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Review

Human Milk Oligosaccharides Modulating Inflammation in Infants, Adults, and Older Individuals—From Concepts to Applications

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A B S T R A C T

The increasing global prevalence of inflammatory diseases, such as ulcerative colitis and irritable bowel syndrome, represents a challenging task for healthcare systems. Several approaches to disease management target the intestinal microbiome, which plays a key role in health and disease. One promising approach is modulating the microbiome using human milk oligosaccharides (HMOs). Originating from human milk, HMOs are indigestible carbohydrates that act in a host-optimized prebiotic fashion by providing an energy source for health-promoting intestinal bacteria and exhibiting systemic effects. Commercial products supporting infant health and development have been the primary fields of HMO application. Advancements in the large-scale production of HMOs through bioengineering and precision fermentation have led to evaluation of their potential for managing inflammatory diseases. Several in vitro studies and observations on model systems have been clinically validated in infants, resulting in a large body of evidence supporting the safety and efficacy of HMOs in inflammatory disorders. Although novel approaches seek to explore interventions in adults, the primary goal for the future is to provide cost-efficient, safe, and reliable healthcare compounds across all age groups.

Keywords: human milk oligosaccharides, inflammation, prebiotics, infants, adults, older individuals

Statement of significance

Although several reviews on human milk oligosaccharides (HMOs) and inflammation are available, they mostly focus on infants and few include studies in adults, but no reviews span all age groups by including older individuals. Here, we provide a unique and comprehensive overview of the present and future applications of HMOs in treating inflammation across all age groups.

Introduction

Over the last decades, the prevalence of inflammatory diseases has displayed a significant increase in prevalence, requiring global healthcare systems to address these novel challenges. This is evident in conditions such as inflammatory bowel disease (IBD) as well as in related functional disorders such as irritable bowel syndrome (IBS). The prevalence of IBS has been estimated to increase by 25% in the next decade, as recently reported in Norway [1]. The increasing prevalence of IBS has far-reaching effects, including economic, quality of life, workforce, psychological, healthcare utilization, and diagnostic challenges [2]. According to a recent meta-analysis including 184 studies, the worldwide prevalence of IBS is ~9% [3]. Similar trends have been observed for IBD, which was classified as a rare disease in 1990 [4], with prevalence rates increasing from 200 per 100,000 in the early 2000s to 320 per 100,000 reported recently in an Italian population [5]. Globally, its prevalence in

Abbreviations: BMO, bovine milk oligosaccharide; DSS, dextran sulfate sodium; EFSA, European Food Safety Agency; FDA, US Federal Drug Administration; FOS, fructo-oligosaccharides; FL, fucosyllactose; FMT, fecal microbiota transplantation; GOS, galacto-oligosaccharides; GRAS, generally recognized as safe; HMO, human milk oligosaccharide; IBD, inflammatory bowel disease; IBS, irritable bowel syndrome; LNT, lacto-N-tetraose; LNnT, lacto-*N*-neotetraose; NEC, necrotizing enterocolitis; SL, sialyllactose.

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industrialized countries is stabilizing, whereas that in newly industrialized countries is rapidly increasing [4]. The resulting economic burden is substantial, with estimates for annual direct healthcare costs in Europe ranging from €900 to €2100 [6] per patient with IBS and annual direct healthcare costs ranging from €2000 to €3500 per patient with ulcerative colitis or Crohn's disease, respectively [7].

Considering the growing population, as well as the societal and public health effects of the increased prevalence rates, it becomes apparent why funding initiatives such as the European Innovative Medicines Initiative, as part of the Horizon 2020 program, target noncommunicable inflammatory diseases. Most funded projects focus on biomarkers, improving diagnostics, and adjusting systemic therapy, because these measures can be addressed in clinical scenarios [8]. In contrast, preventive or control measures taken outside clinical settings are less prominent, particularly since they target individuals who do not require systemic treatment, have less severe symptoms, or are in a preclinical state. Strategies aimed at avoiding progression from a preclinical to a clinical state, although promising, are challenging to implement. Similar to many other inflammatory diseases and related functional disorders, IBS and IBD have complex etiologies, in which genetic predisposition is not the major contributor to disease susceptibility, manifestation, and progression. In contrast, environmental and lifestyle factors are discussed to play a strong role [9,10]. Consequently, recent advances in risk management for inflammatory diseases and related functional disorders aim to modulate this environment by altering smoking habits, alcohol consumption, physical activities, and many more, although dietary changes remain the primary target [11,12].

Risk management and preventive measures addressing these inflammatory scenarios must have a low impact on daily routines and be applicable in nonclinical settings, such as dietary interventions. One of the primary goals of several dietary interventions is modulating the microbiome. Microorganisms are ubiquitous in the gut, tissues, and body surfaces; they serve as a central connection between the environment, diet, and patient [13]. Before the availability of microbiome profiling methods utilizing high-resolution sequencing techniques such as 16S rRNA and bacterial metagenomic sequencing, unraveling this interconnection was practically impossible. Rapid progress in the last 2 decades resulted in a refined picture of inflammatory disease pathophysiology. Initially, reports suggested a substantial difference between the gut microbiome of healthy individuals [14] and those associated with diseases such as obesity, diabetes, cardiovascular disease, and kidney disease [15]. Recently, IBD and IBS phenotypes have been associated with changes in the composition and function of the gut microbiome and their relationship with the gut immune system [16–20].

