

Pre-, probiotics and synbiotics in constipation

3RD INTERNATIONAL SYMPOSIUM OF
PP
robiotics
rebiotics
in **P**ediatrics
2016



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Outline of the presentation

- **Definition**
- **Normal flora**
- **Prebiotics, healthy infants**
- **Prebiotics, constipation**
- **Probiotics, constipation**
- **Synbiotics, constipation**
- **Dessert**

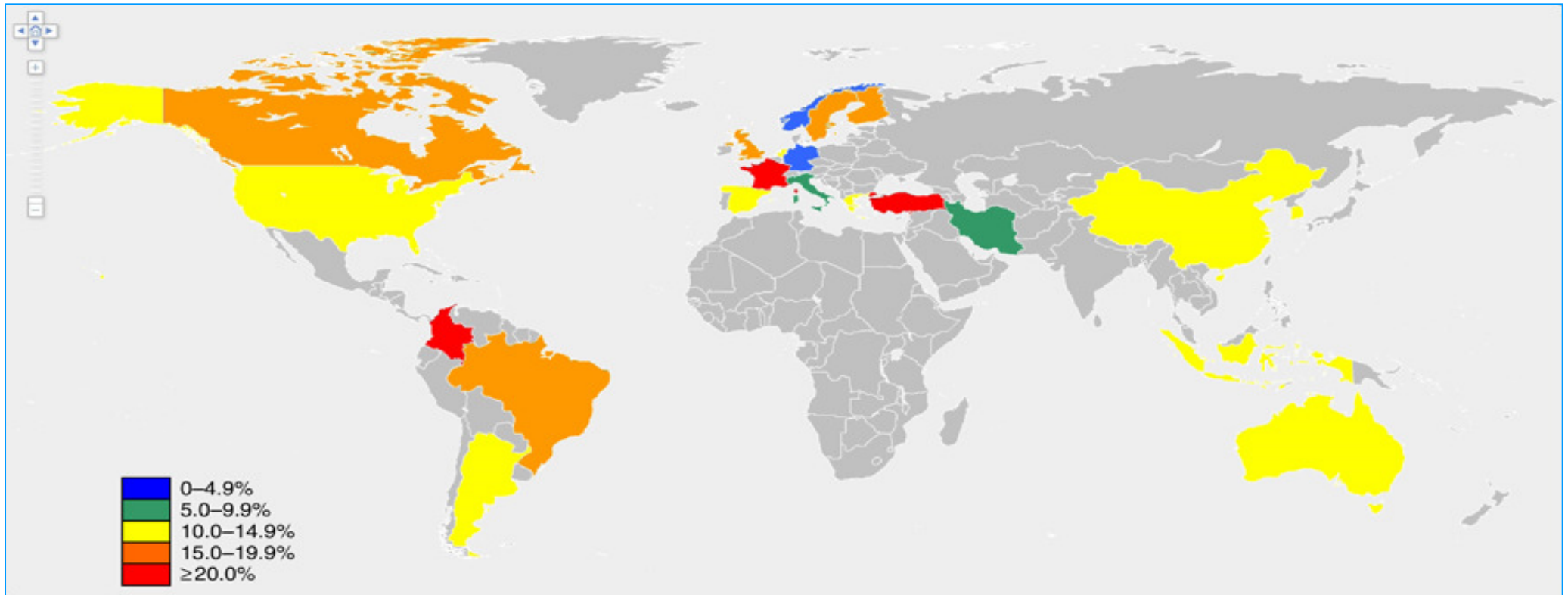
Functional constipation

- Must include one month of at least two of the following in infants, toddlers, children and adolescents:
 - 1. Two or fewer defecations per week
 - 2. History of excessive stool retention
 - 3. History of painful or hard bowel movements
 - 4. History of large diameter stools
 - 5. Presence of a large fecal mass in the rectum

