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Beneficial Effects of Prebiotic Oligosaccharides added to Infant Formulas

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contents

- Human milk oligosaccharides
- Concept of scGOS/lcFOS
- Prebiotic effects of scGOS/lcFOS
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- Conclusions

human milk oligosaccharides

- quantitatively the 3rd fraction in human milk (after lactose and lipids, before protein)

	Human milk (g/L)	Cow's milk (g/L)
Lactose	**55-70**	**40-50**
Oligosaccharides	**6.0-12.0**	**Traces**

- resist digestion in the upper part of the GI tract
- (partly) fermented in the colon by endogenous microflora
- considered to represent the “bifidus factor” in human milk

~ But:

- a very heterogeneous fraction with > 100 different structures (analyses with Maldi-MS).
- variability: genetic control, time of lactation

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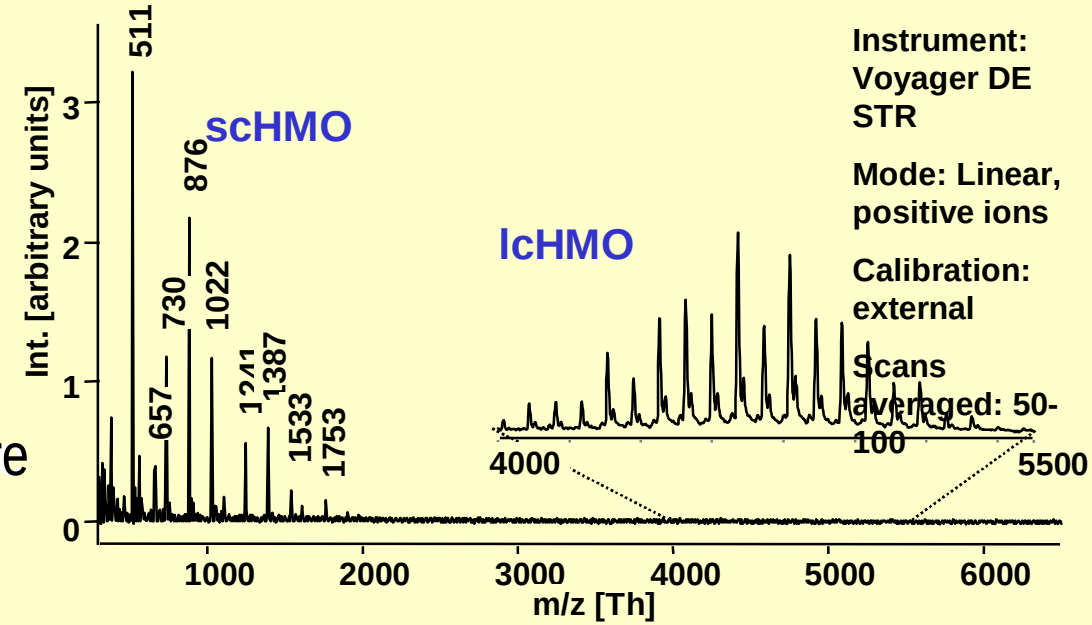
human milk oligosaccharides

structure



Fucose a1-2 a1-4/3 a1-2 a1-3 Linkage

[Gal(b1- 3/4)GlcNAc b1–]$_{n=1-30}$ Gal(b1-4)Glc Core

Linkage

Neu5Ac a2-3/6 a2-6 a2-3/6

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human milk oligosaccharides

- biological functions
  - è Highly specific:
    receptors analogues for pathogenic bacteria and viruses
  - è Generalistic:
    - 4 substrate for specifically bifidobacteria and lactobacilli and thus act as prebiotics (cf. human milk fibre)

- what can we learn from human milk oligosaccharides ?
  - è the generalistic functionality may be simulated by food prebiotics
  - è heterogeneity probably needed for broad activity spectrum
  - è 90% neutral charge
    - 4 high amount of short chain length structures
    - 4 low amount of higher chain length structures
  - è 10% negatively charged (acidic structures)

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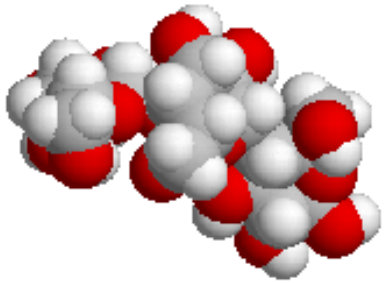
concept of scGOS/lcFOS

90 % scGOS:
short-chain b-**G**alacto-**O**ligo**S**accharides **(from lactose)**

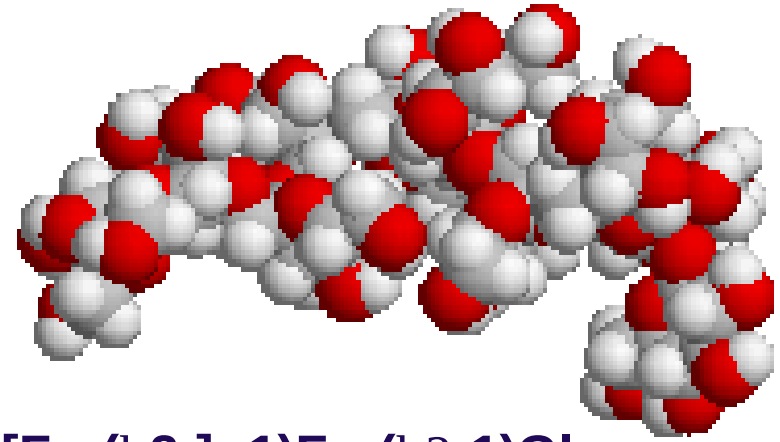
10 % lcFOS:
long-chain b-**F**ructo-**O**ligo**S**accharides **(from chicory)**

lcFOS e.g. 10mer (DP10)

GOS e.g. 3mer (DP3)



[Gal(b1-4)Gal(b1-4)Glc



[Frc(b2-]$_8$ 1)Frc(b2-1)Glc

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concept of scGOS/lcFOS

why is the scGOS/lcFOS concept so special ?

- short chain GOS
  - è the most natural “lactose-derived” oligosaccharide
  - è the lowest incidence of side effects (gas production / bloating) compared to similar short-chain oligosacharides
- long chain FOS
  - è the most suitable slowly fermentable substrate to allow fermentation all over the full length of the large intestine
- extensive portfolio of experimental research and clinical studies

