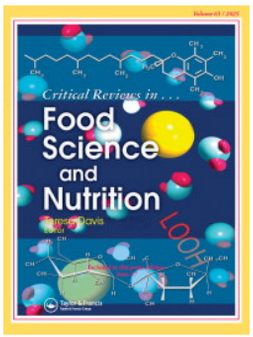

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Impact of non-digestible carbohydrates and prebiotics on immunity, infections, inflammation and vaccine responses: a systematic review of evidence in healthy humans and a discussion of mechanistic proposals

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REVIEW ARTICLE

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Impact of non-digestible carbohydrates and prebiotics on immunity, infections, inflammation and vaccine responses: a systematic review of evidence in healthy humans and a discussion of mechanistic proposals

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ABSTRACT

Prebiotics, particularly non-digestible carbohydrates (NDCs), are increasingly recognized for their role in modulating immune responses in the gut, lungs, and urinary tract. This review systematically evaluates evidence from human studies on the effects of NDCs and prebiotics on immune markers, infection risk and severity, inflammation, and vaccine responses. Prebiotics such as inulin, galactooligosaccharides (GOS), and fructooligosaccharides (FOS) positively influence gut microbiota by promoting beneficial species like *Bifidobacteria*. They also enhance the production of short-chain fatty acids (SCFAs) like butyrate, which interact with immune cells via G-protein-coupled receptors, inducing anti-inflammatory effects. In addition to microbiota-mediated mechanisms, NDCs and prebiotics may directly affect immune and epithelial cells by interacting with pattern recognition receptors (PRRs), enhancing gut barrier function, and modulating immunity. A systematic review of human studies showed that prebiotics, including GOS, FOS, and 2′-fucosyllactose (2FL), reduced infections and increased IgA in healthy infants, while yeast β-glucan reduced respiratory infection symptoms in healthy adults. Yeast β-glucan and GOS supplementation resulted in improvements in NK cell activity. Some effects on vaccine efficacy were noted in young adults, but the overall impact of NDCs and prebiotics on vaccination and systemic inflammation was inconsistent. Further research is needed to clarify the mechanisms involved and to optimize health applications.

KEYWORDS

prebiotic; non-digestible carbohydrates; immunity; infection; inflammation; microbiota

1. Introduction

A well-functioning immune system will promote infection resistance and protect the human body against harmful pathogens, such as viruses or bacteria. Adequate nutrition will support the immune system, but lifestyle, physical exercise, and stress also impact immunity. During aging, there is a decline in specific immune responses which can lead to weaker vaccine responses and an increased susceptibility to and severity of infections. Infancy and childhood are also phases of life in which weaker immune responses may be expected due to immaturity. Infectious diseases are caused by pathogenic microorganisms, such as bacteria and viruses which can be spread between persons via different routes. The gastrointestinal, respiratory and urinary tracts are particularly susceptible to infections. All these tracts have a significant surface area with immunologically active tissue, sampling the external environment, and the gastrointestinal (GI) tract in particular is inhabited by trillions of bacteria that play an important role in determining health and disease. Consequently, pathogens that enter the body via mucus membranes in the intestine, lungs and urinary tract, comprise some of the biggest health challenges worldwide according to the World Health Organization (WHO 2017, 2024).

In the Western world, many infectious diseases are considered to be largely under control, due to a hygienic lifestyle and the availability of vaccines and antimicrobial or

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antiviral pharmaceuticals. Still, respiratory tract viruses like influenza can have serious consequences and even common colds cause sickness and lost work/school days and elevate health care costs annually. More must be done to promote immune defence, as was illustrated by the devastating impact that the emergence of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) had on health in immunocompromised individuals and on the global economy.

Prebiotics are defined as substrates that are selectively utilized by host microorganisms conferring a health benefit (Gibson et al. 2017; Chen, Heyndrickx, et al. 2023). This definition includes, but is not limited to, non-digestible carbohydrates (NDCs). The International Scientific Association for Pro- and Prebiotics (ISAPP) has recently provided scientific criteria to support classification of compounds as prebiotics with emphasis on selectivity, measurable microbiota modulation and association with health outcomes (Hutkins et al. 2025). Compounds such as polyphenols and polyunsaturated fatty acids may also act as prebiotics, although the evidence base for this remains less robust. For this reason, and because of their established safety, widespread use in food and supplements, and consistent clinical outcomes in the context of infection and immunity, this review focuses exclusively on prebiotic carbohydrates. These include well-characterized oligosaccharides such as galactooligosaccharides (GOS), fructooligosaccharides (FOS), inulin, and emerging candidates like β-glucans and resistant starches. Their ability to modulate the gut microbiota and to generate bioactive metabolites further strengthens their relevance in this context (Rastall, Gibson et al. 2022). Key areas of prebiotic research, and findings to date in relation to prebiotics and digestive, immunity, metabolic and cognitive health, as well as some regulatory requirements for health claims are provided in recent reviews (Chen et al. 2023; Tuohy et al. 2024).

There are new data on the human intestinal microbiota and its metabolites which are increasingly implicated in immune effects within the body. Dietary prebiotics, especially NDCs, can modify the microbiota of the intestinal tract. NDCs include dietary fiber and non-digestible oligosaccharides (NDOs), which include molecules of a degree of polymerization (DP) of 2 or more. Dietary fibers, as defined by the European Food Safety Authority (EFSA), include a range of NDCs and lignans from DP3 upwards (EFSA 2010). Some well-studied prebiotics include inulin-type fructans (see below), GOS, pectins and specific human milk oligosaccharides (hMOs) but there are many more prebiotics, some of which are not carbohydrate in nature. Inulin-type fructans comprise structures which are of different chain lengths, such as inulin (degree of polymerization (DP) 2–60), long-chain inulin, oligofructose (DP 2–10) and scFOS (DP 2–5). The term lcFOS describes long-chain inulin in infant formula (often used in combination with GOS [i.e., GOS:lcFOS]), and the term FOS alone may describe scFOS or oligofructose. In the large intestine, NDC-type prebiotics are fermented and metabolized by the microbiota and are transformed into microbial metabolites such as organic acids or short chain fatty acids (SCFAs) and gases, or together with other dietary molecules into indole derivates, all of which are strongly implicated in host immune effects (Martin-Gallausiaux et al. 2021; Ratajczak et al. 2019; Roberfroid 1998). There is also an emerging understanding of host-microbe cross-talk along the gut-lung axis which affects respiratory immunity and inflammation (Dang and Marsland 2019).

The effects of NDC-type prebiotics on immunity were reviewed some time ago (Lomax & Calder, 2009; Roberfroid et al. 2010). Other reviews have focused on predictive markers which can be used to assess immunity and inflammation and provided guidance on the assessment and interpretation of nutritional modulation of immune functions in the general population (Albers et al. 2013; Calder et al. 2013). Recent reviews on prebiotics did not cover infectious diseases in depth (Blaak et al. 2020; Rastall et al. 2022). Overall, the recent research including human clinical research, gut microbiota effects and resultant metabolites suggests a beneficial effect of NDC-type prebiotics on immunity and resistance to infections. Therefore, it is timely to focus on this specific subject of the impact of NDC-type prebiotics on immunity, infections, inflammation and vaccine responses in detail and to perform a systematic review of current evidence for impact of prebiotics and NDCs on these outcomes in humans.

In this context, the goal of this review is to assess the scientific evidence for the effects of NDCs and prebiotics on markers of immunity and inflammation, response to vaccination and outcomes related to infection in generally healthy humans (infants, children, adults, older people). We include a systematic review of the relevant literature on these outcomes in humans. This is followed by a proposal for mechanisms by which NDCs and prebiotics can act either via effects in the gastrointestinal GI tract or via crosstalk with the lungs and urinary tract (Fleming 2024).

1.1. Gastrointestinal, respiratory and urinary tract immunology

To gain a clearer understanding of how prebiotics might influence immunity, we reviewed the current research on the potential targets of action in the gut, lungs, and urinary tract.

1.1.1. Gastrointestinal tract immunology

Most prebiotic NDCs are considered to have a profound impact on the microbiota within the GI tract, especially the colon (Beukema, Faas, and de Vos 2020; Swanson et al. 2020). The GI immune barrier starts from the luminal side with a mucus layer, followed by a monolayer of tightly connected epithelial cells and the lamina propria in which 80% of the human body's immune cells reside (Mowat and Agace 2014). The mucus also serves as a substrate for many gut microbes (Figueroa-Lozano et al. 2020; Gasaly, de Vos, and Hermoso 2021; Jakobsson et al. 2015; Kong et al. 2020; Peterson and Artis 2014) In addition to colonizing the GI lumen, microbes also reside in the mucus layer and can interact with pattern recognition receptors (PRRs) on immune or epithelial cells or produce immune-active microbial products such as SCFAs (Jung et al. 2015). Dietary NDC

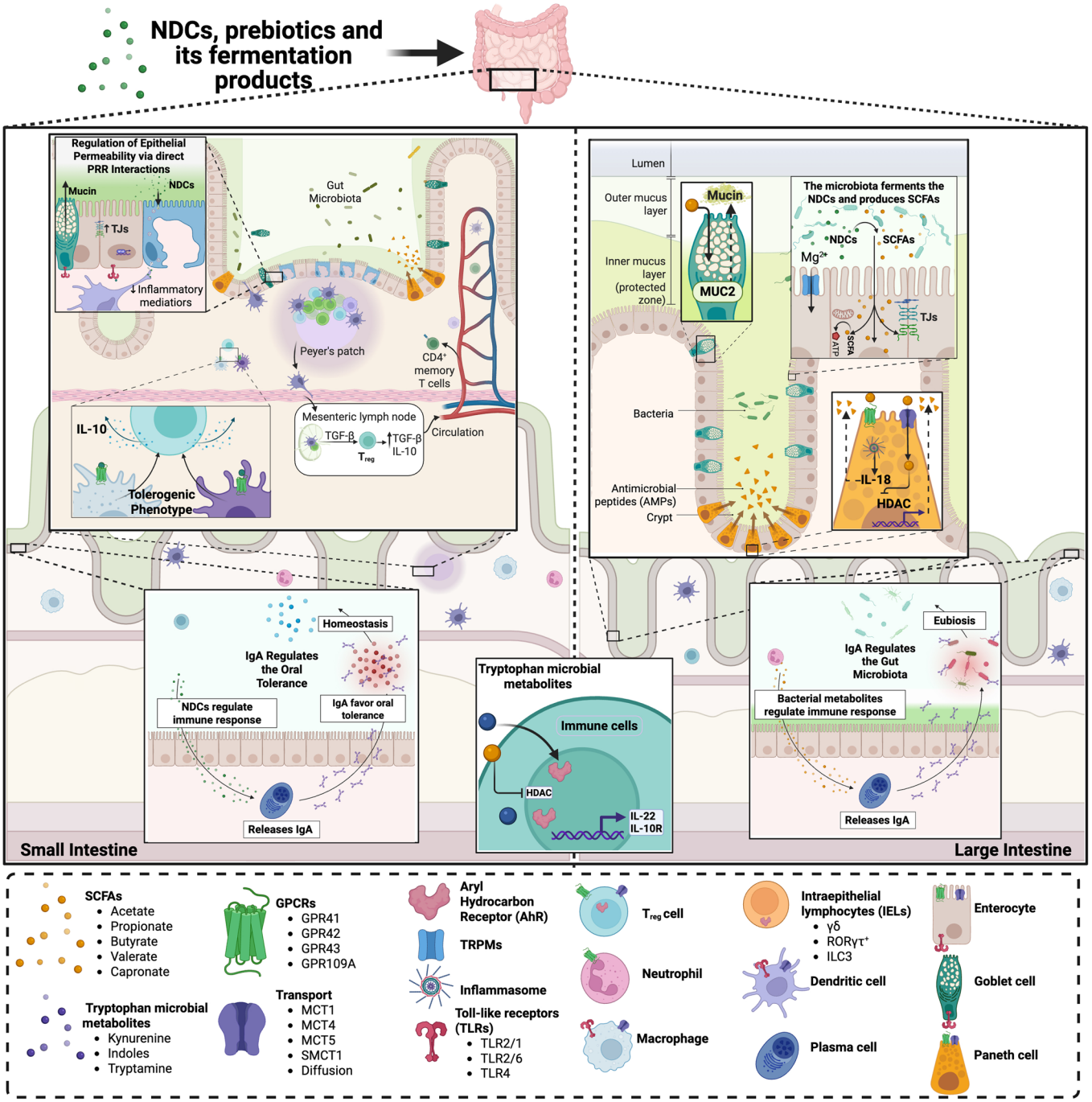

Figure 1. The gastrointestinal (GI) immune barrier and key elements influenced by prebiotics and non-digestible carbohydrates (NDCs) and their fermentation products. The figure illustrates key components of the intestinal immune system, including the mucus layer, epithelial cells, and the lamina propria, which houses a large portion of the body's immune cells. NDCs and prebiotics support gut health by influencing the gut microbiota and promoting the production of short-chain fatty acids (SCFAs), which can regulate immune responses via G-protein coupled receptors (GPRs). The microbiota also interacts with pattern recognition receptors (PRRs) on immune cells, contributing to immune homeostasis and tolerance. Immune cells like dendritic cells (DCs) and macrophages play a critical role in detecting harmful microbes and orchestrating tailored immune responses. The gut's complex immune network is further illustrated through the interaction of microbial metabolites with immune cells, demonstrating the close connection between gut microbiota and intestinal immunity.

prebiotics or fibers can both act on PRRs and promote SCFA production (Figure 1). The mucus layer is also a reservoir for immunoglobin A (IgA) and Paneth cell-derived anti-microbial components that promote immune defenses (Faderl et al. 2015) which also can be supported by NDCs (Wang et al. 2017).

The mucus layer is in close connection with the gatekeeper of the human intestine, the epithelial immune barrier. Within the epithelial layer are dendritic cells (DCs) and intraepithelial lymphocytes. In some regions, an additional epithelial cell type called microfold (M) cells can be found within subepithelial lymphoid structures called Peyer's patches (PP). These M cells are antigen sampling cells and present antigens to underlying immune cells (Dillon and Lo 2019). The permeability of the epithelial layer is highly regulated by a network of desmosomes and tight junctions that

regulate the paracellular passage of luminal components to the lamina propria (Arrieta, Bistritz, and Meddings 2006). NDCs can influence this process by PRR activation or through SCFA-induced G-protein coupled receptor (GPR) activation (Abreu 2010; Chen et al. 2018).

Most of the human body's immune cells are located in the lamina propria, PP and mesenteric lymph nodes (MLNs) (Mowat and Agace 2014). The lamina propria is the homing site for many types of innate immune cells such as macrophages, innate lymphoid cells, DCs, and granulocytes. Also, adaptive immune cells, such as B cells and T cells are found in large numbers in the lamina propria. Through PRRs, DCs and macrophages can recognize harmful microbes and phagocytose them, subsequently presenting the derived antigens to T cells in the lamina propria, PP or MLNs, together termed the gut-associated lymphoid tissue (GALT). This can induce tailored immune responses (Joeris et al. 2017). Many of the immune cells in the lamina propria are equipped with receptors for microbial metabolites such as GPRs for microbial-derived SCFAs or aryl hydrocarbon receptors for microbial indoles (Pezoldt et al. 2018) illustrating the close connection between the gut microbiota and intestinal immunity.

The immune responses in the intestine are highly regulated and allow adequate proinflammatory responses to pathogens but at the same time permit a fast tolerance to food components or commensal microbiota (Agace and McCoy 2017). Tolerance is induced to different antigens in the small and large intestine. In the small intestine, tolerance induction is more directed to dietary antigens while in the large intestine, where most of the microbiota resides, it is more directed to tolerance for intestinal microbiota (Agace and McCoy 2017; Mann et al. 2016). NDCs support this tolerance by either direct interaction with PRRs or by supporting the production of tolerance-inducing microbial metabolites.

1.1.2. Respiratory tract immunology

The lung immune barrier consists of similar physical and cellular effector mechanisms as the GI tract. The gradually thinning compartments of the lungs, i.e., trachea, bronchi, bronchioles and finally microscopic air-filled alveoli, are covered in mucus (Hewitt and Lloyd 2021). The underlying epithelium is composed of ciliated and mucus-producing epithelial cells, interspersed with lymphocytes, antigen-sampling DCs and other immune cells (Figure 2) (Hewitt and Lloyd 2021). Although the lungs possess a low-density microbiota, the primary role of airway mucus is to trap and remove inhaled particles and chemicals, via cilia-assisted expulsion (Fahy and Dickey 2010). While airway mucus production is central to pulmonary health, mucus hypersecretion is associated with poor health outcomes (Fahy and Dickey 2010; Li and Tang 2021; Zanin et al. 2016).

Unlike the GI tract, the airway lumen, specifically the alveolar space, contains immune cells at a steady state, primarily alveolar macrophages (AMs) (Figure 2) (Hussell and Bell 2014). Alveolar macrophages act as immune sentinels and efficiently kill invading microorganisms, but also actively inhibit proinflammatory responses to innocuous inhaled antigens or particles (Hussell and Bell 2014). Although AMs make up the largest population of pulmonary macrophages, interstitial macrophages (IMs) reside in the lung parenchyma and perform additional regulatory functions (Figure 2) (Byrne et al. 2015). Following injury or infection, AMs and IMs are functionally assisted by infiltrating monocyte-derived macrophages (Bain and MacDonald 2022).

Adaptive immune responses to pulmonary insults and pathogens are typically initiated by AMs and/or DCs (monocyte-derived, plasmacytoid or conventional) located in the lung parenchyma (Guilliams, Lambrecht, and Hammad 2013). Similarly to gastrointestinal adaptive immune responses, PRR engagement, antigen processing and presentation eventually lead to T and B cell activation in bronchus-associated lymphoid tissue (BALT) or lung-draining lymph nodes (Chiu and Openshaw 2015). BALT has recently been shown to be particularly common in early human life and the inducible formation of BALT throughout life, predominantly upon respiratory infection, is an active topic of investigation (Matsumoto et al. 2023; Silva-Sanchez and Randall 2020). NDCs support the periodic recruitment of circulating immune cells to the lung and BALT through the gut-lung axis mentioned earlier, which involves the modulation of hematopoiesis in the bone marrow (Dang and Marsland 2019; Martin-Gallausiaux et al. 2021; Ratajczak et al. 2019; Roberfroid 1998).

1.1.3. Urinary tract immunology

The urinary tract is composed of the kidneys, two ureters, the bladder and the urethra and, apart from the urethra, is believed to be largely sterile. Although the distal urethra is constantly exposed to microorganisms that naturally colonize the GI tract (Flores-Mireles et al. 2015), it only forms tertiary lymphoid structures upon infection, except for prostate-associated lymphoid tissue (PALT) found in humans (Di Carlo et al., 2007; Silva et al. 2020). The urinary tract predominantly relies on innate immune defenses to protect itself from urinary tract infections (UTIs), which are particularly common among the elderly and certain patient groups, and which occur 30-times more frequently in women than in men (Tan and Chlebicki 2016; Soudais et al. 2021).

The epithelium that lines the urinary tract is impermeable, a necessary function to safely contain any noxious substances contained in urine and a physiological barrier protecting against pathogens and their aggregation is the strong flushing effect of urine (Song and Abraham 2008). As in other systems of the human body, the epithelial cells lining the urinary tract express PRRs capable of recognizing pathogen-associated molecular patterns (PAMPs) for a variety of pathogens, including, similarly to the gut and lungs, toll-like receptor (TLR) 2 (recognizes bacterial lipoteichoic acid or lipoprotein), TLR3 (recognizes double stranded RNA), TLR4 (recognizes lipopolysaccharide [LPS]), TLR5 (recognizes flagellin), TLR9 (recognizes unmethylated CpG DNA of bacteria and viruses), and TLR11 (recognizes profiling of parasites). Upon stimulation, urinary tract epithelial cells release pro-inflammatory cytokines, such as interleukin (IL)-1ß, IL-6 and IL-8, as well as anti-microbial peptides and effector molecules (Abraham and Miao 2015). Similarly to the lungs, macrophages constitute the first line of

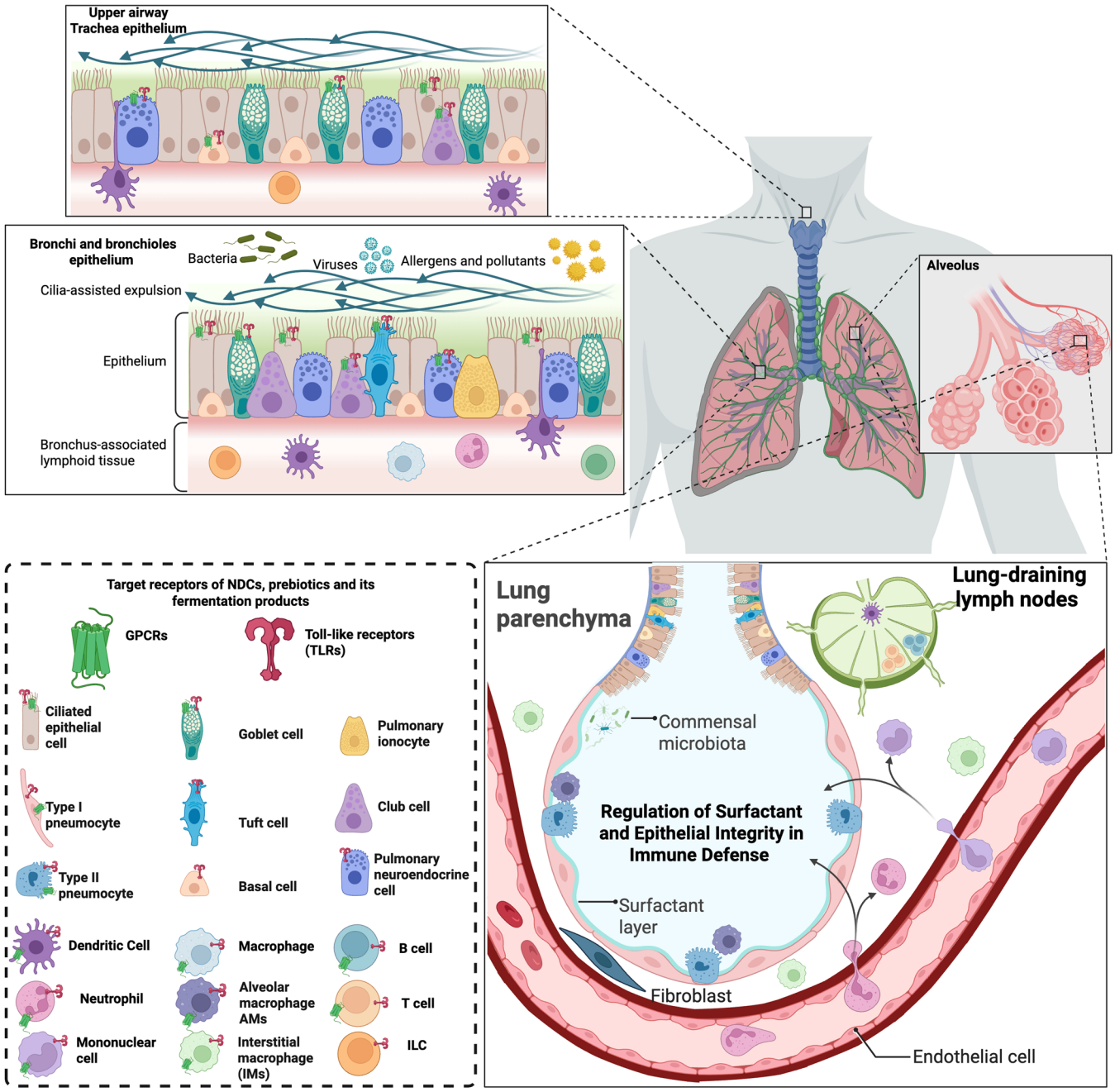

Figure 2. The respiratory tract and lung-associated immune system. The lungs are structurally divided into the upper and lower repiratory airways, forming the tracheobronchial tree. The right and left lobes are connected to the trachea by a bronchus. Each bronchus further branches into bronchioles which, after several generations of branching, are terminated by clusters or sacs of alveoli. The tracheobronchial tree is lined by specialized epithelial cells, including ciliated epithelial cells, goblet cells, tuft cells, ionocytes, club cells, basal cells and neuroendocrine cells, each with distinct functionalities which support pulmonary homeostasis. In contrast, the alveolar epithelium is exclusively composed of type I and type II pneumocytes and is covered in surfactant, which supports gas exchange. Bronchus-associated lymphoid tissue is located just beneath the pulmonary epithelium, adjacent to major airways and arteries to facilitate pulmonary immune defence. Alveoli are additionaly protected by alveolar macrophages, which reside in the alveolar space. Target receptors of prebiotics and NDCs, such as G-protein coupled receptors (GPCRs) and toll-like receptos (TLRs) are widely expressed throughout pulmonary epithelial cells and lung resident or trafficking immune cells, providing a mechanistic framework for gut-lung crosstalk.

professional immune defense in the urinary tract. These macrophages populate the submucosa and can initiate further immune cell recruitment and inflammatory immune responses through the release of chemokines. The steady-state immune surveillance of the urinary tract is complemented by mast cells, another innate immune cell able to release pre-stored inflammatory effector molecules such as tumor necrosis factor alpha (TNF-α) and histamine. Adaptive immune responses are limited, and even actively inhibited, within the urinary tract, possibly to limit extensive inflammation which could damage the epithelium and put the host at risk (Abraham and Miao 2015) (Figure 3).

In summary, the gut, lungs and urinary tract have characteristically distinct immune systems which are each designed to optimally protect these organs from their respective common immunological threats while balancing the need to

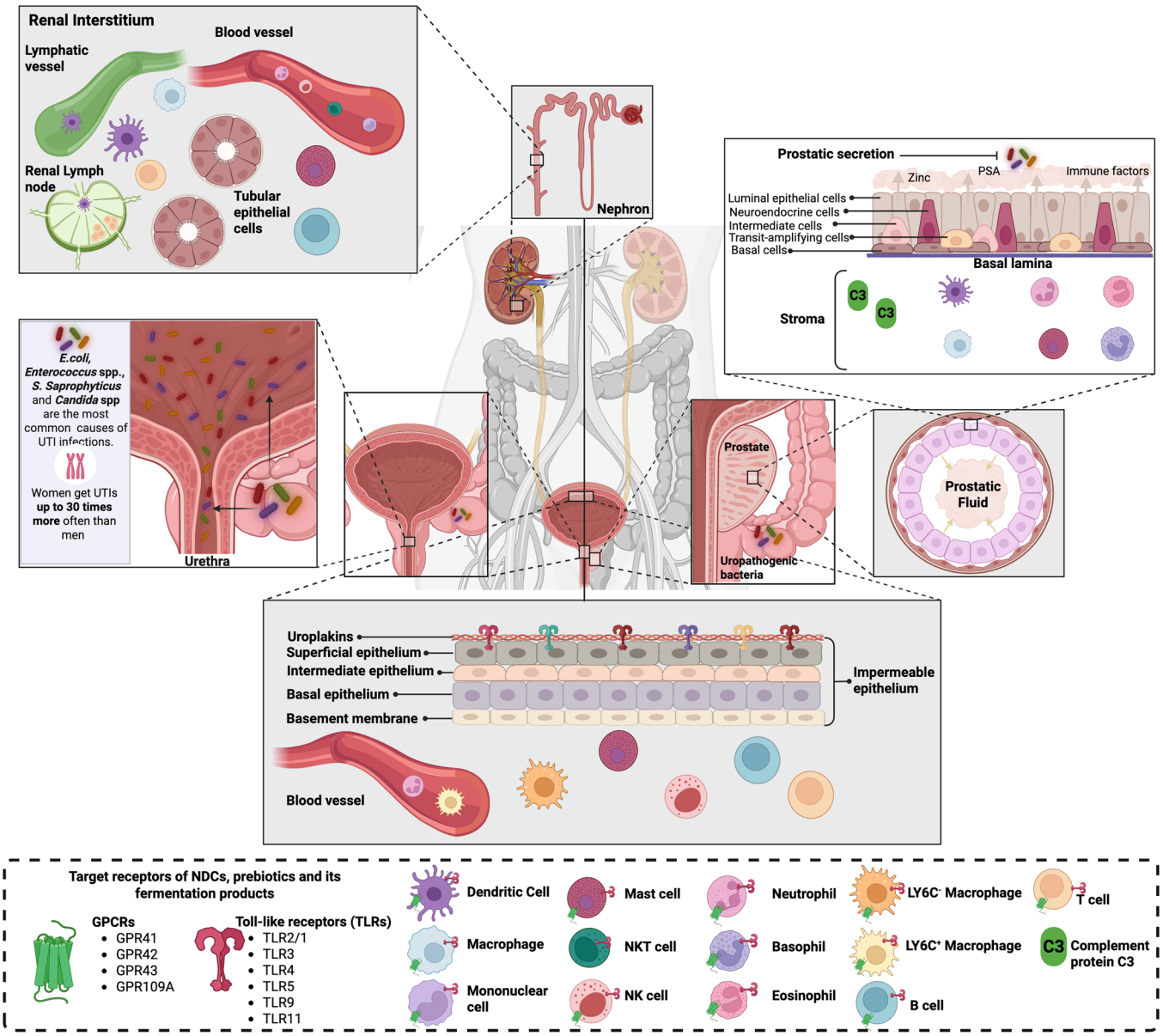

Figure 3. The urinary tract and immune system cells. The urinary system can be divided into the upper and lower urinary tract. The upper urinary tract consists of the kidneys, in which the basic filtration unit is the nephron, which consists of a glomerulus and a renal tubule. Dendritic cells and macrophages accumulate in large numbers in the interstitial tissue of the kidneys. In addition, renal parenchyma is a tissue densely supplied with lymphatic vessels and lymph nodes. The lower urinary tract consists of the ureters, urinary bladder, and urethra. The impermeable epithelium lining the urinary tract consists of layers of stratified epithelial cells, which is the first biological barrier. Below the basal epithelium are numerous mast cells and LY6C$^-$ macrophages. These cells recognize infectious agents and are responsible for the recruitment of natural killer (NK) cells and LY6C$^+$ macrophages to the urinary bladder. In men, the prostate gland is also distinguished as an element of the urinary system. The prostate gland is made up of epithelial cells in the glandular part and stromal cells. Toll-like receptors (TLRs) are widely expressed in both epithelial and stromal cells. The innate component of the immune system in the prostate is the complement system protein C3 (C3). The prostate gland is inhabited by macrophages, neutrophils, dendritic cells (DCs), mast cells, basophils and eosinophils. Prostate fluid contains factors which have antimicrobial and immunomodulatory functions.

maintain homeostasis and prevent the breakdown of their physiological functions due to uncontrolled inflammation. It follows that the ability of NDCs and prebiotics to independently influence innate and adaptive components of human immunity will differentially impact these organs.