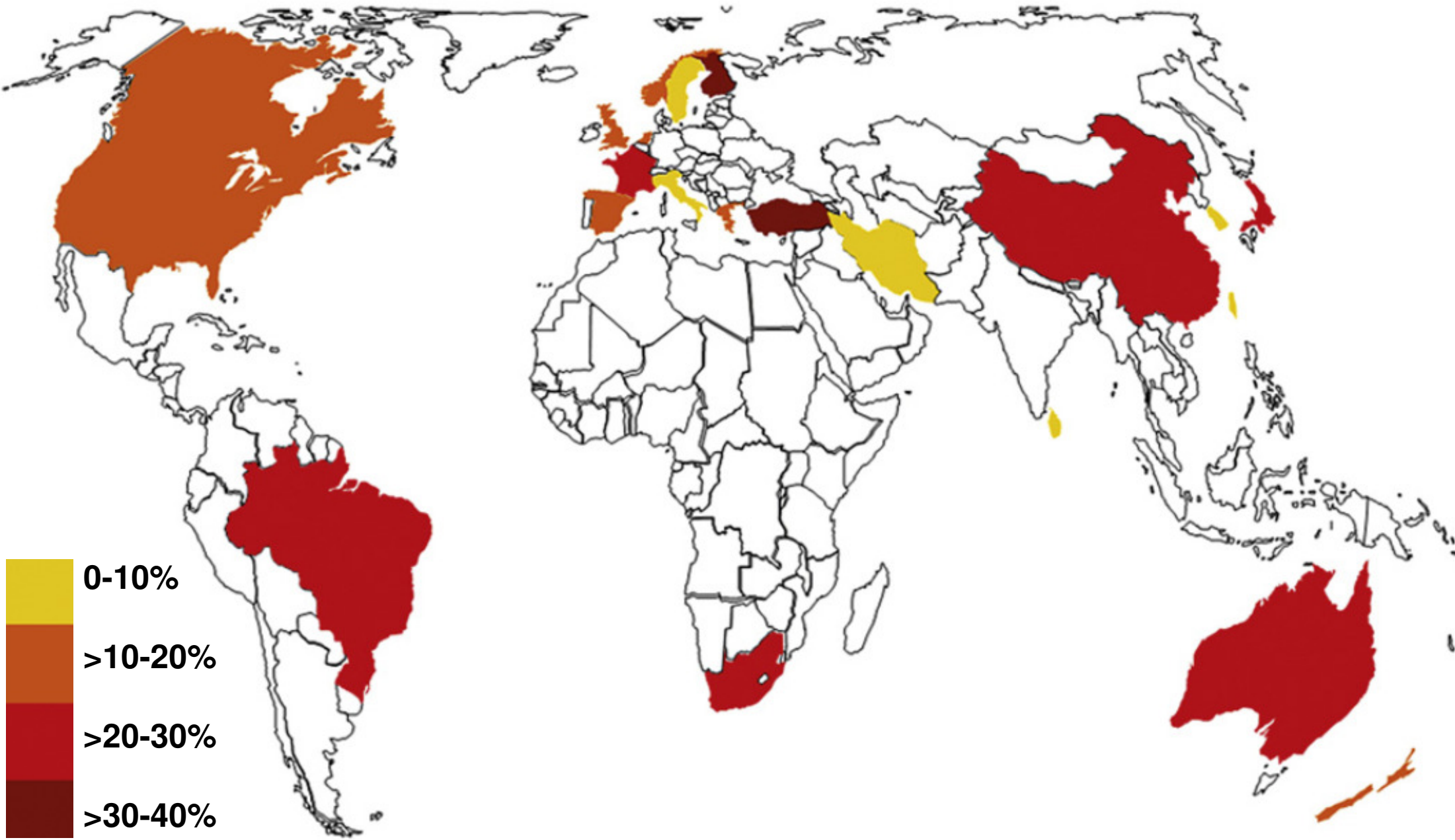
In toilet trained children the following additional criteria may be used

- *6. At least 1 episode/week of incontinence after the acquisition of toileting skills*
- *7. History of large diameter stools which may obstruct the toilet*

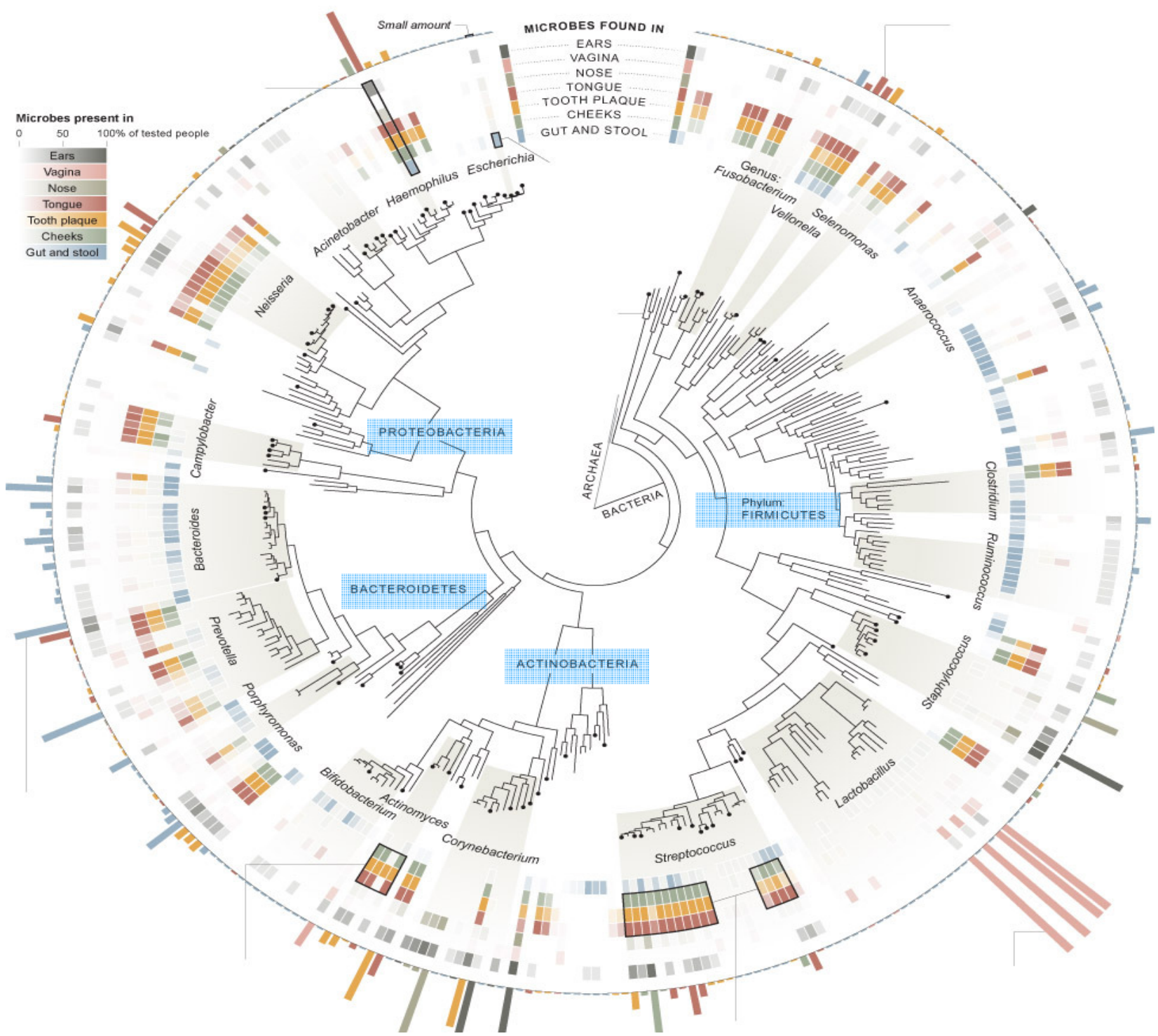
Prevalence of chronic idiopathic constipation according to country