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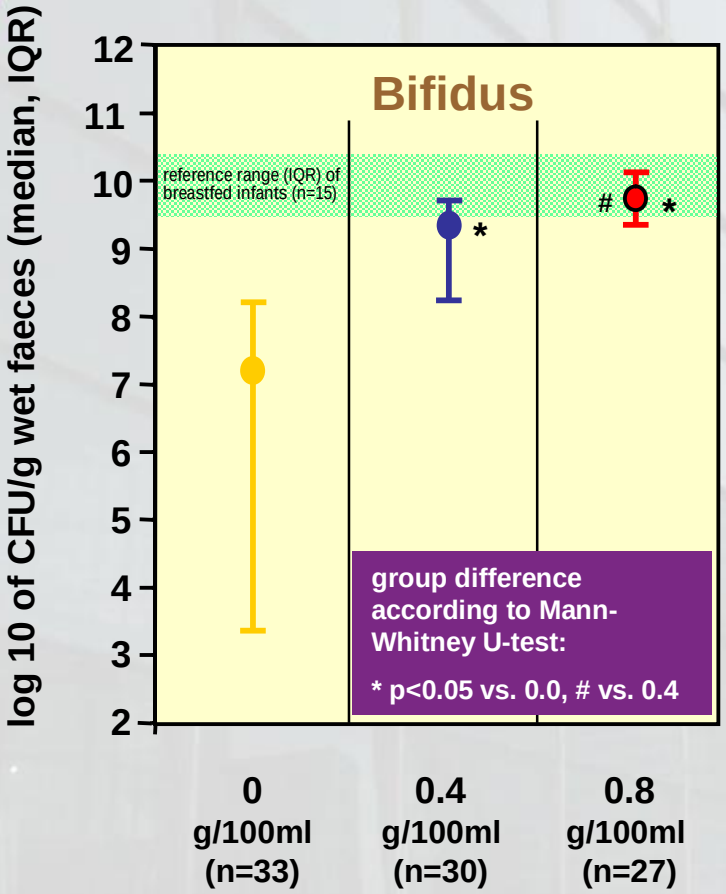
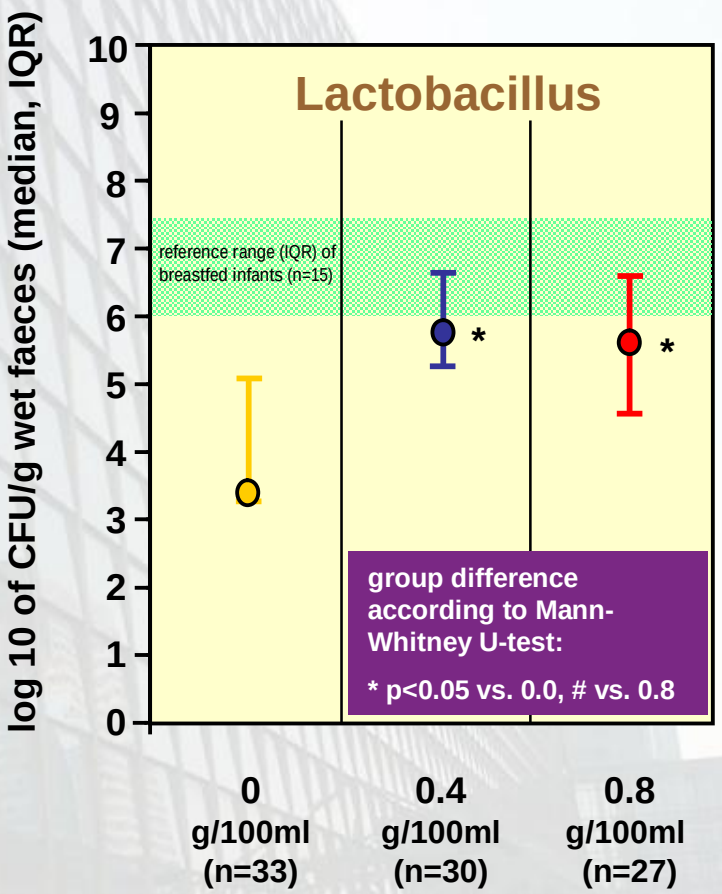
prebiotic effects of scGOS/lcFOS

effect on gut microflora

(term infants after 28 days formula feeding)

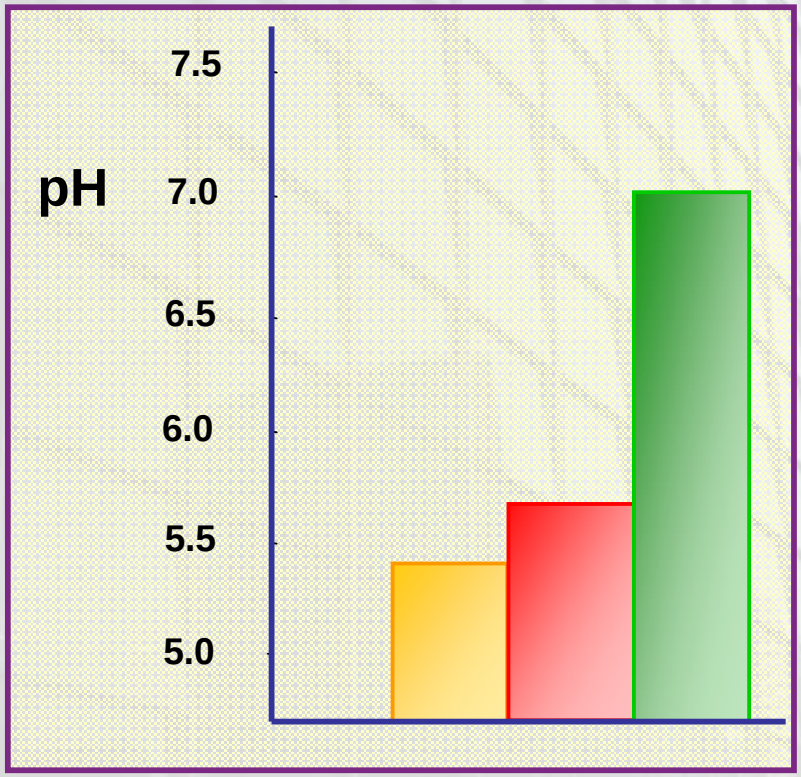




Moro et al. (2002) JPGN 34: 291-295

prebiotic effects of scGOS/lcFOS

effect on fecal pH



- Breastfeeding (n=39)
- Prebiotic (n=16)
- Standard (n=30)

Data averaged from samples obtained at ages 4, 8, 12 and 16 wk.

Bakker-Zierikzee et al. (2005) Br J Nutr 94: 783-790

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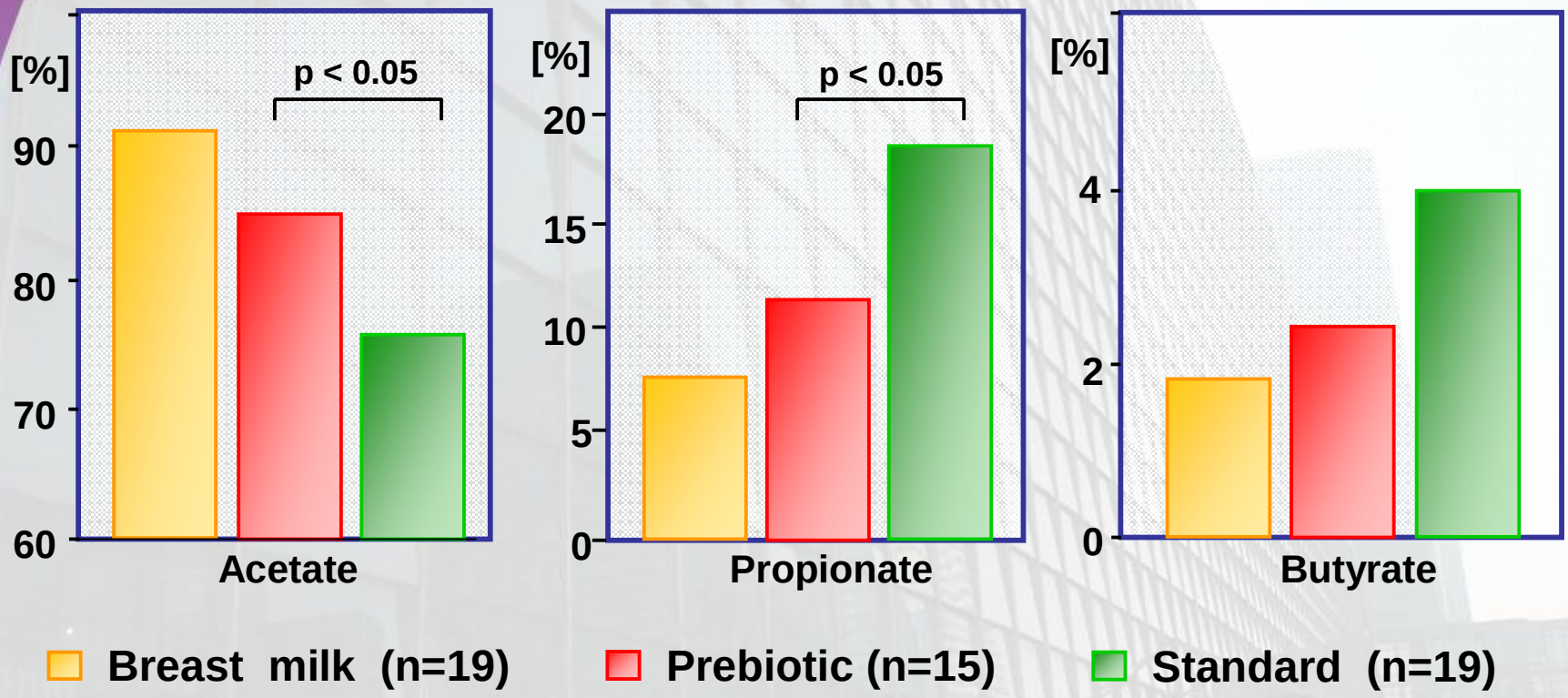
prebiotic effects of scGOS/lcFOS

effect on fecal short chain fatty acids

(formula fed term infants after 6 weeks study formula)