1.2. Microbiota and immunity

The food we eat directly influences host immunity and other biological processes and indirectly influences these processes via effects on the microbiome (Calder 2013). Diet plays the most significant role in shaping the composition of the gut microbiota. Non-digestible dietary components are metabolized by the microbiota, producing signaling molecules in the process. These dietary components include NDCs, proteins, and amino acids. Other intestinal molecules secreted by the host, such as bile acids and hormones, are also metabolized by microbes. Depending on the origin, microbial metabolic products are divided into four categories (Figure 4). The first family of microbial metabolites that influence immunity consists of products transformed from host-derived molecules, such as SCFAs but also bile acids. In both humans and mice, the most abundant SCFAs are acetic

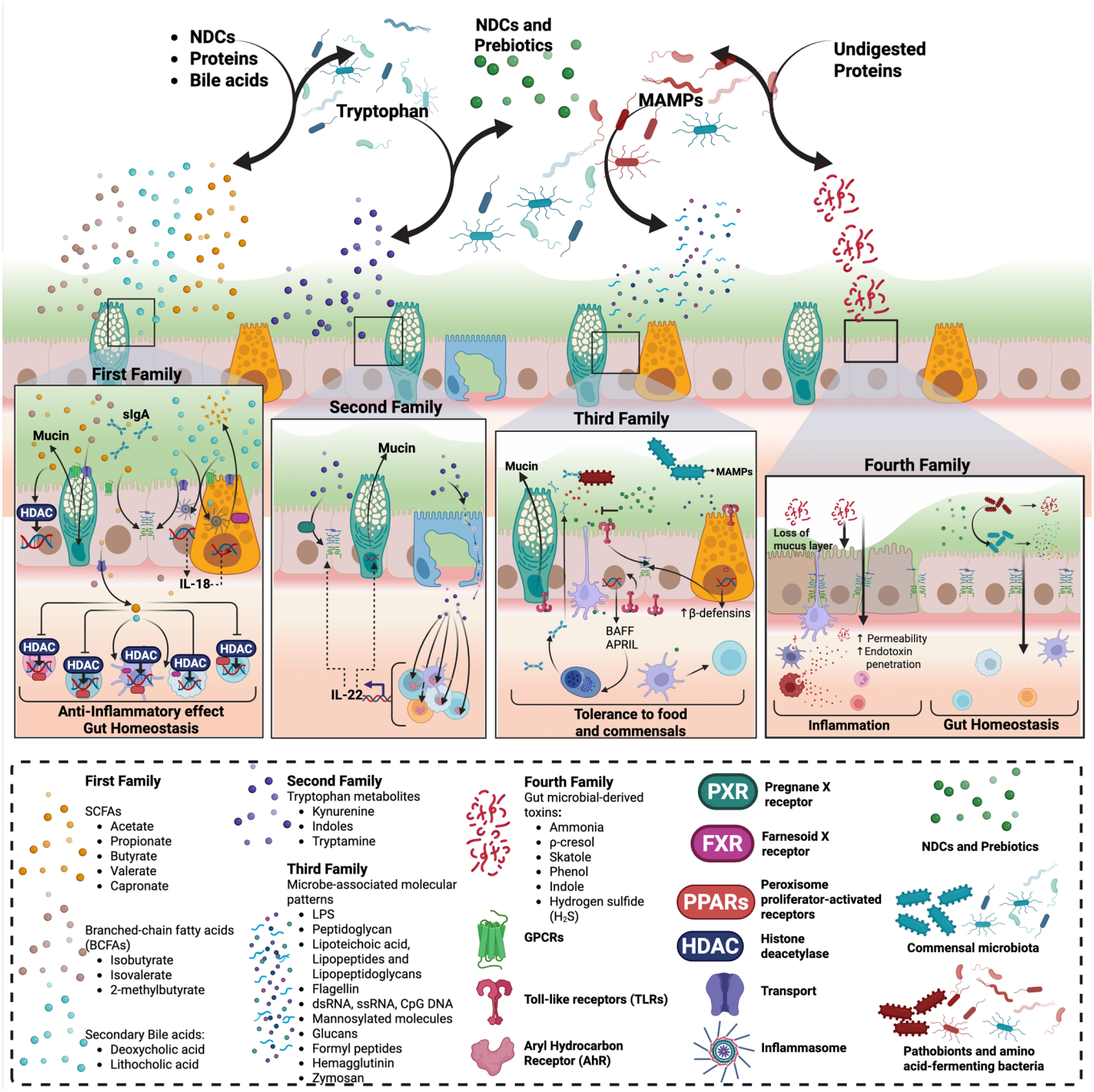

Figure 4. The four families of microbial metabolites and their effects on gut immunity and homeostasis. The first family consists of short-chain fatty acids (SCFAs) and secondary bile acids, which are produced by the metabolism of host-derived molecules like NDCs and bile acids. These metabolites play a role in maintaining gut homeostasis by modulating inflammation through mechanisms such as G-protein coupled receptor (GPR) activation and histone deacetylase inhibition (HDACi). The second family consists of microbial metabolites derived from dietary components such as tryptophan, which influence immune responses via aryl hydrocarbon receptors (AhRs). The third family includes classical microbe-associated molecular patterns (MAMPs) such as lipopolysaccharides (LPS) and peptidoglycans, which can induce immune responses by interacting with pattern recognition receptors (PRRs). The fourth family consists of microbial-derived toxins that negatively impact gut immunity, potentially leading to inflammation and compromised barrier function. The interaction between NDCs, gut microbiota, and the immune system illustrates the complex role of diet in regulating intestinal health and immunity.

acid (C2), propionic acid (C3), and butyric acid (C4) (Cummings and Macfarlane 1991). While the highest concentrations of these metabolites exist at the site of production (the intestinal lumen), they are actively transported from the gut (McNeil, Cummings, and James 1978) into the bloodstream, and circulate systemically, allowing them to interact with, and influence, multiple cells and tissues within the body (Cummings et al. 1987). SCFAs are sensed by cells via two known mechanisms: receptor-mediated (e.g., via GPRs) and histone deacetylase inhibition. There are three SCFA-sensing GPR classes: GPR41 (*FFAR3*), GPR43 (*FFAR2*), and GPR109a (*HCAR2*) (Brown et al. 2003; Ganapathy et al. 2013). These receptors are found on a variety of cell types, including mucosal cells and immune cells with both

overlapping and distinct patterns of expression (Yip et al. 2021). They vary in their affinity for their ligands (including both SCFA and non-SCFA ligands). Signaling through these receptors generates a broad range of responses, the result of which is generally to dampen inflammation (Parada Venegas et al. 2019). SCFAs are also sensed via peroxisome proliferator-activated receptors (PPARs), a family of ligand activated transcription factors (Byndloss et al. 2017; Kinoshita, Suzuki, and Saito 2002). Like SCFA-sensing GPRs, this receptor family is broadly expressed across different cell types, including both immune and non-immune tissues. Activation of PPARs exerts broad anti-inflammatory effects (Grygiel-Górniak 2014). Gut microbes can also convert bile acids into secondary bile acids, which then activate bile acid receptors found on host cells (Baars et al. 2018). The second family of metabolites are those derived from the diet. An example of this family is microbial metabolites of dietary tryptophan such as kynurenine, indoles, and tryptamine (Gasaly, de Vos, and Hermoso 2021), which act on aryl hydrocarbon receptors to regulate immunity. The third family of molecules are the classical microbe-associated molecular patterns such as LPS and peptidoglycans. These potent immune-modulatory molecules act on host cells via PRRs. These three families act in combination to fine-tune immune responses. The fourth family of molecules that are gaining more attention are toxins that are transformed by microbes and negatively impact immunity. NDCs are known to work through various mechanisms, potentially affecting all four categories both locally and systemically, and can also interact directly with human cells.

In addition to supporting immunity, NDCs also may promote health by acting competitively to provide stereospecific protection against a variety of pathogens (Walsh et al. 2020). Glycan structures, particularly those found on hMOs, can be similar in structure to those used by pathogenic bacteria to attach to gut epithelial cells (Laucirica et al. 2017). Soluble glycans can therefore act as decoy receptors, binding potentially harmful bacteria and viruses to prevent them from infecting the host.

Another mechanism by which NDCs (via microbiota) might influence health is by regulating histone modification induced by microbial products. Histone modification is an epigenetic process by which histones are covalently modified to change the way they interact with DNA, determining the accessibility of the DNA for transcription. Generally, acetylation of histones is associated with increased transcriptional activation. This reaction is catalyzed by histone acetyltransferases (HATs), and the reversal by histone deacetylase complexes (HDACs) (Hamminger, Rica, and Ellmeier 2020). SCFAs inhibit HDAC activity (Waldecker et al. 2008). Therefore, the overall effect of SCFAs is to promote gene transcription. Butyrate is the most potent inhibitor of HDACs, followed by propionate (Waldecker et al. 2008). The net result of HDAC inhibition via SCFAs on the immune-cell transcriptional profile is anti-inflammatory (Tan et al. 2014). In addition to histone modification, HDACs have also been found to modify non-histone targets, including transcription factors, modifying their stability and function (Singh et al. 2010).

1.2.1. Compromised gut barrier function

The gut barrier is comprised of commensal microbiota, mucus, epithelial cells and the GALT. The barrier is selectively permeable to bacteria and bacterial products from the intestinal lumen due to the intracellular protein structures, tight-cell junctions (TCJs), desmosomes, and adherence junctions, that lie between adjoining epithelial cells. Disruption to this barrier can occur following the production of proinflammatory cytokines such as IL-1β, TNF-α and IFN-γ by immune cells in response to the presence of non-tolerated antigens in the LP (Amasheh et al. 2009; Moretó and Pérez-Bosque 2009). These cytokines generate a downstream response within epithelial cells which ultimately leads to the internalization of intracellular tight-cell junction proteins (Bruewer et al. 2003; Hu et al. 2013). This process increases gut permeability and can lead to a condition also known as "leaky gut". This is a bidirectional relationship, as reduced barrier function leads to greater numbers of antigens or endotoxins entering the LP which initiate an inflammatory response, which may further increase permeability. Certain dietary patterns may act as instigators for the increased intestinal permeability that leads to the above immune responses. High fat diets can reduce barrier function in vivo and the fermentation of dietary protein produces metabolites associated with increased permeability of cell lines in vitro (Geypens et al. 1997; Hang et al. 2013; McCall et al. 2009). Both these effects are negated with the introduction of specific prebiotics (Cani et al. 2008; Delzenne, Neyrinck, and Cani 2011; Xuedan, Manuela, and Stephan 2020). This provides evidence for the influence of the microbiota on the integrity of gut barrier function.

1.2.2. Gut – lung axis concept

The oral and nasal cavities are the main entry sites of colonizing bacteria for lung and gut ecosystems which partially share taxonomic patterns, e.g., *Bacteroidetes*, *Firmicutes* phyla (Budden et al. 2017). Despite having similar mucosal structures, the lung and gut ecosystems differ significantly, particularly at the species level. For example, the lungs host species like *Pseudomonas* spp. and *Streptococcus* spp., whereas the gut contains species such as *Faecalibacterium prausnitzii*, *Bacteroides thetaiotaomicron*, and *Bifidobacterium longum*. These differences are primarily due to specific local conditions, including oxygen availability, pH and nutrient exposure. Notably, the lung microbiota is considered more adaptable or versatile in response to these conditions (Bingula et al. 2017; Dumas et al. 2018). These seemingly distant microbial ecosystems are at least partially interconnected. It has been suggested that bacteria and viruses can be transferred from the lungs to the gut, likely due to the bidirectional nature of pulmonary respiration, in contrast to the one-way movement of gut transit (Samuelson, Welsh, and Shellito 2015). Modulation of lung microbiota as a result of manipulating the gut microbiota has been suggested, though the mechanisms remain unclear and are likely to be indirect. Both the gut and lung microbiota, along with their metabolites, particularly SCFAs, have shown significant ability to reprogram, fine-tune, and alter the immune system,

both locally and systemically, through various pathways. For instance, luminal antigens are recognized by TLRs on DCs, triggering immune responses. Additionally, exposure to specific gut bacteria influences immune cells and cytokine production, while gut-derived SCFAs can stimulate hematopoietic precursors in the bone marrow (Baradaran Ghavami et al. 2021; Bingula et al. 2017; Budden et al. 2017; Dang and Marsland 2019; Samuelson, Welsh, and Shellito 2015). The concept of the gut-lung axis, primarily developed over the past five years, suggests that the gut ecosystem can modulate lung immunity, and that a reciprocal connection may also exist. Studies have highlighted correlations between various respiratory tract infections, including influenza, tuberculosis, and COVID-19, and gut microbiota composition (Baradaran Ghavami et al. 2021; Enaud et al. 2020; Saint-Criq, Lugo-Villarino, and Thomas 2021; Samuelson, Welsh, and Shellito 2015; Yeoh et al. 2021). While correlations between gut and lung microbiota have been well established, the causal relationship remains poorly understood and warrants further investigation. Current evidence points to crosstalk between the gut, lung, and their local immune systems, facilitated by the exchange of immune cells and immunological compounds (such as cytokines) through blood and lymphatic pathways. This suggests that, beyond systemic immune modulation, the gut may exert a direct immunological influence on lung tissue. Several hypotheses propose that migrating immune cells, cytokines, and other compounds play a role in this interaction, with variations depending on factors like age or immune status (e.g., infection *versus* allergy). From the gut to the lung, key players such as activated and differentiated T cells (e.g., regulatory, type 17 (Th17) and type 1 (Th1) $CD4^+$ T cells), interferons (IFN-α, IFN-β, IFN-γ), TNF-α, NF-κB, and various interleukins (e.g., IL-6, IL-13, IL-25) are thought to be involved in this process (Baradaran Ghavami et al. 2021; Bingula et al. 2017; Enaud et al. 2020; Samuelson, Welsh, and Shellito 2015; Willis and Ambalavanan 2021). Building on this concept of gut-lung immune interaction, two recent in vivo studies in mice have provided further evidence of specific migrations from the gut to the lungs in the context of infection. In one study, group 2 innate lymphoid cells (ILC2) were shown to migrate from the gut to the lungs, a process triggered by gut *Proteobacteria* and the production of IL-33 (Pu et al. 2021). In another study, gut-derived LPS and SCFAs were found to act on specific receptors in pulmonary alveolar cells, particularly macrophages, leading to the upregulation of local IL-1β (Liu et al. 2021). These findings highlight the potential pathways through which gut microbiota can influence lung immune responses during infection (Liu et al. 2021; Pu et al. 2021). Moreover, it has been proposed that bacterial translocation from the gut lumen to the lungs may occur due to increased intestinal permeability, particularly in cases of sepsis and acute respiratory distress syndrome (ARDS). This suggests a potential pathway through which gut barrier dysfunction could contribute to lung infections and complications (Baradaran Ghavami et al. 2021). In a reciprocal manner, crosstalk from the lungs to the gut has also been observed, involving differentiated B and T cells, as well as cytokines like IL-6, IFN-γ, and TNF-α. This further reinforces the concept of the gut-lung axis, where the lung ecosystem may play a role in supporting gut immunity, highlighting the bidirectional nature of these interactions (Bingula et al. 2017; Enaud et al. 2020; Pu et al. 2021; Saint-Criq, Lugo-Villarino, and Thomas 2021; Zhang et al. 2020).

2. A Systematic review of effects of NDCs on immunity, inflammation, vaccine responses and infection in humans

2.1. Methodology

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews (PRISMA-SR) guidelines (Page et al. 2021).

2.1.1. Information sources

A systematic search was performed to identify all human randomized controlled trials (RCTs) that evaluated the effects of NDCs and prebiotics on markers of immunity, infections, inflammation, and vaccine responses. A comprehensive literature search was performed using PubMed, Scopus and Embase to identify human RCTs published up to January 28th 2025.

2.1.2. Search and selection criteria

The search strings applied to identify relevant literature can be found in Supplemental Table 1. All identified records were imported into Covidence software (Covidence, 2024) which was then used to remove duplicates. Titles and abstracts were screened by two independent reviewers and conflicts were solved during meetings with all coauthors. The remaining full-text papers were screened again by two independent reviewers. Any remaining duplicates were removed at this stage.

Inclusion criteria were the following: RCT conducted in humans; conducted in healthy participants (including those with obesity but without any diagnosed co-morbidities); included a control or placebo group/arm; a measure of immunity, inflammation, infection or vaccination was mentioned in the title or abstract; full text availability; published in the English language.

Studies were excluded if they were in vitro or animal studies; epidemiological studies; abstracts, reviews, case reports or commentaries; involved enteral feeding or non-oral intake; had only a single administration; used whole foods, dietary intervention, or a substance not listed in the prebiotic search terms; did not report relevant outcomes. Figure 5 shows the flow of the selection of publications for inclusion.

2.1.3. Quality assessment, data extraction and synthesis

The Cochrane Risk of Bias Tool for randomized trials (RoB2) was used to assess the quality of the studies (Sterne et al. 2019). Quality assessment of the included studies was conducted independently by two authors. Any disagreements were resolved through discussions within the review team.

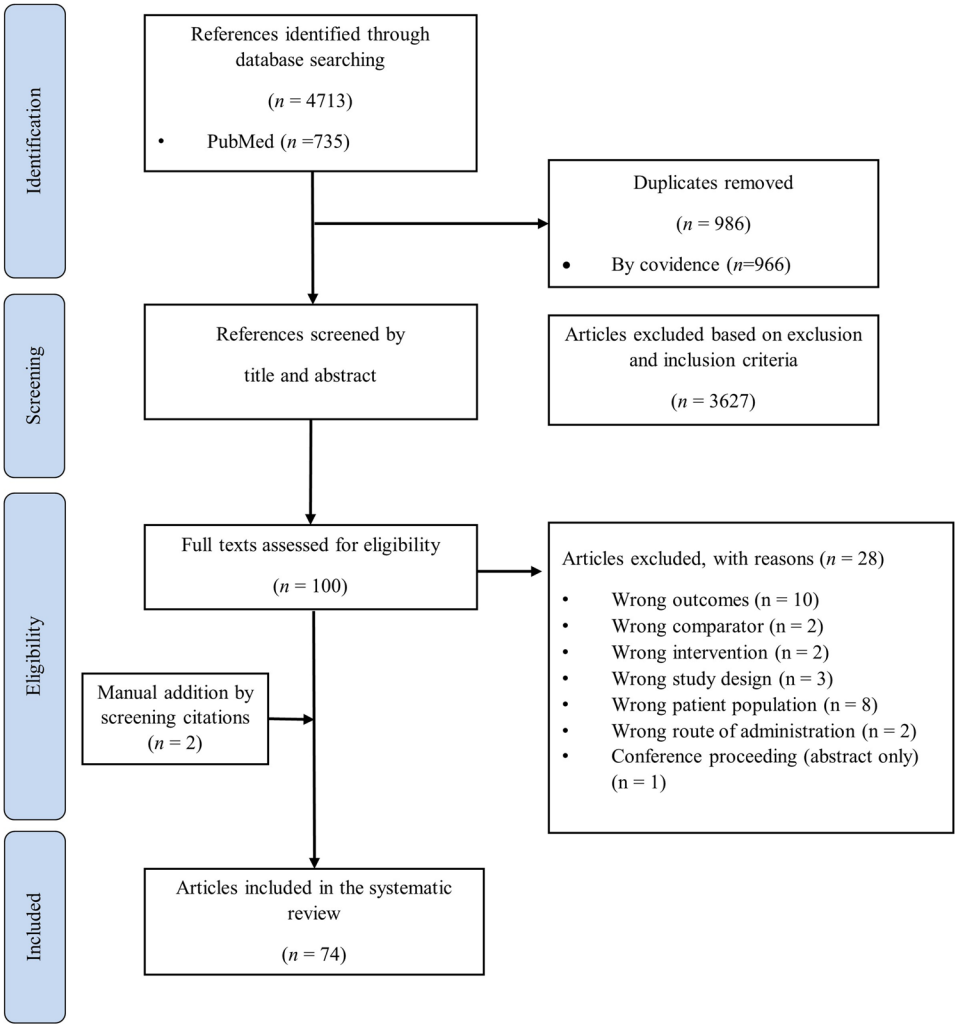

Figure 5. PRISMA flow diagram showing the selection of articles for inclusion in the review.

The tool is structured into five domains; these are the risk of bias arising from the randomization process, risk of bias due to deviations from the intended interventions (effect of assignment to intervention applied herein), missing outcome data, risk of bias in the measurement of the outcome, and risk of bias in the selection of the reported result. Domain-level judgements provide the basis for an overall risk-of-bias judgment. To visualize the risk-of-bias results, traffic light plots and bar plots were generated using the robvis tool (McGuinness and Higgins 2021). Traffic Light Plots show each individual study's domain-level judgements. The judgments are categorized as low risk of bias, some concerns, or high risk of bias. These were visually represented as green, yellow, and red color, respectively. Bar plots show the distribution of risk-of-bias judgements within each bias domain.

Data extraction was performed by first importing the list of included studies from Covidence into an Excel spreadsheet. The data were extracted and collated from the selected publications by two independent reviewers, with a review of the data by all researchers. The studies were categorized according as follows (examples of their related reported outcomes are provided): Immunity: immune cell numbers, T cell proliferation, T cell and monocyte response to stimulation, immunoglobulins (faeces, blood, saliva); Infection: incidence, duration, severity, viral and bacterial titer; Vaccination: anti-vaccine antibodies, seroprotection, seroconversion; Inflammation: cytokines, C-reactive protein (CRP), calprotectin, transcriptomics. The extracted data also included the type of population studied (i.e., life stage, health status), prebiotic type and dose, placebo type and dose, duration of intervention, study country, as well as study design and sample size (Supplemental Table 2).

2.2. Immunity

40 studies investigated the effect of NDCs and prebiotics on markers of immunity (Table 1). Nine studies were conducted in older adults, 20 in adults, 10 in infants and one in children. Studies in older adults used GOS ($n=4$), β-1,3–1,6-glucan ($n=1$), inulin ($n=1$), FOS ($n=2$) or compared multiple prebiotics including soluble and insoluble β-1,3–1,6-glucans ($n=1$). Studies in adults predominantly used β-glucans (from oat ($n=1$), from yeast ($n=3$) as pleuran (β-1,3–1,6-glucan) ($n=2$), from *Agrobacterium* sp. R259 (β-1,3 glucan) ($n=1$), from Reishi (β-1,3–1,6-glucan) ($n=1$), from *Euglena gracilis* ($n=1$) or of unspecified origin ($n=1$)),

Table 1. Effects of NDCs/prebiotics on immune outcomes.

Author, Year	Population	Population description and health status at enrolment/ baseline	Description and dose of NDC/prebiotic intervention	Duration of intervention	Endpoints	Assessment methodology	Time points assessed	Effect on immune outcome(s)
Alliet et al. (2022)	Infants	Healthy; Age at enrolment (days): Formula-fed infants: ≤14; Treatment: M = 6.8 (SD = 3.98); Control: M = 6.7 (SD = 3.80); Sex (% female): Treatment: 52.1; Control: 53.1; Birth weight (kg): Treatment: M = 3.3 (SD = 0.44); Control: M = 3.4 (SD = 0.42)	Milk-based formula with probiotic + 2′FL (1 g/L)	180 days	Faecal sIgA	ELISA	1, 2, 3 months	NS
					Faecal b-defensin	ELISA	1, 2, 3 months	NS
Bosheva et al. (2022)	Infants	Healthy; Age (days): Dose 1 of hMOs (1.5 g/L): M = 14.7 (SD = 4.5); Dose 2 of hMOs (2.5 g/L): M = 14.3 (SD = 4.5); Control: M = 14.5 (SD = 4.6); Breast-fed: M = 15.4 (SD = 3.8); Sex (% female): Dose 1 of hMOs (1.5g/L): 50.6; Dose 2 of hMOs (2.5g/L): 49.7; Control: 48.4; Breast-fed: 39.1	Infant formula with hMOs (2′FL, DFL, lacto-N-tetraose, 3′ sialyllactose and 6′ sialyllactose); 1.5 g/L and 2.5 g/L	6 months	Faecal SIgA	ELISA	0, 3, 6 months	↑ at 3 months for both doses ($p < .01$; $p < .05$) ↑ at 6 months for high dose ($p < .05$)
					Cytokines: IFN-γ, IL-4	PBMC culture in the absence or presence of influenza antigen	Week 0 (basal); week 2 (vaccination); week 8 (6 weeks after vaccination)	NS
					Lymphoctye proliferation			NS
Ivakhnenko and Nyankovskyy (2013)	Infants	Healthy newborns; No details reported, but based on inclusion criteria: Birth weight > 2500 g; No differences between groups in "…age at the enrolment, gender, physical and social settings."	Formula with GOS/lcFOS; (9:1); 8 g/L	At least 2 months (with average approx. 8 months) plus 18 month follow-up	Salivary sIgA	ELISA	After 2 months	↑
					Salivary a-1–3 defensins	ELISA	After 2 months	↓
					Faecal lysozyme	ELISA	After 2 months	↑
Neumer et al. (2021)	Infants	Healthy; < 4 months of age; Age (days): Treatment: M = 67.9 (SD = 39.7) ; Control: M = 60.0 (SD = 41.4); Sex (% female): Treatment: 52.3; Control: 50.8; Weight at inclusion (kg): Treatment: M = 5.2 (SD = 1.34); Control: M = 5.1 (SD = 1.53) Birth weight (kg): Treatment: M = 2.9 (SD = 1.08); Control: M = 3.7 (SD = 1.24)	Infant and follow-on formulas with 0.8 g/100 mL of chicory-derived oligofructose-enriched inulin (short chain oligofructose (DP < 10) and long chain inulin (DP ≥ 10) in an approximate 50:50 ratio ± 10% each)	Until the age of 1 year	Faecal IgA	Indirect enzyme immunoassay	2, 6, 12 months	NS

(*Continued*)

Table 1. Continued.

Author, Year	Population	Population description and health status at enrolment/ baseline	Description and dose of NDC/prebiotic intervention	Duration of intervention	Endpoints	Assessment methodology	Time points assessed	Effect on immune outcome(s)
Raes et al. (2010)	Infants	Healthy; At birth Sex (% female): Treatment: 43.0; Control: 45.6 Birth weight (kg): Treatment: M = 3.5 (SD = 0.4); Control: M = 3.6 (SD = 0.4); Breast feeding (%): Treatment: 38.7; Control: 35.5; Mean duration breast feeding (weeks): Treatment: M = 11.5 (SD = 10.0); Control: M = 10.3 (SD = 9.0)	Formula with GOS/lcFOS (9:1); 6 g/L	26 weeks from birth	Serum IgE	Fluoro-enzyme immunoassay (EliA)	8, 26 weeks	NS
					Serum IgG	Rate nephelometry	8, 26 weeks	NS
					Serum IgA			NS
					Serum IgM			NS
					White blood cell count	Flow cytometry	8, 26 weeks	NS
					Lymphocyte count			NS
					Blood lymphocyte subsets % $CD2^+$, $CD3^+$, $CD4^+$, $CD4^+/CD25^+$, $CD8^+$, $CD8^+/CD38^+$, $CD8^+/CD25^+$, $CD19^+$, $CD22^+$, $CD38^+$,			All NS
					NK cells			
					Blood lymphocyte subset % $CD4^+/CD38^+$	Flow cytometry	8, 26 weeks	↑ at week 8 (p = .02)
Salvini et al. (2011)	Infants	Healthy; born from hepatitis C virus-infected mothers; At birth: Sex (% female): Treatment: 50; Control: 80; Weight (kg): Treatment: M = 3.3 (SD = 0.7); Control: M = 3.3 (SD = 0.3)	Regular bovine milk formula with GOS/ lcFOS (9:1); 8g/L	6 months with further 6 month follow-up	Serum total IgE	ELISA	Unclear	NS
					Blood leukocyte populations	Flow cytometry	Birth, 3, 6, 12 months	NS apart from ↑ $CD3^+$ at 12 months
Scalabrin et al. (2012)	Infants	Healthy; Age (days): 21–30 (mean not reported) Sex (% female): Treatment: 46; Control: 60; Weight (kg): Treatment: M = 4.3 (SEM = 0.5); Control: M = 4.2 (SEM = 0.5)	Formula with GOS and polydextrose (1:1); 4 g/L	60 days	Faecal sIgA	ELISA	Baseline, 30, 60 days	NS

(*Continued*)

Table 1. Continued.

Author, Year	Population	Population description and health status at enrolment/ baseline	Description and dose of NDC/prebiotic intervention	Duration of intervention	Endpoints	Assessment methodology	Time points assessed	Effect on immune outcome(s)
Scholtens et al. (2008)	Infants	Healthy; At birth Sex (% female): Treatment: 43.0; Placebo: 45.6 Birth weight (kg): Treatment: M = 3.5 (SD = 0.4); Placebo: M = 3.6 (SD = 0.4); Breast feeding (%): Treatment: 38.7; Placebo 35.5; Mean duration breast feeding (weeks): Treatment: M = 11.5 (SD = 10.0); Placebo: M = 10.3 (SD = 9.0)	Infant milk formula with GOS/lcFOS (ratio 9:1); 6 g/L	6 months	Faecal sIgA	ELISA	8, 26 weeks	NS at 8 weeks ↑ at 26 weeks (whole group: $p < .05$; sub-group $p < .001$)
Sierra et al. (2015)	Infants	Healthy; Average age (days): Treatment: M = 29.4 (SD = 17.7); Control: M = 32.2 (SD = 18.2); Sex (% female): Treatment: 43.1; Control: 45.8 Birth weight: Treatment: M = 3.2 (SD = 0.5); Control: M = 3.2 (SD = 0.4), formula-fed only for 15 d prior to trial	4.4 g/L GOS in infant formula until 6 months of age, then 5.0 g/L in follow-on formula until 12 months of age	Before 8 weeks to 12 months of age; ≥ 10 months of supplementation	Faecal sIgA	ELISA	Baseline, 4 months	NS
van Hoffen et al. (2009)	Infants	Infants at high risk of allergy; Age (days): Treatment: M = 11.2 (SD = 7); Placebo: M = 11.8 (SD = 9.2); Sex (% female): Treatment: 49.6, Placebo: 51.5. Birth weight (g): Treatment: M = 3344 (SD = 456); Placebo: M = 3376 (SD = 482)	Hypoallergenic whey formula with GOS/ lcFOS (9:1); 8 g/L	6 months	Plasma total IgE, IgG1, IgG2, IgG3, IgG4 Plasma cow's milk protein-specific IgE, IgG1, IgG4	ELISA	6 months	↓ Total IgE, IgG1, IgG2 and IgG3 ($p < .01$) ↓ Cow's milk protein specific IgG1 ($p < .05$)
Jesenak et al. (2013)	Children	Children; aged 2–10 years; with a history of RRTIs; Age (years): Treatment: M = 5.78 (SD = 2.53); Placebo: M = 5.51 ± (SD = 2.22); Sex (% female): Treatment: 42.6; Placebo: 46.9; Weight (kg): Treatment: M = 27.52 (SD = 27.24); Placebo: M = 26.54 (SD = 22.61); Number of RTIs/12 months before the study: Treatment: M = 6.27 (SD = 2.10); Placebo: M = 6.86 (SD = 2.58)	β-1,3-1,6-glucan (pleuran); 10 mg + vitamin C; 10 mg in 1mL of syrup per 5 kg body weight daily	6 months intervention + 6 months follow-up	$CD3^+$; $CD4^+$; $CD8^+$ T-lymphocytes [%]; $CD8^+$ T-lymphocytes [10^9/L], $CD15CD56^+$ NK cells [%]; $CD19^+$ B-lymphocytes [%] $CD19^+$ B-lymphocytes [10^9/L] $CD3^+$ T-lymphocytes [10^9/L] $CD4^+$ T-lymphocytes [10^9/L] $CD8^+$ T-lymphocytes [10^9/L] $CD15CD56^+$ NK cells [10^9/L]	Flow cytometry	0, 6, 12 months	No comparison between groups; however, there were changes over time in some parameters sometimes in both groups.