Suares NC & Ford AC, Am J Gastroenterol 2011



Mugie SM, et al. Best Pract & Res Clin Gastroenterol 2011



Rationale for the use of prebiotics in constipation

- **Nonstarch polysaccharides or other substance supplements poorly digested by human enzymes that nurture probiotic organisms**
 - **Fructo-oligosaccharides / Inulin / Galacto-, galactosyllactose-, xylo-, isomalto and soya oligosaccharides / Pyrodextrins (glucose oligosaccharides) / Lactulose / Breast milk oligosaccharides**
- **Promote growth of bifido-and lactobacilli**
- **Lower colon pH**

Rationale for the use of probiotics

- **Differences in the intestinal microbiota in healthy and constipated subjects**
 - ↓ bifidobacteria
 - ↑ non-pathogenic *E coli*, bacteroides
 - ↑ total number of microorganisms
- **Improved transit time**
 - Several studies involving *B. animalis* DN 173 010

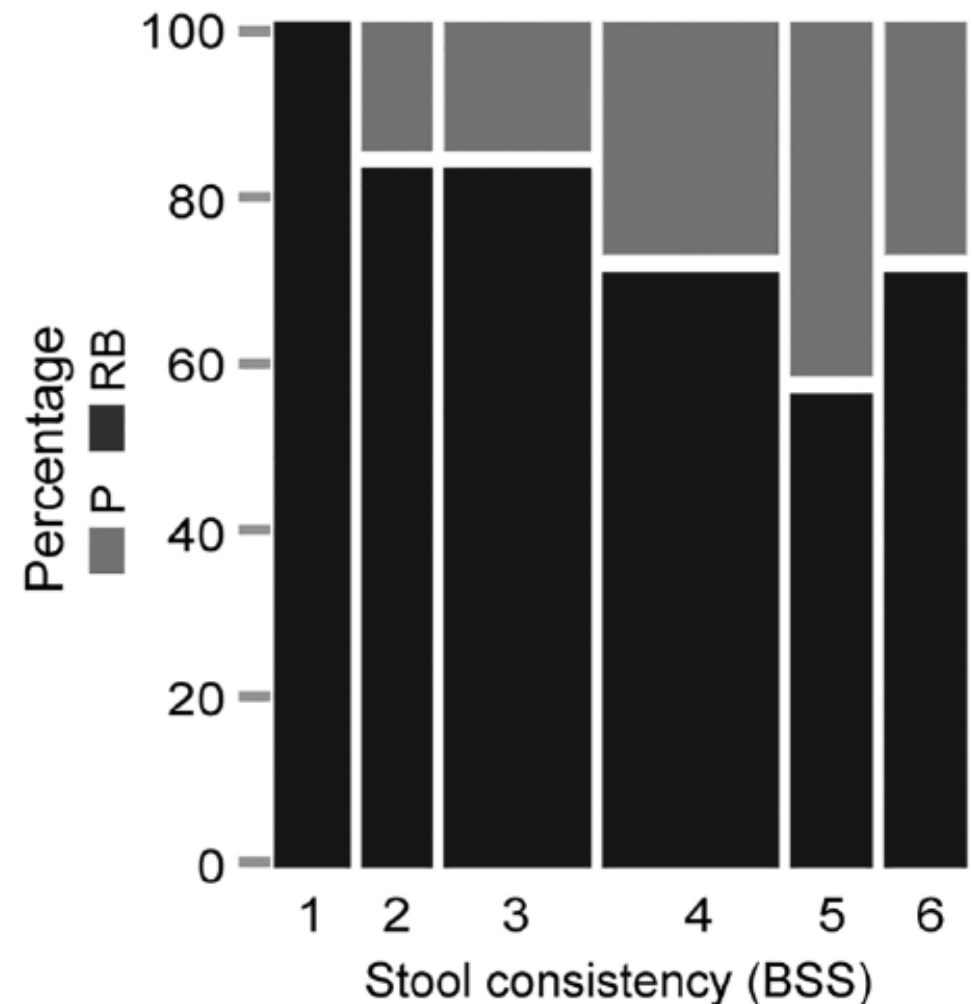
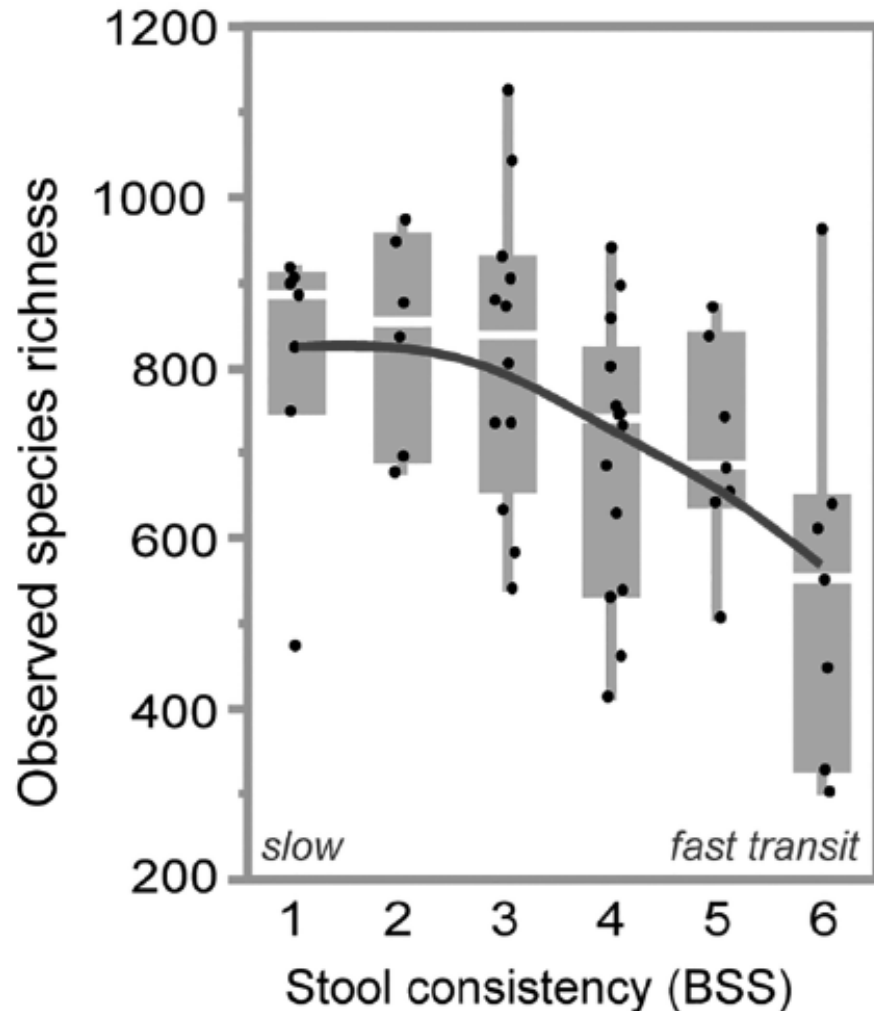
Zoppi, et al. Acta Paediatr 1998

