Nutrición Hospitalaria

Nutr Hosp. 2010;25(3):341-349
ISSN 0212-1611 • CODEN NUHOEQ
S.V.R. 318

Revisiones

# Immunomodulatory effect of fibres, probiotics and synbiotics in different life-stages

J. Romeo[1], E. Nova[1], J. Wärnberg[1,2], S. Gómez-Martínez[1], L. E. Díaz Ligia[1] and A. Marcos[1]

*[1]Immunonutrition Research Group. Department of Metabolism and Nutrition. Instituto del Frío. ICTAN. Scientific National Research Council (CSIC). Madrid. Spain. [2]Department of Preventive Medicine & Public Health University of Navarra. Pamplona. Spain.*

**Abstract**

**Chronic diseases associated to modern lifestyle habits are usually related to immune system malfunction. In this context, since diet is very well-known to modulate host resistance to infectious and inflammatory processes, the consumption of fibre and probiotics seems to be a promising nutritional tool for immune system modulation in different populations. Health effects of dietary fibres and probiotics have been extensively documented in numerous epidemiological and intervention studies, especially their beneficial effect on intestinal microbiota with important clinical implications in the prevention and/or treatment of infectious and inflammatory diseases. Mechanisms may include modulation of the functional properties of the microbiota, epithelial cells, dendritic cells and immune cell types. Prebiotics have been extensively reported to affect the composition of the gut microbiota, stimulating directly or indirectly putative beneficial gut commensals other than lactic acid bacteria, opening promising areas of research for the discovery of new probiotic strains and synbiotic combinations. Age-related changes in gut physiology, microbiota and mucosal immune response are well established. Moreover, exposure to different challenges during life such as early encounter of environmental insults in the newborn, infant formula feeding, antibiotic treatment, gastrointestinal diseases and stress, also interferes with the normal development and balance of the healthy gut microbiota. Therefore, the current short review gives an overview of today's main aspects of the effect of fibres, probiotics and synbiotics on the immune system in different life-stages.**

(*Nutr Hosp*. 2010;25:341-349)

**DOI:10.3305/nh.2010.25.3.4517**

Key words: *Immunomodulation. Fibre. Probiotics. Lifespan.*

**Correspondence:** Ascensión Marcos.
Tesorera de la FENS. Ex-Presidenta de la SEN.
Profesora de Investigación del CSIC.
Grupo de Inmunonutrición. Dpto. Metabolismo y Nutrición.
ICTAN. Instituto del Frío. CSIC.
C/ José Antonio Novais, 10.
28040 Madrid. Spain.
E-mail: amarcos@if.csic.es - ascenmarcos@telefonica.net

Recibido: 18-IX-2009.
Aceptado: 2-XI-2009.

**EFECTO INMUNOMODULADOR DE LA FIBRA, PROBIÓTICOS Y SIMBIÓTICOS EN LAS DIFERENTES ETAPAS DE LA VIDA**

**Resumen**

**Las enfermedades crónicas relacionadas con el estilo de vida frecuentemente están asociadas con una alteración del sistema inmunológico. En este sentido, ya que la dieta es capaz de modular la resistencia a infecciones y procesos inflamatorios, el consumo de fibra y probióticos parece ser una herramienta prometedora en la modulación del sistema inmune en diferentes poblaciones. Los efectos saludables de la fibra dietética y los probióticos han sido documentados en numerosos estudios epidemiológicos y de intervención, especialmente sus efectos beneficiosos sobre la microbiota del intestino con implicaciones clínicas importantes en la prevención y/o tratamiento de enfermedades infecciosas e inflamatorias. Los mecanismos incluyen la modulación de las propiedades funcionales de la microbiota, células epiteliales, dendríticas e inmunológicas. Se han estudiado en profundidad cómo los prebióticos afectan a la composición de la microbiota del intestino, estimulando beneficiosamente a otros comensales además de las bacterias acido lácticas, abriendo así una futura línea de investigación con nuevas cepas de probióticos y combinaciones de sinbióticos. Por otro lado, están bien establecidos los cambios en la fisiología del intestino, microbiota y respuesta inmune atribuidos al envejecimiento están bien establecidos. Además, las agresiones externas en los primeros días de vida, la alimentación con formulas infantiles, el tratamiento con probióticos, las enfermedades gastrointestinales y el estrés, también alteran el desarrollo y equilibrio de la microbiota intestinal. Por todo ello, esta revisión ofrece una visión actual sobre los aspectos mas relevantes del efecto de la fibra, probióticos y simbióticos sobre el sistema inmune en las diferentes etapas de la vida.**

(*Nutr Hosp*. 2010;25:341-349)

**DOI:10.3305/nh.2010.25.3.4517**

Palabras clave: *Inmunomodulación. Fibra. Probióticos.*

## Introduction

Developed societies are facing up to a progressive increase on immune-mediated and gut-related health problems, such as allergies and auto-immune and inflammatory diseases.[1] Recent compelling evidence has suggested that emerging nutritional strategies may contribute to decrease these host-related diseases manipulating the microbiota by diet.[2,3] In this context, the increased use of prebiotic fibres and probiotics has become a major area of interest within the nutrition community[1] and seems to be a promising nutritional tool to modulate the immune system in different populations. These specific nutrients/ingredients are included into several functional foods that may improve the functions of both the immune system and the gut physiology as well as metabolic functions.[4-6]

Mechanisms contributing to altered *in vivo* immune function induced by functional foods may include modulation of the microflora itself, improved barrier function and direct effects of bacteria on different epithelial and immune cell types (monocytes/macrophages, B cells, T cells and NK cells).[3] The increasing incidence of allergies may be explained by a dysregulation in the T helper (Th1/Th2) balance linked to the modern hygienic lifestyle, but this does not explain the increased incidence of other disorders such as inflammatory bowel diseases, which are all primarily driven by Th1 cells.[7-9] In this respect some animal studies have suggested that induction of regulatory T cells by certain microorganisms can prevent or alleviate such diseases.[10] In any case, despite the positive clinical effects on the prevention and treatment of several immune-related diseases, the mechanisms of this type of functional foods are still not completely understood.[11]

