indirect measures such as Bristol stool form scale or complete spontaneous bowel movements are useful surrogates for colonic transit and colorectal motor function
Gut microbiome		
Microbiome analysis (relative/absolute abundance (16S ribosomal RNA amplicon sequencing, metagenomics), indicator taxa, gene functions, metabolomics)	Lack of evidence for clinical utility of microbiome analysis for screening purposes Lack of consensus on what is normal	Screening for pathogens relevant when clinically indicated Multiple microbiome health index tools in development (Box 1)
SCFAs (faecal)	Despite links to nutrition and gut barrier function, SCFA measurement is not clinically useful	Faecal SCFA levels are a poor marker of production, and differential absorption rates confound measurement Beneficial SCFA effects on inflammation, barrier function and nutrition probably contribute to broad gut health benefits
Gut barrier		
Measurements of differential absorption, measured by urinary excretion rates, of sugars of different molecular sizes (typically, mannitol and lactulose) and at different times to reflect small intestinal or colonic permeability	Historical gold standard, requires prolonged urine collection and careful interpretation Putative normal values in healthy cohorts proposed[195]	Early (0–2 h after ingestion) urinary excretion reflects small intestinal permeability and excretion from 8 to 24 h reflects colonic permeability[196]
Faecal zonulin	Commercially available Faecal zonulin levels may be most indicative of permeability in obesity[197]	Faecal zonulin is more reliable than serum zonulin Commercial ELISAs may detect other zonulin family peptides Normal level ≤50 ng/ml
Plasma lipopolysaccharide-binding protein (ELISA)	Indirect measure of lipopolysaccharide and thus permeability and endotoxemia	Moderate test–retest reliability Well correlated with lactulose: mannitol ratio in adults with a healthy normal weight or with obesity[197]
Immune function		
CRP or high-sensitivity CRP (serum), erythrocyte sedimentation rate, white cell and platelet counts	Readily available in clinical practice as non-specific screening tools for whole-body inflammation Normal ranges well established	Non-specific measures of inflammation and/or infection regardless of location
Calprotectin (stool)	Widely available Lack of consensus on upper limit of normal	Marker of mucosal inflammation High levels very suggestive of inflammatory bowel disease[198]
Faecal lipocalin 2	Primarily a research tool and not used in clinical practice	Faecal lipocalin 2 levels reflect intestinal inflammation, making it a potential noninvasive biomarker for inflammatory bowel disease activity
Metabolism		
GLP1 (total or 7–36 amide) (blood) PYY (1–36 or 3–36) (blood)	Not widely available for clinical use Requires specific immunoassay and storage with a peptide hydrolase inhibitor	Post-oral glucose tolerance or post-meal test level of the active form reveals the capacity of L cells to secrete the active form of the peptides Values are lower in individuals with obesity

Table 1 (continued) | Potential metrics of normal gastrointestinal function across six domains

Metric (sample or technique)	Clinical utility	Comments
Gut–brain axis		
Cortisol awakening response (saliva)[199]	Accessible measure of stress response Normal ranges well established[199]	In healthy individuals, cortisol peaks approximately 30 min after waking Blunted response observed in disorders of gut–brain interaction
Perceived stress scale[200]	Readily available Scored into categories of stress severity Normal ranges well established[200]	Valid and reliable scale for measuring stress, although not diagnostic for stress disorders
Host and microbial tryptophan metabolites (stool and blood)	Normal ranges not yet available for all precursors and metabolites[201]	Multiple competing host and microbial pathways[202]
Gut–brain modules (in silico predictions from microbiome sequencing data)	Normal ranges not yet available	Indicates neuroactive potential of the gut microbiome but not validated in clinical setting[203,204]

CRP, C-reactive protein; ELISA, enzyme-linked immunosorbent assay; GLP1, glucagon-like peptide 1; PYY, peptide tyrosine-tyrosine; SCFA, short-chain fatty acid.

great deal of interindividual variability), and what is described as a healthy microbiome in one study can vary tremendously from that in another study, particularly when comparing cohorts across very different environments[39]. At the same time, there is a large degree of overlap between gut microbiome alterations found in different non-communicable diseases[40]. The presence of an altered microbiome is often referred to as a state of 'dysbiosis', which is a problematic term[41] because an altered microbiome in one disease context might be linked with health in another population cohort. Furthermore, most of the variation in the microbiome between healthy individuals is unexplained[38], even within single-country cohorts[33,42], further confounding the definition of a health-associated gut microbiome. A greater understanding of genomic variation within gut commensal microorganisms has shown that clades within taxa that all share the same species label can have strikingly different properties and health associations[43–45]. Simply identifying taxa commonly linked to health has therefore proven difficult[46–48]. However, numerous approaches are emerging based on taxa-dependent and taxa-independent indices, which are anticipated to resolve or at least clarify core microbiome functions and relationships to health (Box 1). At present, the analysis of an individual gut microbiome cannot provide a meaningful index of health or a prediction of disease presence or risk[49], meaning that metrics for this domain lack utility in clinical practice (Table 1).

Intestinal epithelium

The intestinal epithelium has a key role in barrier and endocrine functions, selective permeability, nutrient absorption and mucosal immunity (Fig. 1), and its dysfunction ('leaky gut') has been widely, and at times inappropriately, implicated in a wide range of symptoms and diseases. The epithelium includes diverse cell types and features epithelial, immune, goblet and enteroendocrine cells (EECs) whose dysfunctions have been associated with numerous gastrointestinal infections and chronic diseases[50,51]. Through hormones released by its EECs (alongside other mechanisms), the epithelium has an effect on diseases beyond the gastrointestinal tract, such as obesity and diabetes[52].