Salminen, et al. Scand J Gastro 1997

Picard, et al. Aliment Pharmacol Ther 2005

Stool consistency is strongly associated with gut microbiota richness and composition, enterotypes and bacterial growth rates

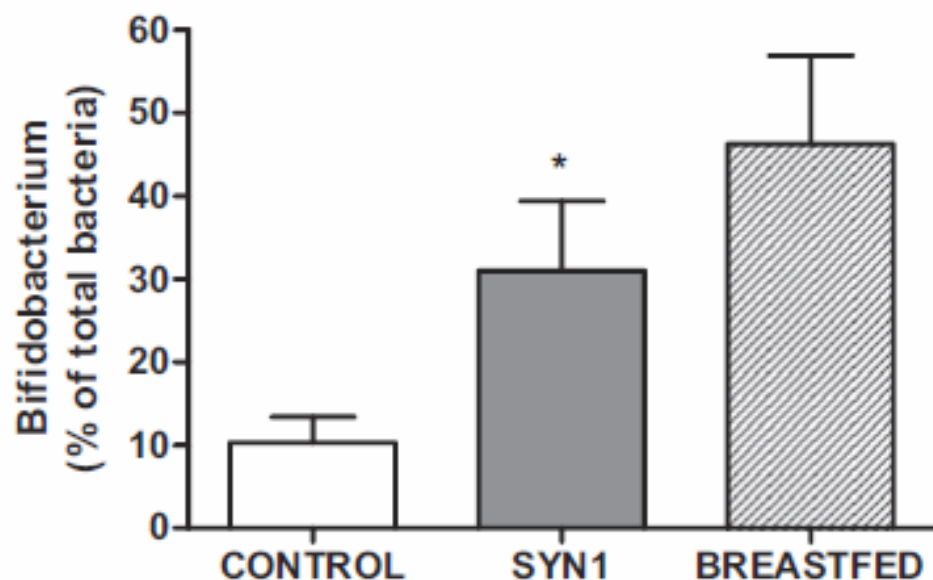
P = Prevotella, RB = Ruminococcaceae-Bacteroides



Safety and efficacy of inulin and oligofructose supplementation in infant formula: Results from a RCT

- **252 formula fed infants were randomized at birth:**
- **124 controls, 128 supplementation formula and 131 BF infants; after 4 months 68 controls, 63 supplementation and 57 BF completed the study**

Safety and efficacy of inulin and oligofructose supplementation in infant formula: Results from a RCT