## Age-related physiological changes

Although relatively little work has been done to describe the gastrointestinal changes associated with normal aging in humans, age-related changes in gut physiology, microflora and mucosal immune response are well established.[12] Exposure to different challenges during life such as early encounter of environmental insults in the newborn, infant formula feeding, antibiotic treatment, gastrointestinal diseases and stress, interfere with the normal development and balance of the healthy gut microflora.[4]

The pattern of intestinal microflora undergoes major ecologic modifications in the early stages of life.[13] Some authors have suggested that adequate establishment of the intestinal flora after birth plays a crucial role in the development of the innate and adaptive immune system.[14] In fact, infants are highly susceptible to infection during early life, which, in large part, is the result of delayed development of the immune function and changes in the composition and number of gut flora after weaning.[15-17] The colonization of the human intestine begins at birth and the composition of the intestinal microbiota is influenced by diet composition.[13] Breast feeding constitutes one route for oral delivery of microbes and antigens. In addition, it has been reported that human milk provides molecules with antimicrobial activity[18] as well as probiotic bacteria such as *Lactobacillus gasseri* and *Lactobacillus fermentum*.[19]

On the other hand, the activity of the immune system and the development of mucosal immune responses to new antigens decline with age.[4,20] The number of factors affecting the idiosyncratic immune characteristics of the individual, such as environmental insults, alteration of the microflora, along with the risk of inflammatory diseases, increase with age.[4,21] For example, numbers of bifidobacteria in the gut decrease markedly after 55-60 years of age.[22] Therefore, prebiotics and probiotics may have a particular interest in this high-risk group, even preventing immune senescence and several age-related diseases.

## Prebiotic and probiotic immune protection in infants and children

Prebiotics target indigenous beneficial bacteria already established in the gut and have become relevant in infant nutrition, as formula-fed infants usually have lower numbers of bifidobacteria compared to the breastfed infants.[23-25] Taking breast-feeding as the natural example of infant nutrition, the prebiotics approach should be considered as a physiological approach to influence intestinal microbiota early in life. In this regard, Bruzzese et al.[13] suggested that the addition of non digestible oligosaccharides and inulin to infant food may exert a comparable effect to human milk. Moreover, prebiotics can simulate the bifidogenic effects of breast milk oligosaccharides and have been shown to exert long-term effects (up to two years) for protecting against infection, lowering the incidence of allergy and also exerting positive consequences for the postnatal development of the immune system.[26,27]

The prebiotic fibres inulin and oligosaccharides have been extensively studied in infants and children. The addition of the inulin/galactooligosaccharides (GOS) mixture in weaning foods of 4- to 6-month-old infants in a daily dose of 4,5 g during 6 wk succeeded in increasing of the faecal percentage of *Bifidobacteria* population (form 43 to 57%) of the fecal flora.[28] Other intervention study in infants receiving an inulin/GOS mixture during 12 months, significantly decreased the episodes of gastrointestinal and respiratory tract infections,[13] also enhancing faecal immunoglobulin (Ig) A levels.[29] Moreover, inulin and oligofructose have also been reported as promoting positive effects as indicated by a lower incidence of febrile episodes in infants.[30] Regarding oligosaccharides alone, a beneficial effect on the immune system of preterm infants due to the specific conditions in the luminal part of the

**Table I**
*Summary of studies reporting effects on immunity with prebiotics, probiotics and synbiotics*

| *Reference* | *Design* | *Population* | *Dose* | *Prebiotic/Probiotic* | *Effect on immunity* |
|---|---|---|---|---|---|
| Scholtens et al., 2006[28] | Double-blind, randomised intervention study for 6 weeks | 38 infants (4- 6 months) | 4.5 g/d | Galacto-oligosaccharides (GOS) and fructo-oligosaccharides (FOS) (9:1) | The level of bifidobacteria in the intestinal microbiota increased |
| King et al., 2007[64] | Randomized crossover intervention study for 3 weeks | 35 subjects (18 lean normotensive and 17 obese hypertensive individuals) (18-49 years) | 30 g/d | Naturally present fibre in diet and supplemented fiber (psyllium) | Reduced levels of CRP in both fibre interventions<br>Greater reduction in lean normotensive compared with obese hypertensive subjects (40% *vs* 10%) |
| Schiffrin et al., 2007[65] | Prospective, randomized, double-blind, controlled intervention study for 12 weeks | 74 elderly subjects (undernourished or at risk of undernutrition) | 1.3 g/250 ml /d (daily liquid supplement) | Oligosaccharides (OS) | Decreased levels of pro-inflammatory gene transcription activation (TNF-α mRNA and IL-6 mRNA) |
| Ma et al., 2008[66] | Cross-sectional observational study during 6 years | 1958 postmenopausal women | 16 g/d of total dietary fibre | Dietary fibre intake by self-report standardized questionnaires | High-fibre diet is associated with lower plasma levels of IL-6 and TNF-α-R2 |
| Shadid et al., 2007[67] | Randomized, double-blind, placebo-controlled study from week 25 of gestation until delivery | 48 pregnant women | 3 g/d (3 times/d) | GOS/lcFOS (9:1) | Increased bifidobacteria counts only in maternal faecal samples. No effects on children immunity |
| Vulevic et al, 2008[32] | Double-blind, placebo-controlled, crossover study for 24 weeks | 44 healthy elderly | 5.5 g/d | GOS mixture | Increases in: phagocytosis, NK cell activity, and IL-10 production<br>Reduction in the production of IL-6, IL-1β, and TNF-α by mitogen stimulated PBMCs |
| Arslanoglu et al., 2008[26] | Prospective, randomized, double-blind, placebo-controlled intervention study for 2 years | 134 healthy infants (aged between 37 and 42 weeks) | 8 g/L scGOS/lcFOS | GOS and FOS | Lower incidence of clinical allergic manifestations and infections until 2 years of life |
| Bruzzese et al., 2009[68] | A multicenter, prospective, randomized, placebo-controlled open trial for 12 months | 342 healthy infants (mean age 53.7+/-32.1 days) | 0.4 g/100 ml/d | GOS/FOS (9:1) | Reduced intestinal and, possibly, respiratory infections in healthy infants during the first year of life. |
| Lee et al., 2001[35] | Randomized prospective clinical study | 100 children (6-60 months of age) for 4 days | One capsule containing $10^9$ viable *LA* and $10^9$ *BI* | *Lactobacillus acidophilus(LA)*<br>*Bifidobacterium infantis (BI)* | Decreased frequency and duration of diarrhoea during hospitalization |
| Solis et al., 2002[69] | Randomized controlled intervention trial. | 22 children (6 and 24 months) malnourished for 2 months | 150 and 200 kcal/kg/day of milk containing probiotics | *Lactobacillus bulgaricus*<br>*Streptococcus thermophilus* | Increased IFN-γ production by PBMC stimulated with yoghurt bacteria |
| Naruszewicz et al., 2002[70] | Randomized, controlled, double blind study for 6 weeks | 36 healthy smoker volunteers (18 women and 18 men) (35–45 years) | 400 mL/d of probiotic formula | *L. plantarum* 299v<br>(5 x $10^7$ colony-forming units/mL) | Decrease in plasma IL-6 concentration (41%) |