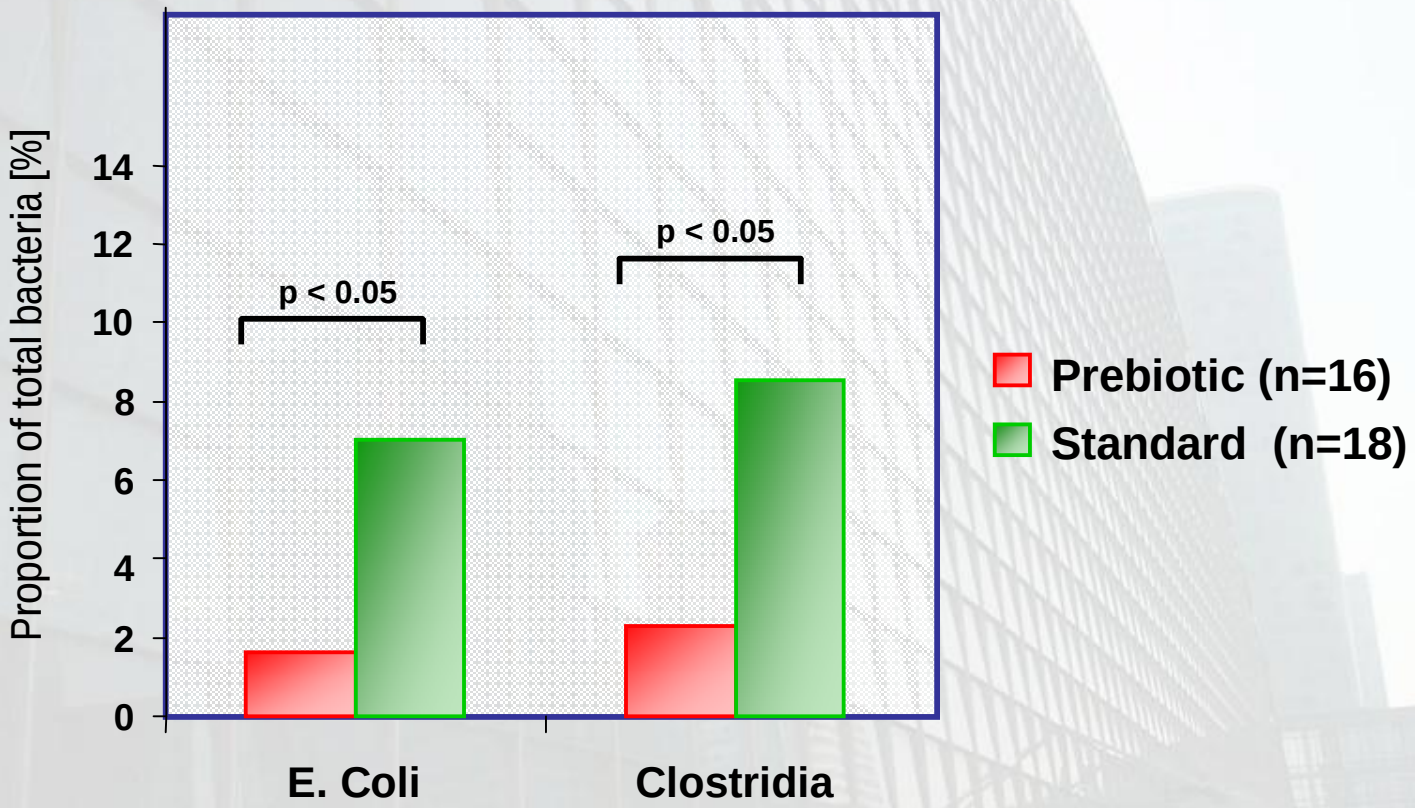
NB: of the SCFA's, acetate most effectively stimulates mucin synthesis

Knol et al. (2005) JPGN 40: 36-42

prebiotic effects of scGOS/lcFOS

effect on reduction of potential pathogens

(formula fed term infants after 6 weeks study formula)



Knol et al. (2003) JPGN 36: 566

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immune-modulating effects of scGOS/lcFOS

immune disorders

Hyper immune- responsiveness:

Allergy

Autoimmunity

Chronic inflammatory diseases

Hypo immune- responsiveness:

Infections

Tumors/metastasis

immune regulation

Resistance to infections
Th1

Allergy
Th2

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immune-modulating effects of scGOS/lcFOS

deviations in t-cell regulation balance

~ Asthma	Th2 -
~ Atopic eczema	Th2 -
~ Coeliac disease	Th1 -
~ COPD	Th1 -
~ Cystic Fibrosis	Th1 -
~ HIV	Th1 ¯, Th2 -, Th1/Th2 ¯
~ Cancer	Th1 ¯
~ Elderly	Th1 ¯
~ Pregnancy	Th1 ¯, Th2 -

the newborn baby, born with a Th2 dominance needs to rapidly develop a proper Th1/Th2 balance to prevent allergy (Th2↓) and to support reactivity to infections (Th1↑)

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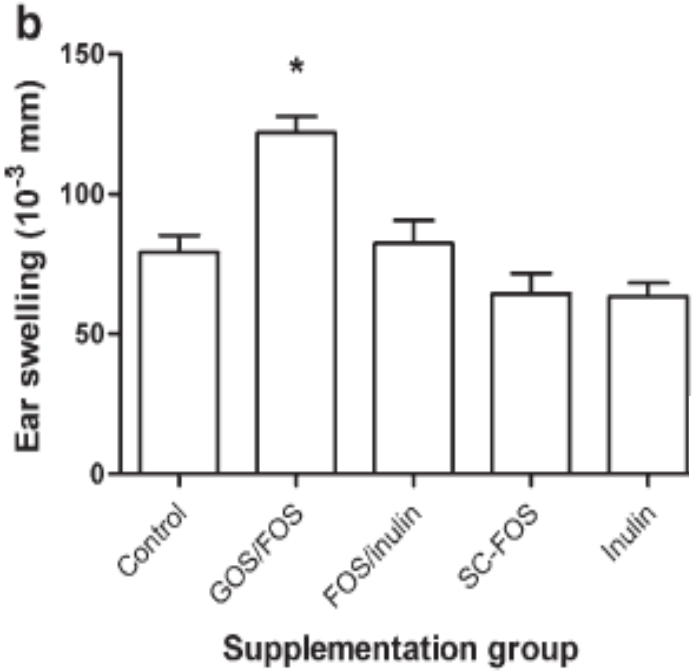
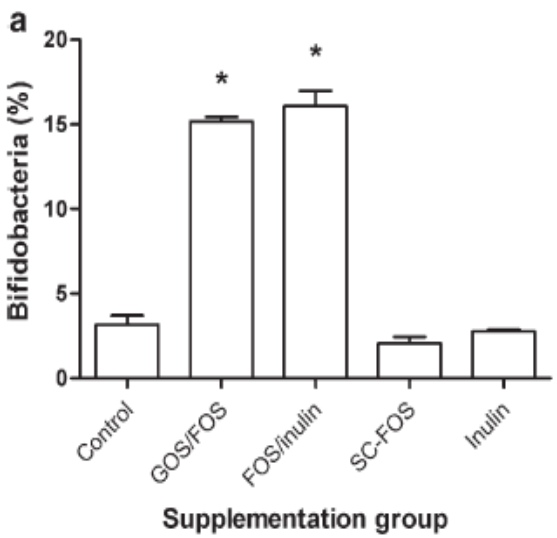
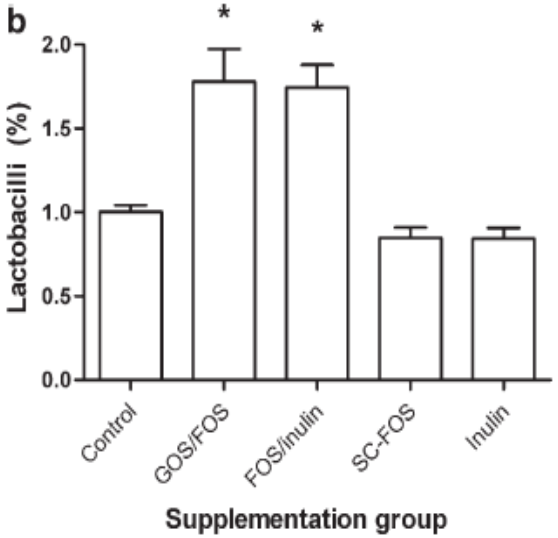
immune-modulating effects of scGOS/lcFOS