We further explored this association and demonstrated that the microbiome has a causative component in ulcerative colitis [21], which is a noncommunicable disease [10]. This complex disease is influenced by many factors; we were able to transfer the phenotype of ulcerative colitis via the gut microbiome from diseased to healthy individuals in a mouse model. Current knowledge suggests a more complex scenario, which includes not only the microbiome and its direct effects on gut functions but also the bidirectional interaction between the host and its microbiome, which results in a balanced system in healthy individuals [22]. Owing to its central role in health and disease, the microbiome has become a prominent target for non-pharmacological interventions; however, it remains challenging to modulate the microbiome in a safe and effective health-promoting way. Pre-, pro-, and postbiotics are being investigated for their beneficial effects on the microbiome, representing an entirely new and innovative field of research. Within this emerging area, human milk oligosaccharides (HMOs) are being discussed as potential agents for modulating, reconstituting, and stabilizing the microbiome, as reviewed by Lê et al. [23]. Gut bacterial species are ecologically and evolutionarily differentiated by their ability to metabolize different glycan structures [24]. HMO structures have evolved into optimum shapes to feed selected indigenous species. In addition, HMOs exhibit systemic effects, as ~1% of the HMOs consumed are absorbed in the upper gastrointestinal tract. They can serve as antiadhesives by binding to the glycocalyx of the epithelial cell surface and preventing viral, bacterial, or protozoan pathogens from attaching to these cells [25]. Although the health benefits of HMOs have been studied since the 1950s [26], currently they are predominantly used as early-life fortifiers in infant formula milk. Beyond this application, researchers are exploring methods to broaden the applicability of this promising group of ingredients. In this review, we outline the current status, recent concepts, and future applications of HMOs in inflammatory diseases and functionally related conditions, such as IBD and IBS.

HMOs, a versatile arsenal with effects on gut microbiota and intestinal epithelial barrier

The history of HMO in science started with pediatric observations wherein breastfed infants showed higher survival rates than bottle-fed infants and that a specific milk fraction selectively promoted the growth of *Bifidobacterium infantis*, which was named the Bifidus factor [27]. Researchers began exploring the highly abundant and functional components of human milk in 1929, leading to the identification of the carbohydrate fraction [28]. Subsequently, the first HMO, 2′-fucosyllactose (2′-FL), was characterized in 1954 [29,30], marking the initiation of a novel research domain including broad applications not limited to the food industry. A brief overview of the history of HMOs and their scientific development is presented in Figure 1.

HMOs are a collection of interconnected carbohydrate structures consisting of the following 5 monosaccharide building blocks: glucose, galactose, *N*-acetyl-glucosamine, *N*-acetylneuraminic acid (sialic acid), and fucose, which are characteristically

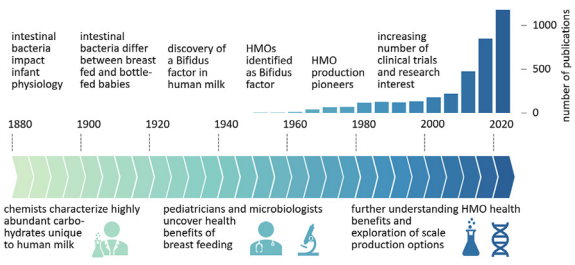

FIGURE 1. A brief history of human milk oligosaccharides (HMOs) from discovery in the late 19th century to today's exploration of large-scale production options. The number of publications was retrieved from PubMed (search term "human milk oligosaccharide"; last updated 2025-02-06: 3254 records).

added onto a lactose core element with a degree of polymerization [31]. Following lipids and lactose, HMOs constitute the third most abundant solid component in human milk, with concentrations between 5 and 15 g/L in mature milk [32]. More than 200 different HMOs have been identified using mass spectrometry [33] and >180 individual HMOs have been structurally characterized [34]. HMOs are defined as indigestible oligosaccharides since they do not directly serve as nutrients for humans [31]. Globally, milk HMO profiles vary significantly among mothers. Here, the impact of factors such as health status and diet has been discussed, but not well established [35–37]. In contrast, the mother's genetic background regarding the glycosyltransferase genes which encode the enzymes creating the characteristic HMO linkages has been well studied as a major factor influencing HMO composition [31]. The FUT2 genotype, which is linked to secretor status (Se), controls the mother's ability to synthesize α1,2-fucosylated HMOs. Similarly, the FUT3 genotype defines the Lewis type (Le), impacting the amount of α1,3- and α1,4-linked fucosylated HMOs found in milk. Variations in Se/Le genotypes result in the following 4 main groups of human milk: Se+Le+, Se-Le+, Se+Le-, and Se-Le- [38]. A study conducted by some authors of this review provided evidence that the FUT2 genotype significantly impacts the human gut microbiome in patients with IBD. Although it is challenging to isolate genotype effects from disease effects, we observed signals belonging to the *Lactobacillus* genus which were positively associated with healthy secretors (functional allele rs601338), and species belonging to the family *Lachnospiraceae* were identified in healthy and diseased nonsecretors (loss-of-function allele). This suggests that the FUT2 genotype may contribute to disease susceptibility by interconnecting with the microbiome [39]. Finally, the HMO composition in human milk varies over the course of lactation [40], following a specific pattern, potentially indicating an adaptation to the altered needs of infants during development (Figure 2).

The diverse molecular arsenal of HMO structures results in 3 major functional mechanisms of HMOs in humans, relevant for all life stages, including infants, children, adults, and older adults. Since HMOs reach the large intestine undigested, they *1*) selectively modulate the microbiota by stimulating the growth of Bifidobacteria (bifidogenic effect) and subsequent cross-feeding mechanism to other bacterial species; *2*) they impact the immune system directly and indirectly through metabolites; and *3*) they support the epithelia by inhibiting the adhesion of or penetration by pathogens [41]. The effects of HMOs beyond these 3 primary categories are largely unexplored but can reach as far as alleviating stress-induced mood, as demonstrated recently [42]. Although HMO science began ~70 y ago, knowledge of the underlying molecular mechanisms of individual HMOs was limited owing to a lack of availability. Technological advances facilitated by the commercialization of selected HMOs have made them available for preclinical and clinical research at scale and purity over the last decade [43].