**Table I** *(continuation)*
*Summary of studies reporting effects on immunity with prebiotics, probiotics and synbiotics*

| *Reference* | *Design* | *Population* | *Dose* | *Prebiotic/Probiotic* | *Effect on immunity* |
|---|---|---|---|---|---|
| Rosenfeldt et al., 2003[71] | Double-blind, placebo-controlled, crossover study for 6 weeks | 43 children with atopic dermatitis (1- 13 years) | $10^{10}$ cfu of each strain | *Lyophilized Lactobacillus rhamnosus 19070-2 Lactobacillus reuteri DSM 122460* | Improved eczema<br>Serum eosinophil cationic protein levels decreased<br>No significant changes in the production of the cytokines IL-2, IL-4, IL-10, or IFN-γ were found |
| Pohjavuori et al., 2004[72] | Randomized, double-blind study design for 4 weeks | 119 infants with cow's milk allergy (age, 1.4-11.5 months; mean, 6.5; 61% boys). | 5 x $10^9$ cfu *LGG*<br><br>MIX group:<br>5x$10^9$ cfu *LGG*<br>5x $10^9$ cfu *LC705*<br>2 x $10^8$ cfu *BBb99*<br>2 x $10^9$ cfu *PJS* | *Lactobacillus rhamnosus GG (ATCC53103)*<br>MIX group:<br>*Lactobacillus rhamnosus GG (ATCC53103) L rhamnosus LC705 Bifidobacterium breve Bbi99 Propionibacterium freudenreichii ssp shermanii JS* | Increased levels of secreted IFN-γ by mitogen-stimulated PBMC in the LGG group<br><br>Increased levels of secreted IL-4 by mitogen-stimulated PBMC in the MIX group |
| Bakker-Zierikzee et al., 2006[29] | Randomized, double-blind intervention study for 32 weeks | 57 healthy infants at birth | 100 ml/d of prebiotic formula<br>100 ml/d of probiotic formula | 0.6 g GOS/FOS (90/10%)/100 ml<br>6.0 × $10^9$ cfu *Bifidobacterium animalis*/100 ml formula | Higher faecal SIgA levels in the prebiotic group compared with the control |
| Nova et al., 2006[37] | Prospective, randomised, controlled and parallel trial for 10 weeks | 30 adolescents with anorexia nervosa (13-19 years) | Yoghurt (375 g/day) containing probiotics $10^7$-$10^8$ cfu/ml each | *Lactobacillus delbrueckii subsp. bulgaricus; Streptococcus thermophilus* | Higher CD4/CD8 ratio<br>Increased IFN-γ production by PHA stimulated PBMCs |
| Passeron et al., 2006[38] | Double-blind prospective randomized study for 3 months | 41 children aged at least 2 years with atopic dermatitis | 1.2 x $10^9$ colony-forming units 3 times per day | *Lactobacillus rhamnosus* Lcr35 plus prebiotics (from fermentation broth for *L. rhamnosus* Lcr35)<br>Prebiotics alone | Improve the manifestations of atopic dermatitis measured by Scoring Atopic Dermatitis (SCORAD) score (both synbiotics and prebiotics interventions used alone) |
| Lara-Villoslada et al., 2007[36] | Intervention longitudinal controlled trial for 6 weeks | 30 children (3-12 years) with no gastrointestinal pathology | 1,8 x $10^7$ cfu/g *L*CECT5711<br>0,2 x $10^7$ cfu/g *LCECT5716* | *L. coryniformis CECT5711 L. gasseri CECT5716* | Higher faecal and saliva IgA levels |
| Uchida et al., 2007[40] | Intervention longitudinal controlled trial for 1 year | 4 paediatric patients with short bowel syndrome (2-13 years) | 3.0 g per day of probiotics (1.0 g of *BB* and *LC)* ($10^9$cfu).<br>3.0 g per day of GOS | *Bifidobacterium breve (BB)*, *Lactobacillus casei* (*LC)* and GOS | CD4(+) and CD8(+) T-cells increased |
| Hol et al., 2008[73] | Double-blind, randomized, placebo controlled study for 12 months | 119 infants with cow's milk allergy (mean age, 4.2 months; 55% boys) | $10^7$ cfu/g formula for each bacteria | *Lactobacillus casei* CRL431 and *Bifidobacterium lactis* Bb-12 | Higher percentages of CD3+ and CD3+CD4+ lymphocytes only in the placebo group |
| Kopp et al., 2008[74] | Double-blind, placebo-controlled prospective intervention study from 4 to 6 weeks of gestation until delivery and for 6 months within infants | 105 pregnant women from families with >= 1 member (mother, father, or child) with an atopic disease | 5x$10^9$ cfu | *Lactobacillus GG* | No clinical effects (atopic symptoms, total IgE concentrations, upper respiratory tract infections, fever) |