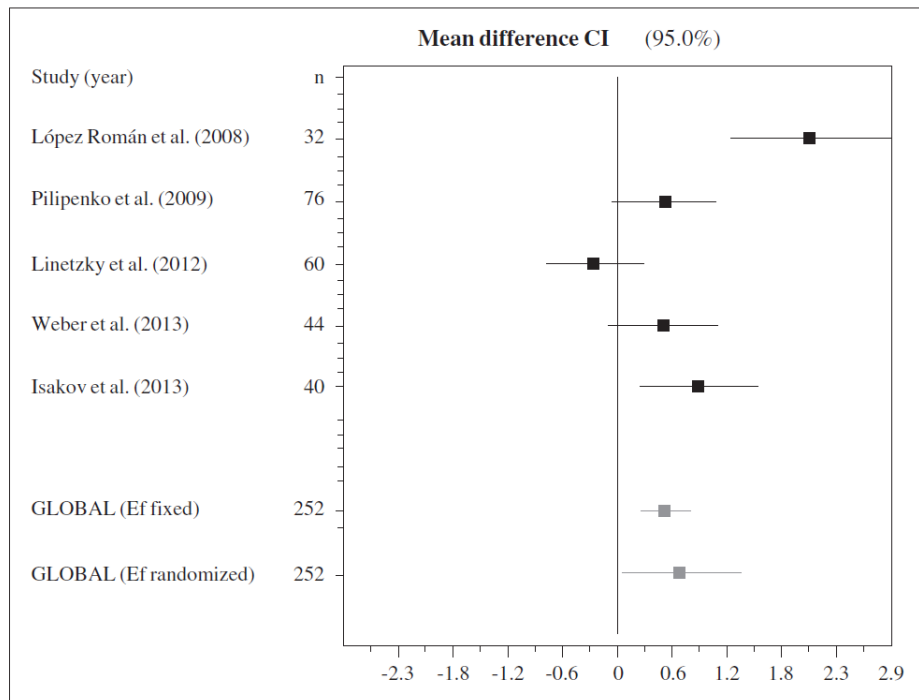


Stool frequency and consistency by feeding groups (mean of 2-days diary).

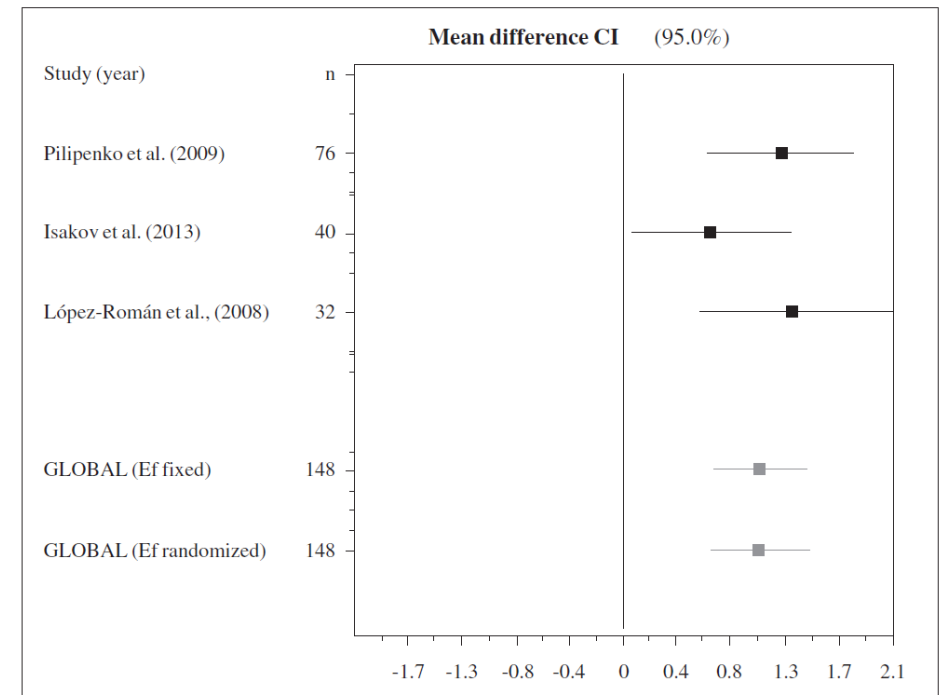
	Control ^a	SYN1 ^b	Breastfed
	Median (IQR)	Median (IQR)	Median (IQR)
MONTH 1			
Stool frequency (n/day)	2.5 (2.0, 4.0)	4.0 (2.5, 5.1) ^{***}	5.0 (2.5, 7.0)
Stool consistency score (1–7)	6.0 (4.7, 6.0)	6.0 (6.0, 6.0) ^{***}	6.3 (6.0, 7.0)
MONTH 2			
Stool frequency (n/day)	2.0 (1.5, 3.0)	2.5 (2.0, 3.5) ^{**}	3.0 (1.5, 5.0)
Stool consistency score (1–7)	6.0 (4.3, 6.0)	6.0 (6.0, 6.0) ^{****}	6.8 (6.0, 7.0)
MONTH 3			
Stool frequency (n/day)	2.0 (1.5, 2.5)	2.5 (1.5, 3.0) ^{**}	2.0 (1.0, 4.0)
Stool consistency score (1–7)	6.0 (4.0, 6.0)	6.0 (6.0, 6.0) ^{***}	6.5 (6.0, 7.0)
MONTH 4			
Stool frequency (n/day)	2.0 (1.5, 2.5)	2.5 (1.5, 3.0) [*]	1.5 (1.0, 3.0)
Stool consistency score (1–7)	6.0 (4.0, 6.0)	6.0 (6.0, 6.0) ^{***}	6.5 (6.0, 7.0)