Several effects of HMOs have been studied using in vitro systems including intestinal cell lines such as Caco-2 cells, human intestinal epithelial cells, and HT-29 cells, which are used as models for cell-specific conditions, such as IBD, IBS, and colorectal cancer. These HMOs include 2′-FL, 3-fucosyllactose (3-FL), 3′-sialyllactose (3′-SL), and 6′- SL salts, which were studied in vitro for selectively supporting the growth of beneficial commensals—*B. bifidum* strain CNCM I-4319 and *Bacteroides* [44–46], although not stimulating growth of the opportunistic pathogen, *Streptococcus* [47,48]. Similarly, some beneficial bacteria, such as *Akkermansia muciniphila* present in mucus can utilize specific HMOs, namely 2′-FL, lacto-*N*-tetraose (LNT), and LNT2, as those structurally resemble mucus [49]. Correspondingly, the immune modulatory functions of HMOs have been demonstrated in vitro, where these oligosaccharides exhibit anti-inflammatory effects by decreasing the expression of proinflammatory genes such as IL-12p35, IL-8, IL-1β, and TNFα [50,51]. In vitro effects on the epithelial barrier have been demonstrated for 3'-SL, which can modify cellular glycan profiles, resulting in a reduced abundance of enteropathogenic *Escherichia coli* [52]. Additionally, 3-FL can modulate albumin absorption [53] and different HMO fractions can inhibit the growth of intestinal cells in vitro although removing damaged and abnormal cells via apoptosis in these models [54]. This is supplemented by other HMOs that induce differentiation [55],

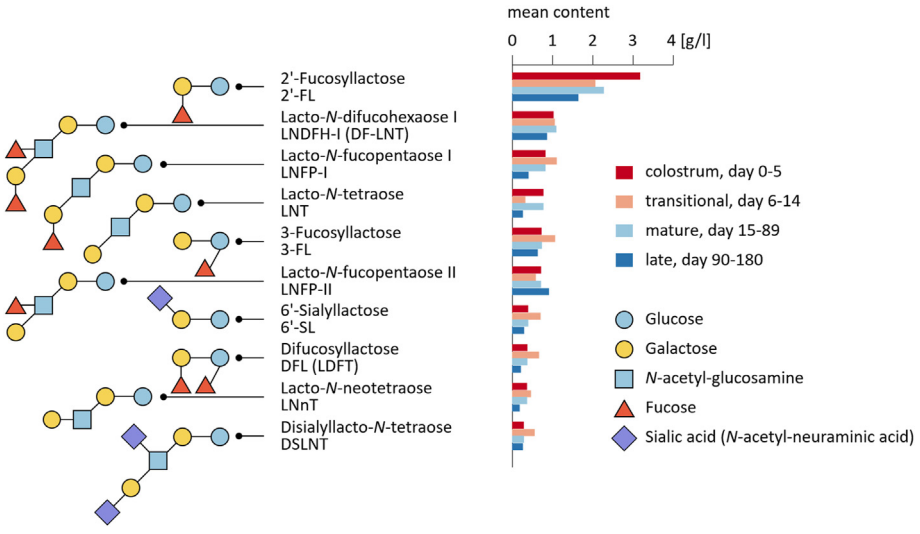

FIGURE 2. Top 10 human milk oligosaccharides (HMOs), which are the most abundant in human milk during first 6 mo of lactation; the graph is based on previously published data [36].

indicating their potential role in the maturation and maintenance of the intestinal epithelial barrier. Further studies using cell lines and intestinal organoids have attributed HMOs to the production of mucin [56], which is the main protein component of mucus and protects against intestinal infections [57]. Moreover, in vitro studies have demonstrated that 2′-FL, which is one of the most abundant HMO in human milk from secretor mothers [58], can improve intestinal barrier integrity by improving tight junctions via inducing the expression of claudin-8 [59], which encodes for an integral tight junction protein. The dysregulation and genetic variants of claudin-8 are associated with IBD pathogenesis [60]. Generally, in vitro studies can differentiate between the indirect effects of HMOs through microorganisms (and metabolites) and direct effects occurring without bacterial involvement. It is unclear whether the direct effects observed in simplified in vitro settings are also relevant to the complex in vivo setting; assessing the nature of the impact of HMOs in a scenario involving various human cell types, environmental factors, and several bacterial species will have to be deciphered via carefully designed experiments.

Taken together, numerous in vitro studies have demonstrated the beneficial effects of various HMOs on the intestinal microbiota, immune system, and epithelial barrier. Further studies, including mice, rats, pigs and cell-based models, are required to further disentangle the complex molecular interactions between HMOs, intestinal microbiota, immune system, and intestinal barrier.

HMOs and their role among pre-, pro- and postbiotics

The group of biotics can be considered as a continuum. According to the International Scientific Association for Probiotics and Prebiotics (ISAPP), prebiotics are substrates that are selectively utilized by host microorganisms conferring a health benefit [61], whereas probiotics are live microorganisms which, when administered in adequate amounts, confer health benefits to the host [62]. Postbiotics are considered a preparation of inanimate microorganisms and/or their components, conferring host health benefits, whereas synbiotics are defined as a mixture of live microorganisms and substrate(s) selectively utilized by host microorganisms, which confer health benefits to the host. Several of these definitions as well as new biotic classes are being discussed in this emerging field [63].