Collectively, the epithelium provides a physical and chemical barrier that facilitates the selective absorption of diverse nutrients and other molecules into the body[53]. Physical barriers include secreted mucin, which expands up to 1,000-fold in volume forming a gel-like network structure to physically entrap bacteria and prevent them from reaching the epithelial cell surface[54]. Another is provided by the selective maintenance of cell-to-cell contact by tight junctions comprising proteins, including occludin and members of the claudin family of transmembrane proteins, that regulate permeability of the paracellular space to ions and small molecules (<8 Å)[55]. The barrier can also permit passage of larger macromolecules (up to ~100 Å), although this 'leak pathway' is less well defined and its regulation incompletely understood[50]. This term 'leak pathway' is not to be confused with the controversial term 'leaky gut'. The epithelium also provides chemical barriers such as antimicrobial peptides (AMPs), including α-defensins and β-defensins, released by enterocytes and Paneth cells, respectively[56], which serve to fend off pathogens, maintain microbial balance and support intestinal barrier integrity. Other AMPs include lysozyme, phospholipase A2 and regenerating islet-derived protein 3α (REG3α)[57], as well as a highly glycosylated glycosylphosphatidylinositol-anchored membrane protein (LYPD8) that binds to flagellin of Gram-negative bacteria to prevent transit of flagellated bacteria through colonic mucus[58].

The interaction of the epithelial barrier with the mucosal immune system is crucial to providing a measured defensive and inflammatory response to threats presented by pathogens and toxins[59]. This dynamic host interaction can also shape the gut microbiome through production of antimicrobials, and, conversely, the gut microbiome regulates the intestinal barrier by production of bioactive metabolites. Immune cells in the intestine have a key role in regulating expression of mucin, tight junction proteins and antimicrobials to maintain homoeostasis with the microbiome[7,60,61]. Inflammation can markedly compromise the quality of mucin and also activates the tight junction leak pathway through activation of myosin light chain kinase, leading to cytoskeletal contraction and weakening of tight junctions[62].

Several methodologies can be employed to assess intestinal barrier function in humans (Table 1). Common research methods include measuring transepithelial resistance in biopsy samples mounted in Ussing chambers and direct in vivo visualization of leakage from the epithelium utilizing confocal laser endomicroscopy. More relevant to current clinical practice are metrics quantifying differential movement of molecules (for example, lactulose versus mannitol) across the intestinal epithelium and assessing noninvasive markers such as levels of lipopolysaccharide-binding protein, soluble CD14, syndecan 1, and intestinal-type fatty acid-binding protein in blood or zonulin and αI antitrypsin in stool[63–66]. However, it is important to note that these approaches measure different attributes of epithelial barrier function. For example, implications of permeability assays used in humans will depend on probe size, absorption mechanism, site and distribution kinetics[65].

A misinterpretation of these studies and a failure to recognize that intestinal permeability is a dynamically regulated process, varying through the day in response to meals, stress, exercise and other stimuli, has led to the profusion of the concept of leaky gut in the media and medical literature. All guts are 'leaky'; it is only when the selective permeability (or 'leakiness') that characterizes the normal epithelium is compromised that it can potentially lead to disease. For many of the pathologies that a leaky gut has been proposed to cause, evidence is scarce or non-existent[65]. Studies comparing barrier function in health and a disease state must be performed in similar experimental conditions, with strict adherence to the study protocol[67] and interpreted cautiously based on known limitations of the tests applied and what exactly they measure.

Immune system

The gut-associated lymphoid tissue (GALT) is the primary immune interface with dietary and microbial antigens, playing a vital role in immune regulation. This intricate cellular network is crucial for maintaining immune homeostasis and preventing pathological inflammation while ensuring effective responses to pathogen or toxin incursion.

Tolerance to harmless dietary and microbial antigens is essential for maintaining gut health. The default immune response to these antigens involves both local and systemic unresponsiveness, an essential physiological process in the small intestine known as oral tolerance[68,69]. Disruptions in oral tolerance can have serious pathological consequences and promote the development of food allergies, coeliac disease and IBD[70–72]. The key cellular mediators that maintain oral tolerance are peripheral regulatory T (T_{reg}) cells and $CD103^+$ dendritic cells[69,70]. Gut microbiome-derived metabolites, such as short-chain fatty acids (SCFAs) and secondary bile acids, promote tolerogenic functions of mucosal peripheral T_{reg} cells and dendritic cells[72,73] (Fig. 1).

Another primary function of the GALT is to detect and eliminate pathogens, such as *Salmonella* and norovirus. To mount a response to pathogens, immune cells, including macrophages and mucosal antigen-presenting cells, detect microbial threats through pattern recognition receptors and then initiate protective responses. Furthermore, other components of the immune system including secretory IgA (sIgA) block pathogen adhesion[68], and effector T cells clear infections to maintain mucosal integrity[71,74]. Notably, inflammation triggered by enteric pathogens can shift the immune response from tolerance to a T helper cell-driven inflammatory state, leading to loss of oral tolerance[71,72,75].

Several metrics to assess gut immune homeostasis and detect inflammation have been established (Table 1). The current gold standard is to measure architectural changes and inflammation of gut tissue via histological analysis, necessarily an invasive approach[76,77]. Serum or plasma and stool markers have also been used as non-specific, noninvasive indicators of intestinal inflammation, including white cell and platelet counts, erythrocyte sedimentation rate, and C-reactive protein (CRP)

Box 1 | Approaches to define a health-associated microbiome

Microbiome profiling produces lists of taxa that can be examined for compositions or species linked to an ostensibly healthy state. Another approach is to identify a core microbiome. Combining the microbiome response to a fibre intervention in type 2 diabetes mellitus with 26 case–control datasets from 15 other diseases identified two groups of core taxa, one associated with fermentation and short-chain fatty acid production, the other with virulence and antibiotic resistance[205]. Machine learning models based on these guilds successfully identified cases and controls when tested for multiple diseases and successfully predicted outcomes of cancer immunotherapy. Others have described 'enterosignatures', five co-abundance groups of microbial species whose weighted abundance correlate with host health[206]. The HACK index is based on taxon prevalence or community association in individuals without disease with longitudinal stability, and correlation with host health, facilitating comparison of microbiomes for their ability to promote gut health[207]. A theoretical framework was proposed for scoring the health association of a given microbiome based on functional scoring of symbiotic innovations for delineating health or disease[208]. The approach ignores taxonomic composition and relies instead on scoring a microbiome for genetic loci in pathways that constitute evolutionary innovation of symbiosis between humans and gut microbiotas[208].