**Table I** *(continuation)*
*Summary of studies reporting effects on immunity with prebiotics, probiotics and synbiotics*

| *Reference* | *Design* | *Population* | *Dose* | *Prebiotic/Probiotic* | *Effect on immunity* |
|---|---|---|---|---|---|
| Ivory et al., 2008[75] | Double-blind, placebo-controlled intervention study for 5 months | 20 adults with seasonal allergic rhinitis (18-45 years) | $6.5x10^9$ *LcS*/ 65 mL probiotic drink | *Lactobacillus casei Shirota (LcS)* | Levels of antigen-induced IL-5, IL-6 and IFN-γ production decreased<br>Levels of specific IgG increased and IgE decreased |
| Lee et al., 2008[33] | Meta-analysis of ten double-blind randomized controlled clinical trials | Paediatric populations | | *Lactobacillus*<br>*Bifidobacterium* | Probiotics are efficient in prevention of paediatric atopic dermatitis (prenatal and postnatal regimen) for pregnant women |
| Marschan et al., 2008[11] | Randomized double-blind placebo-controlled study | 98 infants with a family history of allergy for 6 months | $5 \times 10^9$ cfu *(LGG)*<br>$5 \times 10^9$ cfu *(LC705)*<br>$2 \times 10^8$ cfu *(Bb99)*<br>$2 \times 10^9$ *(PJS)* | *Lactobacillus rhamnosus GG (ATCC 53103)*<br>*L rhamnosus LC705*<br>*Bifidobacterium breve Bb99*<br>*Propionibacterium freudenreichii ssp. Shermanii JS* | Increased IgE, IgA and IL-10 plasma concentrations |
| Prescott et al., 2008[79] | Randomized double-blind, placebo-controlled trial for 6 months | 153 children from birth to 6 months | $3 \times 10^9$ cfu | *L acidophilus* LAFTI® L10 | No significant effect on allergy outcomes (innate responses to toll-like receptor (TLR) function) |
| Ogawa et al., 2006[76] | Longitudinal intervention trial for 1 week | 8 healthy adult (six males, two females; average age 34.9 years) | $1 \times 10^{10}$ cfu of *LCC*<br>1 g of dextran | *L. casei ssp. casei (LCC)*<br>Dextran | Increase of NK cell activity |
| Kukkonen et al., 2007 and 2008[42,77] | Randomized, double-blind, placebo-controlled study with 2 parallel groups. Intervention from week 35 of gestation until delivery and for 6 months within infants | 1223 pregnant women<br><br>925 infants at risk for allergy | Women: $5 \times 10^9$ cfu *LGG*, $5 \times 10^9$ cfu *LC705*, $2 \times 10^8$ cfu *BBb99*, $2 \times 10^9$ cfu *PJS*<br><br>Infants: the same probiotics plus 0.8 g GOS | *Lactobacillus rhamnosus GG (ATCC53103)*<br>*L rhamnosus LC705 (DSM 7061)*<br>*Bifidobacterium breve Bb99 (DSM13692)*<br>*Propionibacterium freudenreichii ssp. shermanii JS (DSM 7076)*<br><br>GOS | Probiotic treatment tended to reduce IgE-associated (atopic) diseases<br>Probiotic treatment reduced eczema and atopic eczema<br>Respiratory infection incidence in the first two years of life was lower after synbiotic treatment |
| De Preter et al., 2008[78] | Randomized, crossover intervention study for 4 weeks | 53 healthy volunteers (25 women and 28 men; 19–26 years) | 2 x 10 g lactulose + 2 x 250 mg placebo *SB*<br>2 x 15 g lactulose + 4 x 250 mg placebo *SB*<br>$2 \times 10^9$ *BB* + 2 x 10 g placebo OF-IN<br>$2 \times 6.5 \times 10^9$ *LcS* + 2 x 10 g placebo OF-IN | Lactulose<br>Oligofructose-enriched inulin (OF-IN)<br><br>*Lactobacillus casei shirota, (LcS)*<br>*Bifidobacterium breve (BB)*<br>*Saccharomyces boulardii (SB)* | Lactulose, OF-IN, *L. casei shirota* or *B. breve decreased* beta-glucuronidase activity |

GOS: Galacto-oligosaccharides; FOS: fructo-oligosaccharides; OS: Oligosaccharides; cfu: colony forming units; d: day.

developing gut wall, have also been suggested by Westerbeek et al.[31] after administration of the combination of neutral oligosaccharides with acidic oligosaccharides (maximal dose of 1.5 g/kg/day added to breast milk or preterm formula).

As aforementioned, a well-proven effect of prebiotics has been described in infants but children and adolescents have so far inspired few clinical studies testing the effects of prebiotics on immunity[30] and further studies are needed in this direction.

Probiotics have been more deeply studied in infancy and childhood, particularly in regard to the prevention of allergic diseases and reinforcement of the gut defence, stimulating a low-grade inflammation by activating the innate immune system and further production of IL-10.[1,32] *Lactobacillus rhamnosus* GG (LGG) has extensively been studied on the prevention and treatment of acute infantile diarrhoea, antibiotic associated diarrhoea and atopic dermatitis with very interesting results.[1,4,33,34] Bifidobacteria (i.e. *B. infantis* and *B. bifidum)* in combination with different strains of *Lactobacillus spp*. have been documented to be useful in diarrhoea prevention and treatment[35]. *Lactobacillus coryniformis* CECT5711 and *Lactobacillus gasseri* CECT5714 have also shown beneficial effects on intestinal flora of healthy children.[36]

The inclusion of yoghurt containing probiotics (375 g/day) over 10 weeks in a group of adolescents with anorexia nervosa (AN), showed a positive immunomodulator effect [higher CD4/CD8 ratio and increased IFN-γ production by stimulated peripheral blood mononuclear cells (PBMCs)],[37] suggesting the potential impact of probiotics on this malnourished population.

The synbiotic formed by *L. rhamnosus* LCR35 plus a specific prebiotic preparation containing lactose (that LCR35 is able to hydrolyse) and potato starch used in the fermentation broth and the prebiotic alone composed of the same fermentation broth seem to be able to significantly improve the manifestations of atopic dermatitis in children aged 2 years and over.[38] Moreover, the treatment of the intestinal infections among children with a synbiotic product (containing *B. bifidum, B. longum, L. casei* strains and fibre) reduced the duration of the diarrhoea syndrome and provided a complete recovery of the intestinal microbiota balance.[39] A positive effect on intestinal flora and systemic immune response (counts and activity of lymphocytes) in children with short bowel syndrome has been pointed out after 1 year of synbiotic therapy including *Bifidobacterium breve*, *Lactobacillus casei* and GOS.[40] Other authors have suggested that in ill children receiving antibiotics, synbiotics may confer additional benefits by increasing bifidobacteria levels.[41]

Regarding long-term safety in infants, some aspects remain unclear. While feeding synbiotics to newborn infants has been suggested to be safe and to increase resistance to respiratory infections during the first 2 years of life,[42] the real evidence about their clinical benefits and safety of prenatal and postnatal probiotic treatments still remains unclear.[43] Hence, further research seems to be needed in this direction.