HMOs can serve as natural prebiotics, which were first defined by Gibson and Roberfroid [64] and have since undergone several updates [61,65]. Consumption of mother's milk containing HMOs clearly increases the proportion of HMO-consuming *Bifidobacteriaceae* and *Bacteroidaceae*, which influence gastrointestinal health in neonates by altering the development of the intestinal microbiota and metabolic and immunological systems [66]. The primary source of prebiotics, providing energy for the growth of beneficial microbes, is the human diet. For infants, the main source is breast milk, which is also the main source of HMOs. In contrast, cow milk, as well as milk from other ruminants such as buffaloes and sheep, is devoid of HMOs and contains bovine milk oligosaccharides (BMOs) only, keeping in mind that structurally identical molecules like 3′-SL and 6′-SL exist in both milk types [67,68]. Within the diet, indigestible carbohydrates modulate the intestinal microflora [69]. This fraction contains not only HMOs but also polysaccharides, such as resistant starch, pectins, inulin, beta-glucans, and possibly other fermentable fibers, as well as oligosaccharides, including fructo-oligosaccharides (FOS), galacto-oligosaccharides (GOS), and xylooligosaccharides [61]. Bacteria can process these saccharides into short-chain fatty acids, such as acetic, propionic, and butyric acids, serving as an energy source in the intestinal epithelia [70]. Among these bacteria, *Bifidobacterium* species are very prominent because of their beneficial health effects on infants and adults, mainly by dispelling pathogens or creating an acidic, pathogen-unfriendly environment [71]. It is believed that the HMO composition, in combination with other dietary factors, is potentially responsible for these growth-promoting effects [72].

In contrast to prebiotics, probiotics are defined as "live microorganisms that, when administered in adequate amounts, confer a health benefit to the host," such as bacteria and yeast [73]. *Lactobacillus* and *Bifidobacterium* are common representative probiotics and are prevalent in yogurt products with live cultures or in probiotic food supplements. They are integral components of the natural human intestinal flora and possess beneficial effects on the host when administered at sufficiently high concentrations. The beneficial effects summarized by the ISAPP include supporting the immune system, preventing allergies, managing the intestinal microbiota, and supporting healthy gut microbiota, although the definition of healthy microbiota is still being discussed [73]. Probiotics directly support vitamin synthesis and improve the bioaccessibility and bioavailability of minerals [74,75]. In parallel, probiotic bacteria prevent or reduce the adhesion or colonization of bacterial pathogens in human intestine [76] and have immunomodulatory characteristics that benefit the host by stimulating the production of immunoglobulins and interferons. These effects can occur via components of the probiotic cell walls and their DNA and RNA fragments, all of which are recognized by immune cells [74].

The last category, postbiotics, has been recently defined as the "preparation of inanimate microorganisms and/or their components that confers a health benefit on the host" [62]. Here, a pioneering approach in postbiotics involves the use of inactivated *Lactobacillus* in IBS, exhibiting beneficial effects on fecal incontinence, abdominal pain, and quality of life; however, the strong placebo effects in this study require further validation [77]. Postbiotics can modulate the gut microbiome using bacteriocins or via quorum-quenching molecules [62]. Generally, applications of postbiotics benefit from their high stability during production and storage because they are highly tolerant to temperature and hydrolysis [62]. Specific postbiotics have been recommended for several pediatric conditions, including the use of heat-killed *Lactobacillus acidophilus* (strain LB) for the management of acute diarrhea and heat-killed *L. paracasei* CBA L74 to prevent gastrointestinal and respiratory tract infections [78]. For adults, *Lactobacillus* postbiotics have been suggested as adjuvant therapy for atopic dermatitis, whereas data do not indicate their efficacy in children [79].

All biotics, regardless of whether they are pre-, pro-, or postbiotics, share the goal of providing health benefits to humans, with the microbiome as a central component. Selecting the most suitable agent to achieve the desired effect is crucial; however, several criteria, such as availability, route of administration, regulatory status, price, shelf life, stability, and consistent benefit outcomes with minimal side effects, must be considered. Although probiotic bacteria are beneficial, HMOs

have several advantages over probiotics. Employing probiotics may increase the risk of sepsis and excessive immune responses, representing a rare but serious issue in neonates and immunocompromised patients [80]. Moreover, HMOs are relatively more stable than probiotics, both in the food matrix and in human digestive tract. Simultaneously, HMOs may act synergistically with other probiotics, as illustrated in a recent study [81] and supported by ex-vivo experiments [82]. As functional prebiotics, HMOs represent the beginning of "the food chain," thus addressing health issues at their root. The third advantage of HMOs might be fueled by the increasing public awareness of a healthy digestive system, which may help improve the acceptance of different health measures, yet the acceptability of approaches such as fecal microbiota transplantation (FMT) is still controversial [83]. One challenge in the large-scale applicability of HMOs is their cost-efficient commercial-scale production and availability. These issues are currently being addressed, resulting in the production of some of the most abundant HMOs in human milk, in commercially suitable quantities. Robust and perceptible evidence may play a role in deciding whether to use HMOs over other less cost-intensive products. Finally, characteristic features of HMOs are their additional functions, such as immune system stimulation and their effect on microbiome maturation [84] and bacterial colonization of the intestine [85], which differentiates them from other biotics.