- Influenza vaccination model for Th1 immunity
  - è C57BL/6 mice were prefed with prebiotics during
    2 weeks prior to the first of 2 vaccinations using a 100 fold diluted vaccin
- 4 prebiotic ingredients/mixtures tested
  - è 2 groups showed prebiotic activity
  - è in only 1 group: Th1 immune enhancement





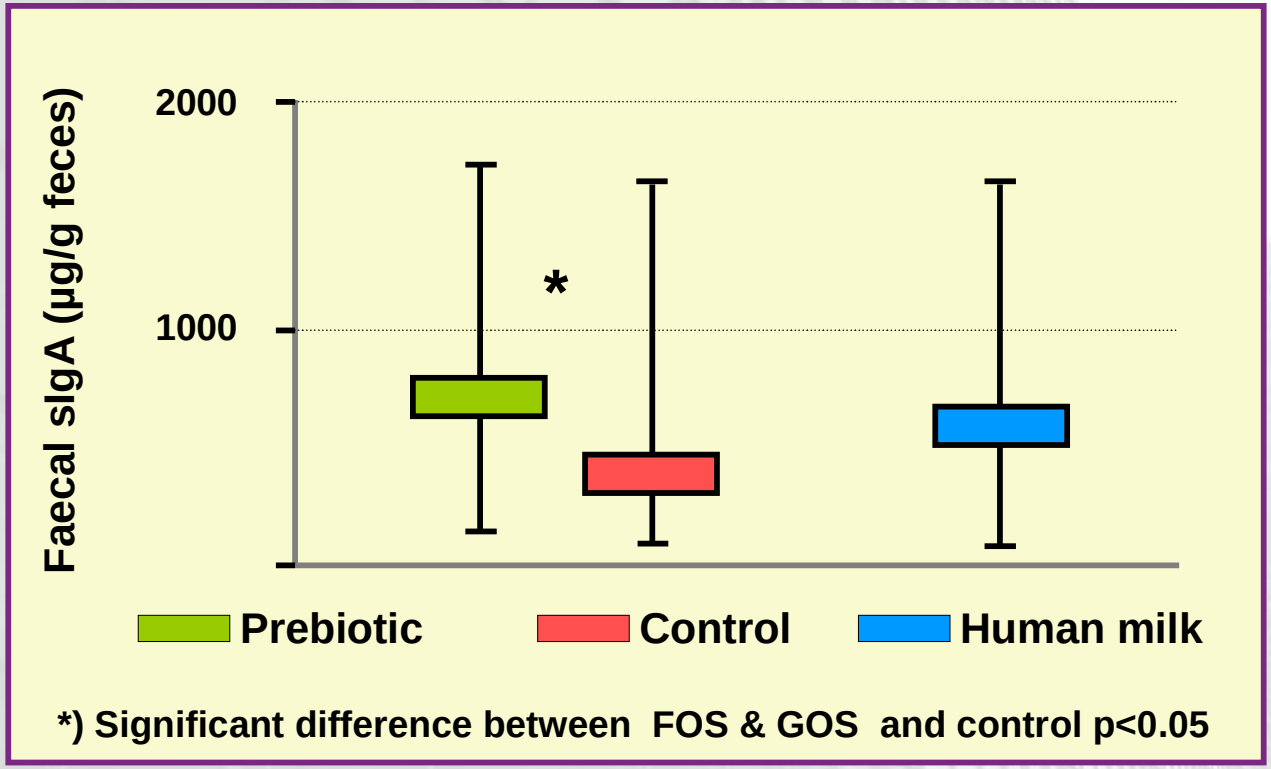


- animal study:
  - not all ingredients giving a prebiotic effects also show similar immune-modulation

Vos et al. (2006) Int Immunopharmacol 6:1277-1286

immune-modulating effects of scGOS/lcFOS

- effect on secretory IgA production at age 26 weeks (assessed as faecal sIgA)

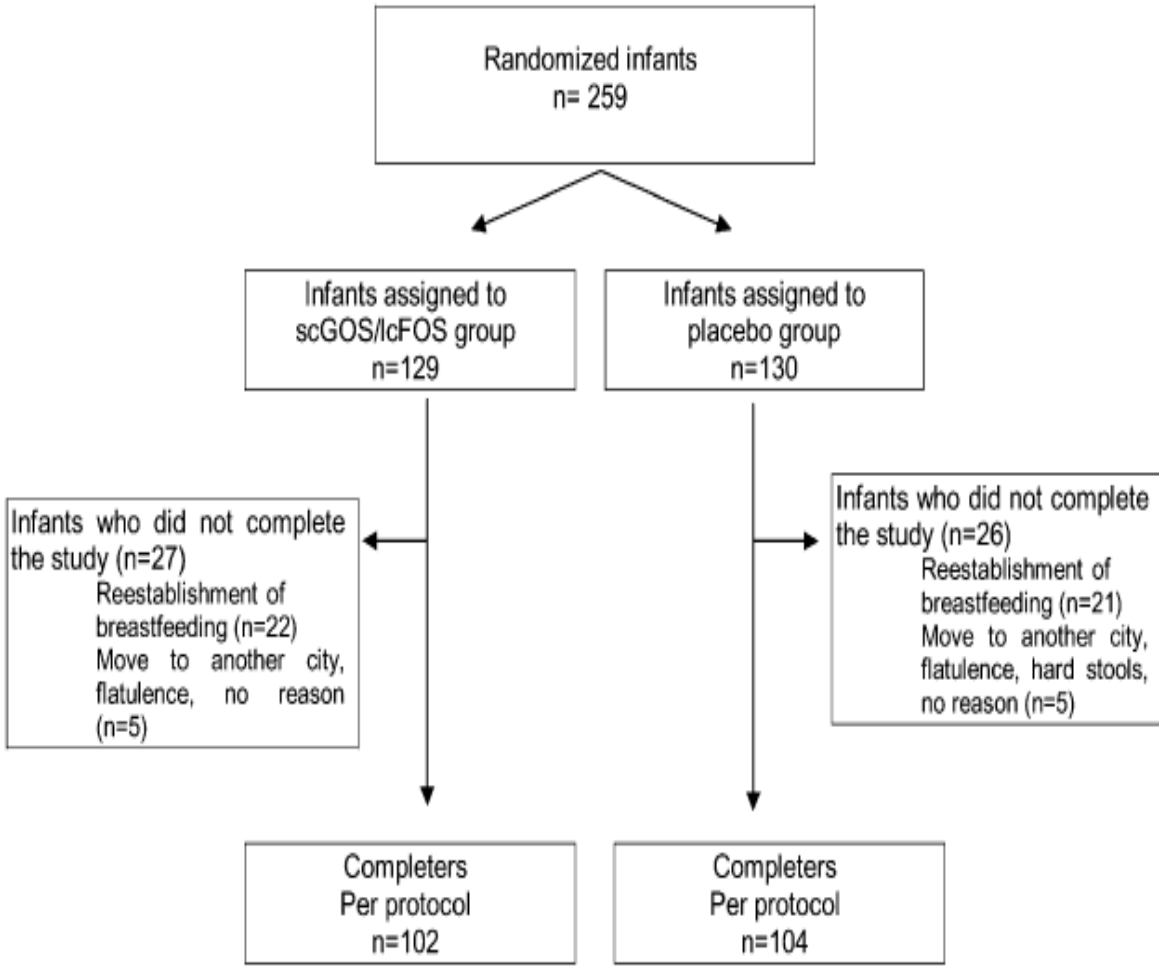


The results represent the median concentration of faecal sIgA with the 10th and the 90th percentiles.