## Prebiotic and probiotic immune protection in adults and elderly

The modulation of the intestinal microbiota by dietary fibre has been established to serve as a useful adjunct in the treatment of gastrointestinal and inflammatory disease in adults.[44-47] Recent evidence even suggests that inhibition of inflammatory processes may be an important mediator in the association between dietary fibre consumption and cardiovascular diseases (CVD). In fact, cross-sectional and randomized crossover intervention trials have demonstrated an association between dietary fibre and clinical inflammation biomarkers, such as C-reactive protein (CRP).[45,49]

In experimental models, prebiotics such as inulin and oligofructose have been associated with reduced mucosal inflammation and may offer an opportunity to

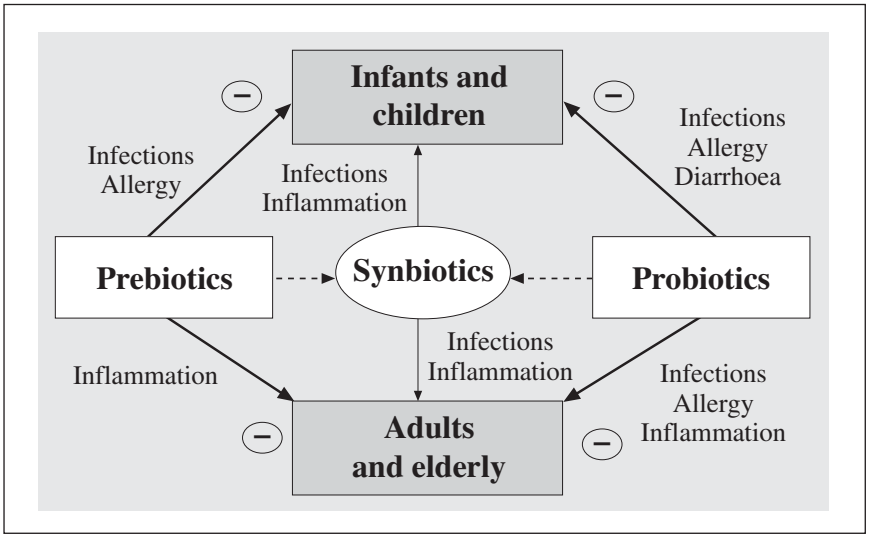


*Fig. 1.—Main effects of fibres, probiotics and synbiotics on the immune system in different life-stages in humans.*

prevent inflammatory bowel disease and other mucosal inflammatory disorders.[50] Other health effects of prebiotics (prevention of diarrhoea, modulation of the intestinal microbiota metabolism, cancer prevention, positive effects on lipid metabolism, stimulation of mineral adsorption) are indirect, i.e. mediated by the intestinal microbiota, and therefore less-well proven.[51] On the other hand, recent studies have shown the potentially extensive impact of prebiotics on gut microbiota composition,[26,52] stimulating directly or indirectly putative beneficial gut commensals other than lactic acid bacteria, opening exciting areas of research for the discovery of new probiotic strains and synbiotic combinations.[53]

Probiotics have been suggested to be capable to modulate the metabolism of short chain fatty acids, amino acids and plasma lipoproteins, demonstrating the diversity of synbiotic co-metabolic connections between the gut microbiota and the host.[54] The prevention and/or treatment of infectious and antibiotic-associated diarrhoea, allergic diseases, inflammatory bowel disorders and prevention of respiratory tract infections by probiotics, have been documented in adults.[51,55,56]

Regular, long-term intake of various synbiotics has been shown to improve adult health by reducing the incidence and severity of respiratory diseases during the cold season,[57] suggesting a synergistic effect of both probiotic and prebiotic ingredients. Synbiotics have also been suggested to alter the composition of the colonic microbiota, reduce inflammatory processes in the gut mucosa, and have the potential to induce disease remission in inflammatory bowel diseases.[58] In surgical patients, evidence from the existing randomized, controlled studies has shown that some synbiotics are able to prevent bacterial infections.[59] Regarding aging, prebiotics, probiotics and synbiotics also might improve gut microbiota and the inflammatory condition of the elderly.[60]

## Summary

There are numerous studies reporting effects on immunity with prebiotics, probiotics and synbiotics (table I). Despite the positive clinical effects on the prevention and treatment of immune-related diseases, the molecular mechanisms by which probiotics affect the immune system remain mostly unknown; further research in this area is needed.[11] The identification of specific strains with anti-allergenic potential and the question, how food matrix and dietary content interact with the most efficacious probiotic strains also require further research.[61]

Prebiotics have been less extensively studied; however, they may become an ideal treatment or co-treatment option in inflammatory bowel disease due to their capacity to increase endogenous lactobacilli and bifidobacteria.[62]

Since the early immune development in infants and the markedly declining immune function (immunosenescence) in the elderly have extensively been studied, prebiotic fibres, probiotics and synbiotics may be targeted for these specific age groups. Although the development of synbiotics to improve prevention and/or treatment of immune-related diseases have emerged as a new strategy for nutritionists and other health professionals, further intervention studies are needed to prove any added benefits or health effects of this combination of ingredients and scientific verification will be critical to the success of this concept[63]. Moreover, further studies to ascertain the mechanisms, the optimal dose/duration and the long-term safety for the intervention in different age groups are also needed.