Effectiveness of inulin intake on indicators of chronic constipation; a meta-analysis of controlled randomized clinical trials

Defecation frequency



Stool consistency

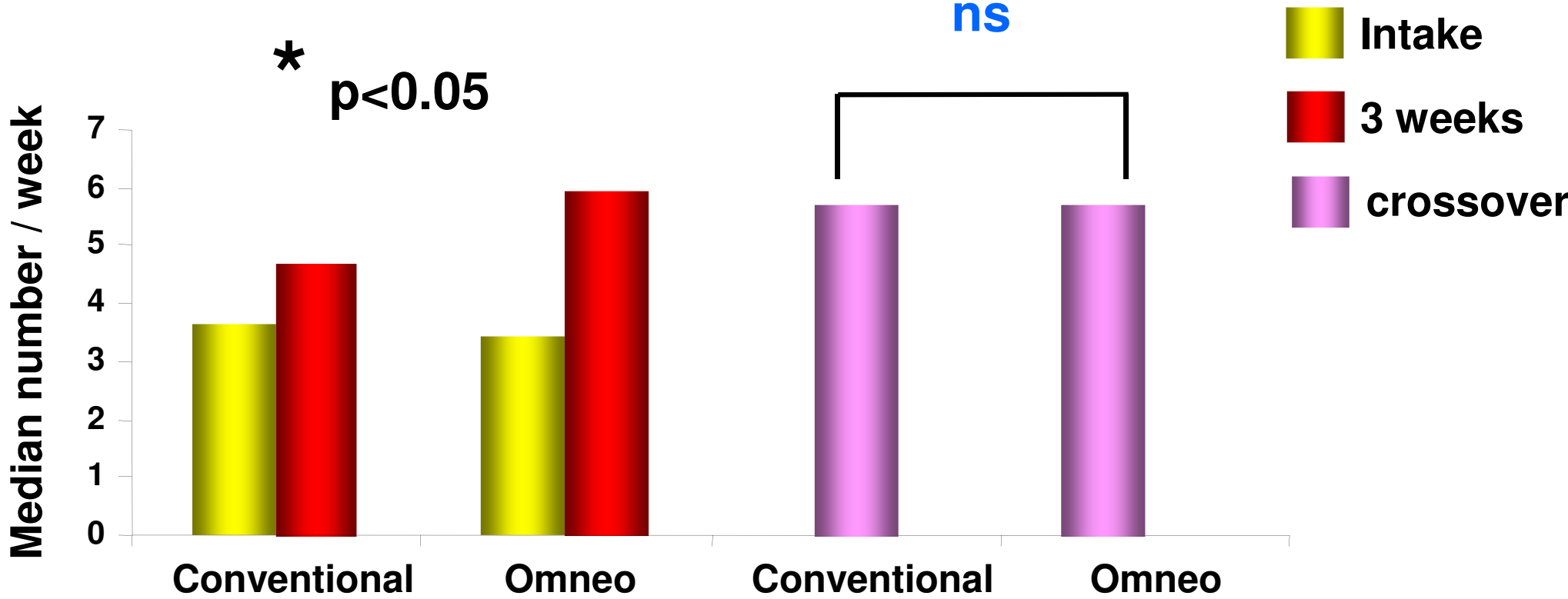


The clinical effect of a new infant formula in term infants with constipation: a double-blind, cross-over trial

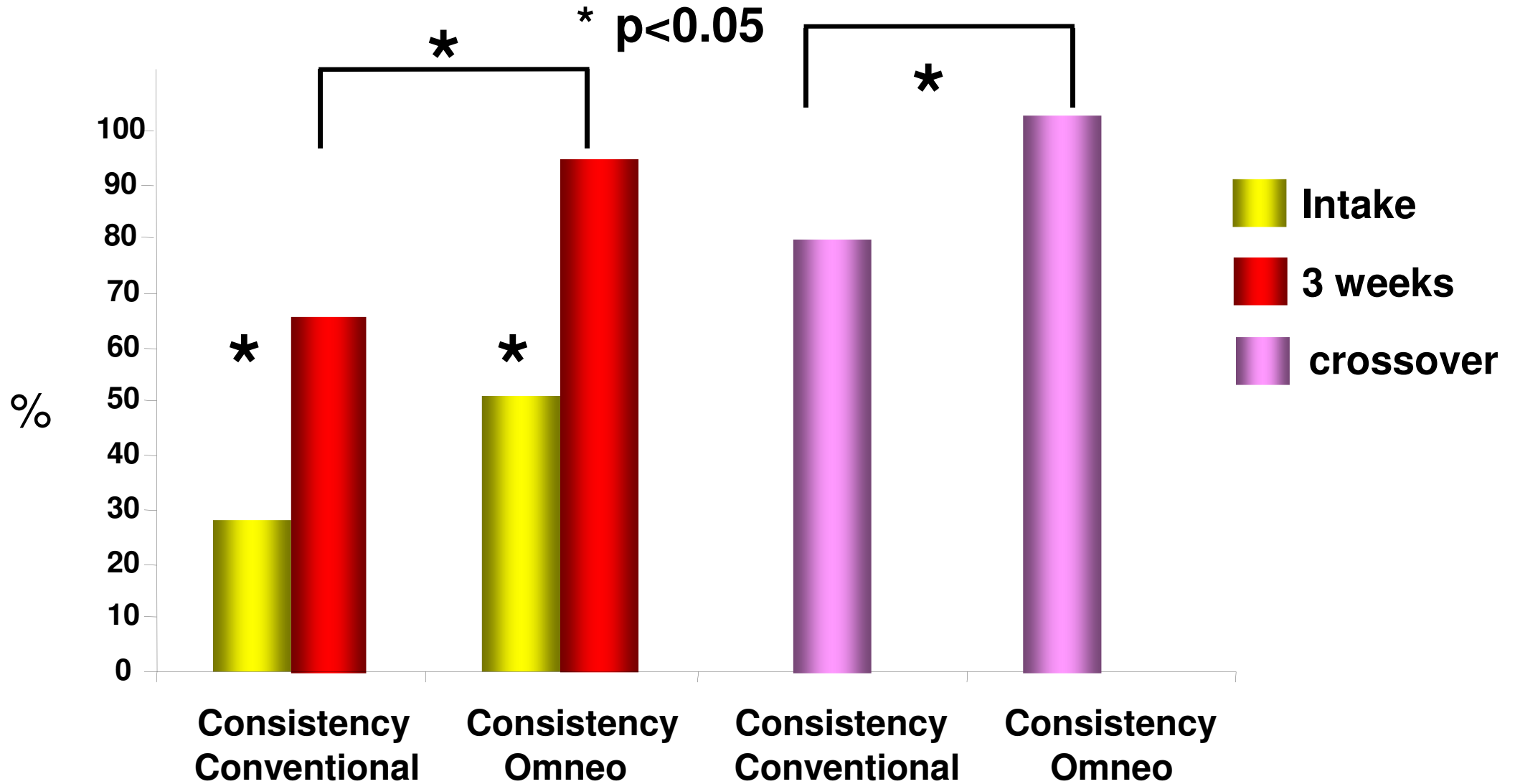
- **High β -palmitic acid level**
- **Non digestible oligosaccharides (GOS and FOS)**
- **N = 38**
- **Only 24 completed the study**