Summary statistics are also convenient descriptors and comparators, and microbiome α-diversity has been adapted or accidentally co-opted as a proxy for health association[9,209–212]. Microbiome uniqueness has been suggested as a convenient single-index marker for unhealthy ageing[213], and Kendall Uniqueness has been suggested as an alternative index that correlates well with maintenance of health-associated commensals and slow gain of pathobionts[36]. The gut microbiome wellness index was developed by machine learning analysis of over 8,000 metagenomes and showed 80% accuracy in separating healthy (no disease) from non-healthy (with disease) individuals[214]. Another gut microbiota well-being index based on microbiota development and health data in a cohort of nearly 1,000 infants successfully predicted general health over the first 5 years of infant life[215]. The current rate of publication of high quality metagenomic datasets from well phenotyped individuals, coupled with the extraordinary analytical power of artificial intelligence, suggests that further testing and refinement of these and other summary statistics and indices will provide robust indicators of the ability of a given microbiome to be associated with health, provided the input study data are well designed. An intriguing microbiome summary statistic that merits further investigation is low gene count (LGC), which was first identified as a predictor of non-responsiveness to therapeutic intervention in individuals with obesity[216], but is also a feature of cirrhosis[217] and non-responsiveness to immunotherapy[218]. LGC is likely to be incorporated into more complex models rather than represent a stand-alone index for microbiome–health associations.

Mindful of the many methodological factors that complicate and confound any attempt to study the microbiome, Joos and colleagues proposed a more rigorous framework for designing studies aiming to identify a health-associated microbiome[191]. Inspired by epidemiological methods, their approach involves an integrated model that combines defining health, reviewing health determinants, cross-cohort comparisons, biomarker identification and follow-up of large cohorts. Importantly, the approach also advocates longitudinal studies, without exclusion criteria, in which the definition of health emerges over time[208].

levels in serum or plasma, and calprotectin and lactoferrin quantities in stool. The latter have emerged as sensitive measures for the detection of IBD[78–80]. Notably, there is no validated noninvasive marker to distinguish acute from chronic inflammation, and histological examination of biopsy samples is therefore required when clinically indicated.

Emerging metrics of gut immune status include local and/or peripheral immunophenotyping to define changes in specific immune cell populations such as tolerogenic T_{reg} cells or pro-inflammatory cells[81,82] and assays for the aryl hydrocarbon receptor, a protein that regulates gene expression and is involved in the immune response and tissue homeostasis[83]. These approaches are not yet available in routine clinical practice.

Gut endocrine function

Gut hormones have a central role in gastrointestinal homeostasis, integrating inputs from the gut lumen with peripheral organs, including the central nervous system (CNS). The results of these coordinated neuroendocrine responses are exemplified by how the gastrointestinal tract reacts to meal ingestion. Messaging to the CNS elicits taste and generates sensations such as pleasure and satiety. Together, these neurohumoral responses generate a normal and enjoyable meal experience. Conversely, disruption of these circuits can lead to symptoms such as early satiety, uncomfortable fullness, nausea and even pain in relation to food ingestion. The disruption of such circuits can also promote overeating, obesity and related cardiometabolic diseases[52,84].

EECs are essential to this response, comprise ~1% of all epithelial cells in the gastrointestinal tract and synthesize and secrete approximately 20 active peptides that regulate key intestinal and systemic functions[85]. A population of EECs, known as neuropod cells, facilitate rapid communication with the enteric nervous system (ENS) and, via the vagus nerve, to the CNS through paracrine effects as well as synaptic connections[86]. Ghrelin, secreted by EECs in the stomach, is an orexigenic (appetite stimulating) peptide, and cholecystokinin primarily secreted from the proximal small intestine by I cells in response to fat and protein promotes the release of bile into the duodenum, inhibits gastric emptying, and stimulates exocrine pancreatic and gastric acid secretion[87]. L cells are a subtype of EECs, which secrete peptides such as glucagon-like peptide 1 (GLP1), GLP2 and peptide tyrosine-tyrosine (PYY)[88,89] (Fig. 1). While GLP1 directly stimulates intestinal motility, it acts in conjunction with PYY to modify efferent signalling to inhibit gastric emptying and reduce nutrient availability[90]. In addition, GLP1 and glucose-dependent insulinotropic peptide (from enteroendocrine subtype K cells) act as incretins, meaning that they promote insulin release by β-cells in the pancreas, thereby decreasing blood sugar levels[91]. GLP2 acts locally to promote intestinal regeneration and repair the epithelial barrier via the G protein-coupled receptor GLP2R[92].

The production of these hormones in the upper part of the gut is stimulated by the final products of host digestive processes, whereas metabolites derived from gut microbial fermentation drive their secretion in the colon[93]. SCFAs such as butyrate or propionate, produced during fermentation of carbohydrates and dietary fibre, as well as other microbially-derived metabolites such as indoles, endocannabinoids and secondary bile acids, can bind to specific receptors on L cells and thereby promote the release of gut hormones, including GLP1, GLP2 and PYY[94] (Fig. 1).

An assessment of gut endocrine function requires blood sampling and adequate sample preparation[92] (Table 1). For example, the active form of GLP1 (GLP1(7–36) amide) in the blood is rapidly cleaved into an inactive form by the activity of dipeptidyl peptidase IV[95]. Furthermore, the levels of several gut peptides are influenced by nutritional status (that is, fasted versus fed state). For these reasons and pending the definition of their implications in diagnosis and management of disease, measures of gut hormones have not achieved a role in everyday clinical practice.

Gut–brain axis

Encompassing enteric, autonomic and central components, the gut–brain axis integrates signals between the gut and brain and influences all domains of gastrointestinal function (Fig. 1). The role of this axis has long been appreciated in gut health and disease[96], with the gut microbiome now recognized as another key node of the gut–brain connection[97] (Box 2).

The CNS influences motor, sensory, autonomic and secretory aspects of the gastrointestinal tract, integrates interoceptive

Box 2 | Pillars of the microbiome–gut–brain axis

The microbiome–gut–brain axis includes the central nervous system (CNS), the sympathetic and parasympathetic limbs of the autonomic nervous system (ANS), the enteric nervous system (ENS), the hypothalamic–pituitary–adrenal axis, the immune system and the gut microbiome. Gut–brain signalling is organized around intrinsic and extrinsic neuronal cell bodies in the gut that interact with the gut musculature and with epithelial and immune cells to monitor and modulate the luminal microbiome and immune states[219]. Representation of information from the gastrointestinal tract in the brain involves complex interactions among affective, cognitive and sensory processes[98]. Top-down regulation of gut health is facilitated by descending pathways from the brain that travel via the ventral, ventrolateral and dorsolateral spinal cord[220].