## References


1. Gil A, Rueda R Interaction of early diet and the development of the immune system. *Nutr Res Rev* 2002; 15 (2): 263-92.
2. Bengmark S, Gil A. Bioecological and nutritional control of disease: prebiotics, probiotics and synbiotics. *Nutr Hosp* 2006; 21( 2): 72-84, 73-86.
3. Ng SC, Hart AL, Kamm MA, Stagg AJ, Knight SC. Mechanisms of action of probiotics: recent advances. *Inflamm Bowel Dis* 2009; 15 (2): 300-10.
4. Nova E, Wärnberg J, Gómez-Martínez S, Díaz LE, Romeo J, Marcos A. Immunomodulatory effects of probiotics in different stages of life. *Br J Nutr* 2007; 98 (1): S90-5.
5. Wolowczuk I, Verwaerde C, Viltart O, Delanoye A, Delacre M, Pot B, Grangette C. Feeding our immune system: impact on metabolism. *Clin Dev Immunol* 2008; 2008: 639-803.
6. Olveira Fuster G, González-Molero I. Probiotics and prebiotics in clinical practice. *Nutr Hosp* 2007; 22 (2): 26-34.
7. Sia C. Imbalance in Th cell polarization and its relevance in type 1 diabetes mellitus. *Rev Diabet Stud* 2005; 2 (4): 182-6.
8. Guarner F. Hygiene, microbial diversity and immune regulation. *Curr Opin Gastroenterol* 2007; 23 (6): 667-72.
9. Svec P, Vásárhelyi B, Pászthy B, Körner A, Kovács L, Tulassay T, Treszl A. Do regulatory T cells contribute to Th1 skewness in obesity? *Exp Clin Endocrinol Diabetes* 2007; 115 (7): 439-43.
10. Elliott DE, Setiawan T, Metwali A, Blum A, Urban JF and Weinstock JV. Heligmosomoides polygyrus inhibits established colitis in IL-10-deficient mice. *Eur J Immunol* 2004; 34 (10): 2690-8.
11. Marschan E, Kuitunenw M, Kukkonenw K, Poussaz T, Sarnesto A, Haahtelaw V, Korpela R, Savilahti E, Vaarala O. Probiotics in infancy induce protective immune profiles that are characteristic for chronic low-grade inflammation. *Clin Exp Allergy* 2008; 38: 611-18.
12. Salles N. Basic mechanisms of the aging gastrointestinal tract. *Dig Dis* 2007; 25 (2): 112-7.
13. Bruzzese E, Volpicelli M, Salvini F, Bisceglia M, Lionetti P, Cinquetti M, Iacono G, Guarino A. Early administration of GOS/FOS prevents intestinal and respiratory infections in infants. *J Pediatr Gastroenterol Nutr* 2006; 42: 2-18.
14. Kirjavainen P, Gibson GR. Healthy gut microflora and allergy: factors influencing development of the microbiota. *Ann Med* 1999; 31: 288-92.
15. Steege JC, Buurman WA, Forget PP. The neonatal development of intraepithelial and lamina propria lymphocytes in the murine small intestine. *Dev Immunol* 1997; 5: 1121-8.
16. Cebra JJ. Influences of microbiota on intestinal immune system development. *Am J Clin Nutr* 1999; 69: 1046S-1051S .
17. Forchielli ML, Walker WA. The role of gut-associated lymphoid tissues and mucosal defence. *Br J Nutr* 2005; 93 (1): S41-8.