Scholtens et al. (2008) J Nutr 138: 1141-1147

immune-modulating effects of scGOS/lcFOS

- The Moro-Arslanoglu study (2004-2008)
- Aim: investigate effect of scGOS/lcFOS on allergy and infection
- Model: Babies with increased family allergy risk
- Formula: Hydrolysate based infant formula +/- scGOS/lcFOS
- Intervention: after BF (<6wk): formula until age of 6 mo
- 4 papers
  - è Moro (2006) Arch Dis Childh
  - è Arslanaglu (2007) J Nutr
  - è Arslanaglu (2008) J Nutr
  - è Van Hoffen (2008) Allergy



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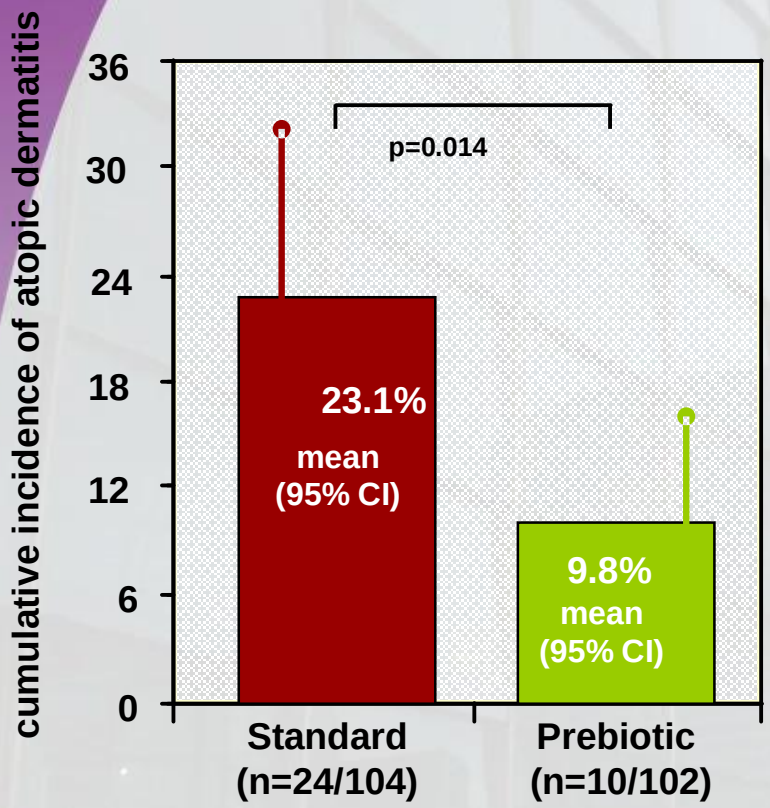
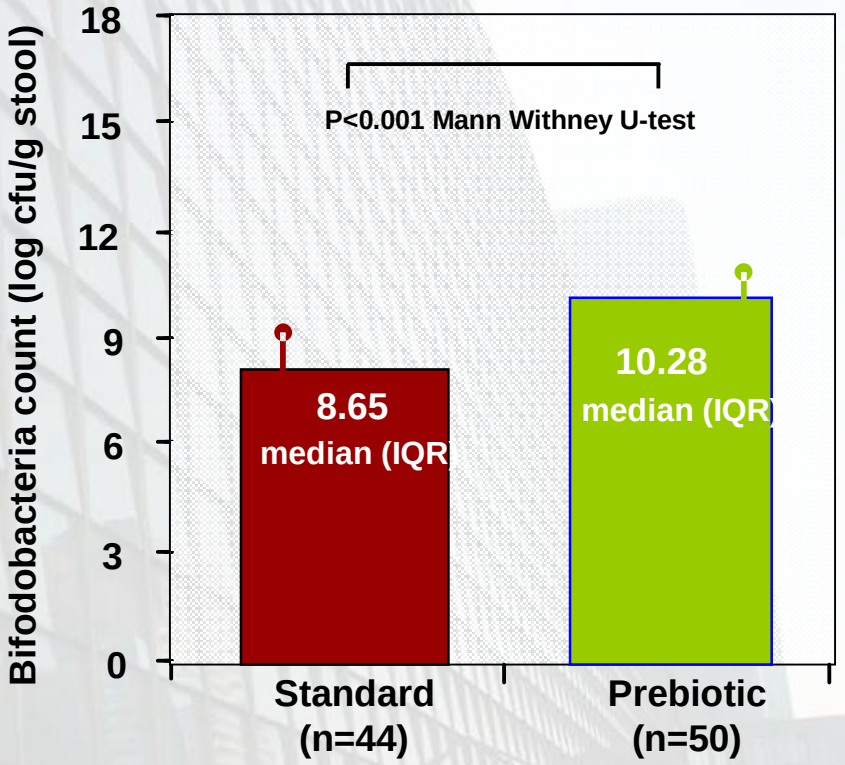
immune-modulating effects of scGOS/lcFOS

effect on atopic dermatitis and bifido counts at age 6 months





Moro G et al. (2006) Arch Dis Child 91: 814-819

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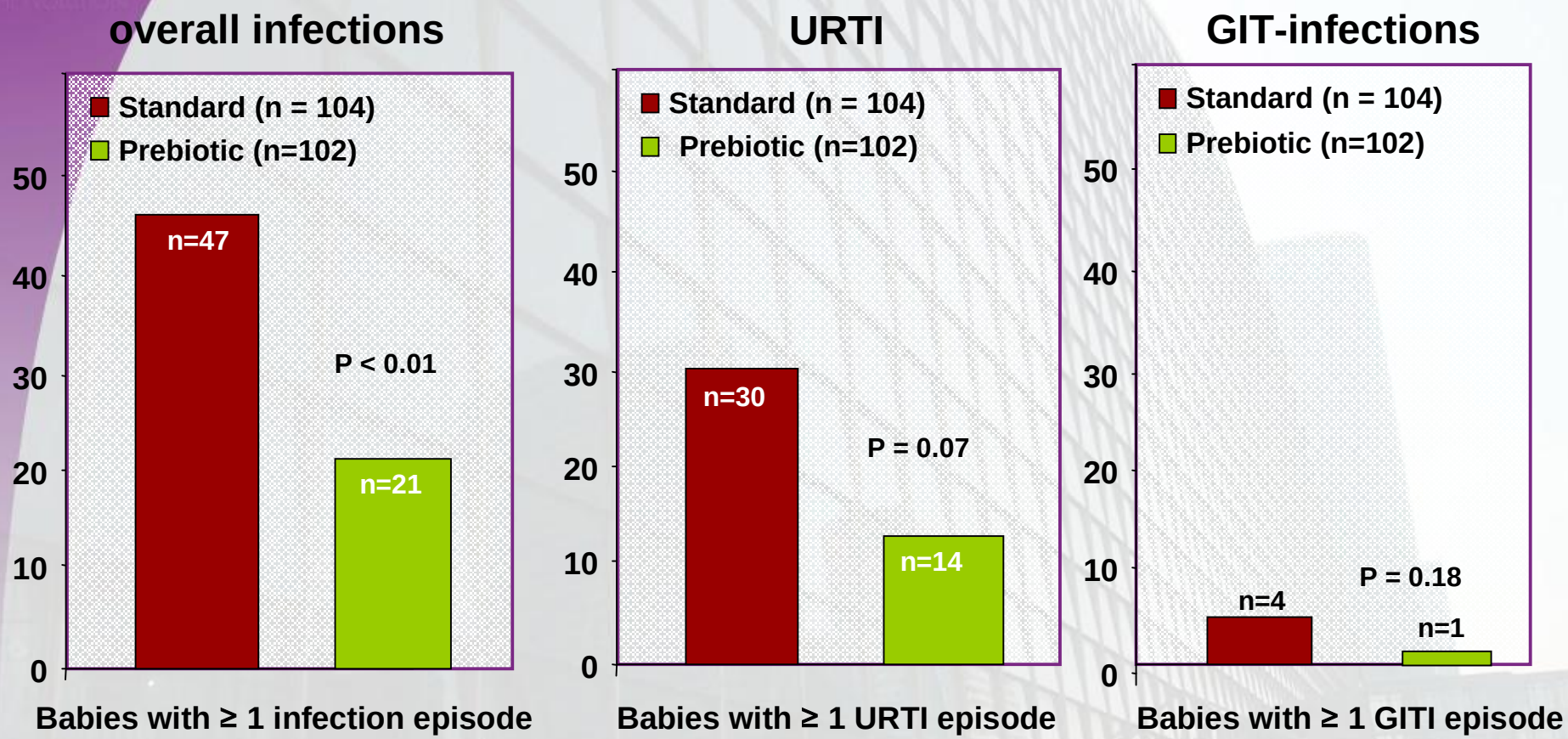
immune-modulating effects of scGOS/lcFOS