(*Continued*)

Table 1. Continued.

Author, Year	Population	Population description and health status at enrolment/ baseline	Description and dose of NDC/prebiotic intervention	Duration of intervention	Endpoints	Assessment methodology	Time points assessed	Effect on immune outcome(s)
					Serum IgE Serum IgG Serum IgA Serum IgM	Immunoassay		Differences between groups unclear, but IgG, IgM and IgA increased in the treatment group (at post-intervention compared to baseline for all, but also at follow-up compared to baseline for IgA and IgG; although IgA also increased in the placebo group at follow-up compared to baseline and between post-intervention and follow-up; no mention of the results for IgE).
Vogt et al. (2017)	Young adults	Healthy; Age (years): Treatment 1: M = 20 (Range = 19–26); Treatment 2: M = 20 (Range = 18–29); Placebo: M = 20 (Range = 18–25); Sex (% female): Treatment 1: 61.5; Treatment 2: 53.8; Placebo: 57.1	Treatment 1: Inulin-type fructans with DP 10–60; Treatment 2: Inulin-type fructans with DP 2–25; 8 g/d	14 days supplementation; vaccination (Hepatitis B) given on day 7, follow-up at days 21 and 35	B cell subsets: Naive non-classed switched B cells Class switched memory B cells Non-classed switched memory B cells Transitional B cells Plasma cells T cell subsets: T cells Th2 cells Th17 cells FOXP3^{+} Th cells CD45 RO^{+} T cells TBET^{+} (Th1) cells NK cells: CD161^{+} NK cells CD335^{+} NK cells NK T cells	Flow cytometry	0, 7, 14, 21, 35 days	No between group comparisons made but for some subsets, there were changes over time.
Bergendiova, Tibenska, and Majtan (2011)	Adults	Healthy athletes; Age (years): Treatment: M = 23.6 (SEM = 0.8); Control: M = 24.0 (SEM = 0.9); Sex (% female): Treatment 56; Control 48; BMI (kg/m^2): Treatment: M = 22.8 (SEM = 0.6); Control: M = 23.7 (SEM = 0.5)	β-1,3-1,6-glucan (pleuran); 100 mg/d plus Vitamin C; 100 mg/d	3 months intervention 3 months follow up	Polymorphonuclear leukocytes phagocytosis	Flow cytometry	Baseline, 3 months and 3 month follow-up	↑ at 3 months ($p < .01$)
					NK cell number	Flow cytometry	Baseline, 3 months and 3 month follow-up	NS

(*Continued*)

Table 1. Continued.

Author, Year	Population	Population description and health status at enrolment/ baseline	Description and dose of NDC/prebiotic intervention	Duration of intervention	Endpoints	Assessment methodology	Time points assessed	Effect on immune outcome(s)
Bobovčák et al. (2010)	Adults	Healthy elite athletes; Age (years): Treatment: M = 23.3 (SEM = 1.7); Placebo: M = 22.4 (SEM = 0.6); Sex (% female): 20 (across both groups; no group specific sex distribution provided); BMI (kg/m^2): Treatment: M = 23.3 (SEM = 0.7); Placebo: M = 22.7 (SEM = 0.6)	β-1,3-1,6-glucan (pleuran); 100 mg/d plus vitamin C; 100 mg/d	2 months	NK cell activity	Flow cytometry NKTEST kit (Orpegen-Pharma, Heidelberg Germany)	Baseline, 2 months, post exercise at 2 months and 1 hour after recovery	↑ at 1 h post exercise (p < .05)
					NK cells count	Blood cell count	Baseline, 2 months, post exercise at 2 months and 1 hour after recovery	NS
					Cell counts of leukocytes, erythrocyte, and lymphocytes, monocytes, granulocytes, T cells (CD3), Th cells (CD3$^+$ CD4$^+$), Tc cells (CD3$^+$ CD8$^+$), B cells (CD19$^+$), NK cells	Blood cell count	Baseline, 2 months, post exercise at 2 months and 1 hour after recovery	NS
Carpenter et al. (2013)	Adults	Recreationally active college students; Age (years): Men – M = 23 (SD = 5); Women – M = 22 (SD = 4); Sex (% female) = 52 (Men: n = 29; Women: n = 31); BMI (kg/m^2): Men – M = 24.4 (SD = 1.7); Women – M = 22.5 (SD = 1.9)	β-1,3-1,6-glucan (*S. cerevisiae*); 250 mg/d	10 d treatment or placebo with 7 day washout in between	Total PBMCs	Flow cytometry	Baseline, pre-exercise, post-exercise, 2 hours post-exercise	Significant condition x exercise time interaction (p = .026); ↑ at 2 h (p value not given)
					Pro-inflammatory PBMCs	Flow cytometry	Baseline, pre-exercise, post-exercise, 2 hours post-exercise	Significant condition x exercise time interaction (p = .033) for pro-inflammatory monocyte concentrations; ↑ at post and 2 h (p value not given)
					Classic PBMCs	Flow cytometry	Baseline, pre-exercise, post-exercise, 2 hours post-exercise	↑ at 2 h post-exercise (p < .05)
					LPS stimulated production of IL-1β, IL-2, IL-6, IL-7, IL-8, IL-10, IL-12, IL-13, GM-CSF, TNF-α	In-vitro stimulation of whole blood with LPS. Cytokine analysis by flow cytometry based multiplex bead array	Baseline, pre-exercise, post-exercise, 2 hours post-exercise	NS

(*Continued*)

Table 1. Continued.

Author, Year	Population	Population description and health status at enrolment/ baseline	Description and dose of NDC/prebiotic intervention	Duration of intervention	Endpoints	Assessment methodology	Time points assessed	Effect on immune outcome(s)
					LPS stimulated production of IL-4	In-vitro stimulation of whole blood with LPS. Cytokine analysis by flow cytometry based multiplex bead array	Baseline, pre-exercise, post-exercise, 2 hours post-exercise	Significant condition x exercise time interaction (p = .025); ↑ at pre-exercise and post-exercise timepoints (p < .05)
					LPS stimulated production of IL-5	In-vitro stimulation of whole blood with LPS. cytokine analysis by flow cytometry based multiplex bead array	Baseline, pre-exercise, post-exercise, 2 hours post-exercise	Significant condition x exercise time interaction (p = .027); ↑ at pre-exercise and post-exercise timepoints (p < .05)
					LPS stimulated production of IFN-g	In-vitro stimulation of whole blood with LPS. cytokine analysis by flow cytometry based multiplex bead array	Baseline, pre-exercise, post-exercise, 2 hours post-exercise	Significant condition x exercise time interaction (p = .011); ↑ at pre-exercise and post-exercise timepoints (p < .05)
Chen, Nan, et al. (2023)	Adults	Men and women; Age (y): Treatment group: M = 37.72, SD = 7.36; Placebo: M = 39.11, SD = 7.52; Sex (% female): Treatment group: 46.8; Placebo group: 41.6 BMI: Not reported	Reishi β-1,3/β-1,6 D-glucan; 200 mg/d	12 weeks	Total Lymphocytes (cells/μL) $CD3^+$ T lymphocytes (cells/μL) $CD4^+$ T lymphocytes (cells/μL) $CD8^+$ T lymphocytes (cells/μL) CD4/CD8 cell ratio NK Cells (cells/μL) NK Cells Cytotoxicity (%) Serum IgA	Lymphocyte subsets: flow cytometry with monoclonal antibodies Cytotoxicity assay IgA: ELISA	Baseline, 12 weeks	↑ at 12 weeks for all (p < .05)

(*Continued*)

Table 1. Continued.

Author, Year	Population	Population description and health status at enrolment/ baseline	Description and dose of NDC/prebiotic intervention	Duration of intervention	Endpoints	Assessment methodology	Time points assessed	Effect on immune outcome(s)
Kawano et al. (2023)	Adults	Men and women who catch a cold every year; Age (y): Treatment group: M = 56.1, SD = 4.6; Placebo: M = 55.7, SD = 4.2; Sex (% female): Treatment group: 54.5; Placebo group: 54.5 BMI (kg/m^2): Treatment group: M = 22.3, SD = 2.6; Placebo group: M = 22.9, SD = 3.3	Paramylon, β-glucan of microalgae Euglena gracilis; 350 mg paramylon/day	12 weeks	Quantification of blood cytokines and immune-related factors: fms-related receptor tyrosine kinase 3 ligand (FLT3LG), colony-stimulating factor (CSF) 3, CSF2, IFNG, IL1B, IL2, IL4, IL6, IL7, CXCL8, IL10, IL13, IL15, IL17A, IL17C, L17F, IL18, IL27, IL33, lymphotoxin-alpha (LTA), CSF1, oncostatin M (OSM), TNF, TNF superfamily (TNFSF) 10, thymic stromal lymphopoietin (TSLP), TNFSF12, chemokine ligand (CCL) 2, CCL3, CCL4, CCL7, CCL8, CCL13, CCL19, C-X-C motif chemokine ligand (CXCL)9, CXCL10, CXCL11, CCL11, CXCL12, hepatocyte growth factor (HGF), matrix metalloproteinase (MMP) 1, MMP12, oxidized ow-density lipoprotein receptor (OLR) 1, epidermal growth factor (EGF), transforming growth factor α (TGFA), and vascular endothelial growth factor A (VEGFA). Quantification of blood immune cells: T cell subset [CD4$^+$ and CD8$^+$ naïve, central memory (Tcm), effector memory (Tem), and terminally differentiated effector memory (Temra)]; Treg; CD4- mucosal-associated invariant T cells/natural killer T cells (MAIT/NKT)]; B cell subsets (naïve and memory, plasmablasts); natural killer (NK) cell subsets; CD38 expression on gamma delta T (gdT) cells; monocyte subsets (classical, intermediate, and non-classical); DCs subsets (plasmacytoid, pDC; myeloid, mDC); granulocytes (basophils and neutrophils); CD38 expression in APC subsets; CD28 and CD38, CD57, and HLA-DR expression on major T cell subsets; CD80, CD86, HLA-DR expression on monocytes before and after intake of PM EOD-1.	Proximity Extension Assay (PEA) Flow cytometry Mass cytometry	Baseline, 12 weeks	↑ (or remained high): IL17A (p = .014), IL27 (p = .019), MMP12 (p = .088), CSF2 (p = .023), FLT3LG (p = .061), IL17C (p = .037). IFNG (p = .020) and chemokines [CCL8 (p = .018), CCL7 (p = .039)] remained low in Treatment group. No marked differences in cell populations, though analysis of cell subsets showed some changes. ↑ HLA-DR, CD38, and CD28 in CD4$^+$ and CD8$^+$ cells in each T cell population. ↑ CD28 in CD4$^+$ and CD8$^+$ naïve T cells (p = .030 and p = .035, respectively). ↓ CD80 (B7-1) on monocytes. ↑ CD38 on T cells, including CD4$^+$ naïve T (p = .018), CD4$^+$ Tcm (p = .011), CD4$^+$ Tem (p = .034), CD8$^+$ naïve T (p = .027), and CD8$^+$ Temra cells (p = .009). ↓ CD28$^-$CD57$^-$ population (p < .001) and a reciprocally ↑ CD28$^+$CD57- population (p < 0.001) in CD4$^+$ T cells. ↓ CD8$^+$ T cells in activated/ early-senescent CD28$^-$CD57$^-$ populations with ↓ T cell function (p = .017) and ↑ in non-activated/ early-activated CD28$^+$CD57$^-$ population in the active state (p = .016). Note: Statistical analysis between groups and time points is unclear.

(*Continued*)

Table 1. Continued.

Author, Year	Population	Population description and health status at enrolment/ baseline	Description and dose of NDC/prebiotic intervention	Duration of intervention	Endpoints	Assessment methodology	Time points assessed	Effect on immune outcome(s)
Ko et al. (2024)	Adults	Overweight and sedentary men and women; Age (y): Treatment: M = 34.68, SEM = 2.85; Placebo: M = 41.46, SEM = 2.9; Sex (%female): Treatment: 57.1; Placebo: 55; BMI (kg/m^2): Treatment: M = 29.8, SEM = 1.37; Placebo: M = 33.78, SEM = 1.39	2′-FL; 3 g/d	12 weeks (follow-up baseline, 6 and 12 weeks), 12 week diet and exercise intervention in both groups	White Blood Cell Count Percentages of monocytes, neutrophils, basophils, lymphocytes, eosinophils	Not stated	Baseline, 6 weeks, 12 weeks	NS NS
Lee et al. (2016)		Healthy; Age (years): Treatment: M = 53.6 (SEM = 1.15); Placebo: M = 54.5 (SEM = 1.35); Sex (% female): Treatment = 89.7; Placebo = 90.9; BMI (kg/m^2): Treatment: M = 23.5 (SEM = 0.30); Placebo: M = 23.5 (SEM = 0.33)	Yogurt with probiotics + citrus hallabong peel polysaccharide providing 60 mg/d rhamnogalacturonan and 5 mg/d polyphenols	2 weeks of run-in, 8 weeks of intervention	NK cell activity E:T ratio 10:1; 5:1; 2.5:1 and 1.25:1 (%)	Nonradioactive cytotoxicity assay kits	Baseline, 8 weeks	↑ ($p < .02$) except NS at E:T ratio 1.25:1
Lee et al. (2017)	Adults	Healthy; Age (years): Treatment: M = 33.0 (SD = 10.0); Placebo: M = 31.3 (SD = 9.5); Sex (% female): Treatment = 37.5; Placebo = 45.9; BMI (kg/m^2): Treatment M = 23.7 (SD = 2.3); Placebo: M = 23.0 (SD = 3.7)	β-1,3-glucan (*Agrobacterium sp. R259*, MW 17-25kDa); 350 mg/d; cellulose 128 mg/d; dextrin 44 mg/d	8 weeks	NK cell activity (%)	Nonradioactive cytotoxicity assay	Baseline, 8 weeks	↑ ($p = .048$ and $p = .009$ after adjustment for smoking and stress status)
					Serum IgG	Immunoassay	Baseline, 8 weeks	NS
Lomax et al. (2012)	Adults	Healthy; Age (years): Treatment: M = 54 (Range = 45–62); Placebo: M = 56 (Range = 45–63); Sex (% female): Treatment = 86.4; Placebo = 61.9; BMI (kg/m^2): Treatment: M = 25.7 (Range = 19.4–33.3); Placebo: M = 25.0 (Range = 17.7–33.8)	Chicory inulin (50% long chain inulin: 50% oligofructose); 8 g/d	8 weeks, but data here at 4 weeks	Salivary sIgA	ELISA	Baseline, 4 weeks	NS
					Blood immune cell phenotypes	Flow cytometry	Baseline, 4 weeks	NS
					Neutrophil and monocyte phagocytosis of *E. coli*	Flow cytometry	Baseline, 4 weeks	NS
					Neutrophil and monocyte oxidative burst	Flow cytometry	Baseline, 4 weeks	NS
					Serum IgA	ELISA	Baseline, 4 weeks	NS
					Serum IgM			NS
					Serum IgG			NS
					NK cell activity	Killing of K562 cells – flow cytometry	Baseline, 4 weeks	NS

(*Continued*)

Table 1. Continued.

Author, Year	Population	Population description and health status at enrolment/ baseline	Description and dose of NDC/prebiotic intervention	Duration of intervention	Endpoints	Assessment methodology	Time points assessed	Effect on immune outcome(s)
					Con A stimulated proliferation of T cells	Flow cytometry post cell culture – CFSE dilution	Baseline, 4 weeks	NS
					Con A stimulated CD69 expression on T cells	Flow cytometry post cell culture	Baseline, 4 weeks	NS
					Con A stimulated production of cytokines (IL-2, IL-4, IL-6, IL-10, TNF-α, IFN-γ) by PBMCs	Flow cytometry post cell culture	Baseline, 4 weeks	NS
Lomax et al. (2015)	Adults	Healthy; Age (years): Treatment: M = 54 (Range = 45–62); Control: M = 56 (Range = 45–63); Sex (% female): Treatment = 86.4; Control = 61.9 BMI (kg/m^2): Treatment: M = 25.7 (Range = 19.4–33.3); Control: M = 25.0 (Range = 17.7–33.8)	Chicory inulin (50% long chain inulin: 50% oligofructose); 8 g/d	8 weeks (only data from last 4 weeks reported in this paper)	Blood immune cell phenotypes	Flow cytometry	Weeks 4, 6 and 8	NS
					NK cell activity	Killing of target cell line	Weeks 4, 6 and 8	NS
					Salivary IgA	ELISA	Weeks 4, 6 and 8	NS
					Serum IgA, IgM, IgG			NS
Lutter et al. (2021)	Adults	Men and women; Age (y): Low dose: M = 35.4, SD = 14.4; High dose: M = 34.5, SD = 14.9; Placebo: M = 38.2, SD = 15.8; Sex (% female): Low dose: 80; High dose: 82; Placebo: 78; BMI (kg/m^2): Low dose: M = 23.5, SD = 2.9; High dose: M = 23.8, SD = 2.7; Placebo: M = 23.2, SD = 2.6	cRG-I (natural extract from carrot [*Daucus carota* subsp. *sativus*]); Low dose: 0.3 g/d; High dose: 1.5 g/d; appropriate amounts of maltodextrin and 0.5 g of caramel colour were added to each dose to obtain a total of 3.5 g of powder per intervention	8 weeks then response phase of 2 weeks (exposure at day 0 to RV16 + course of infection) and follow-up phase of 3 weeks	Non-epithelial cells in nasal lavage	Not reported	Baseline, 8 weeks Change at d3, d6, d9, d13 vs pre-infection (d-1) throughout response phase (13 days)	NS High dose resulted in a higher number of cells in a time-dependent ($p < .03$) parabolic fashion
					Macrophages in nasal lavage	Not reported	Baseline, 8 weeks Change at d3, d6, d9, d13 vs pre-infection (d-1) throughout response phase (13 days)	NS Higher doses (only High dose?) resulted in a higher number of cells in a time-dependent ($p < .001$) parabolic fashion
					Lymphocytes in nasal lavage	Not reported	Baseline, 8 weeks Change at d3, d6, d9, d13 vs pre-infection (d-1) throughout response phase (13 days)	NS Low dose resulted in a higher number of cells vs High dose and Placebo in a time dependent ($p < .02$) parabolic fashion

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Table 1. Continued.

Author, Year	Population	Population description and health status at enrolment/ baseline	Description and dose of NDC/prebiotic intervention	Duration of intervention	Endpoints	Assessment methodology	Time points assessed	Effect on immune outcome(s)
					Neutrophils in nasal lavage	Not reported	Baseline, 8 weeks Change at d3, d6, d9, d13 vs pre-infection (d-1) throughout response phase (13 days)	NS High dose resulted in a higher number of cells in a time-dependent ($p < .08$ but figure says $p < .008$) parabolic fashion
					Eosinophils in nasal lavage	Not reported	Baseline, 8 weeks Change at d3, d6, d9, d13 vs pre-infection (d-1) throughout response phase (13 days)	NS Higher doses (only High dose?) resulted in a higher number of cells in a time-dependent ($p < .003$) parabolic fashion
					Myeloperoxidase in nasal lavage	Not reported	Baseline, 8 weeks Change at d3, d6, d9, d13 vs pre-infection (d-1) throughout response phase (13 days)	NS NS (trend for same pattern as neutrophil counts)
					Eosinophil Cationic Protein in nasal lavage	Not reported	Baseline, 8 weeks Change at d3, d6, d9, d13 vs pre-infection (d-1) throughout response phase (13 days)	NS NS (trend for same pattern as eosinophil counts)
					Antibody titers to RV16 in blood	Not reported	31 days post-infection	NS
McFarlin et al. (2013)	Adults	Experiment 2: Completed a cycling trial; Age (years): Males: M = 23 (SD = 5); Females: M = 22 (SD = 5); Sex (% female): 51.7; BMI (kg/m^2): Males: m = 24.4 (SD = 1.7); Females: M = 22.5 (SD = 1.9)	Experiment 2: Insoluble β-1,3-1,6-glucan; 250 mg/d	Experiment 2: For 10 days prior to experimental exercise (cycling) trial; 7 day wash-out period between study arms	Salivary IgA	Luminex MagPix platform and EMD Millipore Milliplex kit	Baseline, prior to supplementation (BL), after supplementation and prior to exercise (PRE), immediately after exercise (POST), 2 hours after exercise (2 h)	↑ at 2 h ($p < .05$)
McFarlin et al. (2017)	Adults	Healthy; Age (years): Males: M = 22.0 (SEM = 3.0); Females: M = 21.0 (SEM = 3.0) Sex (% female): 54.1 BMI (kg/m^2): Males: M = 24.74 (SEM = 0.40); Females: M = 23.29 (SEM = 0.53)	β-1,3-1,6-glucan (*S. cerevisiae*); 250 mg/d	10 days for each intervention followed by 90 min exercise challenge and 4 hour follow-up; 7 days washout	Total monocytes	Flow cytometry	Baseline, 10 days, then post exercise at 10 days and 2 and 4 h post exercise	↑ post, 2 h and 4 h post exercise; $p < .05$ for each

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Table 1. Continued.

Author, Year	Population	Population description and health status at enrolment/ baseline	Description and dose of NDC/prebiotic intervention	Duration of intervention	Endpoints	Assessment methodology	Time points assessed	Effect on immune outcome(s)
					Classical monocytes	Flow cytometry	Baseline, 10 days, then post exercise at 10 days and 2 and 4 h post exercise	↑ 2 and 4 h post exercise; $p < .05$ for each
					Non-classical monocytes	Flow cytometry	Baseline, 10 days, then post exercise at 10 days and 2 and 4 h post exercise	NS
					CD38 MFI on classical monocytes	Flow cytometry	Baseline, 10 days, then post exercise at 10 days and 2 and 4 h post exercise	↓ at 10 days, post exercise and 2 and 4 hours post exercise, all $p < .05$
					CD80 MFI on classical monocytes CD86 MFI on classical monocytes TLR4 MFI on classical monocytes CD38 MFI on non-classical monocytes CD80 MFI on non-classical monocytes	Flow cytometry	Baseline, 10 days, then post exercise at 10 days and 2 and 4 h post exercise	NS NS NS NS NS
					TLR2 MFI on classical monocytes	Flow cytometry	Baseline, 10 days, then post exercise at 10 days and 2 and 4 h post exercise	↓ at 10 days and 4 hours post exercise; $p < .05$ for each
					CD86 MFI on non-classical monocytes	Flow cytometry	Baseline, 10 days, then post exercise at 10 days and 2 and 4 h post exercise	↑ at 10 days then post exercise and 2 h post exercise; $p < .05$ for each
					TLR2 MFI on non-classical monocytes	Flow cytometry	Baseline, 10 days, then post exercise at 10 days and 2 and 4 h post exercise	↓ at 10 days, post exercise and 2 and 4 h post exercise; $p < .05$ for each
					TLR4 MFI on non-classical monocytes	Flow cytometry	Baseline, 10 days, then post exercise at 10 days and 2 and 4 h post exercise	↑ at 4 h post exercise; $p < .05$ for each
					Total $CD4^+$ T cells	Flow cytometry	Baseline, 10 days, then post exercise at 10 days and 2 and 4 h post exercise	↑ at 10 days, post exercise and 2 and 4 h post exercise; $p < .05$ for each

(*Continued*)

Table 1. Continued.

Author, Year	Population	Population description and health status at enrolment/ baseline	Description and dose of NDC/prebiotic intervention	Duration of intervention	Endpoints	Assessment methodology	Time points assessed	Effect on immune outcome(s)
					Total EM $CD4^+$ T cells	Flow cytometry	Baseline, 10 days, then post exercise at 10 days and 2 and 4 h post exercise	↑ 2 and 4 h post exercise; $p < .05$ for each
					Total CM $CD4^+$ T cells	Flow cytometry	Baseline, 10 days, then post exercise at 10 days and 2 and 4 h post exercise	↑ at 10 days, post exercise and 2 and 4 h post exercise; $p < .05$ for each
					Total $CD8^+$ T cells	Flow cytometry	Baseline, 10 days, then post exercise at 10 days and 2 and 4 h post exercise	↑ at 10 days, post exercise and 2 and 4 h post exercise; $p < .05$ for each
					Total EM $CD8^+$ T cells	Flow cytometry	Baseline, 10 days, then post exercise at 10 days and 2 and 4 h post exercise	↑ at 10 days and 2 and 4 h post exercise; $p < .05$ for each
					Total CM $CD8^+$ T cells	Flow cytometry	Baseline, 10 days, then post exercise at 10 days and 2 and 4 h post exercise	↑ at 2 h post exercise; $p < .05$
					Total EMRA $CD8^+$ T cells	Flow cytometry	Baseline, 10 days, then post exercise at 10 days and 2 and 4 h post exercise	↑ at 10 days, post exercise and 2 and 4 h post exercise; $p < .05$ for each
					LPS stimulated production of IFN-g by whole blood	Mulitplex bead assay	Baseline, 10 days, then post exercise at 10 days and 2 and 4 h post exercise	↑ at 10 days, $p < .05$
					LPS stimulated production of IL-1β by whole blood	Mulitplex bead assay	Baseline, 10 days, then post exercise at 10 days and 2 and 4 h post exercise	↑ at 2 h post exercise; $p < .05$
					LPS stimulated production of IL-2 by whole blood	Mulitplex bead assay	Baseline, 10 days, then post exercise at 10 days and 2 and 4 h post exercise	↑ at 10 days and 2 and 4 h post exercise; $p < .05$ for each
					LPS stimulated production of IL-4 by whole blood	Mulitplex bead assay	Baseline, 10 days, then post exercise at 10 days and 2 and 4 h post exercise	↑ post exercise and 2 h post exercise; $p < .05$ for each

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Table 1. Continued.

Author, Year	Population	Population description and health status at enrolment/ baseline	Description and dose of NDC/prebiotic intervention	Duration of intervention	Endpoints	Assessment methodology	Time points assessed	Effect on immune outcome(s)
					LPS stimulated production of IL-7 by whole blood	Mulitplex bead assay	Baseline, 10 days, then post exercise at 10 days and 2 and 4 h post exercise	↑ post exercise and 2 h post exercise; $p < .05$ for each
					LPS stimulated production of TNF, IL-10, MCP-3, MIP-1α, MIP-1β by whole blood	Mulitplex bead assay	Baseline, 10 days, then post exercise at 10 days and 2 and 4 h post exercise	NS
Nieman et al. (2008)	Adults	Trained male cyclists; Age (years): Treatment: M = 21.8 (SEM = 0.9); Placebo: M = 25.0 (SEM = 2.2); Sex (% female): 0; Body mass (kg): Treatment: M = 70.7 (SEM = 2.1); Placebo: M = 77.4 (SEM = 1.9) significantly different (p = .026)	Oat β-glucan; 5.6 g/d	14 days; then underwent 3 days of intense cycling; supplementation for one additional day; follow-up of 2 weeks	NK cell activity	K562 killing assay	Baseline, 2 weeks post supplementation, immediately after 3 days of exercise, 14 hours after 3 day exercise (3 day exercise occurred immediately after the first 2 weeks of supplementation; supplementation was continued throughout the 3 days of exercise)	NS
					Leukocyte counts	Haematology lab analyses	Baseline, 2 weeks post supplementation, immediately after 3 days of exercise, 14 hours after 3 day exercise (3 day exercise occurred immediately after the first 2 weeks of supplementation; supplementation was continued throughout the 3 days of exercise)	NS

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Table 1. Continued.

Author, Year	Population	Population description and health status at enrolment/ baseline	Description and dose of NDC/prebiotic intervention	Duration of intervention	Endpoints	Assessment methodology	Time points assessed	Effect on immune outcome(s)
					PHA-induced lymphocyte proliferation	Tritiated thymidine incorporation assay	Baseline, 2 weeks post supplementation, immediately after 3 days of exercise, 14 hours after 3 day exercise (3 day exercise occurred immediately after the first 2 weeks of supplementation; supplementation was continued throughout the 3 days of exercise)	NS
					Neutrophil oxidative burst capacity	PMA stimulation and rhodamine 123 as fluorescent oxidation probe for flow cytometry	Baseline, 2 weeks post supplementation, immediately after 3 days of exercise, 14 hours after 3 day exercise (3 day exercise occurred immediately after the first 2 weeks of supplementation; supplementation was continued throughout the 3 days of exercise)	NS
Park et al. (2004)	Adults	Overweight and obese; Age (years): Treatment: M = 42.3 (SEM = 3.1); Control: M = 43.6 (SEM = 2.8); Sex (% female): 100; BMI (kg/m^2): Treatment: M = 26.6 (SEM = 0.7); Control: M = 27.9 (SEM = 0.5)	Resistant corn starch; 24 g/d	21 days	Serum IgG Serum C3	Rate nephelometry	Baseline, 21 days	Between group comparison not reported

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Table 1. Continued.