18. Newburg DS. Neonatal protection by an innate immune system of human milk consisting of oligosaccharides and glycans. *J Anim Sci* 2009; 87 (13): 26-34.
19. Martín R, Langa S, Reviriego C, Jimínez E, Marín ML, Xaus J, Fernández L, Rodríguez JM. Human milk is a source of lactic acid bacteria for the infant gut. *J Pediatr* 2003; 143 (6): 754-8.
20. Cunningham-Rundles S. The effect of aging on mucosal host defense. *J Nutr Health Aging* 2004; 8 (1): 20-5.
21. Isolauri E, Kirjavainen PV, Salminen S. Probiotics: a role in the treatment of intestinal infection and inflammation? *Gut* 2002; 50 (3): 54-9.
22. Hopkins MJ, Sharp R, Macfarlane GT. Variation in human intestinal microbiota with age. *Dig Liver Dis* 2002; 34 (2): S12-8.
23. Brück WM, Redgrave M, Tuohy KM, Lönnerdal B, Graverholt G, Hernell O, Gibson GR. Effects of bovine alpha-lactalbumin and casein glycomacropeptide-enriched infant formulae on faecal microbiota in healthy term infants. *J Pediatr Gastroenterol Nutr* 2006; 43 (5): 673-9.
24. Penders J, Thijs C, Vink C, Stelma FF, Snijders B, Kummeling I, van den Brandt PA, Stobberingh EE. Factors influencing the composition of the intestinal microbiota in early infancy. *Pediatrics* 2006; 118 (2): 511-21.
25. Haarman M, Knol J. Quantitative real-time PCR assays to identify and quantify fecal Bifidobacterium species in infants receiving a prebiotic infant formula. *Appl Environ Microbiol* 2005; 71 (5): 2318-24.
26. Arslanoglu S, Moro GE, Schmitt J, Tandoi L, Rizzardi S, Boehm G. Early dietary intervention with a mixture of prebiotic oligosaccharides reduces the incidence of allergic manifestations and infections during the first two years of life. *J Nutr* 2008; 138: 1091-5.
27. Boehm G, Moro G. Structural and functional aspects of prebiotics used in infant nutrition. *J Nutr* 2008; 138: 1818S-1828S.
28. Scholtens PA, Alles MS, Bindels JG, Van der Linde EG, Tolboom JJ,Knol J. Bifidogenic effects of solid weaning foods with added prebiotic oligosaccharides: a randomised controlled clinical trial. *J Pediatr Gastroenterol Nutr* 2006; 42: 553-9.
29. Bakker-Zierikzee AM, Tol EA, Kroes H, Alles MS, Kok FJ, Bindels JG. Faecal SIgA secretion in infants fed on pre- or probiotic infant formula. *Pediatr Allergy Immunol* 2006; 17: 134-40.
30. Veereman G. Pediatric applications of inulin and oligofructose. *J Nutr* 2007; 137 (11): 2585S-2589S.
31. Westerbeek EA, van Elburg RM, Van den Berg A, Van den Berg J, Twisk JW, Fetter WP, Lafeber HN. Design of a randomised controlled trial on immune effects of acidic and neutral oligosaccharides in the nutrition of preterm infants: carrot study. *BMC Pediatr* 2008; 8: 46.
32. Savilahti E, Kuitunen M, Vaarala O. Pre and probiotics in the prevention and treatment of food allergy. *Curr Opin Allergy Clin Immunol* 2008; 8 (3): 243-8.
33. Lee J, Seto D, Bielory L. Meta-analysis of clinical trials of probiotics for prevention and treatment of pediatric atopic dermatitis. *J Allergy Clin Immunol* 2008; 121 (1): 116-21.
34. Ruszczynski M, Radzikowski A, Szajewska H. Clinical trial: effectiveness of Lactobacillus rhamnosus (strains E/N, Oxy and Pen) in the prevention of antibiotic-associated diarrhoea in children. *Aliment Pharmacol Ther* 2008; 28 (1): 154-61.
35. Lee MC, Lin LH, Hung KL, Wu HY. Oral bacterial therapy promotes recovery from acute diarrhea in children. *Acta Paediatr Taiwan* 2001; 42: 301-5.
36. Lara-Villoslada F, Sierra S, Boza J, Xaus J, Olivares M. Beneficial effects of consumption of a dairy product containing two probiotic strains, Lactobacillus coryniformis CECT5711 and Lactobacillus gasseri CECT5714 in healthy children. *Nutr Hosp* 2007; 22 (4): 496-502.
37. Nova E, Toro O, Varela P, López-Vidriero I, Morandé G, Marcos A. Effects of a nutritional intervention with yogurt on lymphocyte subsets and cytokine production capacity in anorexia nervosa patients. *Eur J Nutr* 2006; 45 (4): 225-33.
38. Passeron T, Lacour JP, Fontas E, Ortonne JP. Prebiotics and synbiotics: two promising approaches for the treatment of atopic dermatitis in children above 2 years. *Allergy* 2006; 61 (4): 431-7.
39. Usenko DV, Gorelov AV, Bitieva RL. Use of new synbiotics in treatment of the intestinal infections among children. *Vopr Pitan* 2007; 76 (1): 70-5.
40. Uchida K, Takahashi T, Inoue M, Morotomi M, Otake K, Nakazawa M, Tsukamoto Y, Miki C, Kusunoki M. Immunonutritional effects during synbiotics therapy in pediatric patients with short bowel syndrome. *Pediatr Surg Int* 2007; 23 (3): 243-8.
41. Schrezenmeir J, Heller K, McCue M, Llamas C, Lam W, Burow H, Kindling-Rohracker M, Fischer W, Sengespeik HC, Comer GM, Alarcon P. Benefits of oral supplementation with and without synbiotics in young children with acute bacterial infections. *Clin Pediatr (Phila)* 2004; 43 (3): 239-49.
42. Kukkonen K, Savilahti E, Haahtela T, Juntunen-Backman K, Korpela R, Poussa T, Tuure T, Kuitunen M. Long-term safety and impact on infection rates of postnatal probiotic and prebiotic (synbiotic) treatment: randomized, double-blind, placebo-controlled trial. *Pediatrics* 2008; 122 (1): 8-12.
43. Boyle R, Leonardi-Bee J, Bath-Hextall F, Tang M. Probiotics for the treatment or prevention of eczema. *J Allergy Clin Immunol* 2009; 123 (1): 266-7.
44. McRorie JW, Daggy BP, Morel JG, Diersing PS, Miner PB, Robinson M. Psyllium is superior to docusate sodium for treatment of chronic constipation. *Aliment Pharmacol Ther* 1998; 12: 491-7.
45. Marlett JA, Kajs TM, Fischer MH. An unfermented gel component of psyllium seed husk promotes laxation as a lubricant in humans. *Am J Clin Nutr* 2000; 72: 784-9.
46. Fukuda M, Kanauchi O, Araki Y, Andoh A, Mitsuyama K, Takagi K, Toyonaga A, Sata M, Fujiyama Y, Fukuoka M, Matsumoto Y, Bamba T. Prebiotic treatment of experimental colitis with germinated barley foodstuff: a comparison with probiotic or antibiotic treatment. *Int J Mol Med* 2002; 9 (1): 65-70.
47. Kanauchi O, Oshima T, Andoh A, Shioya M, Mitsuyama K. Germinated barley foodstuff ameliorates inflammation in mice with colitis through modulation of mucosal immune system. *Scand J Gastroenterol* 2008; 43 (11): 1346-52.
48. King DE, Egan BM, Geesey ME. Relation of dietary fat and fiber to elevation of C-reactive protein. *Am J Cardiol* 2003; 92: 1335-9.
49. Ma Y, Griffith JA, Chasan-Taber L, Olendzki BC, Jackson E, Stanek EJ, III, Li W, Pagoto SL, Hafner AR, Ockene IS. Association between dietary fiber and serum C-reactive protein. *Am J Clin Nutr* 2006; 83: 760-6.
50. Guarner F. Inulin and oligofructose: impact on intestinal diseases and disorders. *Br J Nutr* 2005; 93 (1): S61-5.
51. De Vrese M, Schrezenmeir J. Probiotics, prebiotics, and synbiotics. *Adv Biochem Eng Biotechnol* 2008; 111: 1-66.
52. Vulevic J, Drakoularakou A, Yaqoob P, Tzortzis G, Gibson GR. Modulation of the fecal microflora profile and immune function by a novel trans-galactooligosaccharide mixture (B-GOS) in healthy elderly volunteers. *Am J Clin Nutr* 2008; 88: 1438-46.
53. Saulnier DM, Spinler JK, Gibson GR, Versalovic J: Mechanisms of probiosis and prebiosis: considerations for enhanced functional foods. *Curr Opin Biotechnol* 2009; 20 (2): 135-41.
54. Martin FP, Wang Y, Sprenger N, Yap IK, Lundstedt T, Lek P, Rezzi S, Ramadan Z, van Bladeren P, Fay LB, Kochhar S, Lindon JC, Holmes E, Nicholson JK. Probiotic modulation of symbiotic gut microbial-host metabolic interactions in a humanized microbiome mouse model. *Mol Syst Biol* 2008; 4: 157.
55. Vliagoftis H, Kouranos VD, Betsi GI, Falagas ME. Probiotics for the treatment of allergic rhinitis and asthma: systematic review of randomized controlled trials. *Ann Allergy Asthma Immunol* 2008; 101 (6): 570-9.
56. Ruemmele FM, Bier D, Marteau P, Rechkemmer G, Bourdet-Sicard R, Walker WA, Goulet O. Clinical evidence for immunomodulatory effects of probiotic bacteria. *J Pediatr Gastroenterol Nutr* 2009; 48 (2): 126-41.
57. Pregliasco F, Anselmi G, Fonte L, Giussani F, Schieppati S, Soletti L. A new chance of preventing winter diseases by the administration of synbiotic formulations. *J Clin Gastroenterol* 2008; 42 (3): S224-33.