Composed of the largest and most diverse collection of neurons outside the CNS, the ENS is often referred to as 'second brain' and is independently capable of integrating signals from other organs and multiple cell types in the gastrointestinal tract to fulfil most baseline functions and responses. Coordination of moment-to-moment aspects of secretory and motor activities by the ENS also occurs in the absence of input from the CNS[219]. Innervating the ENS is the vagus nerve, the main component of the parasympathetic limb of the ANS. The vagus nerve comprises a mixture of afferent sensory and efferent motor nerve fibres connecting the medulla oblongata in the brainstem to the gut. Vagal sensory neurons monitor gastrointestinal mechanosensory, chemosensory, inflammatory and microbial outputs, translating these stimuli into neural signals that both influence local gut function and inform the brain about the constantly fluctuating conditions within the gastrointestinal tract and the status of gut health[221]. Functional implications associated with vagus-mediated signalling extend beyond gut function and immune responses to mood, emotion, reward and cognitive function[222].

information from the gut and returns responses, thus mediating the actions and reactions necessary to support gut and brain health[98]. Representations of visceral sensation, discomfort and pain in paralimbic and limbic structures such as the anterior cingulate cortex provide an emotional context to visceral sensation and pain. Neural relays from the gut governing nausea and hunger tap into CNS subcircuits important for multiple aspects of behaviour[99]. A neural gut–brain circuit for reward has been identified[100], while it has also been proposed that neuropods recruit vagal neurons in a relay circuit connecting the intestinal lumen to the brainstem[101]. Abnormal processing within the reciprocal relays between the gut and CNS can amplify sensory signals including those associated with chronic pain, anxiety and depression[97]. It is noteworthy that anxiety disorders and depression are commonly associated with gastrointestinal symptoms[102].

Stress is a trigger for gut symptoms and a risk factor for disorders of gut–brain interaction (DGBI), previously termed functional gastrointestinal disorders. Physiological consequences of stress initially perceived by the CNS often disrupt gut health, with individual outcomes depending on the nature, duration and type of exposure[103]. Early life stress is an important determinant of gut health in adulthood, where the resultant adult phenotype can vary from resilience to undue susceptibility to symptoms such as abdominal pain[104]. Chronic psychological stress in adulthood is also associated with inflammation and dysmotility relayed via the ENS[105], while stress-sensitive neural circuits facilitate modifications to the gut microbiome[106]. Further, bacteria-derived tryptamine, increased by acute stress[107], can act as a ligand for 5-hyroxytryptamine 4 receptor (5-HT_4) expressed in the gut musculature and epithelium modifying secretion and motility[108,109]. Microbial priming of the hypothalamic–pituitary–adrenal axis highlights the reciprocal nature of this relationship[110–113].

The complex architecture of the microbiome–gut–brain axis has led to numerous metrics that can be viewed as putative biomarkers of gut health (Table 1). These metrics include physiological (for example, stress hormone levels, microbial metabolites, measures of barrier function and immune parameters) and psychological readouts (for example, perceived stress). They have mostly been employed in pathological contexts to monitor responses to therapeutic interventions or in research settings, rather than as validated indicators of gut health per se. It is notable that reliable biomarkers for either DGBI or mental health disorders, both of which rely on symptom-based diagnoses in the absence of 'red flag' indicators of overt pathology[114,115], remain elusive.

Patient-reported symptoms: implications for gut health

Gut-related symptoms are a critical component of our definition of gut health, and are closely associated with the conceptualization of gut health in the mind of the general public[3]. Such gut-related symptoms, or symptoms that are assumed to originate from the gut, are extremely common worldwide[116]. In a study among adults in the Netherlands, the prevalence of gut symptoms was 26%, with bloating, borborygmi (rumbling) and flatulence being the most common[117]. A similar survey in the USA found that 14% of adults had experienced bloating within the previous 7 days[118]. In a random sample of the Swedish population, 27% reported heartburn and 22% acid regurgitation[119] and a survey of 53,046 Danish blood donors found that 68% had experienced at least one of 13 gastrointestinal symptoms in the previous 4 weeks, with bloating, abdominal rumbling and abdominal pain being the most frequently reported[120]. The challenge is therefore to determine when the presence of gut symptoms equates to a loss of gut health. Before we can address this question, some important principles need to be recognized:

- In interpreting sensations originating from the gut, the threshold at which such sensations arouse concern and become 'symptomatic' is subject to considerable variation and is undoubtedly influenced by many personal, environmental, psychosocial and cultural factors. Stool frequency, for example, varies considerably based on habitual diet and what would be interpreted as abnormal in one society might well be regarded as normal in another[121,122].
- Certain symptoms arise in specific contexts. Symptoms related to food consumption are common, and may be occasional, featuring what the lay person refers to as indigestion and physicians term gastroesophageal reflux or dyspepsia[123,124]. It is also well recognized that many people will experience transient changes in bowel habits in relation to a change in diet or situation such as the development of constipation when travelling. In addition, both stool frequency and form can vary through the phases of the menstrual cycle, along with symptoms such as bloating[125,126].
- That gut dysfunction and/or pathology often correlate poorly with symptoms is exemplified by several scenarios. At one end of the spectrum lies the patient with IBD who has objective evidence of active inflammation and reports no symptoms, and at the other end is the very symptomatic patient with irritable bowel syndrome (IBS) with no demonstrable pathology or objective markers of gut dysfunction.
- Gut-related symptoms can manifest outside the gastrointestinal tract if a causal link to the gut is established or at least suspected. For example, neuropsychiatric symptoms, such as headaches, dizziness, light-headedness or faintness, could be gut related if they occur in the postprandial period, in relation to other gut functions or in parallel with gut symptoms, such as pain.
- Mention must also be made of the challenges of interpreting symptoms in infants and children. Here one relies on input from a parent or care-giver and their interpretation of changes in behaviour, feeding or bowel movements. For these reasons, our definition of gut health might require modification in these age groups.