Conventional versus N. Omneo

N = 35



Conventional versus N. Omneo



Conclusions

- **Infant formula containing high proportion of *sn*-2 palmitic acid and prebiotic oligosaccharides resulted in softer stools, but not in a difference in stool frequency**
- **Formula transition to this new formula can be considered as initial treatment step in constipated infants with *hard stools***

Probiotic Supplement Use among Young Children in Taiwan: A Prospective Cohort Study (n = 17.000)

- **~ 50% received probiotic supplements < of 18 months**
- **Firstborn children, native mothers, mothers with higher educational levels, higher family income, and parents who lead healthy lifestyles were positively related to probiotic supplement use among children**
- **Young children who were breastfed, with eczema, or with gastrointestinal tract problems were significantly positively associated with probiotic supplement use**

Maternal use of probiotics during pregnancy (N = 2500) and effects on their offspring's health in an unselected population

- **341 mothers (13.7%) used probiotics during pregnancy**

Consumption of probiotics was significantly associated with:

- **Use of homeopathic products**
- **Maternal history of smoking**
- **Paternal history of smoking**
- **Common disease symptoms during first year of life in the offspring did not differ between both groups**

Prophylactic Use of a Probiotic in the Prevention of colic regurgitation, and Functional Constipation: A RCT

- **589 infants were randomly allocated to receive *L reuteri* DSM 17938 or placebo daily for 90 days**
- **At 3 months of age,**
 - **mean duration of crying time (38 vs 71 minutes; $P < .01$)**
 - mean number of regurgitations per day (2.9 vs 4.6; $P < .01$),**
 - mean number of evacuations per day (4.2 vs 3.6; $P < .01$)**
- **Estimated mean savings per patient of \$118.71 for the family and an additional \$140.30) for the community**

Tolerance and safety of *L. paracasei* ssp. *paracasei* in combination with *B. animalis* ssp. *lactis* in an infant formula: a RCT