effect on infections at age 6 months



Arslanoglu et al. (2007) J Nutr 137: 2420-2424

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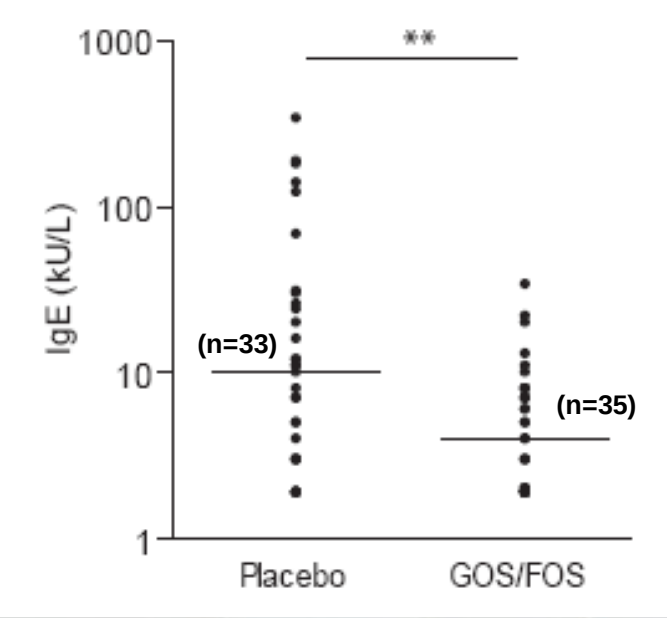
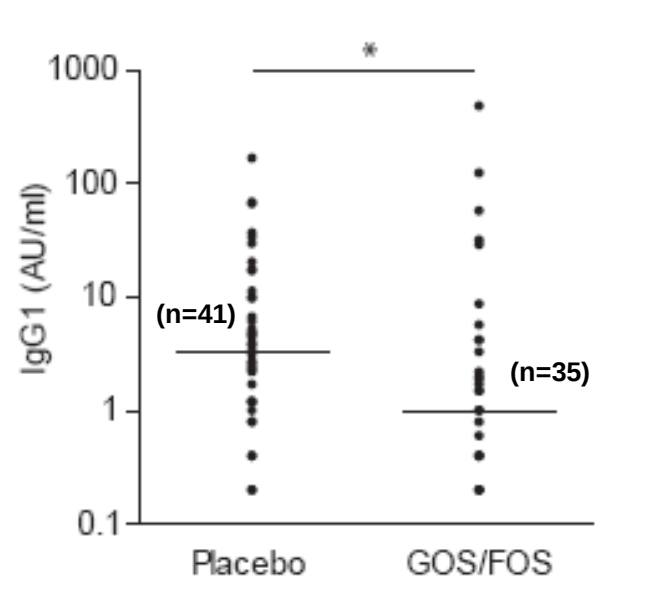
immune-modulating effects of scGOS/lcFOS

effect on immunoglobulin profile at age 6 months: change towards less allergenic risk

Total IgE



CMP-specific IgG1



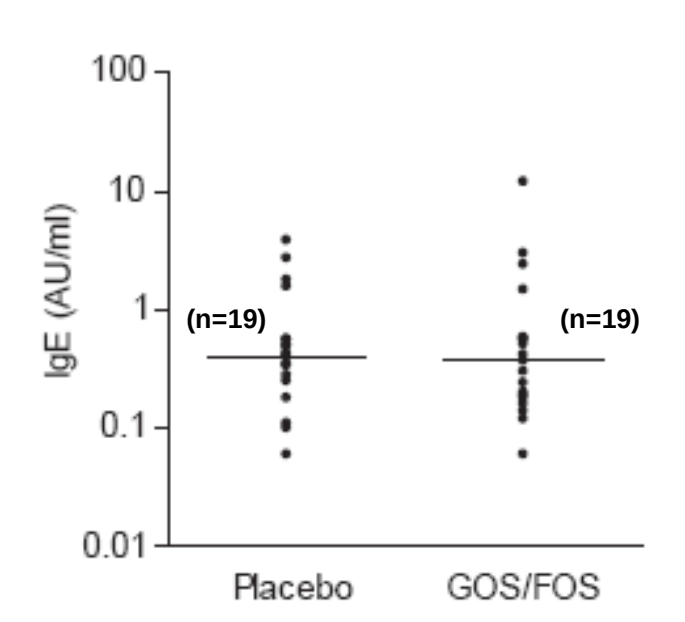
Data represent individual results and median of the placebo group and the GOS/FOS group
** p<0.01; * p<0.05; n.s., not significant

Van Hoffen et al. (2008) Allergy, e-pub

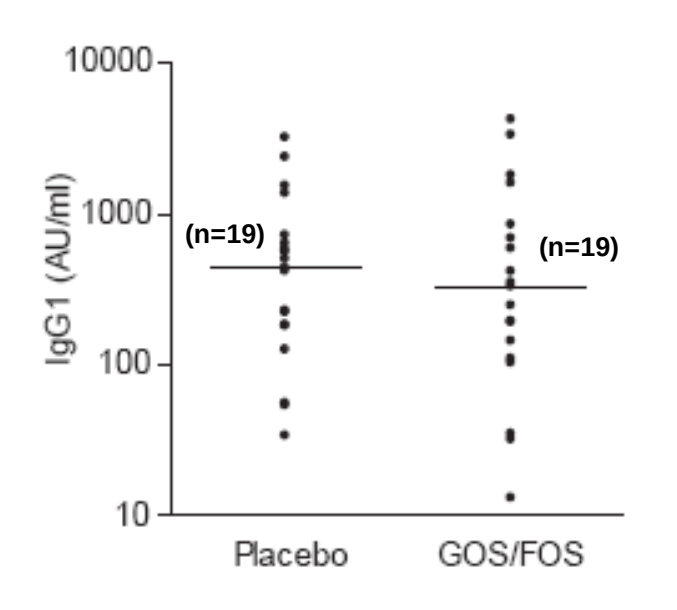
immune-modulating effects of scGOS/lcFOS

effect on immunoglobulin profile at age 6 months:
no effect on routine vaccination efficacy

DTP-specific IgE



DTP-specific IgG1



Data represent individual results and median of the placebo group and the GOS/FOS group

Van Hoffen et al. (2008) Allergy, e-pub

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immune-modulating effects of scGOS/lcFOS

follow-up investigations until the age of 2 years
(between age 7-24 months: no intervention)