When are gut symptoms 'significant'? Occasional gut-related symptoms, which almost all individuals experience from time to time, can be differentiated from those linked to ill health by paying attention to symptom frequency, severity and duration[120], and above all to their effect on daily living as measured by the need to seek medical care or take a medication, as well as bothersomeness and/or deterioration in QOL. The majority of classic gut symptoms such as abdominal pain, constipation, diarrhoea, bloating, nausea, vomiting and heartburn can be assessed by validated symptom-based instruments[127,128], and their effect on QOL by disorder-specific and validated health-related QOL assessment instruments[129]. Indeed, bothersomeness and effect on QOL have emerged as pivotal, given that they reflect the real effect of a symptom or symptoms[116,119,130,131]. For this reason, the definition of gut health proposed specifies "gut-related symptoms that affect quality of life".

For heartburn and some other presumed upper gut symptoms a symptom frequency of at least once a week is regarded as bothersome and has been linked to QOL[132,133]. In relation to other upper gastrointestinal symptoms, efforts to provide objective measures of the ability to accommodate a meal without unpleasant sensations have included invasive tests of gastric accommodation and the much more acceptable nutrient challenge tests. The latter involve the use of a number of drinks

and drinking protocols, with the slow nutrient drink test emerging as the most reproducible and clinically meaningful[134]; however, none has achieved widespread use in clinical practice.

For changes in bowel habits the duration of symptoms is critical, with acute diarrhoea (such as diarrhoea with an infectious aetiology) defined as lasting no longer than 14 days[135] and occasional constipation as an intermittent or occasional symptomatic alteration in bowel habit that may last for a few days or a few weeks[136]. Additional symptom instruments have proven very helpful in the interpretation of bowel habits. The former preoccupation with stool frequency as an indicator of diarrhoea or constipation has been supplanted by the Bristol stool form scale (BSFS), which provides readily accessible and translatable descriptors, in pictogram format, of stool form, ranging from hard constipated stools (BSFS 1) to watery diarrhoea (BSFS 7), with normality in Western populations lying between BSFS 3 and 5 (ref. 137). Accordingly, definitions of functional diarrhoea and constipation now include passing loose or watery (BSFS 6 or 7) or lumpy or hard stools (BSFS 1 or 2) more than 25% of the time, respectively[123]. Furthermore, BSFS correlates with intestinal transit[137], thereby providing a simple, accessible metric of gastrointestinal motility. Recognizing that other symptoms contribute to an individual's experience of constipation, straining, a sensation of incomplete evacuation, sensation of anorectal obstruction or blockage or recourse to manual manoeuvres to facilitate defaecation have been added to the definition, and become syndromic if present more than 25% of the time[133]. To encapsulate these various sensations related to bowel action, the concept of a complete spontaneous bowel movement (CSBM) emerged to describe a bowel movement that does not require stimulation by a laxative, suppository, enema or other agent, and that is perceived by the individual as complete and satisfactory. CSBM has been adopted as a primary end point in clinical trials in constipation-related disorders[138,139], with the normal range for CSBMs lying between three and 21 per week.

To define a DGBI, such as IBS, functional dyspepsia, chronic idiopathic constipation or functional bloating, a component of chronicity (that is, symptoms recurring over at least 3 months) is included by the Rome Foundation in the criteria that have been developed to define these disorders[133]. According to Rome IV criteria, the occurrence of bothersome postprandial fullness, early satiation and belching three or more times per week defines the presence of functional dyspepsia and the occurrence of bloating and/or distension at least 1 day per week defines functional bloating[133]. While any one or a combination of meal-related symptoms might be harbingers of pathology such as peptic ulcer disease or gastric cancer, criteria for the definition of DGBI assume that these entities and other organic diseases have been excluded by appropriate investigation. The frequent association of DGBIs, such as IBS, with systemic and somatic symptoms such as headache, fatigue, migraine and fibromyalgia further exemplifies the broader context in which gut health might be viewed[140]. Table 2 summarizes symptoms and clinical features consistent with gut health.

Table 2 | Clinical features associated with gut health in clinical practice

Health area	Patient presentation
Bowel function	Stool frequency typically ranging from three per day and three per week Having complete spontaneous bowel movements (3 to 21 per week) Stool consistency within the normal range on the Bristol stool form scale (types 3–5)
Eating and satiety	Ability to eat a normal sized meal without discomfort and with a feeling of pleasant satiety Appropriate hunger and satiety responses
Gastrointestinal symptoms	Symptoms such as heartburn, acid regurgitation, belching, burping, bloating, borborygmi, flatulence, abdominal pain or discomfort occur at a frequency that is regarded as normal for age, dietary habit and culture Constipation, diarrhoea, nausea and vomiting are occasional, resolve spontaneously and are explained by dietary indiscretion, travel, stress, medications or other situational issues
Nutritional status and metabolism	Adequate nutritional status Water and electrolyte homeostasis
Growth and development	Age-appropriate growth and development (in children) Body weight appropriate for age and height
Systemic health	Absence of gut-related inflammation Healthy mood and stress responses Absence of health-related anxiety about gastrointestinal symptoms

Dietary determinants of gut health

A comprehensive concept of gut health includes not only functions and subjective manifestations, but also the factors influencing them (Fig. 2). Diet has profound effects on gut health and its influence is mediated by microbiome-dependent and microbiome-independent pathways. A detailed review of the evidence for the effect of specific foods and individual nutrients, food groups and dietary patterns on gut health is beyond the scope of this article; instead, some examples are provided.

At the level of single dietary components, dietary fibre is an important modulator of gut health. There is epidemiological evidence of positive associations between fibre intake and stool frequency[141] and protective effects on the risk for diverticulitis[142] and colorectal cancer[143]. Fibre supplementation can improve symptoms of constipation[144] and IBS[145]. Moreover, a fibre-rich diet might restore gut barrier function[146] and microbiome homeostasis[147]. Accordingly, recommendations for daily intake of fibre have been developed and could be interpreted as a strategy to promote gut health. By comparison, fat intake is commonly implicated by patients as exacerbating their gastrointestinal symptoms. For individuals with functional dyspepsia[148] and IBS[149], upper and lower gastrointestinal symptoms, respectively, are exacerbated by high-fat meals. Based on preclinical studies[150], other dietary components, such as emulsifiers, have been proposed to exert negative effects on the microbiome and the gut barrier. Implications of these findings for risk of human disease continue to be explored[151–153].