Author, Year	Population	Population description and health status at enrolment/ baseline	Description and dose of NDC/prebiotic intervention	Duration of intervention	Endpoints	Assessment methodology	Time points assessed	Effect on immune outcome(s)
Parker et al. (2023)	Adults	Elite rugby union players; Age (y): Treatment: M = 22.4, SD = 3.3; Placebo: M = 24.5, SD = 5.2 Sex (%female): 0 (confirmed by authors) BMI (kg/m^2): not mentioned	GOS; 2.8 g/d	24 weeks (visits: baseline, 12 weeks, 24 weeks)	Saliva sIgA	ELISA	Baseline, 12 weeks, 24 weeks	↑ week 24 ($p < .05$)
Wang et al. (2022)	Adults	Professional table tennis players; Age (years): Treatment: M = 19.79 (SD = 0.89); Placebo: M = 19.38 (SD = 0.96); Sex (% female): Not reported; BMI (kg/m^2): Treatment: M = 22.2; Placebo: M = 23.2 (calculated from weight and height so SD not possible, but recruited based on BMI of 18.5–23.9)	Beverage with β-glucan (origin not described); 2 g/d	4 weeks	Plasma IgM	LC-MS/MS analysis	Baseline; 4 weeks	NS
Williams et al. (2016)	Adults	Healthy (also included a hyperpnoea-induced bronchoconstriction group, but data not reported herein); Age (years) = M = 26 (SD = 4) Sex (% female): 37.5 BMI (kg/m^2): 23.8 (calculated based on weight and height so no SD possible)	GOS; 5.5 g/d	3 weeks; 2 week wash-out period between intervention arms	Serum IgE	ELISA	Pre and post each intervention arm; also pre and 15 min, 60 min and 24 h after eucapnic voluntary hyperpnoea	NS
Wilms et al. (2021)	Adults	Healthy; Age (years): M = 38.2 (SD = 7.8); Sex (% female): 66.7; BMI (kg/m^2): M = 23.1 (SD = 2.6)	GOS; 15 g/d	4 weeks; 4–6 week wash-out period between intervention arms	LPS and PHA stimulated IL-6 production by whole blood after 24 h LPS and PHA stimulated IL-8 production by whole blood after 24 h LPS and PHA stimulated IL-10 production by whole blood after 24 h LPS and PHA stimulated TNF-α production by whole blood after 24 h LPS and PHA stimulated IFN-γ production by whole blood after 24 h	Cytometric bead array	Pre and post each intervention arm	NS NS NS NS NS

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Table 1. Continued.

Author, Year	Population	Population description and health status at enrolment/ baseline	Description and dose of NDC/prebiotic intervention	Duration of intervention	Endpoints	Assessment methodology	Time points assessed	Effect on immune outcome(s)
Bunout et al. (2002)	Older adults	Healthy; Age (years): Treatment: M = 76.2 (SD= 3.9); Placebo: M = 75.2 (SD= 3.8); No data on sex "Both treatment and control groups had a similar sex distribution"; BMI (kg/m^2): Treatment: M = 28 (SD = 5); Placebo: M = 26 (SD = 4)	FOS (70% oligofructose, 30% inulin); 6 g/d	28 weeks	Salivary sIgA; Serum IgG, IgM, IgA	Radial immunodefusion	Week 0 (basal); week 2 (vaccination); week 8 (6 weeks after vaccination)	NS NS
Gaullier et al. (2011)	Older adults	Healthy; > 65 years; Age (years): M = 71.0 (SD = 5.4, Range = 64.9–84.0); Sex (% female): 48; BMI (kg/m^2): M = 24.6 (SD = 2.6, Range = 17.0–29.0)	2.5 mg/d of a product described as a fermentation liquid from *L. edodes* mycelium containing β-1,3-1,6-glucan; the dose of β-glucan used is unclear	6 weeks; 4 week wash-out period between intervention arms	T helper cells (CD4$^+$) Total T cells (CD3$^+$) T cytotoxic cells (CD8$^+$) NK cells (CD56$^+$)	Not stated	Pre and post each intervention arm	NS NS NS NS
					B cells (CD19$^+$)	Not stated	Pre and post each intervention arm	↑ total number and % after 6 weeks (p = .0368; p = .022).
					Immunoglobulins (IgM, IgG, IgA) from blood samples	Not stated	Pre and post each intervention arm	NS
					Complement C3 from blood samples	Not stated	Pre and post each intervention arm	NS
Kiewiet et al. (2021)	Older adults	Healthy; Age (years): Treatment: M = 62.2 (SD = 6.9); Placebo: M = 63.7 (SD = 8.1); Sex (% female): Treatment: 30.8; Placebo: 30.8; BMI (kg/m^2): Treatment: M = 26.1 (SD = 3.6); Placebo: M = 29.7 (SD = 5.6)	Inulin (chicory, long chain inulin DP 10–60); 8 g/d	63 days intervention (7 days of baseline; 154 days of follow up) Vaccination (Hepatitis B): 1st on day 7 from intervention; 2nd 28 days later; 3rd 154 days later	T helper cells (% of CD3$^+$) Cytotoxic T cells (% of CD3$^+$) Regulatory T cells (% of CD4$^+$) Th1 cells (% of CD4$^+$) Memory T cells (% of lymphocytes) Memory Th1 cells (% of CD3$^+$)	Blood count	Run-in phase (-7 days) Intervention, 3 timepoints: Day 7, day 35, day 63 Follow up (day 217)	NS NS NS NS NS NS

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Table 1. Continued.

Author, Year	Population	Population description and health status at enrolment/ baseline	Description and dose of NDC/prebiotic intervention	Duration of intervention	Endpoints	Assessment methodology	Time points assessed	Effect on immune outcome(s)
Laue et al. (2021)	Older adults	Healthy; Men and postmenopausal women, aged 50–79 years; Age (years): Total: Me = 67.9 (IQR = 8.3) Treatment 1: Me = 68.2 (IQR = 9.1) Treatment 2: Me = 67.3 (IQR = 9.8) Treatment 3: Me = 68.0 (IQR = 8.3) Treatment 4: Me = 67.5 (IQR = 7.6) Treatment 5: Me = 66.2 (IQR = 10.1) Control: Me = 69.5 (IQR = 8.3) Sex (% female): Total: 49.4 Treatment 1: 42.5 Treatment 2: 47.5 Treatment 3: 57.5 Treatment 4: 55.0 Treatment 5: 59.0 Control: 35.0 BMI (kg/m^2): Total: M = 27.0 (SD = 3.6) Treatment 1: M = 27.2 (SD = 3.9) Treatment 2: M = 27.0 (SD = 3.1) Treatment 3: M = 26.9 (SD = 3.5) Treatment 4: M = 26.7 (SD = 4.0) Treatment 5: M = 27.3 (SD = 3.7) Control: M = 27.3 (SD = 3.5)	NPS powder containing either Treatment 1: Insoluble β-1,3-1,6-glucan; 500 mg/d), Treatment 2: Soluble β-1,3-1,6-glucan; 500 mg/d, Treatment 3: Oat b-glucan; 10 g/d, Treatment 4: AX from wheat endosperm; 10 g/d, or Treatment 5: EPS preparation from *Limosilactobacillus mucosae;* 2.3 g/d	2 week run-in without supplementation; 5 weeks of supplementation with vaccination at week 2	Culture medium, Con A, and LPS stimulated production of cytokines (IL-1β, IL-2, IL-12, IL-10, TNF-α) in whole blood	Whole blood with culture medium, Con A, or LPS	Baseline, 2 weeks (vaccination) and week 3 (1 week post-vaccination)	NS
					Culture medium, Con A, and LPS stimulated production of IFN-γ in whole blood	Whole blood with culture medium, Con A, or LPS	Baseline, 2 weeks (vaccination) and week 3 (1 week post-vaccination)	Blood incubated with medium, change from baseline to one week post-vaccination significantly different for YBG, OBG, AX, and EPS groups vs control (all uncorrected $p \leq .05$)
Maneerat et al. (2013)	Older adults	Healthy; Age (years): Treatment: M = 70.7 (SEM = 0.69); Placebo: M = 63.0 (SEM = 0.5) ($p < .001$) Sex (% female): Treatment: 66.7; Placebo: 55.6 BMI (kg/m^2): Treatment: M = 28.4 (SEM = 1.1); Placebo: M = 25.6 (SEM = 1.3)	GOS; predominantly galactose (β1-6), (β1-4) and (β1-3) linkages; 8 g/d	21 days; 28 day wash-out period between intervention arms and 28 day follow-up after last intervention arm	Phagocytic activity of monocytes and neutrophils	Phagotest : flow cytometry	Pre and post intervention (baseline and 21 days)	NS
					Oxidative burst activity of monocytes and neutrophils	Flow cytometry	Pre and post intervention (baseline and 21 days)	NS

(*Continued*)

Table 1. Continued.

Author, Year	Population	Population description and health status at enrolment/ baseline	Description and dose of NDC/prebiotic intervention	Duration of intervention	Endpoints	Assessment methodology	Time points assessed	Effect on immune outcome(s)
					Salivary IgA	ELISA	Pre and post intervention (baseline and 21 days)	NS
					LPS stimulated production of cytokines (IFN-γ, IL-1β, IL-6, IL-8, IL-10, TNF-α) in whole blood	ELISA	Pre and post intervention (baseline and 21 days)	NS
Schiffrin et al. (2007)	Older adults	Undernourished or at risk of malnutrition (community dwelling &/ nursing home residents); 70-99 years; Age (years): M = 84 (SD = 7) Sex (% female): 75.7 BMI (kg/m^2): M = 24.9 (±6.2 likely to be SD)	Liquid supplement with FOS; 1.3 g/250 mL – 1.5–3 servings per day (1 serve = 250 mL)	12 weeks	Blood lymphocyte subsets	Flow cytometry	12 weeks	NS
Vulevic et al. (2008)	Older adults	Healthy; Age (years): M = 69.3 (SD = 4.0, Range = 64–79); Sex (% female): 63.6; BMI (kg/m^2): Range = 22–31	GOS; 5.5 g/d	10 weeks intervention with 4 weeks washout period in between	NK cell activity [effector-to-target (E:T) cell in 3 ratios of PBMC:K562 cells, 100:1, 50:1, 25:1]	LDH cytotoxicity detection	Baseline, 5, 10 weeks	↑ at 5 weeks ($p < .05$) ↑ at 10 weeks (E:T 50:1, $p < .001$; E:T 25:1 $p < .01$)
					Phagocytic activity of PBMCs (positive for phagocytosis % (%P)	Phagotest kit	Baseline, 5, 10 weeks	↑ at 5 weeks ($p < .001$) ↑ at 10 weeks ($p < .001$)
					Phagocytosis capacity (PC)	Phagotest kit	Baseline, 5, 10 weeks	↑ at 5 weeks ($p < .05$) ↑ at 10 weeks ($p < .001$)
					LPS stimulated IL-6 production by PBMCs	Immunoabsorbent assay	Baseline, 5, 10 weeks	↓ 5 weeks ($p < .05$) ↓ 10 weeks ($p < .001$)
					LPS stimulated IL-10 production by PBMCs	Immunoabsorbent assay	Baseline, 5, 10 weeks	↑ 10 weeks ($p < .01$)
					LPS stimulated IL-1β production by PBMCs	Immunoabsorbent assay	Baseline, 5, 10 weeks	↓ 10 weeks ($p < .05$)
					LPS stimulated TNF-α production by PBMCs	Immunoabsorbent assay	Baseline, 5, 10 weeks	↓ 5 weeks ($p < .05$) ↓ 10 weeks ($p < .01$)
					LPS stimulated IL-8 production by PBMCs	Immunoabsorbent assay	Baseline, 5, 10 weeks	NS
Vulevic et al. (2015)	Older adults	Healthy; Age (years): 70.4 (SD = 3.8, Range = 65–80); Sex (% female): 62.5; BMI (kg/m^2): Not reported	GOS; 5.5 g/d	4 week run-in; 10 weeks intervention arm with 4 weeks washout period	NK cell activity [effector-to-target (E:T) cell in 3 ratios of PBMC:K562 cells, 100:1, 50:1]	LDH cytotoxicity detection	Baseline, 5 weeks, 10 weeks	↑ at 5 weeks ($p < .001$; E:T 100:1 & 50:1) ↑ at 10 weeks ($p < .001$; E:T 100:1 & 50:1) Follow-up: NS
					Faecal secretory sIgA	ELISA	Timepoints unclear	NS
					LPS stimulated IL-6 production by PBMCs	Immunoabsorbent assay	Baseline, 10 weeks	NS
					LPS stimulated IL-10 production by PBMCs	Immunoabsorbent assay	Baseline, 10 weeks	↑ at 10 weeks ($p < .01$)
					LPS stimulated IL-1β production by PBMCs	Immunoabsorbent assay	Baseline, 10 weeks	↓ at 10 weeks ($p < .001$)
					LPS stimulated TNF-α production by PBMCs	Immunoabsorbent assay	Baseline, 10 weeks	NS

(*Continued*)

Table 1. Continued.

Author, Year	Population	Population description and health status at enrolment/ baseline	Description and dose of NDC/prebiotic intervention	Duration of intervention	Endpoints	Assessment methodology	Time points assessed	Effect on immune outcome(s)
					LPS stimulated IL-8 production by PBMCs	Immunoabsorbent assay	Baseline, 10 weeks	↑ at 10 weeks ($p < .01$)
Wilms et al. (2021)	Older adults	Healthy; Age (years): M = 74.3 (SD = 3.7); Sex (% female): 45; BMI (kg/m^2): M = 26.4 (SD = 3.0)	GOS; 15 g/d	4 weeks; 4-6 week wash-out period between intervention arms	LPS and PHA stimulated IL-6 production by whole blood after 24 h LPS and PHA stimulated IL-8 production by whole blood after 24 h LPS and PHA stimulated IL-10 production by whole blood after 24 h LPS and PHA stimulated TNF-α production by whole blood after 24 h LPS and PHA stimulated IFN-γ production by whole blood after 24 h	Cytometric Bead Array	Pre and post each intervention arm	NS NS NS NS NS

M: Mean; Me: Median; SD: Standard deviation; SEM: Standard error of the mean; IQR: Inter-quartile Range; BMI: Body mass index; RRTIs: Recurrent respiratory tract infections; RTIs: Respiratory tract infections; 2′FL: 2′Fucosyllactose; DFL: 2′,3-di-O-fucosyllactose; hMOs: Human milk oligosaccharides; GOS: Galactooligosaccharides; scGOS: Short chain galactooligosaccharides; FOS: Fructooligosaccharides; lcFOS: Long chain fructooligosaccharides; DP: Degree of polymerization; NPS: Non-digestible polysaccharides; YBG: Yeast-derived β-glucan; SBG: Shiitake-derived β-glucan; OBG: Oat-derived β-glucan; AX: Arabinoxylan; EPS: Exopolysaccharide; cRG-I: carrot rhamnogalacturonan-I; PBMC: Peripheral blood mononuclear cells; CD: Cluster of differentiation; NK: Natural killer; T cell/s: T lymphocyte/s; Th: T helper; Th1: Subset of $CD4^+$ T helper cells; CM: Central memory; EM: Effector memory; EMRA: Terminal effector memory; B cell/s: B lymphocyte/s; TC cells: Cytotoxic T cells; PMA: Phorbol Myristate Acetate; MW: Molecular weight; kDa: KiloDaltons; Ig: Immunoglobulin; sIg: Secretory immunoglobulin; PHA: Phytohaemagglutinin; ConA: Concanavalin A; IL–: Interleukin–; Con A: Concanavalin A; C3: Complement component 3; IFN-γ: Interferon-γ; TNF-α: Tumor necrosis factor-α; GM-CSF: Granulocyte-macrophage colony-stimulating factor; FOXP3: Forkhead box P3/scurfin; MCP-3 (CCL7): Monocyte-chemotactic protein-3 (CC chemokine ligand 7); MIP-1α: Macrophage inflammatory protein-1α; MIP-1β: Macrophage inflammatory protein-1β; LPS: Lipopolysaccharide; LC-MS/MS: Liquid chromatography tandem mass spectrometry; ELISA: Enzyme-linked immunosorbent assay; LDH: Lactate dehydrogenase; Min: Minute; H/h: Hour; NS: Non-significant.

Figure 6. Traffic Light Plot of the domain-level risk-of-bias judgements for each study included in the review of prebiotics and immunity.

GOS ($n=2$), a mixture of inulin and oligofructose ($n=2$), resistant corn starch ($n=1$), rhamnogalacturonan from either hallabong peel ($n=1$) or carrot ($n=1$), 2′FL ($n=1$) and β-fructans ($n=1$). Studies in infants used mixtures of GOS:lcFOS ($n=5$), mixed hMOs ($n=1$), GOS ($n=1$), oligofructose-enriched inulin ($n=1$), 2′FL ($n=1$) and a mixture of GOS and polydextrose ($n=1$). The single study in children used β-1,3–1,6-glucan as pleuran from *Pleurotus ostreatus* ($n=1$). Fecal IgA was measured in 7 trials (6 in infants and 1 in older adults), while salivary IgA was measured in 7 trials (1 in infants, 4 in adults and 2 in older adults). Circulating immunoglobulins, including IgG, IgM, IgE, and IgA, were quantified in 13 trials (3 in infants, 1 in children, 7 in adults, and 2 in older adults). Other immune-related factors, such as defensins, lysozyme, and calprotectin, were assessed in 2 trials involving infants.

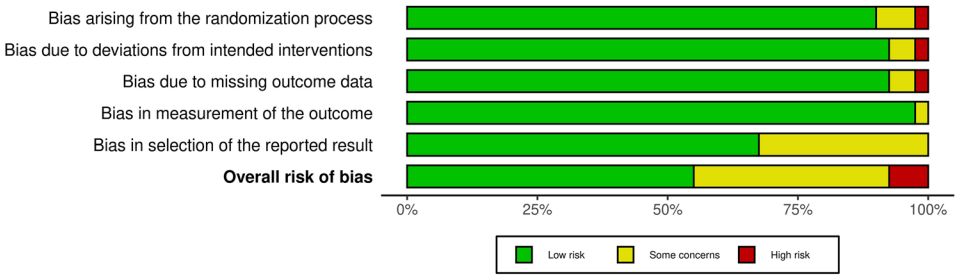

Figure 7. Unweighted bar plots of the distribution of risk-of-bias judgements within each bias domain for studies included in the review of prebiotics and immunity.

Blood complement factor 3 (C3) was measured in 2 trials, 1 in adults and 1 in older adults. Cellular immunity measures were more common in adult populations. NK cell cytotoxicity and/or counts were evaluated in 12 trials, 9 in adults and 3 in older adults. Blood lymphocyte subset counts, with varying levels of detail, were also assessed in 17 trials, 2 in infants, 1 in children, 11 in adults and 3 in older adults, with an additional study ($n = 1$, in adults) quantifying lymphocytes which had infiltrated the nasal cavity upon human challenge with rhinovirus strain 16 (RV16). Functional immune assessments (e.g., cytokine secretion and/or cell proliferation upon stimulation with immunogenic agents (e.g., LPS, phytohaemagglutinin) were conducted in a number of trials. Phagocytosis and oxidative burst assays were performed in 5 trials, 3 in adults and 2 in older adults.

Among the 40 studies reporting on immunity outcomes, 22 (55.0%) showed a low risk of bias, 15 (37.5%) had some concerns, and 3 (7.5%) had a high risk of bias (Figure 6). While the most common reason for the "some concerns" judgment is the bias in the selection of reported results, 39 out of the 40 studies have been classified as low risk of bias in the measurement of the outcome (Figure 7).

In infants, fecal IgA, the most studied marker of immunity in that age group, was increased after supplementation with mixtures of GOS:lcFOS or hMOs (Bosheva et al. 2022; Scholtens et al. 2008). Mixtures of GOS:lcFOS also increased salivary IgA, salivary α1-3 defensin and fecal lysozyme (Ivakhnenko and Nyankovskyy 2013), but did not influence blood immunoglobulins (including IgG, IgA, IgM and IgE) (Raes et al. 2011; Salvini et al. 2011), except in infants at higher risk of developing allergies, where GOS:lcFOS decreased total blood IgE, IgG1, IgG2, IgG3 as well as cow's milk protein specific IgG1 (van Hoffen et al. 2009). In contrast, GOS by itself, GOS with polydextrose, oligofructose enriched inulin or 2′FL neither led to an increase in fecal IgA, nor in the additional markers fecal calprotectin and fecal β-defensin (Alliet et al. 2022; Neumer et al. 2021; Scalabrin et al. 2012; Sierra et al. 2015). GOS:lcFOS had a minor impact on blood lymphocyte populations by increasing the percentage of $CD38^{+}CD4^{+}$ T cells, but none of the various other lymphocyte subsets assessed were affected (Raes et al. 2011). The only trial in children did not find any detectable changes in major T and NK cell subsets in blood after pleuran (β-1,3–1,6-glucan) supplementation, notwithstanding the protective effect observed against recurrent respiratory tract infections (RRTIs) (Jesenak et al. 2013).

In adults, supplementation with β-glucan isolated from *Pleurotus ostreatus* (pleuran; β-1,3–1,6-glucan) mitigated the decline in NK cell numbers and increased NK cell cytotoxic activity after acute bouts of exercise (Bobovčák et al. 2010). Baker's yeast β-1,3–1,6-glucan further influenced the response to acute exercise by increasing monocyte numbers and function, as reflected by enhanced type-1 and -2 cytokine secretion upon LPS-stimulation of peripheral blood (Carpenter et al. 2013; McFarlin et al. 2017). Adult athletes also more generally benefited (outside the period of acute exercise) from pleuran supplementation (100 mg/d) through increased NK cell numbers and peripheral blood mononuclear cell (PBMC) phagocytic activity (Bergendiova, Tibenska, and Majtan 2011). Enhanced NK cell cytotoxic activity was also observed in adult non-athletes following *Agrobacterium* sp.-derived β-1,3-glucan, Reishi-derived β-1,3–1,6-glucan or hallabong peel pectic polysaccharides supplementation (<1 g/d) (Lee et al. 2016; Lee et al. 2017). In addition, Reishi- and *Euglena gracilis*-derived β-glucan influenced the frequencies and phenotypes, respectively, of circulating immune cells after a period of 12 wks (Chen et al. 2023; Kawano et al. 2023), and carrot-derived rhamnogalacturonan selectively altered lymphocyte recruitment to the nasal cavity upon acute RV16 infection (Lutter et al. 2021). In contrast, oat β-glucan (5.6 g/d), 2′FL, and a mixture of inulin and oligofructose (8 g/d) failed to increase NK cell cytotoxicity, lymphocyte counts, lymphocyte cytokine secretion or ability to proliferate upon stimulation, phagocytosis, neutrophil oxidative burst and salivary IgG, IgA and IgM (Lomax et al. 2012, 2015; Nieman et al. 2008). GOS supplementation (15 g/d) failed to alter lymphocyte cytokine secretion (Wilms et al. 2021) as well as blood IgE (Williams et al. 2016), yet increased salivary IgA at lower doses (2.8 g/d) (Parker et al. 2023), while β-glucan (2 g/d, unknown origin) had no impact on blood IgM (Wang et al. 2022). Nevertheless, resistant corn starch (24 g/d) increased blood IgG and C3 (Park et al. 2004).

In older adults, GOS (5.5–8 g/d) consistently increased NK cell cytotoxicity, with mixed effects on PBMC phagocytic activity (Maneerat et al. 2013; Vulevic et al. 2008, 2015). However, GOS, FOS or β-1,3–1,6-glucan (from *Lentinus edodes*) did not enhance fecal or salivary IgA, or blood immunoglobulins (IgG, IgA and IgM) (Gaullier et al. 2011; Maneerat et al. 2013; Schiffrin et al. 2007; Vulevic et al. 2015). Although β-1,3–1,6-glucan (dose unspecified) increased peripheral B cell numbers, it had no effect on other lymphocyte subsets or blood complement factor C3

Table 2. Effects of NDCs/prebiotics on infection outcomes.

Author, Year	Population	Population description and health status at enrolment/baseline	Description and dose of NDC/prebiotic intervention	Duration of intervention	Endpoints	Assessment methodology	Time points assessed	Effect on infection outcome(s)
Arslanoglu, Moro, and Boehm (2007)	Infants	Healthy, with a parental history of atopic eczema, allergic rhinitis or asthma; *Age (days): Treatment: M = 11.2 (SD = 7.0); Control: M = 11.8 (SD = 9.2); *Sex (% female): Treatment: 49.6; Control: 51.5; *Birth weight (kg): Treatment: M = 3.34 (SD = 0.46); Control: M = 3.38 (SD = 0.48) *As reported in a previous paper (Moro et al., 2006)	Extensively hydrolyzed cow's milk whey protein formula with GOS/lcFOS (9:1); 8 g/L	6 months	Infectious episodes (overall types) Infections requiring antibiotic treatment Incidence of infectious episodes	Parental interview (at 3 and 6 months); practitioner documentation	Monthly	↓ at 6 months (p = .01) NS ↓ overall cumulative incidence (>=1 episode), incidence of recurrent infection (>=2), incidence of recurring URTI (p < .05; p = .01; p < .05) NS for otitis media, gastrointestinal infections, and urinary tract infections ↓ incidence of episode during 4th to 6th months of life (p < .05)
Arslanoglu et al. (2008)	Infants	Healthy; with parental history of atopy; Sex (% female): Treatment: 47.6; Placebo: 50; Birth weight (kg): Treatment: M = 3.28 (SD = 0.51); Placebo: M = 3.31 (SD = 0.46)	Hypoallergenic formula with GOS/lcFOS (9:1); 8 g/L	6 months of feeding, follow-up for 2 years	Incidence of any kind of infection Incidence of URTI Incidence of lower respiratory tract infections Incidence of otitis media Incidence of gastrointestinal infection Incidence of urinary tract infections Infections requiring antibiotic prescription Incidence of fever	Physician diagnosed	24 months	↓ (p = .01) ↓ (p < .01) NS NS NS NS ↓ (p < .05)
Berger et al. (2020)	Infants	Healthy; Age (days): Treatment: M = 8.6 (SD = 3.3); Control: M = 7.7 (SD = 3.3); Sex (% female): Treatment: 50.0; Control: 49.4; Breast-fed: 28.6 Weight (kg): Treatment: M = 3.4 (SD = 0.4); Control: M = 3.4 (SD = 0.4); Breast-fed: M = 3.4 (SD = 0.3)	Infant formula with 2'FL; 1.0 g/L + lacto-N-neotetraose; 0.5 g/L	6 months intervention 6 months follow up	Bronchitis LRTI	Parent reported Reported	24 months 0–6 months; 6–12 months	↓ (p < .0001) ↓ at 0–6 and 0–12 months vs control (p < .004; p < .005) NS

(*Continued*)

Table 2. Continued.

Author, Year	Population	Population description and health status at enrolment/baseline	Description and dose of NDC/prebiotic intervention	Duration of intervention	Endpoints	Assessment methodology	Time points assessed	Effect on infection outcome(s)
Duggan et al. (2003)	Infants	Healthy; 6-12 months old, but in a high-risk environment (high burden of GI and other infections); Trial 1: Age (months): Treatment: M = 9.2 (SD = 2.0); Control: M = 8.5 (SD = 1.9); Sex (% female): Treatment: 48.2; Control: 54.6; Weight (kg): Treatment: M = 8.8 (SD = 1.1); Control: M = 8.7 (SD = 1.1) Trial 2: Age (months): Treatment: M = 8.7 (SD = 1.7); Control: M = 8.5 (SD = 1.7); Sex (% female): Treatment: 47.7; Control: 52.6 Weight (kg): Treatment: M = 8.8 (SD = 1.1); Control: M = 8.5 (SD = 1.0)	Oligofructose; 0.55 g/15 g of cereal (approx. cereal intake was 18.4 ± 10.4 g/d; on average 0.67 g oligofructose per day)	6 months	Dysentery Rotavirus infection	Physical examination (no more information). Infant's caretaker was asked about presence of blood, vomiting, cough, other signs of upper respiratory infection, fever, and any visit to health facilities. Physical exam performed if symptoms worsened or new symptom(s).	Throughout the observation period	NS NS
Ivakhnenko and Nyankovskyy (2013)	Infants	Healthy newborns; No details reported, but based on inclusion criteria: Birth weight > 2500 g; No differences between groups in "…age at the enrolment, gender, physical and social settings."	Formula with GOS/lcFOS (9:1); 8 g/L	At least 2 months, with average approx. 8 months, plus 18 month follow-up	Incidence of GI infections Incidence of URTIs	Method not reported	18 months	↓ ($p < 0.001$) ↓ ($p < .001$)
Leung et al. (2020)	Infants	Healthy; 1–2.5 years; Age (months): Formula (a): M = 17.7 (SD = 4.8); Formula (b): M = 17.6 (SD = 4.7); Formula (c): M = 17.7 (SD = 4.7); Formula (d): M = 17.9 (SD = 4.7); Sex (% female): Formula (a): 47.4; Formula (b): 50.0; Formula (c): 50.0; Formula (d): 49.1 Birth weight (kg): Formula (a): M = 3.1 (SD = 0.42); Formula (b): M = 3.18 (SD = 0.42); Formula (c): M = 3.15 (SD = 0.39); Formula (d): M = 3.18 (SD = 0.43)	Formula (b) YCF-A (milk formula with immunoglobulins, lactoferrin, and TGF-β at levels typical for breast milk, 2′-FL at a level found in human milk i.e., 3 g/L, and milk fat) Formula (c) YCF-B (milk formula with lower levels of the bioactive proteins than in formula (b) YCF-A) Formula (d) YCF-C (milk formula with 2′-FL at same level as in formula (b) YCF-A i.e., 3 g/L)	6 months	Total URTI episodes Time to 1st URTI Subjects with ≥ 3 URTI episodes Number of LRTI Total episodes and duration of GITI episodes Severity scores of GITI Antibiotic prescriptions Otitis media	Parent/caregiver reported, investigator verified	6 months	NS NS NS NS NS NS NS NS

(*Continued*)

Table 2. Continued.

Author, Year	Population	Population description and health status at enrolment/baseline	Description and dose of NDC/prebiotic intervention	Duration of intervention	Endpoints	Assessment methodology	Time points assessed	Effect on infection outcome(s)
					Time to first GITI	Parent/caregiver reported, investigator verified	6 months	↓ with 2FL vs control ($p < .05$)
					Duration of URTI Incidence of cough Incidence of runny nose Total number of days with fever	Parent/caregiver reported, investigator verified	6 months	↑ with 2FL vs control ($p < .05$) ↑ with 2FL vs control ($p < .001$) ↑ with 2FL vs control ($p < .001$) ↑ with 2FL vs control ($p < .01$)
Neumer et al. (2021)	Infants	Healthy; < 4 months of age; Age (days): Treatment: M = 67.9 (SD = 39.7) ; Control: M = 60.0 (SD = 41.4); Sex (% female): Treatment: 52.3; Control: 50.8; Weight at inclusion (kg): Treatment: M = 5.2 (SD = 1.34); Control: M = 5.1 (SD = 1.53) Birth weight (kg): Treatment: M = 2.9 (SD = 1.08); Control: M = 3.7 (SD = 1.24)	Infant and follow-on formulas with 0.8 g/100 mL of chicory-derived oligofructose-enriched inulin (short chain oligofructose (DP < 10) and long chain inulin (DP ≥ 10) in an approximate 50:50 ratio ± 10% each)	Until the age of 1 year	Occurrence of infections; measured through the presence of fever >38 °C and: Number of infectious episodes Duration of infectious episodes	Diary	Baseline, 2, 4, 6, 9, 12 months	NS ↓ in Treatment group ($p = .034$)
Paganini et al. (2017)	Infants	Healthy; 6.5–9.5 months old; Age (months): Treatment: Me = 7.3 (Range = 6.9–9.2); Control: Me = 7.5 (Range = 6.9–9.3); Sex (% female): Treatment: 57.7; Control: 48.1	Micronutrient powder including GOS; 7.5 g/d and iron; 5 mg/d	2 week run-in without supplementation; 4 months	VTGs of selected enteropathogens: *B. cereus*, *C. difficile*, *C. perfringens*, EHEC, ETEC, EPEC, Salmonella, *S. aureus*	qPCR	Baseline, 3 weeks, 4 months	All 10 VTGs (combined) ↓ at 3 weeks in Treatment group vs control group (p <.01) EHEC (only considering EHEC positive samples) ↓ at 4 months in treatment group (4.0 (3.6–4.5)) vs control group (4.8 (4.3–5.3)) (p = 0.036)
					Incidence of RTI	Assessed at weekly visits	Month 1, 2, 3, 4	NS
Puccio et al. (2017)	Infants	Healthy; Mean age (days): Treatment: M = 8.6 (SD = 3.3); Control: M = 7.7 (SD = 3.3) Sex (% female): Treatment: 50.0; Control: 49.4 Weight (kg): Treatment: M = 3.4 (SD = 0.4); Control: M = 3.4 (SD = 0.4)	Formula with 2'FL; 1 g/L + lacto-N-neotetraose; 0.5 g/L	Until 6 months of age	Lower respiratory tract infection Upper respiratory tract infection, rhinitis, diarrhoea, otitis	Parent reported (but diagnosed by either primary care physician or study physician)	4, 6, 12 months	↓ reported LRTI events at 12 months; p <.05, OR (95% CI): 0.45 (0.21, 0.95) NS

(*Continued*)

Table 2. Continued.