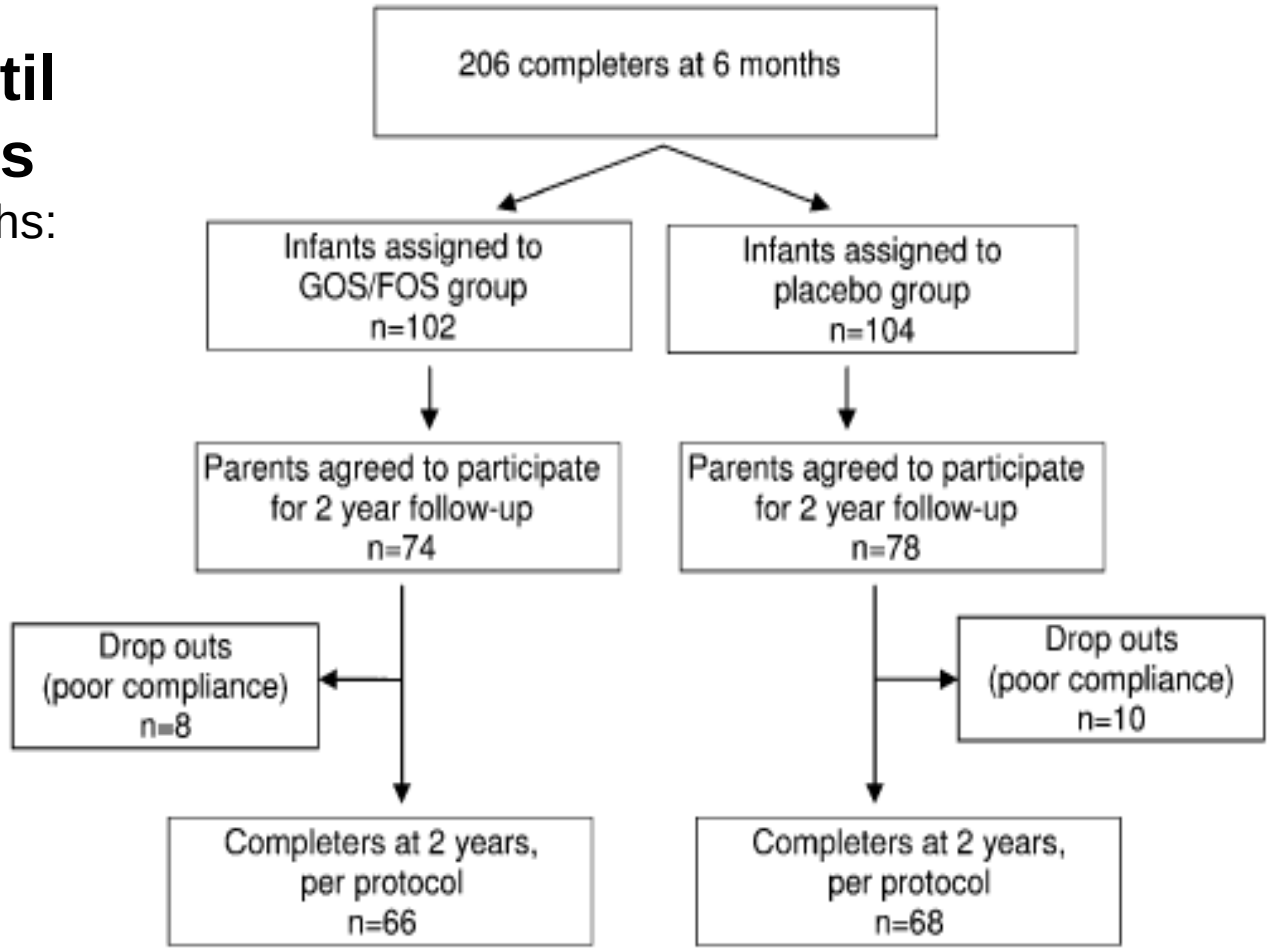

FIGURE 1 Flow chart showing enrollment and disposition of the subjects throughout the study.

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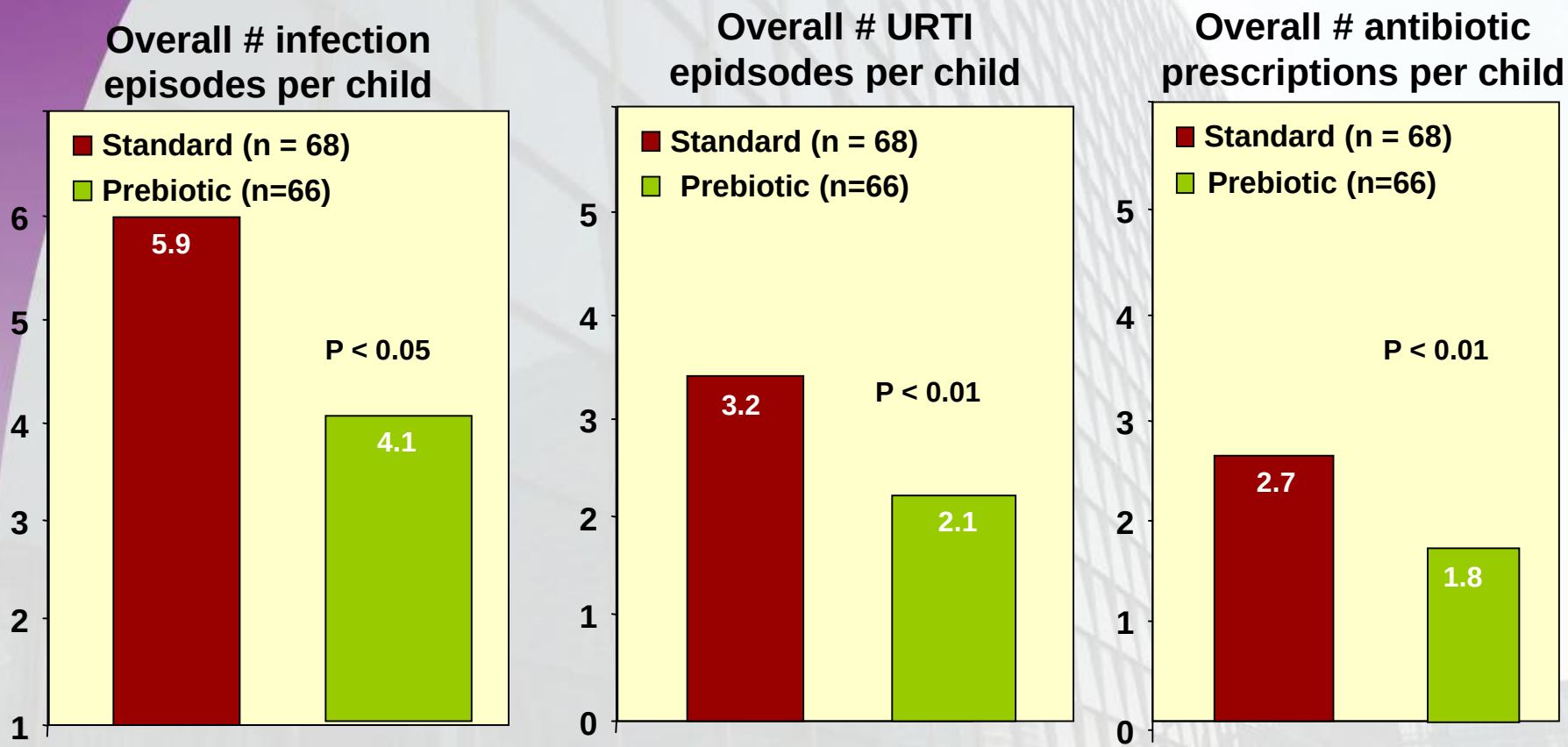
immune-modulating effects of scGOS/lcFOS