At the level of individual food groups, excessive intake of meat and meat products has been associated with increased risk of colorectal cancer[154–156]; however, the strength of this evidence has been questioned[157]. This controversy illustrates the potential for bias in observational studies of diet and health outcomes. Appropriate adjustment is needed for confounders that are present in meat, meat products or meat-containing meals that might also influence gut health (for example, food additives, fat) and for food items that might be inadvertently or preferentially restricted (for example, fish, grains, fibre, fruits and vegetables). Such adjustments are exceedingly difficult to perform. Additionally, there is a risk of bias in retrospective studies resulting from inaccurate recall and dietary changes made by patients in response to symptoms.

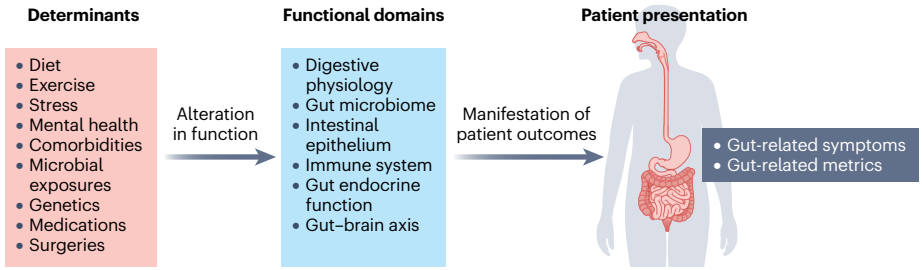

Fig. 2 | A comprehensive concept of gut health. Gut health is a complex, multicomponent concept that is a composite of functional contributions to host health and the subjective experience of the individual, influenced by multiple intrinsic factors and environmental exposures, past and present. Determinants of gut health include intrinsic host factors (such as genetics, immune function and comorbidities) as well as the broader exposome (including diet, stress, medications and environmental exposures). Together, these determinants affect the six key physiological domains, resulting in the patient presentation evaluated by gut-related symptoms.

Dietary patterns are defined as the quantities, proportions and variety of combinations of foods and drinks consumed. A change in dietary pattern could plausibly have considerable implications for gut health. Mediterranean and plant-based diets, both rich in polyphenols and fibre, are associated with microbial communities enriched in fibre-degrading microorganisms[158] and lower circulating levels of inflammation-related molecules including trimethylamine *N*-oxide[159], IL-6 and CRP[160]. These responses might reduce risk for IBD[161] and colorectal cancer[162]. To date, clinical trials of a Mediterranean diet in the prevention or treatment of gastrointestinal disease have been limited[163]. Here again complexities arise as some dietary patterns can have differential effects across gut health domains. For example, a low FODMAP (fermentable oligosaccharides, disaccharides, monosaccharides and polyols) diet, restricted in fermentable carbohydrates, has clear benefits for symptoms in IBS[164], but leads to reductions in *Bifidobacterium*[165], microorganisms that are considered to be beneficial in the gastrointestinal tract.

Despite these general relationships between diet and gut health, responses to dietary manipulation are highly individualized. A prime example is the interindividual variability to extremely controlled dietary interventions[166,167]. In this regard, habitual diet might be important in driving the unique gut health responses to dietary interventions. For example, a higher background intake of dietary fibre has been associated with a magnified bifidogenic response to fibre supplementation in healthy individuals compared with those with lower fibre intakes[168,169]. Predictors of symptom responses to diets in gastrointestinal disease have been evaluated but results to date remain exploratory at best[170]. Specific clinical phenotypes and baseline microbiome profiles have been identified as potential predictors of response to a low FODMAP diet[170], but study populations have been small and findings inconsistent.

Other determinants of gut health

Although studied less extensively than diet, many other factors can influence gut health, including genetic heritability, early life exposures, medications, stress, exercise, smoking and other lifestyle and environmental exposures as well as disease[40] (Fig. 2). Smoking is associated with detrimental shifts in the oral and colonic microbiome and can influence gastrointestinal disease pathogenesis[171].Exercise is associated with a more diverse microbiome[172] and might be beneficial for gut disorders such as constipation[173] and IBS[174]. Exercise has also been shown to accelerate gastric emptying and, in some circumstances, lower the risk of colon cancer[175,176]. In turn, gut health might influence lifestyle behaviour and thereby affect health in general. For example, preclinical data suggest that particular gut microbiota patterns can affect CNS areas that govern exercise behaviour[177]. Bacterial fatty acid amides stimulate the endocannabinoid receptor CB1 of the ENS, which increases neuronal activity during exercise. Activation of sensory neurons in the gut enhances dopamine signalling in the striatum, thereby increasing exercise performance[177]. Such mechanisms might suggest feedforward loops, whereby the determinants interact bidirectionally in the promotion or diminution of gut health. Research remains in the early stages for many determinants, and there are many priorities for further study.

Gut health in research

Dietary intervention trials increasingly refer to gut health or improvement in gut health as a hypothesis to be tested or inferred as an outcome to be evaluated. Similarly, gut health has also been the subject of numerous trials with biotics (encompassing probiotics, prebiotics, synbiotics and postbiotics) and fermented foods. Initially, prebiotics and probiotics, the most studied biotics, focused on gut-specific claims[178–180] but the goals have expanded to health end points beyond the gastrointestinal tract[181]. A wide range of end points are being studied under the umbrella of gut health, ranging from effects of diets on the microbiome of healthy individuals[182,183] to clinical benefits for patients with chronic disease[184,185]. Some diet interventions in these trials can even be labelled in such a way that they imply benefits for gut health (for example, 'gut-focused diet'[186] or 'healthy gut diet'[187]).