Author, Year	Population	Population description and health status at enrolment/baseline	Description and dose of NDC/prebiotic intervention	Duration of intervention	Endpoints	Assessment methodology	Time points assessed	Effect on infection outcome(s)
Raes et al. (2010)	Infants	Healthy; At birth Sex (% female): Treatment: 43.0; Control: 45.6 Birth weight (kg): Treatment: M = 3.5 (SD = 0.4); Control: M = 3.6 (SD = 0.4); Breast feeding (%): Treatment: 38.7; Control: 35.5; Mean duration breast feeding (weeks): Treatment: M = 11.5 (SD = 10.0); Control: M = 10.3 (SD = 9.0)	Formula with GOS/lcFOS (9:1); 6 g/L	26 weeks from birth	Bronchitis	Parent reported (but diagnosed by either primary care physician or study physician)	4, 6 and 12 months	↓ reported bronchitis events at all time points (p <.01); OR (95% CI) for 0–4 months: 0.16 (0.02, 0.78), 0–6months: 0.26 (0.08, 0.74) and 0–12 months: 0.30 (0.11, 0.73)
Ranucci et al. (2018)	Infants	At risk of atopy; Birth weight (kg): Treatment: M = 3.4 (SD = 0.4); Control: M= 3.4 (SD = 0.4)	Formula with GOS/ polydextrose (50:50); 4 g/L	48 weeks; follow up at 24, 36, 48 and 96 weeks	Respiratory infection	Physician diagnosed	Up to 96 weeks	At 48 weeks: Fewer infants with at least one episode and fewer episodes
					Acute gastroenteritis	Parental report	Up to 96 weeks	NS
Ripoll et al. (2015)	Infants	Healthy; Age (weeks): Treatment: M = 17.8 (SD = 0.2); Control: M = 17.8 (SD = 0.1); Sex (% female): Treatment: 48.5; Control: 58.1	Follow-on milk formula with scFOS (from sucrose, DP3-5); 5 g/L	6 months	Incidence of infection	Parental report (but analysed as AE of infectious origin as confirmed by medical expert post-study)	Duration of study period	NS
Shahramian et al. (2018)	Infants	Healthy; Age (days): <14 (mean not reported) Birth weight (kg): Treatment: M = 3.36 (SD = 0.31); Control: M = 3.31 (SD = 0.29)	Formula with GOS/lcFOS (9:1); dosage not reported	<14 days of age to 12 months	Incidence of fever Incidence of respiratory tract infection	Physician diagnosed	From birth to 12 months, every 2 months	↓ at 10 months (p = .001); ↓ over 12 months (p = .0001) ↓ at 12 months (p = .01)
Sierra et al. (2015)	Infants	Healthy; Average age (days): Treatment: M = 29.4 (SD = 17.7); Control: M = 32.2 (SD = 18.2); Sex (% female): Treatment: 43.1; Control: 45.8 Birth weight (kg): Treatment: M = 3.2 (SD = 0.5); Control: M = 3.2 (SD = 0.4), formula-fed only for 15 d prior to trial	4.4 g/L GOS in infant formula until 6 months of age, then 5.0 g/L in follow-on formula until 12 months of age	Before 8 weeks to 12 months of age; ≥ 10 months of supplementation	Number of URTI per infant Infants with at least 3 URTI per year	Parent reported and reviewed by a primary care paediatrician	Duration of intervention (throughout the approx. 11 months)	NS NS
van Stuijvenberg et al. (2011)	Infants	Healthy; Age (days): Treatment: Me = 30 (IQR = 22); Control: Me = 32 (IQR = 24); Sex (% female): Treatment: 47; Control: 52; Birth weight (g): Treatment: Me = 3277 (IQR = 645); Control: Me = 3320 (IQR = 695)	Non-hydrolysed cows' milk-based formula with GOS/lcFOS (9:1); 6.8 g/L and citrus pectin acidic OS; 1.2 g/L	Until the age of 1 year	Number of fever episodes (Fever was defined as a peak rectal temperature >38.5°C) + suspected causes: GI; URTI; Otitis; vaccination-related fever	Diary	From enrolment up to the end of the 1st year of life	NS

(*Continued*)

Table 2. Continued.

Author, Year	Population	Population description and health status at enrolment/baseline	Description and dose of NDC/prebiotic intervention	Duration of intervention	Endpoints	Assessment methodology	Time points assessed	Effect on infection outcome(s)
van Stuijvenberg et al. (2015)	Infants	Healthy; < 8 weeks after birth, birth weight > 10th percentile according to local growth charts; Age (days): Treatment: Me = 30 (IQR = 24); Control: Me = 32 (IQR = 25); Sex (% female): Treatment: 51.3; Control: 53.1; Weight (kg): Treatment: Me = 15 (IQR = 2.2); Control: Me = 14.8 (IQR = 2.2)	Infant formula with GOS/lcFOS (9:1); 6.8 g/L and citrus pectin acidic oligosaccharides; 1.2 g/L	Supplementation during the 1st year and follow-up between age of 3 and age of 5	Duration of diarrhoea Use of antibiotics by type Frequency of febrile episodes per year (fever, coughing, wheezing, runny nose, vomiting, diarrhoea) Duration of illness (fever, coughing, wheezing, runny nose, vomiting) Use of antipyretics (paracetamol, ibuprofen)	Questionnaire, parent reported	Period 3-5 years of age	↓ from 2 to 1d ($p < 0.01$) NS NS NS NS
Waligora-Dupriet et al. (2007)	Infants	Healthy; Aged 6–24 months; Age (median ± SD): Treatment: M = 14.2 (SD = 3.5); Placebo: M = 12.6 (SD = 3.4) Sex (% Female): Not reported Weight (Kg): Not reported	Chicory oligofructose; 2 g/d	8 days run-in; 21 days of supplementation; 15 days follow-up	Infectious diseases requiring antibiotic treatment Episodes of vomiting Episodes of fever The number of children who start to vomit	Parent or caregiver reported	Period of 42 days	↓ ($p < .001$) data not reported ↓ ($p < .001$) data not reported ↓ ($p < .05$) data not reported ↓ ($p < .05$) data not reported
Jesenak et al. (2013)	Children	Children; aged 2–10 years; with a history of RRTIs; Age (years): Treatment: M = 5.78 (SD = 2.53); Placebo: M = 5.51 ± (SD = 2.22); Sex (% female): Treatment: 42.6; Placebo: 46.9; Weight (kg): Treatment: M = 27.52 (SD = 27.24); Placebo: M = 26.54 (SD = 22.61); Number of RTIs/12 months before the study: Treatment: M = 6.27 (SD = 2.10); Placebo: M = 6.86 (SD = 2.58)	Insoluble β-1,3-1,6-glucan (pleuran); 10 mg + vitamin C; β-1,3-1,6-glucan 10 mg in 1 mL of syrup per 5 kg body weight daily	6 months intervention + 6 months follow-up	No. of children with respiratory infections Incidence of flu and flu-like disease Incidence lower RTIs Respiratory morbidity	Self-reported Self-reported Self-reported Paediatrician evaluated	For 6 months 12 months 12 months Unclear	↓ ($p < .05$) ↓ ($p < .05$ data not shown) ↓ ($p < .05$) ↓ ($p < .001$)
Lohner et al. (2018)	Children	Healthy; 3–6 years old; Age (years): Treatment: Me = 4.93 (IQR = 1.54); Placebo: Me = 4.97 (IQR = 1.72); Sex (% female): Treatment: 47.3; Placebo: 47.7; Weight (kg): Treatment: Me = 18.8 (IQR = 4.50); Placebo: Me = 18.0 (IQR = 6.00)	Inulin-type fructan mix of shorter and longer chains (DP ≥11 approx. 25%–30%; average DP of about 7–8); 6 g/d	24 weeks	Overall number of infections requiring physician consultation Tonsillopharyngitis acuta Laryngitis acuta Otitis media Bronchitis acuta Pneumonia Gastroenteritis acuta Urinary tract infection Total number of URTIs Total number of LRTIs	Physician diagnosed	Duration of intervention (throughout the 24 weeks)	NS NS NS NS NS NS NS NS NS NS
					Number of febrile infections requiring physician consultation Sinusitis maxillaris	Physician diagnosed	Duration of intervention (throughout the 24 weeks)	↓ ($p = 0.04$) ↓ ($p = .03$)

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Table 2. Continued.

Author, Year	Population	Population description and health status at enrolment/baseline	Description and dose of NDC/prebiotic intervention	Duration of intervention	Endpoints	Assessment methodology	Time points assessed	Effect on infection outcome(s)
					Episodes with respiratory symptoms	Parent reported	Duration of intervention (throughout the 24 weeks)	NS
					Episodes with gastrointestinal symptoms			NS
					Fever episodes			NS
					Infections requiring antibiotic prescription			NS
					Infections requiring hospitalization			NS
Sudarmo et al. (2019)	Children	Healthy; Age (months): Treatment: 38.57 ± 11.8; Control: 36.75 ± 12.9 (unclear whether SD or SEM is reported); Sex (% female): Treatment: 41.5; Control: 60.4; Weight (kg): Treatment: 13.62 ± 3.5; Control: 12.77 ± 3.1 (unclear whether SD or SEM is reported)	GOS; as much as 840 mg was given per feeding	26 weeks	ARI incidence rates	Daily questionnaire		NS
					RRR			NS
					ART			NS
					NTT Average duration of ARI (days)			NS
Urbancikova et al. (2020)	Adolescents and young adults	Healthy with herpes (herpes simplex facialis/labialis); Age (years) Acute Treatment Phase: Treatment: M = 25.3 (SEM = 2.3); Control: M = 17.4 (SEM = 1.5); Preventative Phase: Treatment: M = 26.1 (SEM = 2.5); Control: M = 17.6 (SEM = 1.4); Sex (% female): Acute Treatment Phase: Treatment: 65.3; Control: 51.2; Prevention Phase: Treatment: 64.1; Control: 52.6; BMI: Not reported	Acute treatment of herpes: β-1,3-1,6-glucan (pleuran); 300 mg, vitamin C; 160 mg and zinc; 10 mg Prevention period: β-1,3-1,6-glucan (pleuran); 100 mg and vitamin C; 100 mg	Intervention during acute treatment: 10 days Intervention during prevention period: 120 days	Duration of infection (days)	Daily diary cards	Overall from day 1 to 10	↓ (p = .046)
					Herpes symptoms score			NS
					Antiherpetic use			NS
					Symptomatic herpes patients (n)	Daily diary cards	Daily from day 1 to 10	↓ day 5 and 6 (p = .027; p = .013)
					Duration of acute respiratory symptoms and intercurrent diseases (days)	Daily diary cards	Overall from day 10 to 120	↓ of rhinitis and cough (p = .05; p = .024) ↓ of cough (p = .035)
					Acute respiratory symptoms and intercurrent diseases score			

(*Continued*)

Table 2. Continued.

Author, Year	Population	Population description and health status at enrolment/baseline	Description and dose of NDC/prebiotic intervention	Duration of intervention	Endpoints	Assessment methodology	Time points assessed	Effect on infection outcome(s)
Auinger et al. (2013)	Adults	Healthy (at least 3 common cold episodes in last 6 months); Age (years): Treatment: M = 43.7 (SD = 15.1); Placebo: M = 42.7 (SD = 16.3); Sex (% female): Treatment: 71.6; Placebo: 66.7; BMI (kg/m^2): Treatment: M = 25.3 (SD = 5.4); Placebo: M = 25.1 (SD = 4.9)	Insoluble β-1,3-1,6-glucan (*S. cerevisiae*); 900 mg/d	16 weeks	Incidence of common cold Subjects with at least 1 severe episode (achieving maximum scale) Mean total symptom score Duration of episodes	Characterised during visits (physician?)	Visits at baseline, 8 and 16 weeks + visit at 5th day of each infection episode – Primary endpoint	↓ in PP population (1.06 ± 0.89 and 1.36 ± 0.94; p = .041) ↓ incidence (p = .028) NS NS
Bergendiova, Tibenska, and Majtan (2011)	Adults	Healthy athletes; Age (years): Treatment: M = 23.6 (SEM = 0.8); Control: M = 24.0 (SEM = 0.9); Sex (% female): Treatment 56; Control 48; BMI (kg/m^2): Treatment: M = 22.8 (SEM = 0.6); Control: M = 23.7 (SEM = 0.5)	β-1,3-1,6-glucan (pleuran); 100 mg/d and vitamin C; 100 mg/d	3 months intervention 3 months follow up	URTI symptoms score	Invalidated physical health questionnaire	0, 3, 6 months	↓ at 3 months (p < .001)
Cummings, Christie, and Cole (2001)	Adults	Healthy; Age (years): Treatment – M = 49.9 (SD = 14); Placebo – M = 50 (SD = 12.4); Sex (% female): Treatment = 45.3; Placebo = 47.2 BMI (kg/m^2): Not reported	FOS (not described); 10 g/d	5 weeks: 1 week run-in (baseline) period (no supplement taken) 2 weeks pre-holiday period (taking supplement) 2 weeks during holiday (taking supplement)	Total number of stools during 2 week holiday period Size of each stool (3 point scale) during the 2 week holiday period (adjusted for number of stools) Stool consistency of each stool (3 point scale) during the 2 week holiday period (adjusted for number of stools)	Self-report diary	Baseline, pre-holiday, holiday	FOS ↑ stool frequency in the pre-holiday period (adjusted for baseline stool frequency; 6%, p = 0.02) NS NS
Dharsono et al. (2019)	Adults	Healthy adults with reduced immunity (defined by susceptibility to URTIs); Age (years): Treatment – M = 37.6 (SD = 14.3); Placebo – M = 40.5 (SD = 16.4); Sex (% female): Treatment = 68; Placebo = 68; BMI (kg/m^2): Treatment – M = 23.8 (SD = 3.3); Placebo – M = 23.2 (SD = 3.0)	Insoluble β-1,3-1,6-glucan (*S. cerevisiae*); 900 mg/d	16 weeks (visits at baseline, 8 weeks, 16 weeks and 3rd/4th day of each URTI episode)	Incidence of URTIs	Self-report questionnaire – WURSS-21, most episodes also clinically confirmed at site	Daily for duration of study i.e., 16 weeks	NS

(*Continued*)

Table 2. Continued.

Author, Year	Population	Population description and health status at enrolment/baseline	Description and dose of NDC/prebiotic intervention	Duration of intervention	Endpoints	Assessment methodology	Time points assessed	Effect on infection outcome(s)
					Global severity (AUC) of URTIs (primary outcome) – Overall analysis Global severity (AUC) of URTIs (primary outcome) – severity of sickness episodes Global severity (AUC) of URTIs – severity of episodes lasting >7 days. Global severity (AUC) of URTIs (primary outcome) – subject level (Severity data from subjects experiencing several episodes was summed on subject level, with focus on physical symptoms WURSS (Q2-11) over defined time intervals)	Self-report questionnaire – WURSS-21 and Jackson score	Daily for duration of study i.e., 16 weeks	NS ↓ during the first days of episodes (↓ severity of physical symptoms for all time intervals within 7 days ($p < .05$) ↓ severity in first week ($p < .05$); Total WURSS-21 score ↓ days 1–2, days 1–3, days 1–4 ($p < .05$). ↓ for the time intervals up to 4 days (days 1–2, days 1–3, days 1–4: $p < .05$)
					Duration of URTIs	Self-report questionnaire – WURSS-21 and Jackson score	Per episode for duration of study i.e., 16 weeks (defined as from the beginning of an episode (as defined by the questionnaires), to the end of an episode (as defined by 2 consecutive days of no symptoms but longest for a period of 14 days)	NS

(*Continued*)

Table 2. Continued.

Author, Year	Population	Population description and health status at enrolment/baseline	Description and dose of NDC/prebiotic intervention	Duration of intervention	Endpoints	Assessment methodology	Time points assessed	Effect on infection outcome(s)
Drakoularakou et al. (2010)	Adults	Healthy adults aged 18+ years who travelled for a minimum of 14 (and maximum of 60) days to a country of low/high risk of TD (Travellers' diarrhoea); Age (years): Treatment – M = 38; Placebo – M = 39 (SD or SEM not reported); Sex (% female): Treatment = 44.4; Placebo = 41.0; BMI (kg/m^2): Not reported	GOS; 2.64 g/d	7 day run-in period taking intervention (pre-holiday period), followed by the intervention period (holiday period: varied between 14 and 60 days)	Incidence of TD Duration of TD Duration of GI symptoms associated with TD & QoL	Clinical report form (self-report)	Holiday period	↓ (p <.05). ↓ (p < .05). ↓ duration of abdominal pain and ↑ QoL (p < .05).
Feldman et al. (2009)	Adults	Healthy; Age (years): Treatment – M = 30.3 (SD = 11.4); Placebo – M = 36.4 (SD = 16.2); Sex (% female): Treatment = 67; Placebo = 74; BMI (kg/m^2): Treatment – M = 23.6 (SD = 2.5); Placebo – M = 25.1 (SD = 4.3)	β-1,3-1,6-glucan (*S. cerevisiae*); 500 mg/d	90 days	Incidence of SRI Duration of SRI	Clinical evaluation	Onset of symptoms and twice daily for 7 days (7–10 days)	NS NS
					Duration of SRI symptoms SRI symptom severity	Self-report daily symptom diary	Onset of symptoms and twice daily for 7 days (7–10 days)	NS NS
Fuller et al. (2012)	Adults	Healthy with at least 1 self-reported cold in the last 12 months; Age (years): Treatment: M = 21.9 (SD = 4.8); Placebo: M = 21.3 (SD = 2.7); Sex (% female): Treatment = 50; Placebo = 50; BMI (kg/m^2): Treatment: M = 23.5 (SD = 2.7); Placebo: M= 23.1 (SD = 2.6)	β-1,3-1,6-glucan (*S. cerevisiae*); 250 mg/d	90 days	Number of days of URTI symptoms	Self-report questionnaire (daily health log)	Daily throughout intervention period and reported as total across the 90 days	NS
					URTI symptom severity	WURSS-21 questionnaire	URTI severity – each symptomatic day after a confirmed reporting of a URTI (with episodes confirmed by medical assessment)	Ability to "breathe easily" was significantly better in the treatment group compared to placebo (p = .049)

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Table 2. Continued.

Author, Year	Population	Population description and health status at enrolment/baseline	Description and dose of NDC/prebiotic intervention	Duration of intervention	Endpoints	Assessment methodology	Time points assessed	Effect on infection outcome(s)
Hasle et al. (2017)	Adults	Healthy travellers (>= 16 years) with intermediate or high risk of traveller's diarrhoea; 3 populations: ITT, CE (Conditionally Evaluable), PP; ITT: Age (years): Treatment: M = 42.0; Placebo: M = 43.2 (no SD or SEM reported); Sex (% female): Treatment = 52.4; Placebo = 50; CE: Age (years): Treatment: M= 43.3; Placebo: M = 43.8 (no SD or SEM reported); Sex (% female): Treatment = 55.1; Placebo = 50.9; PP: Age (years): Treatment: M = 44.0; Placebo – M = 43.8 (no SD or SEM reported); Sex (% female): Treatment = 56.3; Placebo = 49.7; BMI (kg/m^2) : Not reported	GOS; 2.7 g/d	5 days prior to departure and during travel period which varied across participants between 7 and 15 days	Incidence of diarrhoea	Self-reported via questionnaire	Daily throughout intervention period (5 days prior to travel and 7–15 days of travel)	ITT: NS PP: ↓ odds ratio (0.56); total number of participants who experienced diarrhoea: GOS (19.2%) and placebo (28.7%); p = .03; number of cases lasting only 1 day (PP: GOS = 6, placebo = 20, OR = 0.25, p = .004); and incidence of diarrhoea beginning later than a week after starting supplementation, (also in CE population); ↓risk of contracting diarrhoea (HR = 0.62, p = .039) and diarrhoea lasting only 1 day (HR = 0.35, p = .012) as well as for diarrhoea starting more than a week after beginning supplementation (0.50, p = .020 also for CE: 0.56, p = .032 population).
					Duration of diarrhoea, fever, number of bowel movements during diarrhoea	Self-reported via questionnaire	Daily throughout intervention period (5 days prior to travel and 7–15 days of travel)	NS
Hughes et al. (2011)	Adults	Healthy; Age (years): Dose 1 of treatment (2.5 g): M = 19.9 (SEM = 0.1); Dose 2 of treatment (5 g): M = 19.6 (SEM = 0.1); Placebo: M = 20.1 (SEM = 0.1); Sex (% female): Dose 1 of treatment (2.5 g): = 50; Dose 2 of Treatment (5 g): = 51.1; Placebo = 50.7; BMI (kg/m^2): Dose 1 of treatment (2.5 g): M = 23.9 (SEM = 0.3); Dose 2 of treatment (5 g): M = 23.4 (SEM = 0.3); Placebo: M = 23.8 (SEM = 0.3)	Fibre supplement containing 86% GOS (DP2 = 21%, ≥DP3 = 65%); 2.5 g or 5 g/d	8 weeks	Number of cold/flu symptoms Ratings of symptom intensity for each cold/flu symptom were collected from which an overall cold/flu symptom intensity (SI) score was calculated based on the sum of intensities for each individual symptom	Self-report questionnaire	Daily over the 8 weeks	NS 2.5 g GOS ↓ SI across all levels of stress; 5g GOS ↓ SI at lower levels of daily stress (2.5g GOS ↓ SI than 5g at stress levels; 2, 4, 5).

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Table 2. Continued.

Author, Year	Population	Population description and health status at enrolment/baseline	Description and dose of NDC/prebiotic intervention	Duration of intervention	Endpoints	Assessment methodology	Time points assessed	Effect on infection outcome(s)
					% sick days	Self-report questionnaire	Daily over the 8 weeks	Probability of having a sick day was significantly positively related to stress level and significantly associated with GOS supplementation for different BMI categories: 18.5–24.9 kg/m^2 5 g GOS ↓ cold/flu days than 2.5 g and placebo (40% reduction; CI: 2.9, 7.2). 25–29.9 kg/m^2 2.5 g GOS ↓ cold/flu days than 5 g (not with placebo) >30 kg/m^2 2.5 g GOS ↓ cold/flu days than 5 g and placebo
Kawano et al. (2023)	Adults	Mean and women who catch a cold every year; Age (y): Treatment group: M = 56.1, SD = 4.6; Placebo: M = 55.7, SD = 4.2; Sex (% female): Treatment group: 54.5; Placebo group: 54.5 BMI (kg/m^2): Treatment group: M = 22.3, SD = 2.6; Placebo group: M = 22.9, SD = 3.3	Paramylon, β-1,3-1,6-glucan of microalgae *Euglena gracilis*; 350 mg paramylon/dat	12 weeks	Number of days of: Chills Fever Runny nose Stuffy nose Sneezing Cough Sore throat	Self-reported	Duration of intervention	↓ (p < .001) ↓ (p < 0.001) NS NS NS ↓ (p = .025) ↓ (p < .001)
Lutter et al. (2021)	Adults	Men and women Age (y): Low dose: M = 35.4, SD = 14.4; High dose: M = 34.5, SD = 14.9; Placebo: M = 38.2, SD = 15.8; Sex (% female): Low dose: 80; High dose: 82; Placebo: 78; BMI (kg/m^2): Low dose: M = 23.5, SD = 2.9; High dose: M = 23.8, SD = 2.7; Placebo: M = 23.2, SD = 2.6	cRG-I (natural extract from carrot [*Daucus carota* subsp. *sativus*]); Low dose: 0.3 g/d; High dose: 1.5 g/d; appropriate amounts of maltodextrin and 0.5 g of caramel colour were added to each dose to obtain a total of 3.5 g of powder per intervention	8 weeks then response phase of 2 weeks (exposure at day 0 to RV16 + course of infection) and follow-up phase of 3 weeks	Respiratory symptoms: Score Duration Severity	WURSS-21 symptom score (items 2–11) and full WURSS-21 symptom score (all items, including QoL questions) for 13 days following infection with RV16: Duration – Symptom peak (day); pharmacokinetic modelling of the t1/2 (symptom elimination half-life when symptoms reduced to 50%; day) Severity – Peak score (score) and AUC (score/13 days)	Post infection period (13 days)	ITT: WURSS-21 items 2-11: Shorter duration of symptoms for low dose vs both other groups (symptom peak: 25% earlier onset of decline of symptoms vs placebo, p< .001; although rate of decline similar for all groups; t1/2 symptoms: 28% reduction vs placebo, p < .001) Less severe symptoms for Low dose vs both other groups (20% reduction in peak symptom scores vs Placebo, p < .001; AUC: NS) Full WURSS-21: Similar pattern of results as above i.e., parabolic dose-dependent outcome favouring the Low dose, p < .001 (full WURSS-21 score and peak score were lower and reduced earlier)

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Table 2. Continued.

Author, Year	Population	Population description and health status at enrolment/baseline	Description and dose of NDC/prebiotic intervention	Duration of intervention	Endpoints	Assessment methodology	Time points assessed	Effect on infection outcome(s)
					RV16 viral load in nasal lavage	PCR titer	Post infection period (13 days)	Between groups: NS; Post-hoc analysis: Greatest increase in viral load D1-D3 was in Low dose vs other groups ($p <$ .02)
					Duration of infection	Duration of infection based on a composite of symptom score and viral load	Integrated over 13 days	NS
Mah et al., 2020a	Adults	Healthy; Marathon runners; Age (years): Treatment: M = 37.4 (SD = 10.3); Control: M = 39.2 (SD = 10.2); Sex (% female): Treatment = 49.3; Control = 51.1 BMI (kg/m^2): Not reported	Dairy-based beverage containing insoluble β-1,3-1,6-glucan; 250 mg/d	45 days prior to, day of, and 45 days after marathon (91 days total)	Total symptomatic days	Daily Health log online questionnaire	91 day period	↓ symptomatic days (3.43 vs 3.84; p = .0346)
					Severity of URTI: Total score	Jackson index rating via the daily health log	91 day period	↓ total score (4.52 vs 5.60; $p <$ .0184)
					Severity of URTI: Nasal discharge			↓ nasal discharge score (1.07 vs 1.38; p = .0008)
					Severity of URTI: Sore throat			↓ sore throat score (0.28 vs 0.64; $p <$ .0001)
					Duration of URTI episodes	Online Health Log/ questionnaire, reviewed by study physician	91 day period	NS
					Total number of URTI episodes			NS
					Nasal obstruction			NS
					Sneezing			NS
					Malaise			NS
					Headache			NS
					Cough			NS
					Chilliness			NS
					Severity of URTI			
Mah et al. (2020)	Adults	Healthy; Marathon runners; Age (years): Treatment 1: M = 37.4 (SD = 10.3); Treatment 2: M = Not reported; Placebo: M = 39.2 (SD = 10.2) Sex (% female): Treatment 1: 49.3; Treatment 2: Not reported; Placebo: 51.1	Dairy-based beverage containing insoluble β-1,3-1,6-glucan (treatment 1) or soluble β-1,3-1,6-glucan (treatment 2)	45 days prior to, day of, and 45 days after marathon (91 days total)	Nasal discharge Sore throat	Self-reported, reviewed by study physician	Daily for duration of intervention	↓ severity in the soluble and insoluble beta-glucan groups ($p <$ .05) ↓ severity in the insoluble group only ($p <$ .05)
					Nasal obstruction	Self-reported, reviewed by study physician	Daily for duration of intervention	NS
					Sneezing			NS
					Malaise			NS
					Headache			NS
					Cough			NS
					Chilliness			NS

(*Continued*)

Table 2. Continued.

Author, Year	Population	Population description and health status at enrolment/baseline	Description and dose of NDC/prebiotic intervention	Duration of intervention	Endpoints	Assessment methodology	Time points assessed	Effect on infection outcome(s)
McFarlin et al. (2013)	Adults	Experiment 1: Marathon runners; Age (years): Treatment 1: M = 34 (SEM = 9); Treatment 2: M = 34 (SEM = 11); Placebo: M = 35 (SEM = 11); Sex (% female): Treatment 1 = 52.7; Treatment 2 = 43.8; Placebo = 42.9 BMI (kg/m^2): Not reported	Experiment 1: Soluble β-1,3-1,6-glucan; 250 mg/d (Treatment 1), Insoluble β-1,3-1,6-glucan (Treatment 2)	Experiment 1: For 28 days post-marathon	URTI symptoms	Daily health log WURSS-44 if ill	1, 2, 3, 4 weeks post-marathon	↓ number of symptomatic days in both treatment groups (p = .026) NS (data not reported)
Nieman et al. (2008)	Adults	Trained male cyclists; Age (years): Treatment: M = 21.8 (SEM = 0.9); Placebo: M = 25.0 (SEM = 2.2); Sex (% female): 0; Body mass (kg): Treatment: M = 70.7 (SEM = 2.1); Placebo: M = 77.4 (SEM = 1.9) significantly different (p = 0.026)	Oat β-glucan; 5.6 g/d	14 days; then underwent 3 days of intense cycling; supplementation for one additional day; follow-up of 2 weeks	URTI	Self-reported "health log"	Baseline, 2 weeks, immediately after the 3 day exercise, 14 hours after 3 day exercise	NS
Parker et al. (2023)	Adults	Elite rugby union players; Age (y): Treatment: M = 22.4, SD = 3.3; Placebo: M = 24.5, SD = 5.2 Sex (%female): 0 (confirmed by authors) BMI (kg/m^2): not mentioned	GOS: 2.8 g/d	24 weeks (visits: baseline, 12 weeks, 24 weeks)	Daily upper respiratory symptoms: Incidence Severity Duration	Self-reported	Duration of intervention	NS NS ↓ (p < .05)
Talbott and Talbott (2012)	Adults	Marathon runners; Age (years): M = 36 (SD = 9); Sex (% female): 53.3 (35 male, 40 female); BMI (kg/m^2): Not reported	β-1,3-1,6-glucan (*S. cerevisiae*); 250 or 500 mg/d	4 weeks	URTI symptoms	DHL (10 upper respiratory symptoms)	2, 4 weeks post-marathon	↓ for both doses after 2 and 4 weeks (p < .05)
Talbott and Talbott (2012)	Adults	Healthy stressed women; Age (years): M = 41 (± 11 unknown if SD or SEM), Range = 18–65 Sex (% female): 100 BMI (kg/m^2): Not reported	β-1,3-1,6-glucan (*S. cerevisiae*); 250 mg/d	12 weeks	11 upper respiratory symptoms: nasal congestion, runny nose, sore throat, sneezing, cough, chest congestion, fatigue, headache, fever, body aches, and general malaise	Daily health log (frequency assessment ranging from no symptoms to multiple symptoms per day)	4, 8, 12 weeks	↓ upper respiratory symptoms (p < .05)

(*Continued*)

Table 2. Continued.