HMOs and their role in healthy immune system development and protection from infection in infants

The WHO states that breast milk is the optimal food for infants and includes everything required for a child's healthy development [86]. Although HMOs play a significant role in conferring these health-promoting properties [85], documenting their effects can be challenging because of the need for studies involving infants as participants. In concordance with in vitro findings, clinical trials have documented that HMOs modulate the microbiota of preterm and breastfed caesarian-born infants to more closely resemble the microbiota of vaginally born infants by promoting the growth of *Firmicutes* and Bifidobacteria, whereas reducing the abundance of pathogenic bacteria, such as some *Enterococcus* strains [87,88]. Health benefits attributed directly and indirectly to HMOs in infants are numerous, whereas most benefits are closely linked to the potential of HMOs to modulate and stabilize the microbiota [89] and their overall ability to reduce infections in infants, as reviewed by Schönknecht et al. [90]. In general, HMOs may act as growth-supporting factors influencing infant gut development and maturation, as well as anti-inflammatory and immune components modulating the intestinal immune system [54], which is also reflected by the association of specific HMOs with reduced overall child mortality [91]. As part of this process, HMOs have been shown to affect the adhesion of monocytes, lymphocytes, and neutrophils to endothelial cells, which is one of the primary steps in tissue invasion during inflammatory reactions. These results indicate that specific acidic oligosaccharides in human milk may serve as anti-inflammatory components and may therefore contribute to the lower incidence of inflammatory diseases in human milk-fed infants [92]. Along the same lines, HMOs have been shown to control the expression of inflammatory markers and regulate the type 1 T helper/type 2 T helper lymphocyte balance [93]. In atopic dermatitis, one of the most prevalent inflammatory diseases in children (prevalence $\leq$20%) [94], clinical data have suggested the protective effects of HMOs [95]. Although not life-threatening, this condition represents a substantial burden, considering its high prevalence. This is also in concordance with studies in murine models, in vitro studies, and observations in infants, which attribute a potential protective effect of HMOs against asthma [96]. Although several clinical trials have hypothesized and evidenced the protective effects of HMOs against allergies, some studies in infants have revealed contradictory findings [85]. The different findings may result from different experimental setups which vary in the type and concentration of HMOs, as well as the time of treatment. Therefore, further validation of the interaction between HMOs and allergies is required. One of the most severe diseases for which limited progress in mortality rates has been made over the last decades is highly complex necrotizing enterocolitis (NEC), wherein formula milk consumption is one of the risk factors. Although the WHO discourages bottle milk feeding [97], the worldwide prevalence of 59% in children receiving formula milk instead of breast milk in their first year of life illustrates the potential impact of this risk factor [98]. In contrast to formula milk, mother's milk reduces the risk of NEC by factors 6–10, as shown in a multicenter cohort study of low-birth-weight infants [99]. In animal models, this effect has been attributed to HMOs and extracellular vesicles in human milk [100,101]. Pathogens are highly relevant for many severe conditions, such as infectious diarrhea, respiratory tract infections, and sepsis, which manifest in early childhood. In addition, diarrhea is the result of pathogens adhering to the mucosal, with subsequent dissemination, colonization, and invasion (for example, *E. coli*, *Helicobacter jejuni*, *Shigella* strains, *Vibrio cholerae*, and *Salmonella* species) [102,103]. Some HMOs have exhibited protective effects against infant diarrhea [104], urinary tract infections [105], and sepsis [106]. Moreover, 2'-FL and lacto-*N*-neotetraose (LNnT) in formula milk have been observed to result in fewer incidences of bronchitis and respiratory tract infections among infants [107]. In the same study, children receiving 2'-FL and LNnT in formula milk required fewer antipyretics and fewer antibiotic interventions than those in the formula-only fed control group, which was recently validated independently [108]. *Clostridiodes difficile* (formerly *Clostridium difficile*) infections are nosocomial infections caused by dysbiosis or antibiotic intervention. A recent study demonstrated the antimicrobial activity of HMOs against *C. difficile* [109], further supporting the hypothesis that HMOs act as stabilizers of health-promoting microbiota. Excessive LPS-mediated inflammatory signaling during *E. coli* invasion of intestinal epithelial cells can be inhibited by HMOs [105]. In the same context, observations in preterm infants suggested that HMOs can reduce intestinal permeability during the first month of life [110], further preventing epithelial penetration by pathogens and subsequent inflammation. Furthermore, biofilm formation of *Staphylococcus aureus*, which is responsible for skin infections, toxic shock syndrome, postsurgical infections, and sepsis [111], has been shown to be inhibited by HMOs in vitro [112].

In summary, many studies provide scientific support for the hypothesis that HMOs protect against inflammation in children and are relevant for infant development. Although observations have expanded to many different fields, including studies suggesting a potential effect of HMOs on cognitive development [31,

113–115], the primary focus is often on inflammatory disorders and manifestations with an inflammatory component. Another example is obesity risk, where it is known that the microbiome, inflammation, and obesity are closely linked [116] and that HMOs could potentially exhibit a modulatory role via their impact on intestinal *Bacteroides* and Bifidobacteria. Although HMOs presumably play a role in the risk of infant obesity, the available evidence is inconsistent [117,118]. Despite preventing inflammation, several of the above-mentioned studies have also reported that HMOs can reduce inflammatory symptoms such as the invasion of inflammatory cells, fever, diarrhea, and impaired intestinal function due to mucosal inflammation. Several questions need to be addressed when considering HMOs for the dietary management of inflammation or as a component of formula milk: which component(s) should be added, what is the appropriate dosage, what is the metabolic fate of HMOs, and which infants should receive it? Further studies will help address these queries. Nevertheless, the field of HMO applications in children is very active, and rapid progress is currently being made.