Major factors that limit the design and interpretation of these studies are the absence of a standardized definition of gut health and the accuracy and reproducibility of metrics with which to evaluate it. For example, one study might designate gut health solely based on changes to the gut microbiome, whereas another defines gut health by a reduction in constipation. Furthermore, the heterogeneous nature of study end points makes synthesis of current literature challenging. The availability of an agreed-upon definition and framework for gut health provides an opportunity for researchers to more deliberately target specific components of gut health, with more consistent and accepted study end points and validated measures. In the discussion of the various functional domains that contribute to gut health, we have attempted to highlight areas of importance that are potential targets for diagnostic testing and therapeutic intervention. More fundamental research identifying biomarkers for gut health and

developing tests to quantify them is needed. By clearly defining the target of an intervention and its scientific basis (be it microbiome, gut barrier and so on), we will arrive at a more precise approach to gut health research and accordingly provide clarity in communications about interventions to clinicians, regulators, industry and the general public alike.

Gut health in clinical practice

For the medical practitioner, it is essential to be able to distinguish abnormal gut health from normal variations in signs and symptoms. This is largely based on assessment of patient-reported symptoms and appropriate implementation of diagnostic testing in response to reported symptoms. In most situations, outcomes and assessments that are relevant to the patient assume priority over disease-oriented or biomarker-oriented outcomes[188]. Thus, a definition of gut health that emphasizes function and QOL, rather than stringent testing criteria, should be relevant and impactful. A concept of gut health that considers the health of the whole person and includes an emphasis on nutrition and lifestyle will resonate with primary care clinicians who are dedicated to caring for the whole person rather than a discrete diagnosis. Although the practice of gastroenterology should, by definition, be dedicated to restoring or maintaining gut health, a formal definition of gut health has been elusive among gastroenterologists. Traditionally, the focus of the gastroenterologist has been on the detection and management of gastrointestinal disease. While some of the tools in the gastroenterologist's armamentarium, such as imaging and endoscopy, might well provide indicators of dysfunction in one or more of the domains of gut health (such as motility or immune function) described above, other approaches (Table 1) may be required to provide a more complete and in-depth assessment of gut health.

Furthermore, as exemplified by the paucity of formal or case-based education in nutrition in a gastroenterologist's training, the specialty has not widely embraced a more holistic view of gut health. Accordingly, the definition and framework described here could provide those clinicians with an opportunity to think more broadly about gut health and going on to partner with other providers, such as primary care physicians, dietitians and psychologists, to help patients achieve gut health. Establishing measurable norms for gut health will facilitate defining shared goals of care for patients and providers.

We believe that the definition should provide clarity to the general public and clinicians alike on what this term should mean and how claims for products or other interventions in regard to gut health should be interpreted. Similarly, the discussion of the domains that relate most directly to gut health and, in particular, of the limitations of several metrics that claim to accurately assess the status of gut health is particularly important in addressing the many half-truths and misinterpretations that occupy this area.

Limitations and future directions

Consensus process

The process used to produce this statement was a consensus meeting/conference method[189], including preparation from participants on a set of prompts, a semi-structured face-to-face group meeting with presentations from each participant, followed by individual synthesis of manuscript sections, aggregation of group content, online review meetings and a final vote on the definition. In comparison with other more structured consensus methodologies, such as the Delphi process, our semi-structured process has several strengths and limitations. The strengths of our method included the combination of both individual contemplation and face-to-face group discussion, which facilitated the synthesis and sharing of diverse perspectives and rationales, as well as reflection upon them. The limitations included the lack of anonymity and possible promotion of conformity[190]. While a semi-structured approach might have enabled unexpected perspectives to emerge, the use of structured questions for all participants might have better identified where divergent views existed. Our panel was chosen to represent the key disciplines and expertise identified as relevant to the study of gut health, with a group size conducive to face-to-face discussion, and included 13 scientists and clinicians from three continents. However, inclusion of a broader number of perspectives from additional geographies, disciplines and professions, might have altered the conclusions of the panel. Further discussion of these consensus findings with researchers and clinicians globally will be likely to lead to further evolution and refinement of these concepts.

Incorporating risk into the gut health concept

For now, the presence or absence of risk factors is not considered within the definition of gut health. As predictors for future states of gastrointestinal health and disease are further delineated, whether they be determined by host genome, gut microbiome, diet or environmental exposures, one could envisage their incorporation into a broader definition of gut health. From a preventative perspective, validated assessments of future health risk would be a valuable tool — for example, assisting clinicians to answer the question of whether a patient's current state is on a trajectory towards continued health or will result in the development of disease. The concept of 'wellness' and taking proactive steps for health maintenance has assumed an ever-increasing importance among patients and the general public alike, and a goal of achieving gut health (however conceived) is often a focus for intervention. Given the far-reaching effects of gut functions on systemic health, the potential effect of gut health for preventative approaches in other organs is an attractive area for further research.

Where normal ranges are available for some putative metrics of gut health (Table 1), these ranges are typically derived from cross-sectional or short-term follow-up of cohorts demonstrating an absence of measurable disease or symptomatology at a given time point. It is likely that some values within a range considered normal for cross-sectional correlation might represent degrees of dysfunction in other contexts which are predictors and/or contributors to future disease. Measurements of longer-term effects will also progress our understanding of individualized gut health responses to diet. Progress in this area must await a more complete understanding of the mechanisms through which diet affects gut physiology and function, together with large-scale longitudinal studies in which comprehensively phenotyped participants are provided with controlled diets. Such research on diet and other determinants might also provide a path forward to approach validated screening tools for gut health risk factors within a preventative health model.

Development of validated assessments and normal ranges

Defining metrics that accurately assess gut health remains a substantial challenge. The difficulties inherent to relying on just one parameter and one that has assumed such prominence, the gut microbiome, have already been stressed[38,191]. Most biomarkers that were derived from laboratory and clinical research also require further exploration and validation in long-term studies, with subsequent refinements of normal ranges to capture subclinical changes indicative of risk of poor outcomes[192]. The application of the gut health concept based on

objective, measurable parameters will therefore remain incomplete as long as we remain unable to comprehensively define normality and to reliably predict clinical scenarios and patient outcomes from physiological measures alone. Further, given the primacy of subjective experiences to the perception of health, symptom assessment is an important component of any definition of gut health.