effect on infections at 2 yr. follow-up



Arslanoglu et al. (2008) J Nutr 138: 1091-1095

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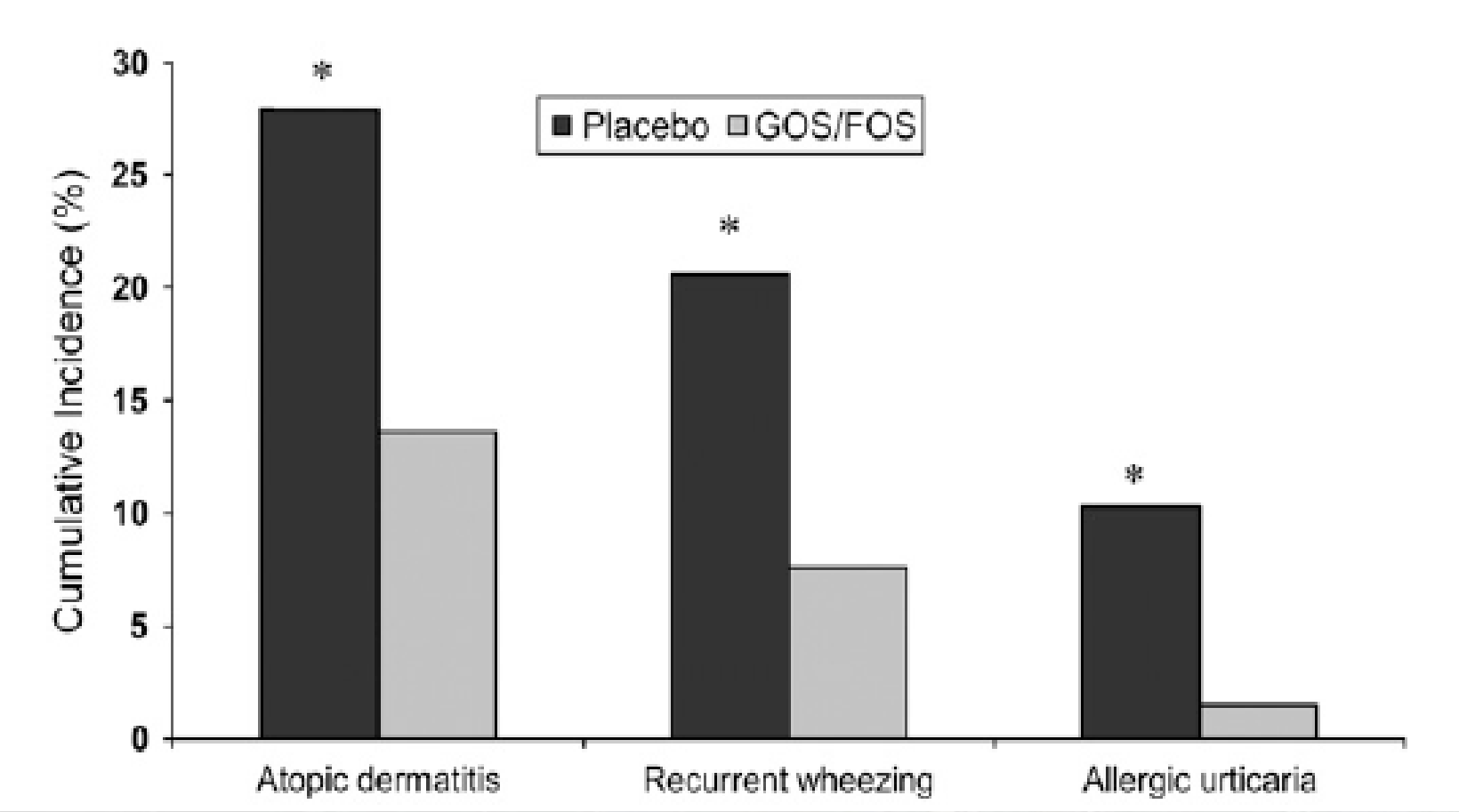
immune-modulating effects of scGOS/lcFOS

effect on allergy at 2 yr. follow-up



Arslanoglu et al. (2008) J Nutr 138: 1091-1095

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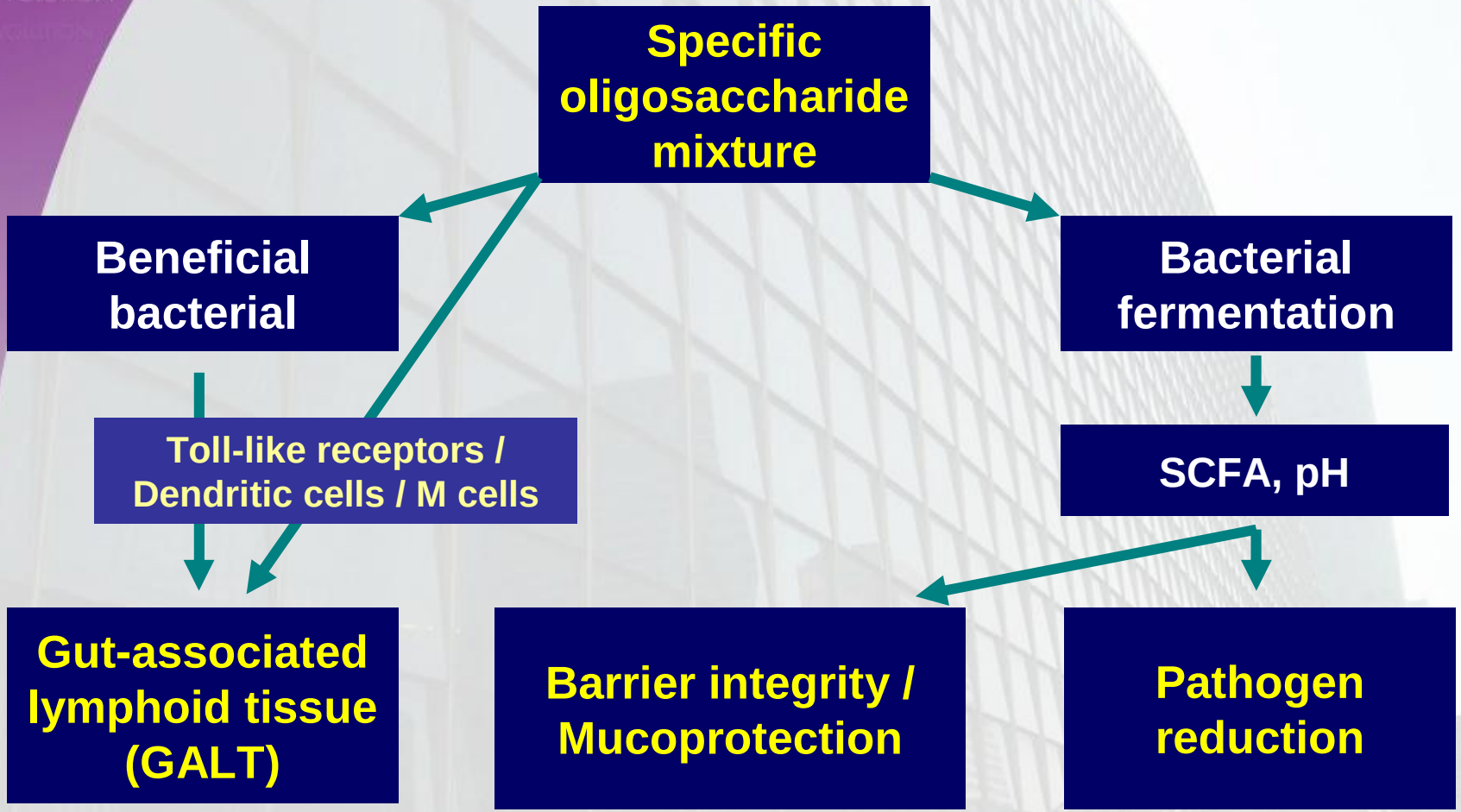
conclusions

tentative mechanism



Boehm et al.(2005) Nutrafoods 4: 51-57

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conclusions

- The scGOS/lcFOS concept for infant nutrition was developed to maximally emulate the prebiotic functionality of human milk oligosaccharides
- Prebiotic characteristics and effects on colonic fermentation ecology have been demonstrated for the scGOS/lcFOS concept
- The scGOS/lcFOS concept for infant nutrition exhibits immune-modulatory characteristics by supporting Th1 and down regulating Th2 immunity, similar to human milk oligosaccharides
- Clinical endpoints for relevant immune-modulation in early life, reduction in risk for allergy (Th2↓) and infections (Th1↑) are substantiated
- Current insights suggest an indirect mode of action via an effect on the intestinal flora and a direct effect via Toll-like receptors, dendritic cells and M-cells
- Immune-modulatory characteristics are rather specific and are not general characteristics of prebiotic ingredients
- The claim "naturally strengthens your baby's the immune system" has been submitted to EFSA for infant formulas with adequate amounts of scGOS/lcFOS