HMOs and their potential applications addressing inflammation in adults

The vast majority of the available clinical trial data cover the effects of HMO on preterm infants and infant development. These studies were largely driven by the objective of improving formula milk composition or substituting essential components required for the healthy development of children. Because adults do not consume formula milk, study data covering the effects of HMOs on health and disease in adults are limited. However, some observations from clinical trials in infants are similar to those in adults, such as the ability of HMOs to inhibit pathogen growth [87,88]. Simultaneously, findings from children cannot be simply transferred to adults, as the microbiome matures and changes with age, paralleled by altered diet and physiological changes [119]. Consequently, the composition of commensals confronted with bacterial pathogens differs and exhibits different protective properties. This is well illustrated by Bifidobacteria, which represent ~90% of the total intestinal microbiota in children, decreasing to 5% in adults, and decreasing even more in older individuals [120]. Interestingly, decreased levels of Bifidobacteria have been linked to IBS, IBD, obesity, and allergies [120,121], and HMOs are known to modulate the abundance of Bifidobacteria, as described above. A double-blind, placebo-controlled study from Denmark supplementing 100 healthy adult volunteers with 2′-FL and LNnT at a daily dose of $\leq$20 g reported modulation of the microbiome by increasing the levels of *Bifidobacterium* without showing adverse effects [122]. Considering the decrease in *Bifidobacterium* abundance in older individuals, these results encourage further research on HMO administration in older individuals. This study also established that dietary HMO supplementation is a suitable and safe approach to shaping the adult microbiota in a beneficial manner. Addressing safety is an important step toward application in larger population groups such as individuals with obesity or metabolic syndrome. Here, several studies have shown that HMO-treated mice exhibit reduced body weight, adipose tissue weight, and fasting blood glucose levels, whereas reducing low-grade inflammation observed in obesity [123,124]. Keeping in mind the limitations of animal models, these findings are relevant not only for obesity but also for type 2 diabetes mellitus and metabolic syndrome. A recent study supports these findings by observing microbiome changes in human adults in response to HMO treatment, which may protect against obesity and metabolic syndrome [84]. Despite these pilot findings, clinical studies with larger cohorts are required to validate the beneficial effects of HMOs in the context of obesity, metabolic syndrome, and type 2 diabetes mellitus. Finally, the observation of the beneficial effects of HMOs in infants and children should be addressed by corresponding clinical studies in adults. In addition to the anti-inflammatory properties, such studies should also focus on the beneficial effects of HMOs on the cognitive system observed in children [113–115], which may be of similar relevance in adults.

Patients with IBS are often considered for nonpharmacological dietary interventions or diet supplementation, including HMOs. A mixture of 2'-FL and LNnT administered at a dose of 5 g/d for 4 wk did not show any impact, whereas a 10 g/d dose substantially increases the abundance of the genera *Actinobacteria*, *Bacteroides,* and *Prevotella*. However, after a subsequent wash-out phase of 4 wk, the microbiome profiles returned to a state close to the initial state, where the beneficial effects of HMOs were not measurable, indicating the necessity of continuous supplementation to maintain the effect on the intestinal microbiome [125]. On the basis of these findings, analysis of the fecal and mucosa-associated microbiome in adult patients with IBS has revealed an increase in the abundance of *B. adolescentis* and *B. longum*, paralleled by an increase in the abundance of the *Faecalibacterium* genus and *Lachnospiraceae* family in stool samples, and an increased abundance of the genus *Blautia* in mucosal biopsies from the colon [126]. In another study, the administration of a dose (4 g/d) 2′-FL over 6 wk instead of 4 wk could modulate the microbiome by increasing the fecal abundance of *B. longum* and *Faecalibacterium prausnitzii* [127], both of which are beneficial in inflammatory scenarios [128]. Overall, these results in the field of IBS open new avenues for future interventional studies with HMOs.

Celiac disease, an inflammatory enteropathy triggered by dietary wheat proteins and prolamins from cereals, represents the primary focus of dietary interventions and could thus be a target for HMO-based interventions. However, a recent study could not show any effects of 2′-FL on celiac disease, whereas patients with IBS and IBD who participated in the same study showed improvements in intra- and extraintestinal symptoms [127]. In contrast, children from the PreventCD cohort demonstrated that *Methylobacterium komagatae*, *Methylocapsa palsarum,* and the fucosylated HMOs consuming *Bacteroides vulgatus* are more abundant in mothers milk of children who developed celiac disease, suggesting that this might be the result of vertical transmission of bacteria from mother to child. This further illustrates the challenges in studying the anti-inflammatory effects of HMOs in adults, particularly because observations from breastfeeding cannot be translated to HMO supplementation in adults.

Despite the substantial progress in IBD management, limited studies have explored the suitability of HMOs for intervention or for supporting established therapies. Particularly in adults, disentangling the contribution of HMOs and other dietary modulations or interventions is clinically challenging [129]. Despite the lack of clinical trials, a large body of evidence indicate that the pathology of IBD is a suitable environment for HMO applications. Mice treated with dextran sulfate sodium (DSS) develop colitis-like symptoms and are therefore used as models for