Author, Year	Population	Population description and health status at enrolment/baseline	Description and dose of NDC/prebiotic intervention	Duration of intervention	Endpoints	Assessment methodology	Time points assessed	Effect on infection outcome(s)
Laue et al. (2021)	Older adults	Healthy; Men and postmenopausal women, aged 50–79 years; Age (years): Total: Me = 67.9 (IQR = 8.3) Treatment 1: Me = 68.2 (IQR = 9.1) Treatment 2: Me = 67.3 (IQR = 9.8) Treatment 3: Me = 68.0 (IQR = 8.3) Treatment 4: Me = 67.5 (IQR = 7.6) Treatment 5: Me = 66.2 (IQR = 10.1) Control: Me = 69.5 (IQR = 8.3) Sex (% female): Total: 49.4 Treatment 1: 42.5 Treatment 2: 47.5 Treatment 3: 57.5 Treatment 4: 55.0 Treatment 5: 59.0 Control: 35.0 BMI (kg/m^2): Total: M = 27.0 (SD = 3.6) Treatment 1: M = 27.2 (SD = 3.9) Treatment 2: M = 27.0 (SD = 3.1) Treatment 3: M = 26.9 (SD = 3.5) Treatment 4: M = 26.7 (SD = 4.0) Treatment 5: M = 27.3 (SD = 3.7) Control: M = 27.3 (SD = 3.5)	NPS powder containing either Treatment 1: Insoluble β-1,3-1,6-glucan ; 500 mg/d, Treatment 2: Soluble β-1,3-1,6-glucan; 500 mg/d, Treatment 3: Oat b-glucan; 10 g/d, Treatment 4: AX from wheat endosperm; 10 g/d, or Treatment 5: EPS from *Limosilactobacillus mucosae;* 2.3 g/d	2 week run-in without supplementation; 5 weeks of supplementation with vaccination at week 2	Common cold incidence	Diary	Baseline, 2 weeks (vaccination), week 3 (1 week post-vaccination) and week 5 (3 weeks post-vaccination	Overall: NS (chi-square test); Pairwise comparisons (uncorrected Fisher exact test): ↓ subjects in AX vs control group according to Jackson criteria (p = .029)

M: Mean; Me: Median; SD: Standard deviation; SEM: Standard error of the mean; IQR: Inter-quartile Range; BMI: Body mass index; RTI: Respiratory tract infection; RRTIs: Recurrent respiratory tract infections; URTI: Upper respiratory tract infection; LRTI: Lower respiratory tract infection; SRI: Symptomatic respiratory infection; ARI: Acute respiratory infection; GI: Gastrointestinal; GITI: Gastrointestinal Tract Infection; TD: Travellers' Diarhoea; QoL: Quality of life; AE: Adverse Event; RRR: Relative risk reduction; ART: Absolute risk reduction; NTT: Number needed to treat; 2'FL: 2'Fucosyllactose; OS: Oligosaccharides; GOS: Galactooligosaccharides; scGOS: Short chain galactooligosaccharides; FOS: Fructooligosaccharides; scFOS: Short chain fructooligosaccharides; lcFOS: Long chain fructooligosaccharides; cRG-I: carrot rhamnogalacturonan-I; TGF-β: Transforming growth factor β; DP: Degree of polymerization; YCF: Young child formula; NPS: Non-digestible polysaccharides; YBG: Yeast-derived β-glucan; SBG: Shiitake-derived β-glucan; OBG: Oat-derived β-glucan; AX: Arabinoxylan; EPS: Exopolysaccharide; AUC: Area under the curve; qPCR: Quantitative polymerase chain reaction; VTGs: Virulence & toxin genes; EHEC, ETEC, EPEC: E. Coli pathotypes; DHL: Daily health log; WURSS: Wisconsin Upper Respiratory Tract Infection Severity Score/Wisconsin Upper Respiratory Symptom Survey questionnaire; NS: Non-significant; ITT: Intention-to-treat; PP: Per protocol.

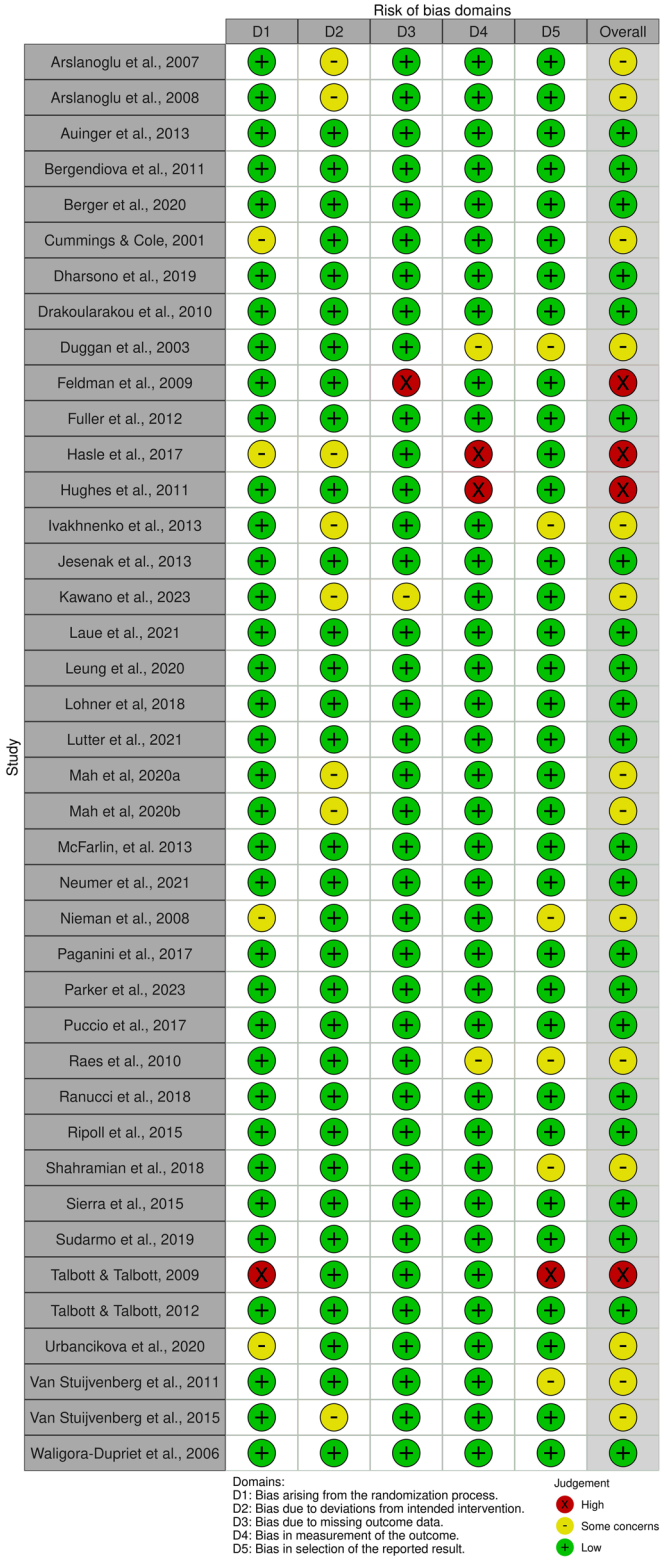

Figure 8. Traffic Light Plot of the domain-level risk-of-bias judgements for each study included in the review of prebiotics and infection.

(Gaullier et al. 2011). Similarly, FOS (1.9–3.9 g/d) did not alter the frequency of major lymphocyte subsets, including T cells, B cells, and NK cells (Kiewiet et al. 2021; Schiffrin et al. 2007; Vogt et al. 2017).

In summary, mixtures of GOS:lcFOS (9:1, 8 g/L in infant formula) have consistently been shown to increase fecal or salivary IgA levels in infants, while supplementation with β-glucan (less than 1 g/d) from specific sources in adults and with GOS in older adults has been consistently found to enhance NK cell function. Findings with other prebiotics are inconsistent or suggest little immune impact.

2.3. Infection

Of 40 intervention trials focused on the effect of NDCs and prebiotics on infection, 17 studied infants, 3 children, 1

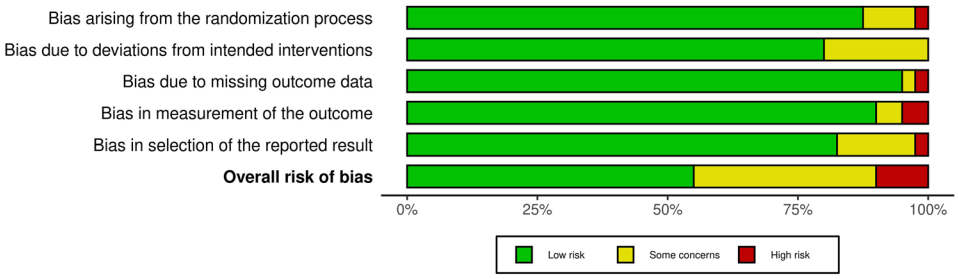

Figure 9. Unweighted bar plots of the distribution of risk-of-bias judgements within each bias domain for studies included in the review of prebiotics and infection.

adolescents and young adults, 18 adults and 1 older adults (Table 2). Among these 40 studies, 22 studies (55.0%) were classified as low risk of bias, 14 studies (35.0%) had some concerns, and 4 studies (10.0%) were at high risk of bias (Figure 8). All studies, except for one with a high risk of bias and another with some concerns (due to missing outcome data, Domain 3), have been classified as low risk of bias (Figure 9).

A GOS:lcFOS formula (9:1; 8 g/L) resulted in fewer infectious episodes at 4 and 6 months and less recurrent infection in infants (Arslanoglu, Moro, and Boehm 2007). At a later follow up (2 years) there were fewer infections, lower incidence of upper respiratory tract infections (URTIs) and less fever (Arslanoglu et al. 2008). Reduced URTI outcomes with a GOS:lcFOS formula have been observed by others (Ivakhnenko and Nyankovskyy 2013; Raes et al. 2010; Shahramian et al. 2018). However, in a multi-cohort study, this prebiotic preparation led to no significant difference in fever incidence (van Stuijvenberg et al. 2011) although after a 3–5 year follow up, less diarrhea was reported (van Stuijvenberg et al. 2015).

Sierra et al. (2015) identified no difference in infection incidence in infants fed GOS-containing infant formula (4.4–5 g/L) over 10 months. On the other hand, Paganini et al. (2017) observed GOS (7.5 g/d) to reduce expression of virulence and toxin genes, along with reducing Enterohemorrhagic *Escherichia coli* (EHIC) positive fecal samples, whilst Ranucci et al. (2018) observed reduced URTI incidence following GOS/polydextrose (50:50; 4 g/L) intervention.

In a study in healthy infants in a high infection risk environment, oligofructose (on average 0.7 g/d) resulted in no differences in dysentery or rotavirus occurrence. However, some of these infants were breast fed, so previously had received "native" hMOs (Duggan et al. 2003). At a higher dosage, oligofructose (2 g/d) was demonstrated to reduce infections, vomiting and fever, concurrent with increased fecal *Bifidobacterium* (Waligora-Dupriet et al. 2007). In a poliovirus vaccination study, scFOS or placebo was administered during the vaccination regime; however, no significant difference in infection incidence was observed between the groups but it is worth noting that some infants in this study were previously breastfed (Ripoll et al. 2015). A further study in infants (Neumer et al. 2021) reported a significant reduction in infection duration in infants taking an oligofructose-supplemented formula (8 g/L). In a study in older infants (1–2.5 years), where some participants were previously breast fed (Leung et al. 2020), an hMO and bioactive protein formula, resulted in no differences in URTIs, GI infections, or otitis media. In younger infants, (<2 wks) 2′FL and lacto-n-neotetroase (1.5 g/L in total) led to a lower bronchitis incidence at 6 and 12 months (Berger et al. 2020), and less lower respiratory tract infection (LRTI) at 12 months (Puccio et al. 2017).

Of the three studies that focused on children, GOS alone was observed to lead to no differences in infectious incidence (Sudarmo et al. 2019), whilst 2 mg/kg body weight/day (= on average 55 mg/d) of an insoluble β-glucan led to fewer respiratory like infections and lower influenza incidence (Jesenak et al. 2013) and 6 g/d of inulin was reported to reduce febrile infections (Lohner et al. 2018). In adolescents undergoing treatment for herpes, 300 mg β-glucan daily resulted in shorter infection duration and fewer URTI symptoms (Urbancikova et al. 2020).

In adults, two studies evaluated the effect of GOS on traveller's diarrhea (Drakoularakou et al. 2010; Hasle et al. 2017). A dose of 2.7 g/d supplemented to participants 7 and 5 days before travel departure resulted in reduced incidence and duration of traveller's diarrhea (Drakoularakou et al. 2010) associated with reduced duration of abdominal pain and improved quality of life. Hasle et al. (2017) reported the incidence of diarrhea to be reduced in the per protocol population. No other significant effect on the duration of diarrhea, fever and number of bowel movements during traveller's diarrhea episodes was observed. Cummings, Christie, and Cole (2001) tested a 10 g FOS supplement daily for 2 wks before and 2 wks during travel in healthy adults; the intervention led to a small increase in stool frequency 2 wks before holidays, but no effect on the number and consistency of stools during the holidays (Cummings, Christie, and Cole 2001).

In a small study on 33 elite rugby players, 2.8 g GOS per day led to reduced duration of URTIs, whilst there was no impact reported on incidence or severity (Parker et al. 2023). In 427 healthy adults supplemented with either 2.5 g or 5 g GOS per day or placebo for eight weeks (Hughes et al. 2011) no difference was observed in the number of cold symptoms. However, 2.5 g/d of GOS reduced symptom intensity scores across all the levels of stress, whilst 5 g/d of GOS was only protective at lower levels of stress. A carrot-based oligosaccharide (0.3 g/d rhamnogalacturonan-I) decreased symptoms of acute respiratory viral infection in a controlled infection study in adults (Lutter et al. 2021).

Table 3. Effects of NDC/prebiotics on inflammatory outcomes.

Author, Year	Population	Population description and health status at enrolment/baseline	Description and dose of NDC/prebiotic intervention	Duration of intervention	Endpoints	Assessment methodology	Time points assessed	Effect on inflammatory outcome(s)
Alliet et al. (2022)	Infants	Healthy; Age at enrolment (days): Formula-fed infants: ≤14; Treatment: M = 6.8 (SD = 3.98); Control: M = 6.7 (SD = 3.80); Sex (% female): Treatment: 52.1; Control: 53.1; Birth weight (kg): Treatment: M = 3.3 (SD = 0.44); Control: M = 3.4 (SD = 0.42)	Milk-based formula with probiotic + 2′FL; 1 g/L	180 days	Faecal myeloperoxidase, calprotectin, neopterin	ELISA	1, 2, 3 months	NS
Bosheva et al. (2022)	Infants	Healthy; Age (days): Dose 1 of treatment (1.5 g/L): M = 14.7 (SD = 4.5); Dose 2 of treatment (2.5 g/L): M = 14.3 (SD = 4.5); Control: M = 14.5 (SD = 4.6); Breast-fed: M = 15.4 (SD = 3.8); Sex (% female): Dose 1 of treatment (1.5 g/L): 50.6; Dose 2 of treatment (2.5 g/L): 49.7; Control: 48.4; Breast-fed: 39.1	Infant formula with hMOs (2′FL, DFL, lacto-N-tetraose, 3′ sialyllactose and 6′ sialyllactose); 1.5 g/L and 2.5 g/L	6 months	Faecal calprotectin	ELISA	0, 3, 6 months	↓ at 6 months for 1.5 g/L dose ($p < .05$)
Neumer et al. (2021)	Infants	Healthy; < 4 months of age; Age (days):: M = 67.9 (SD = 39.7) ; Control: M = 60.0 (SD = 41.4); Sex (% female): Treatment: 52.3; Control: 50.8; Weight at inclusion (kg): Treatment: M = 5.2 (SD = 1.34); Control: M = 5.1 (SD = 1.53) Birth weight (kg): Treatment: M = 2.9 (SD = 1.08); Control: M = 3.7 (SD = 1.24)	Infant and follow-on formulas with 0.8 g/100 mL of chicory-derived oligofructose-enriched inulin (short chain oligofructose (DP < 10) and long chain inulin (DP ≥ 10) in an approximate 50:50 ratio ± 10% each)	Until the age of 1 year	Faecal calprotectin	ELISA	2, 6, 12 months	NS
Paganini et al. (2017)	Infants	Healthy; 6.5–9.5 months old; Age (months): Treatment: Me = 7.3 (Range = 6.9–9.2); Control: Me = 7.5 (Range = 6.9–9.3); Sex (% female): Treatment: 57.7; Control: 48.1	Micronutrient powder including GOS; 7.5 g/d and iron; 5 mg/d	2 week run-in without supplementation; 4 months	Plasma CRP	ELISA	Baseline, 4 months	NS
					Faecal calprotectin	ELISA	Baseline, 3 weeks, 4 months	NS
Raes et al. (2010)	Infants	Healthy; At birth Sex (% female): Treatment: 43.0; Control: 45.6 Birth weight (kg): Treatment: M = 3.5 (SD = 0.4); Control: M = 3.6 (SD = 0.4); Breast feeding (%): Treatment: 38.7; Control: 35.5; Mean duration breast feeding (weeks): Treatment: M = 11.5 (SD = 10.0); Control: M = 10.3 (SD = 9.0)	Formula with GOS/lcFOS (9:1); 6 g/L	26 weeks from birth	Plasma CRP	Turbidimetry	Weeks 8, 26	NS

(*Continued*)

Table 3. Continued.

Author, Year	Population	Population description and health status at enrolment/baseline	Description and dose of NDC/prebiotic intervention	Duration of intervention	Endpoints	Assessment methodology	Time points assessed	Effect on inflammatory outcome(s)
					Plasma cytokines (IFN-γ, TNF-a, IL-10, IL-5, IL-4, IL-2)	Cytometric bead array	Weeks 8, 26	NS
Carpenter et al. (2013)	Adults	Recreationally active college students; Age (years): Men – M = 23 (SD = 5); Women – M = 22 (SD = 4); Sex (% female) = 52 (Men: *n* = 29; Women: *n* = 31); BMI (kg/m^2): Men – M = 24.4 (SD = 1.7); Women – M = 22.5 (SD = 1.9)	β-1,3-1,6-glucan (*S. cerevisiae*); 250 mg/d	10 d treatment/ placebo; 7 day washout; 10 d treatment/ placebo	Plasma: IL-12 IL-2 IL-13 GM-CSF TNF-α IL-1β IL-6	Cytometeric bead array	Baseline, pre-exercise, post-exercise, 2 hours post-exercise	NS NS NS NS NS NS NS
					Plasma: IL-4 IL-7 IL-8 IL-10 IL-5 IFN-g	Cytometric bead array	Baseline, pre-exercise, post-exercise, 2 hours post-exercise	Condition x exercise time main effect (p = .042). BG group had significantly higher levels at 2 h post exercise (p < .05); also greater for BG vs PL at the PRE timepoint. Condition x exercise time main effect (p = .047). BG group had significantly higher levels at 2 h post exercise (p < .05). Condition x exercise time main effect (p = .049). BG group had significantly higher levels at 2 h post exercise (p < .05) Condition x exercise time main effect (p = .033). BG group had significantly higher levels at 2 h post exercise (p < .05) Condition x exercise time main effect (p = .053); BG group had higher levels at 2 h post exercise (p < .05), also greater for BG vs PL group at the PRE timepoint. Condition x exercise time interaction (p = .047), greater concentration for BG vs PL group at 2 h.
Clarke et al. (2017)	Adults	Age (years): M = 28.2 (SD = 5.1); Sex (% female): 57.7; BMI (kg/m^2): M = 24.5 (SD = 3)	β-2-1 chicory fructan (50:50 mixture of inulin and short chain oligosaccharides); 15 g/d	28 days per intervention period with 14 day (washout)	Serum LPS Serum LBP	ELISA	Pre and post each intervention period	NS NS

(*Continued*)

Table 3. Continued.

Author, Year	Population	Population description and health status at enrolment/baseline	Description and dose of NDC/prebiotic intervention	Duration of intervention	Endpoints	Assessment methodology	Time points assessed	Effect on inflammatory outcome(s)
Fernandes et al. (2016)	Adults	Healthy; Age (years): Treatment = 25.6 ± 1.5; Placebo = 35 ± 15.7 (unclear whether SD or SEM is reported); Sex (% female): Treatment = 67; Placebo = 100; BMI (kg/m^2): Treatment = 21.3 ± 1.7; Placebo = 20.9 ± 2.5 (unclear whether SD or SEM is reported)	FOS (not described); 6 g/d	15 days	Plasma IL-1β Plasma TNF-α Plasma IL-6 Serum CRP Serum albumin CRP/albumin ratio	ELISA ELISA ELISA Immunonephelometry Automated colorimetric method	Baseline and post intervention (15 days)	NS NS NS NS NS NS
Fuller et al. (2012)	Adults	Healthy with at least 1 self-reported cold in the last 12 months; Age (years): Treatment: M = 21.9 (SD = 4.8); Placebo: M = 21.3 (SD = 2.7); Sex (% female): Treatment = 50; Placebo = 50; BMI (kg/m^2): Treatment: M = 23.5 (SD = 2.7); Placebo: M = 23.1 (SD = 2.6)	β-1,3-1,6-glucan (*S. cerevisiae*); 250 mg/d	90 days	Plasma chemokines: MIP-1β, granulocyte colony-stimulating factor, monokine induced by interferon gamma Plasma cytokines: IL-1β, IL-2, IL-4, IL-5, IL-6, IL-8, IL-10, IL-12p70, TNF-α, TNF-β, IFN-γ	Flow-Cytomix Multiplex	Day 0, day 90, and during self-reported URTI episodes	NS NS
					Plasma chemokine: MCP-1	Flow-Cytomix Multiplex	Day 0, day 90, and during self-reported URTI episodes	During self-reported URTI episodes ↓ (p = .006)
Ko et al. (2024)	Adults	Overweight and sedentary men and women; Age (y): Treatment: M = 34.68, SEM = 2.85; Placebo: M = 41.46, SEM = 2.9; Sex (%female): Treatment: 57.1; Placebo: 55; BMI (kg/m^2): Treatment: M = 29.8, SEM = 1.37; Placebo: M = 33.78, SEM = 1.39	2′-FL; 3 g/d	12 weeks (follow-up baseline, 6 and 12 weeks), 12 week diet and exercise intervention in both groups	Serum IL-1β, IL-2, IL-4, IL-5, IL-6, IL- 8, IL-10, GM-CSF, IFN-γ, TNF-α	Luminex kit	Baseline, 6 weeks, 12 weeks	NS
Lee et al. (2016)	Adults	Healthy; Age (years): Treatment: M = 53.6 (SEM = 1.15); Placebo: M = 54.5 (SEM = 1.35); Sex (% female): Treatment = 89.7; Placebo = 90.9; BMI (kg/m^2): Treatment: M = 23.5 (SEM = 0.30); Placebo: M = 23.5 (SEM = 0.33)	Yogurt with probiotics + citrus hallabong peel polysaccharide providing 60 mg/d rhamnogalacturonan and 5 mg/d polyphenols	2 weeks of run-in, 8 weeks of intervention	Serum hs-CRP	CRP-Latex (II) X2 kit	Baseline and 8 weeks	NS
					Serum TNF-a Serum IL-6 Serum IL-1β	Bio-Plex Reagent Kit	Baseline and 8 weeks	NS NS NS
					Serum IL-12 Serum IFN-γ	ELISA ELISA	Baseline and 8 weeks Baseline and 8 weeks	↑ (p = .041) ↑ (p = .029)

(*Continued*)

Table 3. Continued.

Author, Year	Population	Population description and health status at enrolment/baseline	Description and dose of NDC/prebiotic intervention	Duration of intervention	Endpoints	Assessment methodology	Time points assessed	Effect on inflammatory outcome(s)
Lee et al. (2017)	Adults	Healthy; Age (years): Treatment: M = 33.0 (SD = 10.0); Placebo: M = 31.3 (SD = 9.5); Sex (% female): Treatment = 37.5; Placebo = 45.9; BMI (kg/m^2): Treatment M = 23.7 (SD = 2.3); Placebo: M = 23.0 (SD = 3.7)	β-1,3-glucan (*Agrobacterium sp. R259*, MW 17–25 kDa); 350 mg/d, cellulose; 128 mg/d, dextrin; 44 mg/d	8 weeks	Serum IL-10	Luminex kit	0, 8 weeks	↑ (p = .029 without adjustment; p = .094 with adjustment for smoking and stress)
					Serum cytokines (IFN-γ, IL-2, IL-4, IL-6, IL-12 and TNF-α)	Luminex kit	0, 8 weeks	NS
Lutter et al. (2021)	Adults	Men and women; Age (y): Low dose: M = 35.4, SD = 14.4; High dose: M = 34.5, SD = 14.9; Placebo: M = 38.2, SD = 15.8; Sex (% female): Low dose: 80; High dose: 82; Placebo: 78; BMI (kg/m^2): Low dose: M = 23.5, SD = 2.9; High dose: M = 23.8, SD = 2.7; Placebo: M = 23.2, SD = 2.6	cRG-I (natural extract from carrot [*Daucus carota* subsp. *sativus*]); Low dose: 0.3 g/d; High dose: 1.5 g/d; appropriate amounts of maltodextrin and 0.5 g of caramel colour were added to each dose to obtain a total of 3.5 g of powder per intervention	8 weeks then response phase of 2 weeks (exposure at day 0 to RV16 + course of infection) and follow-up phase of 3 weeks	CXCL-8 (IL-8) in nasal lavage	Not reported	Baseline, 8 weeks Change at d3, d6, d9, d13 vs pre-infection (d-1) throughout response phase (13 days)	NS Low dose showed earlier increase vs High dose and Placebo and higher peak than Placebo (p < .01)
					CXCL-10 (IP-10) in nasal lavage	Not reported	Baseline, 8 weeks Change at d3, d6, d9, d13 vs pre-infection (d-1) throughout response phase (13 days)	NS Both doses led to earlier responses (p < .001)
McFarlin et al. (2017)	Adults	Healthy; Age (years): Males: M = 22.0 (SEM = 3.0); Females: M = 21.0 (SEM = 3.0) Sex (% female): 54.1 BMI (kg/m^2): Males: M = 24.74 (SEM = 0.40); Females: M = 23.29 (SEM = 0.53)	β-1,3-1,6-glucan (*S. cerevisiae*); 250 mg/d	10 days for each intervention followed by 90 min exercise challenge and 4 hour follow-up; 7 days washout	Serum: IL-4 IL-5 IL-7 IL-8	Multiplex kit	Pre and post intervention and after exercise challenge and 2 and 4 hour follow-up	NS NS NS NS
					Serum IFN-γ Serum IL-2	Multiplex kit	Pre and post intervention and after exercise challenge and 2 and 4 hour follow-up	↑ 2 and 4 hours after end of exercise challenge ↑ only at 4 hours after end of exercise challenge

(*Continued*)

Table 3. Continued.

Author, Year	Population	Population description and health status at enrolment/baseline	Description and dose of NDC/prebiotic intervention	Duration of intervention	Endpoints	Assessment methodology	Time points assessed	Effect on inflammatory outcome(s)
Mosikanon et al. (2017)	Adults	Overweight and obese; Age (years): M = 41.27 (SD = 10.71); Sex (% female): 70.5; BMI (kg/m^2): Baseline data: Treatment: M = 27.22 (SD = 3.64); Placebo: M = 28.19 (SD = 2.52)	β-1,3-1,6-glucan (*S. cerevisiae*); 2 weeks at 477 mg/d then 4 weeks at 954 mg/d	6 weeks (first 2 on lower dose)	Plasma: TNF-α IL-6 IL-10	ELISA	0, 2 and 6 weeks	↓ at week 2 (p = .037) ↓ at week 6 (p = .005) ↑ at week 2 and 6 (p < .001; p < .001)
Nieman et al. (2008)	Adults	Trained male cyclists; Age (years): Treatment: M = 21.8 (SEM = 0.9); Placebo: M = 25.0 (SEM = 2.2); Sex (% female): 0; Body mass (kg): Treatment: M = 70.7 (SEM = 2.1); Placebo: M = 77.4 (SEM = 1.9) significantly different (p = .026)	Oat β-glucan; 5.6 g/d	14 days; then underwent 3 days of intense cycling; supplementation for one additional day; follow-up of 2 weeks	Plasma cytokines (IL-1ra, IL-6, IL-8, IL-10)	ELISA	Baseline, 2 weeks post supplementation, immediately after 3 days of exercise, 14 hours after 3 day exercise (3 day exercise occured immediately after the first 2 weeks of supplementation; supplementation was continued throughout the 3 days of exercise)	NS
					Leukocyte IL-1ra, IL-8, IL-10 gene expression	qPCR	Baseline, 2 weeks post supplementation, immediately after 3 days of exercise, 14 hours after 3 day exercise (3 day exercise occurred immediately after the first 2 weeks of supplementation; supplementation was continued throughout the 3 days of exercise)	NS
Parker et al. (2023)	Adults	Elite rugby union players; Age (y): Treatment: M = 22.4, SD = 3.3; Placebo: M = 24.5, SD = 5.2 Sex (%female): 0 (confirmed by authors) BMI (kg/m^2): not mentioned	GOS; 2.8 g/d	24 weeks (visits: baseline, 12 weeks, 24 weeks)	Plasma CRP Plasma TNF-α	ELISA	Baseline, 12 weeks, 24 weeks	NS NS
Rajkumar et al. (2015)	Adults	Healthy; Age (years): Range = 20–25; Sex (% female): 53.3; BMI (kg/m^2): Synbiotic: M = 22.23 (SEM = 0.44); Probiotic: M = 22.34 (SEM = 0.44); Control: M = 22.72 (SEM = 0.35)	Synbiotic: FOS; 10 g/d + *L. salivarius*	6 weeks	Serum: CRP IL-6 IL-1β TNF-α	Krishgen kit	Baseline; Week 6	↑ versus Probiotic group (p < .05) ↑ versus Probiotic group (p < .05) NS ↑ versus Probiotic group (p < .05)

(*Continued*)

Table 3. Continued.