Consistency and precision in research design and reporting

Outcome reporting in gut health research remains inconsistent, limiting comparability across studies and practical applications in clinical and public health settings. Core outcome sets (COS), developed through initiatives such as COMET, aim to standardize outcome selection and reporting by defining a minimum set of outcomes relevant across studies. A COS is an agreed-upon set of outcomes deemed essential for a specific condition, population or intervention, typically including outcomes that reflect both benefits and harms to offer a balanced assessment of interventions relevant to clinical practice[193]. Creation of tailored COS can help to standardize the meaning of gut health — improving comparability, reducing reporting bias and supporting the development of preventive strategies — especially when adapted to different age groups and life stages. Furthermore, COS would focus on outcomes that are most relevant to patients, clinicians and other stakeholders, enhancing the practical effect of research. Advancing this work will require interdisciplinary collaboration. In the current absence of such standardized measures, it is imperative that research and lay communications clearly specify which component of gut health is being referred to.

Conclusions

Providing a consensus definition of gut health represents a starting point for the development of a more comprehensive framework for understanding what contributes to a healthy gut and how it influences the homeostasis and overall health of the individual. While several functional domains contribute to gut health, they are intimately interrelated and interdependent and should be viewed as an integrated system that sustains gut health. Further, combining this physiological lens with the subjective patient experience of gut health is critical for a comprehensive understanding of the manifestations, effects and measurement of gut health. Given the wide range of component concepts within the composite of gut health, we encourage stakeholders to clarify the relevant domains of gut health for specific research and communications. Basic and clinical research have provided an array of putative markers of normal gut function, and we look forward to the validation of existing instruments and the discovery of novel indicators. These approaches should ultimately lead to a truly inclusive and meaningful concept of gut health and the development of substantiated recommendations on how to achieve and maintain gut health and prevent future diseases.

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Competing interests

M.L.M. is a member of the board of the International Scientific Association for Probiotics and Prebiotics, a non-paid voluntary position. She serves on the scientific advisory board for NURA USA and Cosun. M.C. serves as Executive Director for the International Scientific Association for Probiotics and Prebiotics and has previously been employed by manufacturers and distributors of probiotic and nutritional products. G.C. has received honoraria from Janssen, Probi, Apsen, Heel Pharmaceuticals and Boehringer Ingelheim as an invited speaker; is in receipt of research funding from Pharmavite, Fonterra, Reckitt, Tate and Lyle and Nestle; and is or has been a paid consultant for Yakult, Heel Pharmaceuticals, Bayer Healthcare and Zentiva; this support neither influenced nor constrained the contents of this review. N.D. has been a member of the scientific advisory board and consultant for Danone and Cosun; she worked with industrial partners in the context of European research consortia, including Mondelez, Kitozyme and Cargill. J.D.L. consulted or served on an advisory board or data monitoring committee for Amgen, Arena Pharmaceuticals, Bristol-Myers Squibb, Celgene, Crohn's & Colitis Foundation, Eli Lilly and Company, Galapagos, Gilead, Janssen Pharmaceuticals (Johnson & Johnson), Merck, Odyssey Therapeutics, Pfizer, Protagonist Therapeutics, Sanofi and Spyre Pharmaceuticals; he has had research funding or in-kind support from Nestlé Health Science, Takeda, Janssen Pharmaceuticals, AbbVie and Eli Lilly and Company; he has had educational grants from Janssen; he has performed legal work on behalf of manufacturers of generic ranitidine and 3M; and he owns stock in Dark Canyon Labs. D.M. has provided submissions for legal proceedings on behalf of VSL#3 and Golo Health; and is a member of the board of the International Scientific Association for Probiotics and Prebiotics, a non-paid voluntary position. P.W.O'T. has active research funded by Fonterra New Zealand and the US Highbush Blueberry Council; he is a co-founder of Carabia, a University College Cork campus company developing products for healthy ageing. H.M.S. is currently funded by the National Health and Medical Research Council (APP2018118); and has previously received research funding from the British Dietetic Association, Microba, the Rome Foundation and DSM Pharmaceuticals; and non-financial support from VSL pharmaceuticals. H.S. serves as a board member of the International Scientific Association for Probiotics and Prebiotics, a role which is unpaid and voluntary; she has participated as a clinical investigator, advisory board member, consultant and speaker for several companies, including Arla, BioGaia, Biocodex, Danone, Dicofarm, Nestlé, NNI, Nutricia, Mead Johnson, Novalac and Winclove. J.M.W. has previously received research funding from Nestec, Nutrileads, Cortecs and Chr. Hansen; and has acted in an advisory capacity for Yakult, Nestec and Nutrileads. E.M.M.Q. serves as a consultant to Atmo Biosciences, Biomerica, Nimble Science, Novonesis and Vibrant; is a member of the board of the International Scientific Association for Probiotics and Prebiotics, a non-paid voluntary position; and has received research support from 4D Pharma, Atmo Biosciences, Biomerica, Nimble Science, Novonesis, Takeda and Vibrant. S.C.B. and M.M. declare no competing interests.

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[1]Department of Food Science and Technology, University of California, Davis, CA, USA. [2]International Scientific Association of Probiotics and Prebiotics, Brisbane, Queensland, Australia. [3]Institute of Nutritional Medicine, University of Hohenheim, Stuttgart, Germany. [4]Department of Psychiatry and Neurobehavioural Science and APC Microbiome Ireland, University College Cork, Cork, Ireland. [5]Metabolism and Nutrition Research Group, Louvain Drug Research Institute, UC Louvain, Brussels, Belgium. [6]Division of Gastroenterology and Hepatology, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA. [7]Department of Immunology, University of Pittsburgh, Pittsburgh, PA, USA. [8]Department of Family Medicine, Georgetown University Medical Center, Washington, DC, USA. [9]School of Microbiology and APC Microbiome Ireland, University College Cork, Cork, Ireland. [10]Department of Medicine, School of Translational Medicine, Monash University, Melbourne, Victoria, Australia. [11]Department of Paediatrics, The Medical University of Warsaw, Warsaw, Poland. [12]Host-Microbe Interactomics, Department of Animal Sciences, Wageningen University & Research, Wageningen, Netherlands. [13]Division of Gastroenterology and Hepatology, Lynda K and David M Underwood Center for Digestive Health, Houston Methodist Hospital and Weill Cornell School of Medicine, Houston, TX, USA.