ulcerative colitis. In such a model, 2'-FL supplementation could reduce various parameters of disease activity coupled with the enhanced expression of MUC2 and NLRP6. MUC2 is the main gel-forming mucin in the intestine, whereas NLRP6 is a negative regulator of proinflammatory toll-like receptor 4 [130]. In a separate study employing a DSS mouse model for colitis, 2′-FL was found to be more effective than galacto-oligosaccharide when applied at the same dose, whereas both modulated the intestinal microbiome and reduced inflammatory responses [131]. In humans, HMOs can exert systemic effects that are potentially relevant to IBD treatment. A recent study employing organoids originating from adult human colon biopsies showed that claudin-5 and claudin-8 are upregulated in response to the bacterial metabolization of 2'-FL [59]. Claudin-5 and claudin-8 are tight junction proteins that strengthen barrier function and are found in many endothelial cells, making them key players in maintaining intestinal integrity and protecting against inflammation [132]. Our own group could document that the FUT2 genotype, encoding α-1,2-fucosyltransferase and relevant for HMO composition, has a substantial impact on the microbiome in healthy individuals and patients with Crohn's disease. In addition, we identified a significant disease-by-genotype association, indicating that the FUT2 genotype not only influences the composition of bacterial communities but may also partly explain disease susceptibility [39]. Although it is tempting to speculate on the potential applications of HMOs to compensate for this FUT2 effect, the findings of our study are insufficient to support such a suggestion, and further studies are required to address this specifically. This observation is further supported by studies showing that the FUT2 genotype not only modulates the risk for Crohn's disease but also for ulcerative colitis [133]. In an open-label pilot trial, patients with ulcerative colitis reported improved intra- and extraintestinal symptoms on 2′-FL administration, assessed based on the IBD Questionnaire domain score [127]. Although the small sample size of this pilot trial requires validation in a larger cohort, these findings represent a promising starting point for further exploration. Considering the large body of evidence available for infants, the observation that NEC shares pathways with Crohn's disease, as identified via RNA sequencing [134], suggests that the above-mentioned HMO--based strategies developed for NEC in infants could represent a starting point for novel applications in adult patients with Crohn's disease. Moreover, in addition to HMOs, other prebiotics, such as FOS, GOS, chitosan-oligosaccharide, and others are being discussed as functional foods and used as adjuncts for ulcerative colitis therapy [135], as reviewed by Liu et al. [136]. Similar to HMOs, the promising results from initial clinical trials require further validation before effective implementation. Keeping the limited clinical data on HMOs in adults in mind, all studies share initial findings on the beneficial effects of HMOs on inflammatory disorders in adults. These findings should encourage future research on HMOs to expand beyond the realm of infant development. For adults and older individuals, HMOs may be a valuable addition to the arsenal of tools for inflammation management, particularly in nonclinical scenarios.

HMOs as future agents addressing inflammaging and dysbiosis in older adults

A largely unexplored field is currently the application of HMOs in the context of older adults. Gut microbiota is considered a central player in healthy aging. The current hypothesis expands this to the concept that age-associated dysbiosis seen in many older individuals is the primary cause of age-associated morbidities, many of which have an inflammatory component [137]. The Western diet is being discussed as a driver of these microbiome changes [138], where the abundance of beneficial bacteria decreases, and is replaced by bacteria driving chronic inflammation [139].

Our own studies on healthy aging, including 250 individuals aged 20–104 y, have shown that the phenotype of longevity is associated with a reduction in metabolism-associated processes, potentially linked to a specific lifestyle, including a specific diet. Individuals who did not achieve longevity did not display these specific patterns [140]. Reduced dietary variation, often observed in older adults [141] is a known risk factor for dysbiosis, representing a possible connection between host metabolism and the microbiome. Consequently, dysbiosis with all its downstream effects could be addressed via HMOs as a stabilizing or even reconstituting component. Currently, only a single model system-based study employing cultured fecal microbiota derived from older adults has explored this concept, investigating the ability of HMOs to induce changes in the microbiota, such as *Bifidobacterium* expansion and decreasing the abundance of *Bacteroides* and *Roseburia* [84]. At the same time, the model system employed does not reflect the complex environment found in human intestine, mandating further studies. Similarly, little is known about the exact nature of the decline in gut barrier function observed in older adults. However, in vitro studies and findings in model systems indicate the involvement of tight junction proteins [142]. Joining these findings with the above-mentioned upregulation of tight junction proteins claudin-5 and claudin-8 by 2′-FL [59], administering HMOs would represent a promising setup to reduce the leaky gut observed in older individuals.

One phenomenon commonly found in older adults is chronic low-grade inflammation, also called inflammaging, a term first introduced by Franceschi et al. [143]. Although it is unclear whether the dysbiosis observed in parallel is the cause or consequence of inflammation [144,145], it is agreed that these 2 events are closely interconnected. A large body of evidence suggest that various pre- and probiotics can reduce low-grade inflammation [139]. Among these, GOS potentially protect against inflammatory diseases by increasing the relative levels of *Bifidobacterium*, *Lactobacillus–Enterococcus* spp., and *Clostridium coccoides–Eubacterium rectale* in older adults [146]. Similarly, probiotics have been reported to have a positive effect on exhaustion and handgrip strength, which are 2 criteria of frailty [147]. Other studies have reported the effects of probiotics on the microbiome in older adults [148,149]; however, the downstream impact on healthy aging remains to be explored [150]. In contrast to that, no data are currently available on how HMOs can affect inflammation in older adults or inflammaging. On the basis of the studies on infants, children, and adults listed above, it is tempting to speculate that HMOs would exhibit similar beneficial effects, thus reducing both, inflammaging and dysbiosis in older adults. Available safety data for adults, where 5–20 g/d of indigestible carbohydrates has been shown to be tolerable [151], will promote potential implementation in older adults. Many age-associated diseases, such as Alzheimer's, Parkinson's, cardiovascular, and chronic obstructive pulmonary disease, along with diabetes, [152], have either an inflammatory

component or are linked to the microbiome, and HMOs could address both these issues; the concepts outlined here are based on observations in infants, children, and adults. To our knowledge, clinical data on the effects of HMOs on older individuals are unavailable. This further emphasizes the urgent need to conduct pilot studies followed by larger validation approaches. Although HMOs may not completely replace systemic therapies or biologics, a strategy to safely modulate the microbiome in a beneficial manner for healthy aging represents a promising approach that could be achieved by employing HMOs.

Considering the promising potential of HMOs in addressing inflammaging, dysbiosis, and healthy aging in older adults, one can expect that this field will receive increased attention in the future, finally leading to the routine application of HMOs in adults. Coupled with demographic changes and increased health awareness in this age group [153], health-promoting HMOs for older adults should not be disregarded, and require clinical evaluation. These trials will generate reliable evidence and grant older individuals access to the beneficial effects of HMOs.