58. Steed H, Macfarlane GT, Macfarlane S. Prebiotics, synbiotics and inflammatory bowel disease. *Mol Nutr Food Res* 2008; 52 (8): 898-905.
59. Rayes N, Seehofer D, Neuhaus P. Prebiotics, probiotics, synbiotics in surgery-are they only trendy, truly effective or even dangerous? *Langenbecks Arch Surg* 2009; 394 (3): 547-55.
60. Guigoz Y, Doré J, Schiffrin EJ. The inflammatory status of old age can be nurtured from the intestinal environment. *Curr Opin Clin Nutr Metab Care* 2008; 11 (1): 13-20.
61. Isolauri E, Kalliomäki M, Laitinen K, Salminen S. Modulation of the maturing gut barrier and microbiota: a novel target in allergic disease. *Curr Pharm Des* 2008; 14 (14): 1368-75.
62. Geier MS, Butler RN, Howarth GS. Inflammatory bowel disease: current insights into pathogenesis and new therapeutic options; probiotics, prebiotics and synbiotics. *Int J Food Microbiol* 2007; 115 (1): 1-11.
63. Douglas LC, Sanders ME. Probiotics and prebiotics in dietetics practice. *J Am Diet Assoc* 2008; 108 (8): 1381.
64. King DE, Egan BM, Woolson RF, Mainous AG, 3rd, Al-Solaiman Y, Jesri A. Effect of a high-fiber diet vs a fiber-supplemented diet on C-reactive protein level. *Arch Intern Med* 2007; 167: 502-6.
65. Schiffrin EJ, Thomas DR, Kumar VB, Brown C, Hager C, Van't Hof MA, Morley JE, Guigoz Y. Systemic inflammatory markers in older persons: the effect of oral nutritional supplementation with prebiotics. *J Nutr Health Aging* 2007; 11 (6): 475-9.
66. Ma Y, Hébert JR, Li W, Bertone-Johnson ER, Olendzki B, Pagoto SL, Tinker L, Rosal MC, Ockene IS, Ockene JK, Griffith JA, Liu S. Association between dietary fiber and markers of systemic inflammation in the Women's Health Initiative Observational Study. *Nutrition* 2008; 24 (10): 941-9.
67. Shadid R, Haarman M, Knol J, Theis W, Beermann C, Rjosk-Dendorfer D, Schendel DJ, Koletzko BV, Krauss-Etschmann S. Effects of galactooligosaccharide and long-chain fructooligosaccharide supplementation during pregnancy on maternal and neonatal microbiota and immunity—a randomized, double-blind, placebo-controlled study. *Am J Clin Nutr* 2007; 86 (5): 1426-37.
68. Bruzzese E, Volpicelli M, Squeglia V, Bruzzese D, Salvini F, Bisceglia M, Lionetti P, Cinquetti M, Iacono G, Amarri S, Guarino A. A formula containing galacto- and fructo-oligosaccharides prevents intestinal and extra-intestinal infections: an observational study. *Clin Nutr* 2009; 28 (2): 156-61.
69. Solis B, Nova E, Gómez S, Samartín S, Mouane N, Lemtouni A, Belaoui H, Marcos A. The effect of fermented milk on interferon production in malnourished children and in anorexia nervosa patients undergoing nutritional care. *Eur J Clin Nutr* 2002; 56 (4): 27S-33S.
70. Naruszewicz M, Johansson ML, Zapolska-Downar D, Bukowska H. Effect of Lactobacillus plantarum 299v on cardiovascular disease risk factors in smokers. *Am J Clin Nutr* 2002; 76 (6): 1249-55.
71. Rosenfeldt V, Benfeldt E, Nielsen SD, Michaelsen KF, Jeppesen DL, Valerius NH, Paerregaard A. Effect of probiotic Lactobacillus strains in children with atopic dermatitis. *J Allergy Clin Immunol* 2003; 111 (2): 389-95.
72. Pohjavuori E, Viljanen M, Korpela R, Kuitunen M, Tiittanen M, Vaarala O, Savilahti E. Lactobacillus GG effect in increasing IFN-gamma production in infants with cow's milk allergy. *J Allergy Clin Immunol* 2004; 114 (1): 131-6.
73. Hol J, van Leer EH, Elink Schuurman BE, de Ruiter LF, Samsom JN, Hop W, Neijens HJ, de Jongste JC, Nieuwenhuis EE. Cow's Milk Allergy Modified by Elimination and Lactobacilli study group. The acquisition of tolerance toward cow's milk through probiotic supplementation: a randomized, controlled trial. *J Allergy Clin Immunol* 2008; 121 (6): 1448-54.
74. Kopp MV, Hennemuth I, Heinzmann A, Urbanek R. Randomized, double-blind, placebo-controlled trial of probiotics for primary prevention: no clinical effects of Lactobacillus GG supplementation. *Pediatrics* 2008; 121 (4): 850-6.
75. Ivory K, Chambers SJ, Pin C, Prieto E, Arqués JL, Nicoletti C. Oral delivery of Lactobacillus casei Shirota modifies allergen-induced immune responses in allergic rhinitis. *Clin Exp Allergy* 2008; 38 (8): 1282-9.
76. Ogawa T, Asai Y, Tamai R, Makimura Y, Sakamoto H, Hashikawa S, Yasuda K. Natural killer cell activities of synbiotic Lactobacillus casei ssp. casei in conjunction with dextran. *Clin Exp Immunol* 2006; 143 (1): 103-9.
77. Kukkonen K, Savilahti E, Haahtela T, Juntunen-Backman K, Korpela R, Poussa T, Tuure T, Kuitunen M. Probiotics and prebiotic galacto-oligosaccharides in the prevention of allergic diseases: a randomized, double-blind, placebo-controlled trial. *J Allergy Clin Immunol* 2007; 119 (1): 192-8.
78. De Preter V, Raemen H, Cloetens L, Houben E, Rutgeerts P, Verbeke K. Effect of dietary intervention with different pre- and probiotics on intestinal bacterial enzyme activities. *Eur J Clin Nutr* 2008; 62 (2): 225-31.
79. Prescott SL, Wiltschut J, Taylor A, Westcott L, Jung W, Currie H, Dunstan JA. Early markers of allergic disease in a primary prevention study using probiotics: 2.5-year follow-up phase. *Allergy* 2008; 63 (11): 1481-90.