Author, Year	Population	Population description and health status at enrolment/baseline	Description and dose of NDC/prebiotic intervention	Duration of intervention	Endpoints	Assessment methodology	Time points assessed	Effect on inflammatory outcome(s)
Wang et al. (2022)	Adults	Professional table tennis players; Age (years): Treatment: M = 19.79 (SD= 0.89); Placebo: M = 19.38 (SD = 0.96); Sex (% female): Not reported; BMI (kg/m^2): Treatment: M = 22.2; Placebo: M = 23.2 (calculated from weight and height so SD not possible, but recruited based on BMI of 18.5–23.9 according to inclusion criteria)	Beverage with β-glucan (origin not described); 2 g/d	4 weeks	Plasma IL-6 Plasma CRP Plasma TNF-α	Not reported	Baseline; 4 weeks	NS NS NS
Williams et al. (2016)	Adults	Healthy (also included a hyperpnoea-induced bronchoconstriction group, but data not reported herein); Age (years) = M = 26 (SD = 4) Sex (% female): 37.5 BMI (kg/m^2): 23.8 (calculated based on weight and height so no SD possible)	GOS; 5.5 g/d	3 weeks; 2 week wash-out period between intervention arms	Serum CCL11 Serum CCL17 Serum CRP Serum TNF-α	ELISA	Pre and post each intervention arm; also pre and 15 min, 60 min and 24 h after eucapnic voluntary hyperpnoea	NS NS NS NS
Wilms et al. (2021)	Adults	Healthy; Age (years): M = 38.2 (SD = 7.8); Sex (% female): 66.7; BMI (kg/m^2): M = 23.1 (SD = 2.6)	GOS; 15 g/d	4 weeks; 4–6 week wash-out period between intervention arms	Serum CRP	Immunoturbidimetric assay	Pre and post each intervention arm	NS
Chung et al. (2020)	Older adults	Healthy; Age (years): M = 67.67 (SEM = 1, Range = 60–75); Sex (% female): 61.9; BMI (kg/m^2): M = 25.18 (SEM = 0.71, Range = 18.98–31.25)	AXOS (wheat bran, av DP = 5) containing 15% β-glucan); 15 g/d	5 days run-in period; 10 day intervention period; 5 day washout-period; 10 day intervention period; 5 day follow-up period	Faecal calprotectin	ELISA	Both intervention periods and in wash-out period	NS
Gaullier et al. (2011)	Older adults	Healthy; > 65 years; Age (years): M = 71.0 (SD = 5.4, Range = 64.9–84.0); Sex (% female): 48; BMI (kg/m^2): M = 24.6 (SD = 2.6, Range = 17.0–29.0)	2.5 mg/d of a product described as a fermentation liquid from *L. edodes* mycelium containing β-1,3-1,6-glucan; the dose of β-glucan used is unclear	6 weeks; 4 week wash-out period between intervention arms	CRP Cytokines (IL-8, IL-10, IL-12 and TNF-α)	Not stated	Pre and post each intervention arm	NS NS
Maneerat et al. (2013)	Older adults	Healthy; Age (years): Treatment: M = 70.7 (SEM = 0.69); Placebo: M = 63.0 (SEM = 0.5) ($p < .001$) Sex (% female): Treatment: 66.7; Placebo: 55.6 BMI (kg/m^2): Treatment: M = 28.4 (SEM = 1.1); Placebo: M = 25.6 (SEM = 1.3)	GOS; predominantly galactose (β1-6), (β1-4) and (β1-3) linkages; 8 g/d	21 days; 28 day wash-out period between intervention arms and 28 day follow-up after last intervention arm	Plasma chemokines (G-CSF, MCP-1, MIG, MIP-1α, MIP-1β)	Multiplex kit	Pre and post intervention (baseline and 21 days)	NS

(*Continued*)

Table 3. Continued.

Author, Year	Population	Population description and health status at enrolment/baseline	Description and dose of NDC/prebiotic intervention	Duration of intervention	Endpoints	Assessment methodology	Time points assessed	Effect on inflammatory outcome(s)
Schiffrin et al. (2007)	Older adults	Undernourished or at risk of malnutrition (community dwelling &/ nursing home residents); 70–99 years; Age (years): M = 84 (SD = 7) Sex (% female): 75.7 BMI (kg/m^2): M = 24.9 (±6.2 likely to be SD)	Liquid supplement with FOS; 1.3 g/250 mL – 1.5–3 servings per day (1 serve = 250 mL)	12 weeks	Plasma cytokines (IL-2R, TNF-α, sIL-6R, sCD14, LBP)	ELISA	12 weeks	NS
					PBMC gene expression (iNOS, IL-2, TNF-α, IL-1β, IL-6)	PCR	12 weeks	Between group comparison not reported.
Vulevic et al. (2015)	Older adults	Healthy; Age (years): 70.4 (SD = 3.8, Range = 65–80); Sex (% female): 62.5; BMI (kg/m^2): Not reported	GOS; 5.5 g/d	4 week run-in; 10 weeks per intervention arm with 4wk washout period	Faecal calprotectin	ELISA	Timepoints unclear	NS
					Plasma CRP	ELISA	Baseline, 10 weeks	↑ 10 weeks ($p < .01$)
Wilms et al. (2021)	Older adults	Healthy; Age (years): M = 74.3 (SD = 3.7); Sex (% female): 45; BMI (kg/m^2): M = 26.4 (SD = 3.0)	GOS; 15 g/d	4 weeks; 4–6 week wash-out period between intervention arms	Serum CRP	Immunoturbidimetric assay	Pre and post each intervention arm	NS

M: Mean; Me: Median; SD: Standard deviation; SEM: Standard error of the mean; BMI: Body mass index; URTI: Upper respiratory tract infection; 2′FL: 2′Fucosyllactose; DFL: 2′,3-di-O-fucosyllactose; hMOs: Human milk oligosaccharides; GOS: Galactooligosaccharides; scGOS: Short chain galactooligosaccharides; FOS: Fructooligosaccharides; lcFOS: Long chain fructooligosaccharides; DP: Degree of polymerization; AX: Arabinoxylan; AXOS: Arabinoxylan oligosaccharides; cRG-I: carrot rhamnogalacturonan-I; PBMC: Peripheral blood mononuclear cells; iNOS: Inducible nitric oxide synthase; IL–: Interleukin–; sIL–: Soluble IL–; sCD14: Soluble cluster of differentiation 14; IFN-γ: Interferon-γ; CRP: C-reactive protein; hs-CRP: High sensitivity CRP; TNF: Tumor necrosis factor; TNF-α: Tumor necrosis factor-α; TNF-β: Tumor necrosis factor-β; G-CSF: Granulocyte-colony stimulating factor; GM-CSF: Granulocyte-macrophage colony-stimulating factor; MIG (CXCL9): Chemokine ligand 9; MCP-1: Monocyte chemotactic protein-1; MIP-1α: Macrophage inflammatory protein-1α; MIP-1β: Macrophage inflammatory protein-1β; LPS: Lipopolysaccharide; LBP: Lipopolysaccharide binding protein; CCL11: Eotaxin-1; CCL17 (SCYA17): CC chemokine ligand 17; sIL-6R: Soluble interleukin 6 receptor; sCD14: Soluble cluster of differentiation 14; PCR: Polymerase chain reaction; qPCR: Quantitative polymerase chain reaction; ELISA: Enzyme-linked immunosorbent assay; NS: Non-significant.

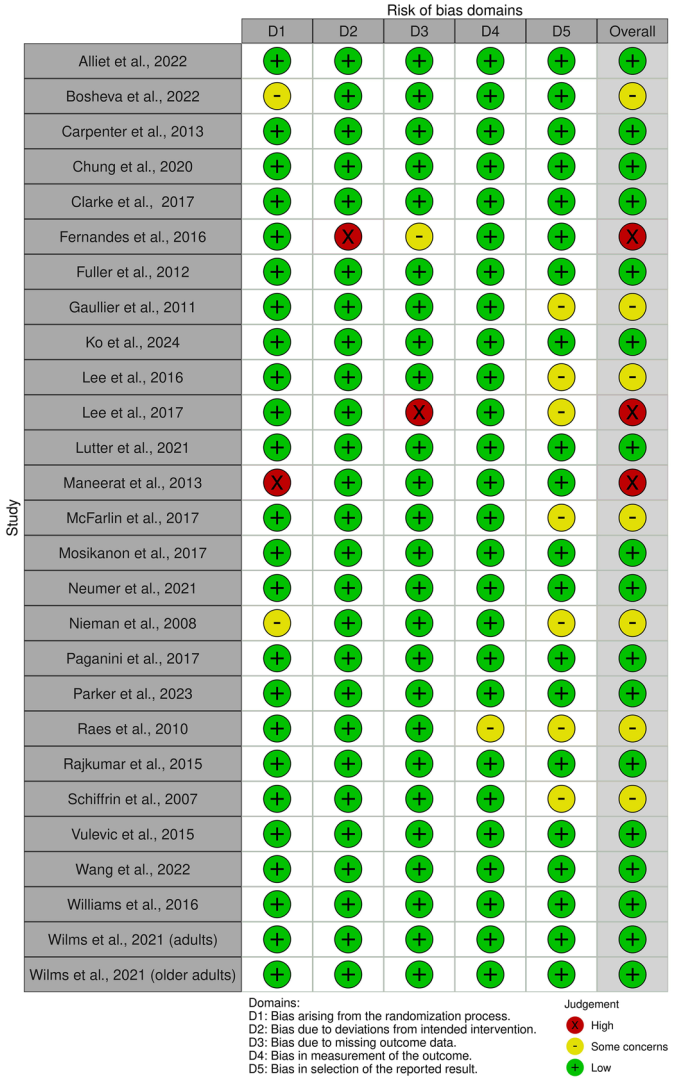

Figure 10. Traffic Light Plot of the domain-level risk-of-bias judgements for each study included in the review of prebiotics and inflammatory outcomes.

12 studies investigated the effect of β-glucans on respiratory infections and cold/flu. Of these, one study used oat β-glucans, one β-glucans from mushroom *Pleurotus ostreatus* (β-1,3–1,6-glucan), one from micro algae and nine β-glucans from yeast (β-1,3–1,6-glucan). All except two of these studies observed some positive impact of the supplementation. Three studies performed in marathon runners with yeast β-1,3–1,6-glucan observed reduced URTI symptoms or a lower number of symptomatic days (Mah et al., 2020; McFarlin et al. 2013; Talbott and Talbott 2012) with doses between 250 and 500 mg/d. Mah et al. (2020) also observed a 250 mg/d dose of soluble or insoluble yeast β-glucans 45 days before and 45 days after the marathon to reduce the severity of nasal discharge and to reduce sore throat with the insoluble fraction only. No other cold symptoms were impacted by the supplementation. For studies performed on healthy adults not involved in marathon running, the results were more mixed. In three studies, no impact of yeast β-1,3–1,6-glucan was observed on the incidence of symptomatic respiratory infections or URTIs with doses from 250 to 900 mg/d (Dharsono et al. 2019; Feldman et al. 2009; Fuller et al. 2012). However, Dharsono et al. (2019) observed reduced severity of URTI with 900 mg of β-1,3–1,6-glucan per day and Fuller et al. (2012) observed an improved ability to "breathe easily" with 250 mg/d. Auinger et al. (2013) tested 900 mg/d yeast β-1,3–1,6-glucan in healthy adults for 16 wks and reported reduced incidence of colds. When tested on healthy though stressed women, 250 mg of yeast β-1,3–1,6-glucan per day for 12 wks reduced the incidence of URTI (Talbott and Talbott 2012). In a small study focused on those who annually catch colds, an intervention of 350 mg/d micro-algae β-glucan led to reduced cold associated symptoms (Kawano et al. 2023). In a study by Laue et al. (2021), supplementation with β-glucan from yeast, mushroom or oat (500 mg daily) or arabinoxylans (10 g daily) in older adults led to no significant difference in common cold incidence post influenza vaccination, although the incidence in the control group was 8 and fewer colds were reported in the other groups. Supplementation with 100 mg/d of β-1,3–1,6-glucan from *Pleurotus ostreatus* provided with vitamin C (100 mg/d) for 3 months to healthy athletes reduced URTI symptom scores when compared to vitamin C only (Bergendiova, Tibenska, and Majtan 2011). Finally, 5.6 g/d of oat β-glucans for 18 days in healthy trained male

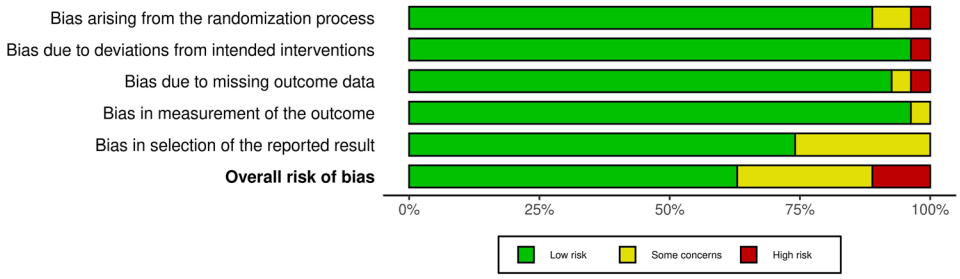

Figure 11. Unweighted bar plots of the distribution of risk-of-bias judgements within each bias domain for studies included in the review of prebiotics and inflammatory outcomes.

cyclists did not induce any significant effect on URTI (Nieman et al. 2008).

In conclusion, the studies that reported on infection following prebiotic and NDC intervention indicate the GOS:lcFOS (9:1) mixture, though not GOS alone, and 2′FL to be effective at reducing infections in infants. Previous breast feeding may impact on the infant in a positive way, meaning that a later prebiotic intervention may not be effective at reducing infection, as infection risk may already be low. Within children, positive effects of β-glucans were reported against infections. Within the adult studies, GOS was reported to help against traveller's diarrhea, whilst GOS in healthy adults showed some evidence of impact on cold symptoms. Yeast β-1,3–1,6-glucan when used in low doses resulted in positive impact at reducing URTI symptoms in athletes, whilst results were more variable in healthy non-athletic adults. Overall, as a strategy of reducing infections, prebiotics and NDCs are emerging as an option showing potential in different population groups.

2.4. Inflammation

Inflammation is part of innate host defence against pathogens and the response to tissue damage through injury. As such, inflammation is protective. However, if uncontrolled or excessive, inflammation can damage host tissues, being linked with autoimmunity, risk of non-communicable diseases and accelerated aging (Calder et al. 2009, 2013, 2017). 27 trials studied the effect of prebiotics on markers of inflammation; five trials were conducted in infants, 16 in young or middle-aged adults and 6 in older adults (Table 3). Trials in infants used GOS ($n=1$), a mix of inulin and FOS ($n=1$), GOS:lcFOS ($n=1$), a single hMO ($n=1$) or a mix of hMOs ($n=1$). Trials in young or middle-aged adults used FOS ($n=3$), GOS ($n=3$), oat β-glucan ($n=2$), yeast β-1,3-glucan ($n=1$), yeast β-1,3–1,6-glucan ($n=4$), 2′FL ($n=1$), carrot-derived rhamnogalacturonan ($n=1$) or hallabong peel pectic polysaccharide ($n=1$). Trials in older adults used GOS ($n=3$), FOS ($n=1$), arabinoxylan oligosaccharides (AXOS) ($n=1$) or yeast β-1,3–1,6-glucan ($n=1$). Circulating CRP was measured as a biomarker of inflammation in 11 trials ($n=2$ in infants, $n=6$ in young and middle-aged adults, $n=3$ in older adults). Circulating cytokines and/or chemokines were measured in 16 trials ($n=13$ in young or middle-aged adults, $n=3$ in older adults). Four trials in infants measured fecal markers of inflammation, all of them measuring calprotectin. Two trials in older adults measured fecal calprotectin. One trial in adults and one in older adults measured blood immune cell gene expression. Three trials in adults included an exercise challenge in the protocol.

Out of these 27 studies, 17 (63.0%) showed a low risk of bias, 7 (25.9%) had some concerns, and 3 (11.1%) were at high risk (Figure 10). Nearly all studies (26 out of 27) had low risk of bias in Domain 2 and Domain 4 (Figure 11).

Neither GOS (7.5 g/d) nor a GOS:lcFOS mixture in infant milk (9:1 ratio, 6 g/L), altered CRP in infants (Paganini et al. 2017; Raes et al. 2010). GOS, inulin:FOS and 2′FL did not alter fecal calprotectin (Alliet et al. 2022; Neumer et al. 2021; Paganini et al. 2017). 2′FL also did not alter fecal myeloperoxidase or neopterin (Alliet et al. 2022). A mix of hMOs decreased fecal calprotectin after six months, but this was observed only for the lower of the two doses used (i.e., 1.5 g/L of infant formula) (Bosheva et al. 2022).

In young and middle-aged adults, GOS (5.5–15 g/d) did not affect CRP in two studies (Williams et al. 2016; Wilms et al. 2021) or circulating cytokines and chemokines (Williams et al. 2016). 2′FL (3 g/d) did not affect inflammatory markers in adults (Ko et al. 2024). FOS (6 g/d) did not affect circulating CRP, albumin or cytokines in one study (Fernandes et al. 2016), while a mixture of inulin and FOS (50:50; 15 g/d) did not affect serum LPS or LPS binding protein (Clarke et al. 2017). FOS (10 g/d) used in conjunction with a probiotic increased circulating CRP, IL-6 and TNF-α compared to probiotic alone, but there was no effect on IL-1β (Rajkumar et al., 2015). Carrot-derived rhamnogalacturonan had a dose-dependent impact on changes of circulating IL-8 and CXCL-10 in response to acute RV16 challenge (Lutter et al. 2021). Hallabong peel pectic polysaccharide (60 mg/d) did not affect CRP, TNF-α, IL-1β, or IL-6 but increased IL-12 and IFN-γ (Lee et al. 2016). β-glucan did not affect CRP (two studies), circulating cytokines (two studies) or immune cell gene expression (Nieman et al. 2008; Wang et al. 2022). The *Agrobacterium* sp. derived β-1,3-glucan at a dose of 350 mg/d had no effect on circulating inflammatory cytokines; however, it increased the anti-inflammatory cytokine IL-10, but this effect was lost after statistical adjustments (Lee et al. 2017). Studies of β-1,3–1,6-glucan report varying outcomes. One study reported decreased TNF-α and IL-6 along with increased IL-10; this study used the highest dose of all studies of this ingredient (Auinger et al. 2013). Other studies report no effect on circulating cytokines following supplementation with β-1,3–1,6-glucan sourced from baker's yeast (250 mg/d) (Carpenter et al. 2013; Fuller et al. 2012), no effect on circulating cytokines and chemokines but

Table 4. Effects of NDCs/prebiotics on response to vaccination.

Author, Year	Population	Population description and health status at enrolment/baseline	Description and dose of NDC/prebiotic intervention	Duration of intervention	Endpoints	Assessment methodology	Time points assessed	Effect on vaccine response(s)
Duggan et al. (2003)	Infants	Healthy; 6–12 months old, but in a high-risk environment (high burden of GI and other infections); Trial 1: Age (months): Treatment: M = 9.2 (SD = 2.0); Control: M = 8.5 (SD = 1.9); Sex (% female): Treatment: 48.2; Control: 54.6; Weight (kg): Treatment: M = 8.8 (SD = 1.1); Control: M = 8.7 (SD = 1.1) Trial 2: Age (months): Treatment: M = 8.7 (SD = 1.7); Control: M = 8.5 (SD = 1.7); Sex (% female): Treatment: 47.7; Control: 52.6 Weight (kg): Treatment: M = 8.8 (SD = 1.1); Control: M = 8.5 (SD = 1.0)	Oligofructose; 0.55 g/15 g of cereal (approx. cereal intake was 18.4 ± 10.4 g/d; on average 0.67 g oligofructose per day)	6 months	Haemophilus influenzae type B vaccine response (antibody titers)	ELISA	5 months (baseline; pre-vaccine) and 6 months (post-vaccine titers)	NS
Paineau et al. (2014)	Infants	Healthy; ITT group: Mean age (days): Treatment: M = 4.0 (SD = 0.8); Control: M = 4.2 (SD = 0.7) Sex (% female): Treatment: 51.6; Control: 48.1 Weight at birth (kg): Treatment: M = 3.6 (SD = 0.5); Control: M = 3.3 (SD = 0.5) significantly different ($p < .05$) Weight at enrolment (kg): Treatment: M = 3.5 (SD = 0.4); Control: M = 3.2 (SD = 0.5)	scFOS (from sucrose, DP 3-5) in infant formula daily; dose 2–4 g/d (0.5-1 L) depending on infant weight	4 months	Faecal anti-poliovirus specific IgA	ELISA	4 months	NS
Ripoll et al. (2015)	Infants	Healthy; Age (weeks): Treatment: M = 17.8 (SD = 0.2); Control: M = 17.8 (SD = 0.1); Sex (% female): Treatment: 48.5; Control: 58.1	Follow-on milk formula with scFOS (from sucrose, DP3-5); 5 g/L	6 months	Faecal poliovirus-specific sIgA	ELISA	1 and 2 months	NS
Salvini et al. (2011)	Infants	Healthy; born from hepatitis C virus-infected mothers; At birth: Sex (% female): Treatment: 50; Control: 80; Weight (kg): Treatment: M = 3.3 (SD = 0.7); Control: M = 3.3 (SD = 0.3)	Regular bovine milk formula with GOS/lcFOS (9:1); 8 g/L	6 months with further 6 month follow-up	Anti-hepatitis B vaccine IgG	ECLIA	12 months	NS
Stam et al. (2011)	Infants	Healthy; Age (weeks): <8 Sex (% female): not reported Birth weight: above 10th percentile Distribution between groups not reported	Standard non-hydrolyzed cow's milk-based formula with GOS/lcFOS (9:1); 6.8 g/L and pAOS (1.2 g/L)	12 months	H. influenza type B vaccine specific IgG (anti-Hib, anti-tetanus)	ELISA	6 and 12 months	NS

(*Continued*)

Table 4. Continued.

Author, Year	Population	Population description and health status at enrolment/baseline	Description and dose of NDC/prebiotic intervention	Duration of intervention	Endpoints	Assessment methodology	Time points assessed	Effect on vaccine response(s)
(van Hoffen et al. (2009)	Infants	Infants at high risk of allergy; Age (days): Treatment: M = 11.2 (SD = 7); Placebo: M = 11.8 (SD = 9.2); Sex (% female): Treatment: 49.6, Placebo: 51.5. Birth weight (g): Treatment: M = 3344 (SD = 456); Placebo: M = 3376 (SD = 482)	Hypoallergenic whey formula with GOS/ lcFOS (9:1); 8 g/L	6 months	Vaccine (diptheria, tetanus, polio) specific Igs (IgE, IgG1, IgG2, IgG3)	ELISA	6 months	NS
Vogt et al. (2017)	Young adults	Healthy; Age (years): Treatment 1: M = 20 (Range = 19–26); Treatment 2: M = 20 (Range = 18–29); Placebo: M = 20 (Range = 18–25); Sex (% female): Treatment 1: 61.5; Treatment 2: 53.8; Placebo: 57.1	Treatment 1: Inulin-type fructans with DP 10–60; Treatment 2: Inulin-type fructans with DP 2–25; both 8 g/d	14 days supplementation; vaccination (Hepatitis B) given on day 7, follow-up at days 21 and 35	Plasma anti-HB antibody	Chemiluminescent microparticle immunoassay	0, 14, 21, 35 days	↑ lc-inulin vs sc-inulin ($p < .05$); NS vs placebo ($p = .1$)
Lomax et al. (2015)	Adults	Healthy; Age (years): Treatment: M = 54 (Range = 45–62); Control: M = 56 (Range = 45–63); Sex (% female): Treatment = 86.4; Control = 61.9 BMI (kg/m^2): Treatment: M = 25.7 (Range = 19.4–33.3); Control: M = 25.0 (Range = 17.7–33.8)	Chicory inulin (50% long chain inulin: 50% oligofructose); 8 g/d	8 weeks (only data from last 4 weeks reported in this paper; vaccination was at 4 weeks so this paper reports the post-vaccination findings)	Antibody response to seasonal influenza vaccine	HI assay	Weeks 4, 6, 8	↑ to H3N2 but not to H1N1 or B; ↑ vaccine-specific IgG1 at week 6 but not week 8; no effect on vaccine-specific IgA, IgM or IgD at either time point
Bunout et al. (2002)	Older adults	Healthy; Age (years): Treatment: M = 76.2 (SD= 3.9); Placebo: M = 75.2 (SD= 3.8); No data on sex "Both treatment and control groups had a similar sex distribution"; BMI (kg/m^2): Treatment: M = 28 (SD= 5); Placebo: M = 26 (SD = 4)	FOS (70% oligofructose, 30% inulin); 6 g/d	28 weeks	Salivary sIgA Serum IgG, IgM, IgA	Radial immunodiffusion	Week 0 (basal), Week 2 (vaccination), Week 8 (6 weeks after vaccination)	NS NS
					Antibody response to influenza and pneumococcus vaccines	ELISA	Week 0 (basal), Week 2 (vaccination), Week 8 (6 weeks after vaccination)	NS
Kiewiet et al. (2021)	Older adults	Healthy; Age (years): Treatment: M = 62.2 (SD = 6.9); Placebo: M = 63.7 (SD = 8.1); Sex (% female): Treatment: 30.8; Placebo: 30.8; BMI (kg/m^2): Treatment: M = 26.1 (SD = 3.6); Placebo: M = 29.7 (SD = 5.6)	Inulin (chicory, long chain inulin DP 10–60); 8 g/d	63 days intervention (7 days of baseline; 154 days of follow up) Vaccination (Hepatitis B): 1st on day 7 from intervention; 2nd 28 days later; 3rd 154 days later	Serum anti-HB antibody	Chemiluminescent microparticle immunoassay	Run-in phase (-7 days) Intervention, 3 timepoints: Day 7, day 35, day 63 Follow up (day 217)	NS

(*Continued*)

Table 4. Continued.

Author, Year	Population	Population description and health status at enrolment/baseline	Description and dose of NDC/prebiotic intervention	Duration of intervention	Endpoints	Assessment methodology	Time points assessed	Effect on vaccine response(s)
Laue et al., (2021)	Older adults	Healthy; Men and postmenopausal women, aged 50–79 years; Age (years): Total: Me = 67.9 (IQR = 8.3) Treatment 1: Me = 68.2 (IQR = 9.1) Treatment 2: Me = 67.3 (IQR = 9.8) Treatment 3: Me = 68.0 (IQR = 8.3) Treatment 4: Me = 67.5 (IQR = 7.6) Treatment 5: Me = 66.2 (IQR = 10.1) Control: Me = 69.5 (IQR = 8.3) Sex (% female): Total: 49.4 Treatment 1: 42.5 Treatment 2: 47.5 Treatment 3: 57.5 Treatment 4: 55.0 Treatment 5: 59.0 Control: 35.0 BMI (kg/m^2): Total: M = 27.0 (SD = 3.6) Treatment 1: M = 27.2 (SD = 3.9) Treatment 2: M = 27.0 (SD = 3.1) Treatment 3: M = 26.9 (SD = 3.5) Treatment 4: M = 26.7 (SD = 4.0) Treatment 5: M = 27.3 (SD = 3.7) Control: M = 27.3 (SD = 3.5)	NPS powder containing either Treatment 1: Insoluble β-1,3-1,6-glucan; 500 mg/d, Treatment 2: Soluble β-1,3-1,6-glucan; 500 mg/d, Treatment 3: oat b-glucan; 10 g/d, Treatment 4: AX from wheat endosperm; 10 gday, Treatment 5: EPS preparation from *Limosilactobacillus mucosae;* 2.3 g/d	2 week run-in without supplementation; 5 weeks of supplementation with vaccination at week 2	H1N1 Titre (MLFI)	HI assay	Baseline, 5 weeks (3 weeks post-vaccination)	↓ in SBG group vs control (p = .044 uncorrected, not significant after correction for multiple testing)
					Seroprotection rate	HI assay	Baseline, 5 weeks (3 weeks post-vaccination)	NS
					Seroconversion rate	HI assay	Baseline, 5 weeks (3 weeks post-vaccination)	NS
					H1N1 Titre (MLFI)	Micro-neutralization assay	Baseline, 5 weeks (3 weeks post-vaccination)	↓ SBG group vs control (p = .014, uncorrected)
					Seroprotection Rate	Micro-neutralization assay	Baseline, 5 weeks (3 weeks post-vaccination)	↓ in the SBG group (30.8%) vs control (61.5%) for H1N1 (p = .012 uncorrected, not significant after correction for multiple testing)
					Seroconversion Rate	Micro-neutralization assay	Baseline, 5 weeks (3 weeks post-vaccination)	NS

M: Mean; Me: Median; SD: Standard deviation; IQR: Inter-quartile Range; BMI: Body mass index; GOS: Galactooligosaccharides; scGOS: short chain galactooligosaccharides; FOS: Fructooligosaccharides; scFOS: short chain fructooligosaccharides; lcFOS: Long chain fructooligosaccharides; AOS: Acidic oligosaccharides; pAOS: Pectin-derived acidic oligosaccharides; OS: Oligosaccharides; NPS: Non-digestible polysaccharides; DP: Degree of polymerization; YBG: Yeast-derived β-glucan; SBG: Shiitake-derived β-glucan; OBG: oat-derived β-glucan; AX: arabinoxylan; EPS: exopolysaccharide; MLFI: mean log2 fold increase; Ig: Immunoglobulin; HB: Hepatitis B; HI: Hemagglutination inhibition; H1N1: Influenza A virus subtype H1N1; H3N2: Influenza A virus subtype H3N2; ELISA: Enzyme-linked immunosorbent assay; ECLIA: Electrochemiluminescence immunoassay; NS: Non-significant.