HMOs as health-supportive interventions in the future

Since their discovery, HMOs have been traditionally applied in the field of infant and child development, today often as supplements in formula milk. The beneficial effects of HMOs in infants include modulation and stabilization of the microbiota to support infant gut development, anti-inflammatory protection, and immune system maturation [89]. Although commercially highly relevant, a major challenge is the cost-efficient production of HMOs, which is the primary requirement for broader applications. Because milk from farmed animals generally contains only BMOs, other approaches such as enzymatic or biotechnological production have been explored in recent years. Among these, production employing bacterial precision fermentation is the most prominent one, resulting in some of the most abundant HMOs now being produced in an industrial. The cell factories used to manufacture these scales are engineered strains of *E. coli*, *Corynebacterium glutamicum*, and *Saccharomyces cerevisiae* [43, 154]. The chemical and enzymatic synthesis of HMOs is a promising yet challenging concept. For specific scenarios, a combination of different methods might be worth considering [155], and further research may help precisely identify which approach best meets all requirements.

The safety of manufactured HMOs and production strains has been scientifically assessed and established globally by multiple jurisdictions [156], including the European Food Safety Agency (EFSA), US Federal Drug Administration (FDA), and Food Standards Australia New Zealand, along with many others from countries such as China, Thailand, Malaysia, Singapore, Taiwan, Canada, Brazil, Russia, Saudi Arabia, India, and the United Kingdom. In the European Union, multiple HMOs are approved as Novel Foods and are listed on the EU Novel Foods Union List, whereas scientific opinions on HMO safety are published in the *EFSA Journal*. In the United States, HMOs that were positively evaluated by the FDA gain the generally recognized as safe (GRAS) status, which is published as FDA "No questions letter" in the FDA GRAS Notice Inventory.

Ongoing studies illustrate the activities in the field of HMO applications; SYMBA (SYMBiosis for Allergy prevention, Trial Identification Number: ACTRN12615001075572) aims to assess the influence of prebiotic supplements provided between the second trimester and month 6 of lactation on the manifestation of infant allergies. Likewise, the PREGRALL (Efficacy Of Antenatal Maternal Supplementation With GOS/Inulin Prebiotics On Atopic Dermatitis Prevalence In High-Risk One-Year-Old Children, Trial Identification Number: NCT03183440) investigates how prebiotics can modify the risk of developing atopic dermatitis in children aged until 12 mo.

The HIBS study (Human milk oligosaccharides for Irritable Bowel Syndrome, Trial Identification Number: NCT05205785) aims to assess the effects of daily HMO administration for 12 wk on IBS symptoms in adults using a treatment compared with placebo setup. Validated findings from such clinical trials, better availability, and more competitive pricing will facilitate the implementation of HMOs in novel application fields, while broadening their use in the current fields of application. One potential future avenue is to make more sophisticated HMO compositions available in the formula milk market.

Future HMO applications may also venture into areas previously restricted to sophisticated methods of microbiome modulation, such as FMT, which can reshape the entire intestinal community in humans. Successful FMT has been reported in the context of *C. difficile* infection, IBS, and IBD [157–159]. However, this method may exhibit several short- and long-term risks, including diarrhea, infection, sepsis, and fever, many of which are explained by unwanted pathogen transmission [159]. Furthermore, some commensal bacterial species from the donor may exhibit more harmful properties in the different environments encountered by a diseased individual. Here, postbiotics and prebiotics, such as HMOs, represent an alternative, particularly in scenarios where microbiota transplantation is considered unsafe, as none of these risks have been described for HMOs. In the same context, public acceptance of interventions is associated with their origin and production process. A recent study showed that patients have substantial doubts regarding the safety of FMT [160], while it is likely that HMOs may have fewer limitations in acceptance. Considering product safety, one of the next steps could be to examine the long-term effects of HMO treatment on both children and adults. This is particularly relevant since a clinical trial in patients with IBS has shown that the beneficial effects are not persistent when discontinuing HMO supplementation [125]. Safety data on long-term supplementation could also facilitate the integration of HMOs into future diet recommendations; however, the available study data indicate no side effects, independent of the time window examined. Taken together, ongoing clinical trials illustrate the dynamics of the research area, fueled by the available promising results, all of which suggest the increasing clinical and commercial relevance of HMOs in the future.

The driving force of HMO applications and implementation is, and will continue to be, the evidence level available, where clinical trials play a key role. Presently, the ClinicalTrials.gov database, maintained by the National Library of Medicine, lists 107 registered trials on covering the topic of HMOs. Of them, 66 studies include children, 57 adults, and 28 older adults. In comparison, probiotics have been studied in 2586 clinical trials (last accessed February 2025). This not only illustrates the limitations when discussing HMOs but also indicates that parts of our current understanding are shaped by in vitro studies, supplemented by postulated statements. Consequently, assumptions

on the anti-inflammatory properties of HMOs have to carefully take the evidence level available into account: it is mandated to emphasize the nature of the corresponding studies when describing HMO attributes (see also: graphical abstract).

In conclusion, although the health benefits of HMOs have been known for decades, the recent successful large-scale production of individual HMOs by precision fermentation has resulted in a rekindling of interest in the mechanisms underlying the health benefits and exploring new applications of this group of molecules. Currently, the vast majority of clinical trials and studies involving human participants include infants and breastfeeding; consequently, it is challenging to disentangle the contribution of individual HMOs to the health benefits observed. Here, in vitro approaches and model systems will help increase the resolution of the HMO interaction map. In contrast to the wide landscape of applications for infants, there is a large, unexplored field of opportunities to employ HMOs for adults and older individuals. Increasing evidence for the potential of HMOs in combating inflammatory conditions, such as IBS or IBD, is paving the way for broader applications, from nonclinical dietary to personalized clinical interventions.

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Conflict of interest

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