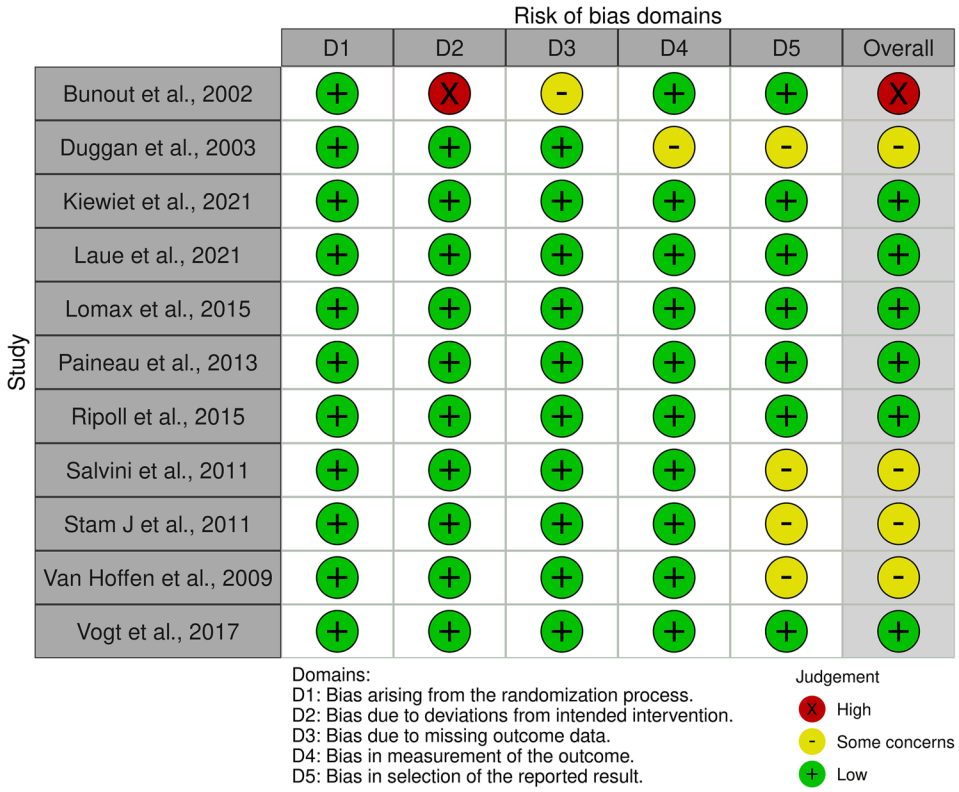

Figure 12. Traffic Light Plot of the domain-level risk-of-bias judgements for each study included in the review of prebiotics and response to vaccination.

a lower monocyte chemoattractant protein 1 (MCP-1) during self-reported URTI (Fuller et al. 2012) and higher IL-2 and IFN-γ in response to exercise (McFarlin et al. 2017).

In older adults, one study of GOS (5.5 g/d, 10 wks) reported increased CRP after 10 wks (Vulevic et al. 2015), but another study of GOS (15 g/d, 4 wks) reported no effect on CRP (Wilms et al. 2021). GOS did not alter plasma chemokines or fecal calprotectin in older adults (Maneerat et al. 2013). There was no effect of FOS on plasma cytokine levels (between-group comparisons of immune cell gene expression were not reported in that study) (Schiffrin et al. 2007), of AXOS on fecal calprotectin (Chung et al. 2020), or of yeast β-1,3–1,6-glucan on CRP or circulating cytokines in older adults (Gaullier et al. 2011).

Overall, the prebiotics and NDCs tested at the given doses and durations seem to have minimal impact on markers of systemic or gut inflammation in healthy participants.

2.5. Vaccination

Eleven trials studied the effects of various (different blends of) prebiotics on vaccination efficacy in different age groups; of these, 6 studies were conducted in infants, 2 in adults, and 3 in older adults (Table 4). Across the 11 studies reporting vaccination outcomes, 6 studies (54.5%) were found to have an overall low risk of bias, 4 studies (36.4%) had some concerns, and 1 study (9.1%) had a high risk of bias (Figure 12). All studies had a low risk of bias arising from the randomization process (Figure 13).

Six trials investigated the effect of prebiotics on vaccination efficacy in infants ranging from newborns to those over 12 months old (Duggan et al. 2003; Paineau et al. 2014; Ripoll et al. 2015; Salvini et al. 2011; Stam et al. 2011; van Hoffen et al. 2009). Trials in infants used oligofructose ($n=1$), scFOS ($n=2$), GOS:lcFOS ($n=2$), and a mix of GOS:lcFOS (9:1) and pAOS ($n=1$). The duration of interventions ranged from four to twelve months. One trial (Duggan et al. 2003) provided the intervention in the form of cereal, whereas the other five studies used formula feeding. There were no significant effects on antibody titers for *Haemophilus influenza* type B, poliovirus, hepatitis B, and DTP (diphtheria, tetanus and polio) vaccine in infants.

There were five trials performed in adults with (blends of) inulin-type fructans for 2–28 wks, and a complex mix of NDCs including β-glucans and other NDCs, reporting on vaccination efficacy at different follow-up times (Bunout et al. 2002; Lomax et al. 2015; Vogt et al. 2017; Kiewiet et al. 2021; Laue et al. 2021). Trials used different chain lengths of inulin ($n=2$) and its combination with varying proportions of oligofructose ($n=2$). One of the studies compared the effects of long and short chain inulin intervention and placebo in young adults (Vogt et al. 2017). The lc-inulin intervention for 14 days resulted in a significant increase in plasma hepatitis B antibody titers (anti-HBsAg) compared to the short-chain inulin group, but this was not significantly different from the placebo group. Another study, this time in older adults, reported that the same dose of lc-inulin had no effect on vaccination response in this age group (Kiewiet et al. 2021). Antibody titers to the influenza H3N2, but not to the H1N1 or B strains, increased following consumption for 8 wks of a blend of oligofructose with lc-inulin by middle aged adults (Lomax et al. 2015). Vaccine-specific IgG

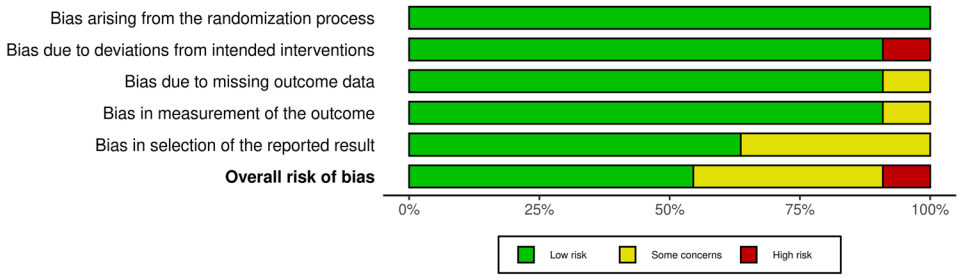

Figure 13. Unweighted bar plots of the distribution of risk-of-bias judgements within each bias domain for studies included in the review of prebiotics and response to vaccination.

was significantly higher in the intervention group, while no significant effects on vaccine-specific IgA, IgM, or IgD were demonstrated (Lomax et al. 2015). There was no significant effect of the complex NDC mix with β-glucans on the H1N1 subtype nor other parameters in older adults after correction for multiple testing (Laue et al. 2021). Although two studies showed that prebiotic intervention showed some impact on vaccine response in young and middle-aged adults, overall, it is considered that it is very difficult to observe any enhancement of vaccination responses, especially in the older adult population.

3. NDC and prebiotic mechanisms

3.1. Mechanism: NDCs and prebiotics on the immune system

A key focus of this review is understanding the mechanisms by which prebiotics, NDCs, and dietary fibers influence the host's immune health. Although the precise ways these ingredients affect physiology, immune pathways, and disease susceptibility remain incompletely understood, a recurring pattern in the literature suggests that their consumption, in certain contexts, can enhance immune function compared to placebo controls (see Section 2). The following section explores the potential mechanisms through which various NDCs and prebiotics may exert these immunological effects.

3.1.1. hMOs

The mechanisms by which hMOs exert protective effects are likely to be both direct on host cells and indirect on microbiota (Figure 14). The strongest direct effects are thought to occur in the gut, where concentrations are the highest. There is also evidence that hMOs are partially incorporated into the systemic circulation of infants, where they can directly interact with cells around the body (Goehring et al. 2014). Transepithelial transfer of hMOs has been demonstrated In vitro, alongside direct immune-modulatory activity on peripheral blood mononuclear cells, suggesting that distant organs such as the respiratory and urinary tracts may benefit from direct protective effects from circulating hMOs (Eiwegger et al. 2010). Some hMOs have also been shown to shed the TNF-receptor 1 and by doing so regulate inflammatory responses (Cheng et al. 2021).

In the gut, hMOs may play a crucial role in health by acting as competitive inhibitors, providing stereospecific protection against a range of pathogens. This competitive interaction could be a key mechanism underlying the health benefits associated with hMOs (Kong et al. 2022; Newburg et al. 2004; Walsh et al. 2020).

In vitro and animal-based studies have found that hMOs act directly on gut epithelial cells to strengthen and protect the epithelial barrier by modifying glycosylation patterns (Angeloni et al. 2005; Kong et al. 2019), increasing mucin production (Wu et al. 2019) and stimulating expression of tight junction proteins (Chichlowski et al. 2012; Kim & Kim, 2017; Otani et al. 2019; Šuligoj et al. 2020). They also act directly on immune cells to induce an anti-inflammatory phenotype (Bode, Rudloff, et al. 2004; Bode, Muhly-Reinholz, et al. 2004; Newburg, Tanritanir, and Chakrabarti 2016; Noll et al. 2016; Thomas et al. 2003).

Although no studies meeting the search criteria specifically addressed the effects of oral prebiotic supplementation on the urinary system, individual studies suggest that such effects may occur. For example, an in vitro study on human urinary bladder epithelial cells (5637 ATCC HTB-9) demonstrated that some hMOs can directly interact with uropathogenic *Escherichia coli* (UPEC, strain CFT073), blocking bacterial attachment to bladder cells (Lin et al. 2014). In addition, hMOs reduced UPEC-induced cytotoxicity, including through caspase-independent pathways, as shown by a decreased percentage of apoptotic cells. hMOs also helped preserve the structural integrity of epithelial cells by inhibiting the degradation of adhesion proteins such as paxillin and β1-integrin. Moreover, hMOs were found to suppress UPEC-induced activation of the MAPK (mitogen-activated protein kinase) and NF-κB pathways, both of which play key roles in inflammation. Collectively, these findings suggest that hMOs can protect bladder epithelial cells from the harmful cytotoxic and pro-inflammatory effects of UPEC infection. This may be one of the mechanisms contributing to the observed reduction in UTIs among breast-fed infants, as highlighted in epidemiological studies (Lin et al. 2014).

Indirectly, hMOs are thought to exert their immune-modulating properties via microbial metabolic products such as SCFAs and specifically succinate and lactic acid (Kong et al. 2021). SCFAs circulate systemically and can therefore significantly influence immune function in the lung and kidney (Dang and Marsland 2019; Yang et al. 2018).

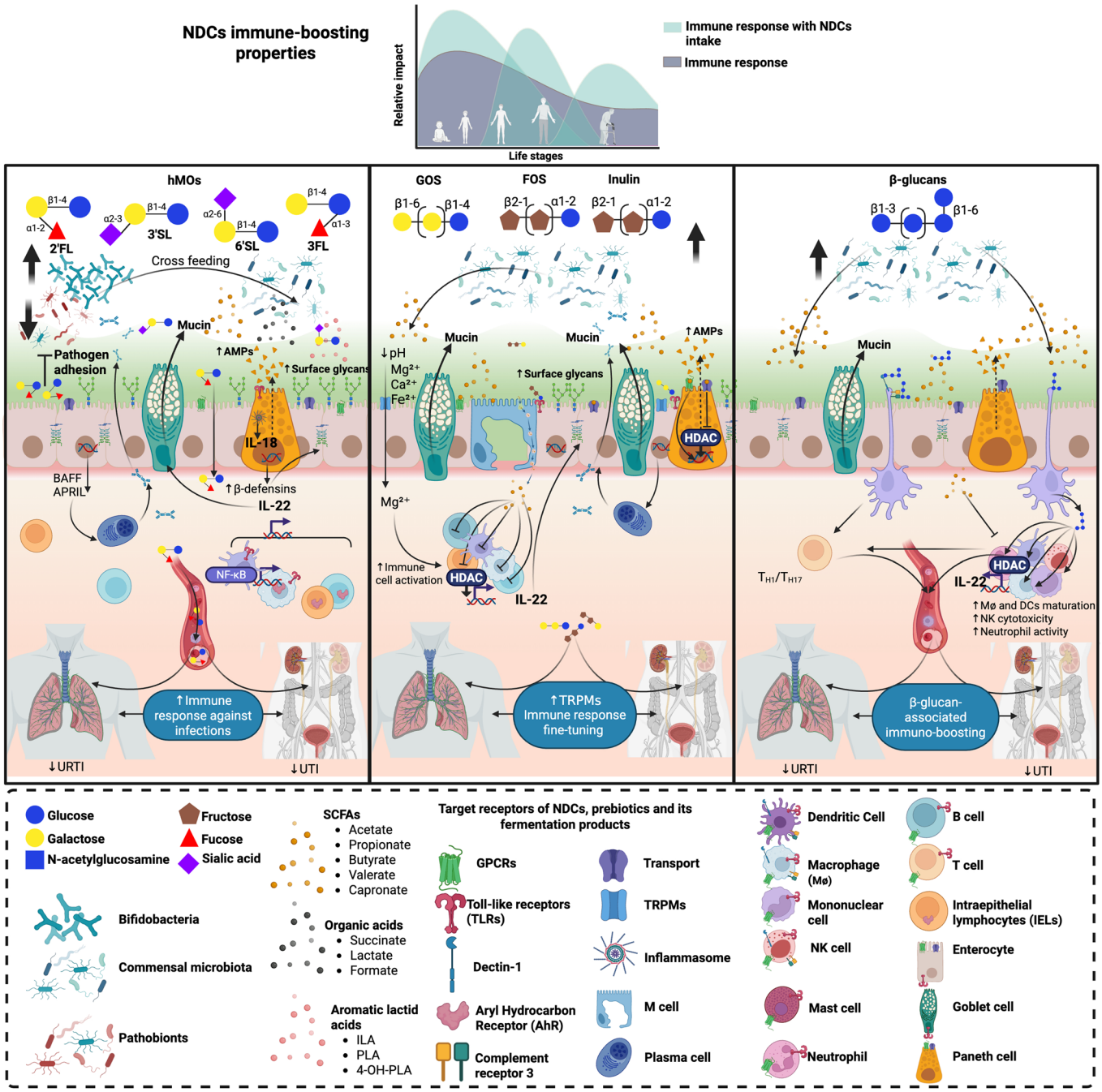

Figure 14. Immune-boosting properties of various non-digestible carbohydrates (NDCs)/prebiotics across life stages. The figure illustrates the mechanisms by which human milk oligosaccharides (hMOs), galacto-oligosaccharides (GOS), fructo-oligosaccharides (FOS), inulin, and β-glucans contribute to immune health. hMOs play a critical role in preventing pathogen adhesion in the gut, boosting mucin and antimicrobial peptide production, and modulating immune responses to protect against infections. GOS, FOS, and inulin enhance the intestinal barrier by promoting tight junction integrity, mucin production, and immune cell activation via receptors like TRPMs and toll-like receptors (TLRs), leading to improved immune responses. β-glucans, recognized by immune cells via Dectin-1 and other receptors, boost immune functions such as macrophage and dendritic cell maturation, neutrophil activity, and natural killer (NK) cell cytotoxicity. These NDCs, through their effects on gut microbiota and immune modulation, contribute to the regulation of immune responses and protection from infections across various life stages (upper panel).

3.1.2. GOS, FOS and inulin

This review identified that prebiotics or combinations thereof showed some enhancement of IgA production and a reduction in infections in infants, as well as modest effects of inulin-type fructans on vaccination titers in young and middle-aged adults. Similar to hMOs, GOS, FOS, and inulin can directly interact with the intestinal epithelial barrier and immune cells. Although GOS-types are frequently described as non-digestible, recent evidence challenges this absolute characterization. In vitro digestion models, rat experiments, and human trials have shown that β-GOS can undergo partial degradation in the small intestine, facilitated by endogenous β-galactosidase activity (Alander et al. 1999; Sako et al. 2021; Mara et al. 2024). These findings imply that structural

modifications to β-GOS may occur prior to fermentation in the colon. In addition, β-GOS produced via enzymatic transgalactosylation of lactose yields a complex array of linkages and chain lengths. The structural diversity among commercially available β-GOS, underscores the need for precise definition and differentiation when interpreting clinical and mechanistic studies (Kittibunchakul et al. 2020).

These interactions may play a role in their immunomodulatory effects, supporting both mucosal immunity and overall immune function. In the gut, these prebiotics modify the glycosylation patterns on cells (Kong et al. 2019), goblet cell activation and function (Bhatia et al. 2015; Hino et al. 2013), and tight junction expression, strengthening the gut barrier and making it more resistant to pathogens (Akbari et al. 2015; Majima et al. 2017). They also act directly on immune cells, mainly via TLRs, to reduce inflammation (Lehmann et al. 2015; Sahasrabudhe et al. 2018). Animal and human studies have shown that lc-inulin ingestion impacts mineral metabolism, e.g., magnesium and calcium absorption (Coudray, Demigné, and Rayssiguier 2003; Holloway et al. 2007). This seems to be mediated by the microbial production of SCFAs in the large intestine, mainly in the cecum, which reduces the luminal pH and consequently increases the soluble fraction of minerals with significant butyrate participation (Scholz-Ahrens and Schrezenmeir 2007). Another established mechanism of inulin's effect involves the modulation of transient receptor potential melastatin 6 and 7 (TRPM6 and TRPM7) expression in the kidneys and large intestine. These proteins are responsible for transporting magnesium (Mg^{2+}) across the apical membrane of epithelial cells in these tissues, playing a crucial role in regulating systemic and cellular magnesium homeostasis (Rondón, Rayssiguier, and Mazur 2008). The importance of cations as basic signaling molecules in immune cell responses has been demonstrated, both for immune cell activation and subsequent immune responses (Feske, Wulff, and Skolnik 2015). Both TRPM6 and TRPM7 function together as a heterotetrameric channel complex, involved in active transepithelial transport. This complex consists of a TRPM channel pore fused with a non-redundant C-terminal serine/threonine protein kinase. While little is known about the specific activation mechanisms or physiological substrates of TRPM6 and TRPM7 kinases, it is suggested that TRPM6 modifies the function of the TRPM7/M6 complex through cross-phosphorylation of TRPM7. This interaction enhances the efficiency of the TRPM7/M6 complex as a divalent ion influx channel, making it more effective than either TRPM6 or TRPM7 functioning alone (Zhang et al. 2014). Adenosine 5′-(tetrahydrogen triphosphate) magnesium salt (MgATP) is a physiological regulator of TRPM6/M7 channel activity (Zierler, Hampe, and Nadolni 2017). TRPM channels are currently being studied in the context of their importance as potential therapeutic targets to combat diseases associated with excess inflammation (Zierler, Hampe, and Nadolni 2017). Changing expression of these proteins could affect cellular functions both physiological and pathophysiological. The examples could be: mast cell reactivity regulation (human lung mast cells and human mast cells lines, LAD2 and HMC-1) (Wykes et al. 2007); inflammation, phagocytosis, proliferation, apoptosis and differentiation via annexin A1 (ANXA1) a substrate for TRPM7's intracellular channel-kinase 1 (ChaK1), elongation factor-2 kinase, myelin basic protein, histone 3, phospholipase Cγ2, and myosin IIA, B and C (Cabezas-Bratesco et al. 2015; Zierler, Hampe, and Nadolni 2017). Moreover, TRPM7 is essential for human leukocyte physiology being involved in T cell signaling, transcriptional regulation and differentiation into the pro-inflammatory Th17 cell type (Nadolni and Zierler 2018) as well as for B cell affinity maturation and antibody production (Krishnamoorthy et al. 2018).

3.1.3. β-glucans

Based on this review, certain β-glucans have demonstrated beneficial effects on upper URTI outcomes in both adults and children. β-glucans have been extensively studied for their immune-supporting properties, with their mechanisms of action largely explored through in vitro and animal studies. These studies suggest that β-glucans can modulate immune responses, making them a promising tool for supporting immune health across various populations (De Marco Castro, Calder, and Roche 2021)

Many β-glucans, such as the β-1,3–1,6-glucans which can be found in the cell wall of fungi, are recognized by the immune system as PAMPs, primarily through Dectin-1 and complement receptor 3 (CR3) (Sukhithasri et al. 2013). They are primarily recognized by the innate compartment: macrophages, neutrophils, monocytes, NK cells and DCs (Del Cornò, Gessani, and Conti 2020). β-glucans derived from different sources (e.g., mushrooms, wheat, oats) differ in their biological activity perhaps because of their different structures (Zeković et al. 2005). In vitro studies suggest that some β-glucans enhance the antimicrobial activity of neutrophils (Chan et al. 2016; Shamtsyan et al. 2004), promote NK cell cytotoxicity (EL-Deeb et al. 2019; Huyan et al. 2014), trigger activation and maturation in macrophages and DCs (Chan et al. 2007), and promote the production of proinflammatory cytokines (Del Cornò, Gessani, and Conti 2020; Zhong et al. 2023). Together, these effects shift the adaptive immune response toward a Th1 and/or Th17 phenotype, promoting a faster and more effective response to infection.

Although the effects observed in clinical studies are not always consistent, this may be due to the limitations of peripheral blood sampling, which may fail to capture changes occurring in tissue that more accurately reflect the immune processes influencing disease outcomes. While the functional modulation of immune cells in peripheral blood may facilitate the systemic dissemination of β-glucan-associated immunomodulation, potentially impacting the respiratory and urinary tracts, the extent to which this activity is directly related to the circulation of free β-glucan remains to be determined (De Marco Castro, Calder, and Roche 2021).

3.2. Fermentation of NDCs and prebiotics by gut microbiota to short chain fatty acids

Many of the NDCs and prebiotics reviewed here have demonstrated selective effects on gut microbiota. Studies

using inulin, GOS, FOS, oligofructose, hMOs and AXOS consistently show an increase in beneficial microbes like *Bifidobacteria* and *Lactobacilli*, along with a reduction in potential pathogens such as harmful *Clostridia* species, *Escherichia*, and *Candida. Bifidobacteria*, which are among the first colonizers of the human infant gut, utilize a variety of strategies to interact with and modulate the host immune system (Alessandri et al. 2019). *Bifidobacteria* possess a range of secreted and surface-associated molecules that play a crucial role in mediating interactions with the host immune system and mucosa-associated immune cells. These include immune-modulating fatty acids (Coakley et al. 2003), sortase-dependent pili (or fimbriae), and Tight Adherence (Tad) pili. The sortase-dependent pili are strongly implicated in priming the infant immune system, while the Tad pili contribute to the maturation of gut epithelial cells (Turroni 2014; O'Connell Motherway 2019). These effector molecules include anti-inflammatory exopolysaccharides, serpins (serine protease inhibitors) and are also implicated in immune dialogue (Fanning 2012; Schiavi et al. 2016). Additionally, the by-products of bifidobacteria's carbohydrate metabolism, such as B-vitamins, lactate, and acetate, not only have antimicrobial properties, but also serve as substrates for other commensal gut bacteria that produce SCFAs, such as butyrate. Butyrate, in particular, is beneficial for intestinal cells and helps support the gut barrier (Pokusaeva, Fitzgerald, and van Sinderen 2011). Commensal urinary *lactobacilli* have demonstrated potent activities in inhibiting uropathogenic strains such as *Escherichia coli* and *Klebsiella pneumoniae* (Johnson et al. 2022). Several mechanisms of action have been reported for *lactobacilli*, including the production of organic acids, hydrogen peroxide, and bacteriocins. Additionally, *lactobacilli* can inhibit pathogen adhesion to mucosal surfaces by competitively binding to host cell receptors, thereby preventing pathogen colonization (Coyte and Rakoff-Nahoum 2019; Patnode et al. 2019). Microbe-to-microbe interactions within the host gut can result in both positive cooperation, such as cross-feeding between different species, and negative interactions, including direct competition for colonization space and exploitative competition for shared nutrients like NDCs. This interplay between microbes further influences the overall balance of the gut ecosystem (Coyte and Rakoff-Nahoum 2019; Patnode et al. 2019). Microbial competition within host niches plays a crucial role in maintaining microbiota homeostasis and controlling pathogen colonization. However, the complexity and variability of these mechanisms, which can change over time and under different conditions, require further investigation. Of particular interest is the nutrient-dependent expression of toxins and the Type VI secretion system (T6SS), which allows microbes to directly translocate toxins into targeted cells or scavenge essential nutrients. These processes are significant drivers of microbiota composition and dynamics, and understanding them is essential for elucidating how the microbiome is shaped (Coyne and Comstock 2019; Fletcher et al. 2021; Gallegos-Monterrosa and Coulthurst 2021; Wood, Aksoy, and Hachani 2020). The observed ability of NDCs and prebiotics to provide protection against disease beyond the intervention period, as reported in several studies, may be partly due to their modification of the microbiome. This aligns with the influence of microbial competition and nutrient-dependent interactions, such as the expression of toxins and the use of the Type VI secretion system (T6SS), in shaping the microbiota. As highlighted elsewhere, the structure-function relationship of these prebiotics is crucial to understanding their long-term impact on health and microbiome composition (Rastall et al. 2022).

Similar phenomena of microbial modulation and competition observed in the gut also apply to the urinary tract, where the microbiome plays a critical role in maintaining health and preventing infection. For instance, a study in a mouse model demonstrated that butyrate influences the expression of GPR109 in podocytes, which are key cells at the glomerular basement membrane. This interaction has been shown to protect podocytes, reducing the risk of glomerulosclerosis and mitigating tissue inflammation, further highlighting the protective effects of microbial metabolites beyond the gut (Felizardo et al. 2019). These findings suggest that a prebiotic capable of promoting high butyrate production by the intestinal microbiota may offer protective effects against kidney disease. Additionally, butyrate has been recognized for its role in stimulating the secretion of antimicrobial cathelicidin peptides from colonocytes, further contributing to its beneficial impact on host health (Raqib et al. 2006; Schauber et al. 2003). In two separate rodent studies, orally administered butyrate and butyrogenic NDCs demonstrated the ability to restore cathelicidin expression in the colon during infection and to activate cathelicidin secretion in monocyte-derived macrophages from the blood, respectively. These findings further underscore the systemic immunomodulatory effects of butyrate and butyrogenic NDCs in enhancing host defense mechanisms (Sarker et al. 2011; Siednamohammeddeen et al. 2022).

4. Conclusion and future perspectives

The findings from the systematic review highlight the potential of NDCs and prebiotics in modulating immune function in humans, also illustrating a structure-function relationship. Evidence from human studies, though variable, suggests that prebiotic interventions, such as supplementation with GOS, FOS, oligofructose, inulin, or mixes thereof, and β-glucans (especially β-1,3–1,6-glucan), can influence immune responses, particularly in infants and children, to a lesser extent in (young) adults with the least effects in older adults. The most consistent results were observed in younger populations, where prebiotics have been shown to increase fecal as well as salivary IgA levels and to reduce infection rates. In adults, however, the effects were less consistent, though some studies reported a reduction of respiratory infection symptoms following β-1,3–1,6-glucan supplementation (primarily in athletic individuals) and a reduction in incidence and duration of traveller's diarrhea with GOS supplementation, as well as improvements in NK cell activity in both younger and older adults following β-glucan and GOS supplementation, respectively. Despite these promising findings, the overall variability in study outcomes warrants further investigation.

One of the proposed mechanisms for the immunomodulatory effects of prebiotics is through their ability to modulate gut microbiota composition. NDCs and prebiotics selectively enhance the growth of beneficial bacterial genera and enhance the production of SCFAs including butyrate, acetate, and propionate. These SCFAs can interact with G-protein-coupled receptors (GPR41, GPR43, and GPR109a) on immune and epithelial cells, promoting anti-inflammatory effects and supporting epithelial barrier function. This microbiota-dependent pathway has been extensively studied in both animal models and in vitro, with human data beginning to show similar trends. However, human trials often show considerable variability in the magnitude of these effects, likely due to differences in individual microbiota profiles, study designs, sample size, participant characteristics and the technical aspects of the measurements made.

In addition to microbiota-dependent mechanisms, prebiotics may also exert direct effects on immune cells and epithelial tissues. These effects include modulation of PRRs, such as TLRs, present on immune cells, which can trigger downstream signaling pathways that regulate cytokine production and immune cell activation. Prebiotics may also enhance the production of mucins and strengthen tight junctions in the intestinal epithelial barrier, reducing gut permeability and protecting against microbial translocation. While these mechanisms are well supported by preclinical studies, the translation to human clinical outcomes remains inconsistent, underscoring the need for more detailed mechanistic studies in human populations.

A critical limitation in evaluating the effects of prebiotics on human immunity is the potential for bias in the studies included in this review. Many human trials on prebiotics have heterogeneous study designs, varying in prebiotic dosage, intervention duration, and participant characteristics, all of which can influence outcomes. Furthermore, differences in immune assessment methodologies present challenges in comparing findings across studies. For instance, the measurement of NK cell cytotoxicity, cytokine production, or lymphocyte populations by flow cytometry often varies significantly between studies in terms of gating strategies and antibody panels, reducing comparability. The choice of biomarkers used to assess immune function also adds complexity to interpreting results. Most studies rely on systemic biomarkers such as blood cytokines or immune cell populations, which are not likely to fully capture local immune responses occurring in the gastrointestinal or respiratory tracts. Moreover, systemic markers may not reflect real-time immune dynamics in response to prebiotics, particularly in the context of mucosal immunity, where prebiotics may exert their most profound effects. Future studies should aim to incorporate more localized immune markers, such as those from fecal or mucosal samples, to better understand the direct and microbiota-mediated effects of prebiotics.

In conclusion, while there is substantial evidence supporting the potential of NDCs and prebiotics to modulate immune function, particularly in younger populations, the variability in outcomes and the presence of methodological bias underscore the need for more standardized research protocols. Future studies should focus on optimizing study designs, including well-defined populations, consistent prebiotic dosages, and standardized immune assessment protocols. Moreover, further research into the localized effects of prebiotics on mucosal immunity and the interaction with the gut microbiota will be crucial for a more comprehensive understanding of their immunomodulatory potential. Our systematic review focused on studies conducted in healthy populations. NDCs and prebiotics may act differently in those with immune impairments or with a heightened state of inflammation. Findings from our systematic review cannot be extrapolated to these other populations.

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Authors contributions

HAT, PCC, OG, and PdV contributed to the study design. PdV, EEV and CT wrote the ILSI activity proposal. HAT, AC, GFD, DG, DJ, KJK, AL, AM, WR, FR, CT, EEV, NV, GW, OG and PdV contributed to data collection, data analysis, and drafting specific sections of the manuscript. PCC, OG and PdV supervised the manuscript development and were responsible for final review and editing of the manuscript. All authors approved the final version of the manuscript.

Disclosure statement

This is an ILSI Europe activity from its Prebiotic Task Force group. HAT, AC, NYIGR, DJ, AL, WR, GW, OG, and PdV have no conflicts of interest to declare. GFD is an employee of Clasado Biosciences. DG is an employee of Nexira. KJK and NV are employees of ILSI Europe. AM is an employee of Mondelez France R&D SAS. FR is an employee of CP Kelco France. CT is an employee of ROQUETTE. EEV is an employee of Sensus. PCC has research funding from Tate and Lyle.

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