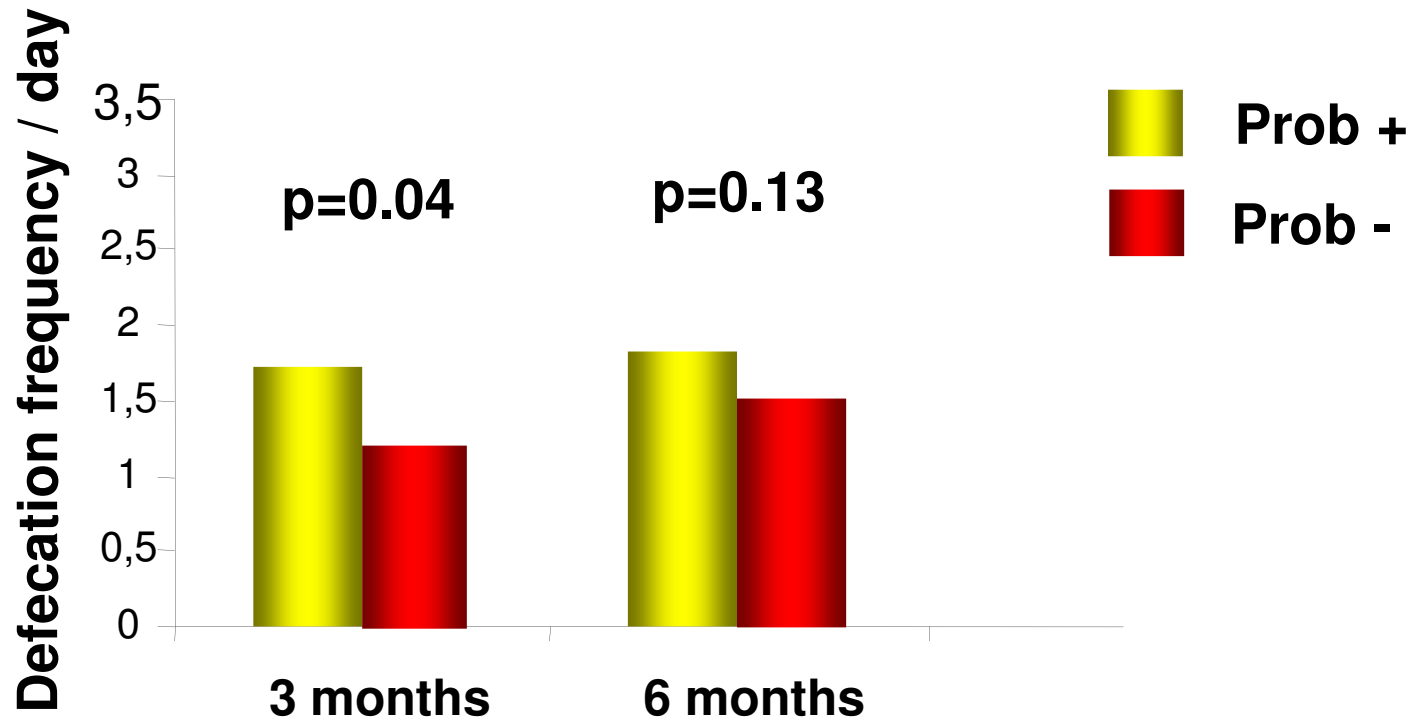
- **126 new borns**
- **RCT:**
 - **Starter formula + *L. paracasei* ssp. *Paracasei* Lactis (1×10^7 CFU /g) and *B. animalis* ssp. *Lactis* (1×10^7 CFU /g)**
 - **Starter formula without probiotics**
- **3 months**

Results

- Normal growths in all infants
- **No difference** between the 2 groups with respect to:
 - gain in weight, length and head circumference
- **No difference** between the 2 groups with respect to:
 - crying and sleeping hours, number of infections, AB use, visits to the general practitioner and number of adverse events

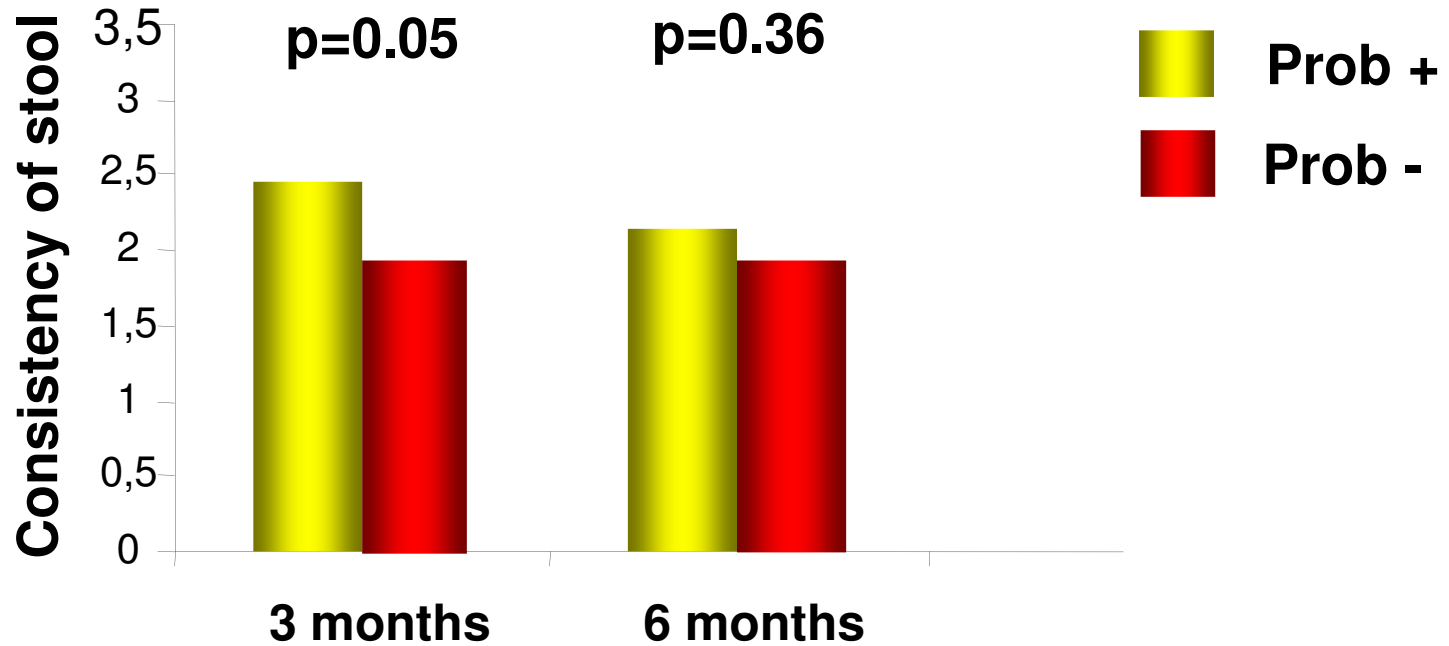
Results

N = 126

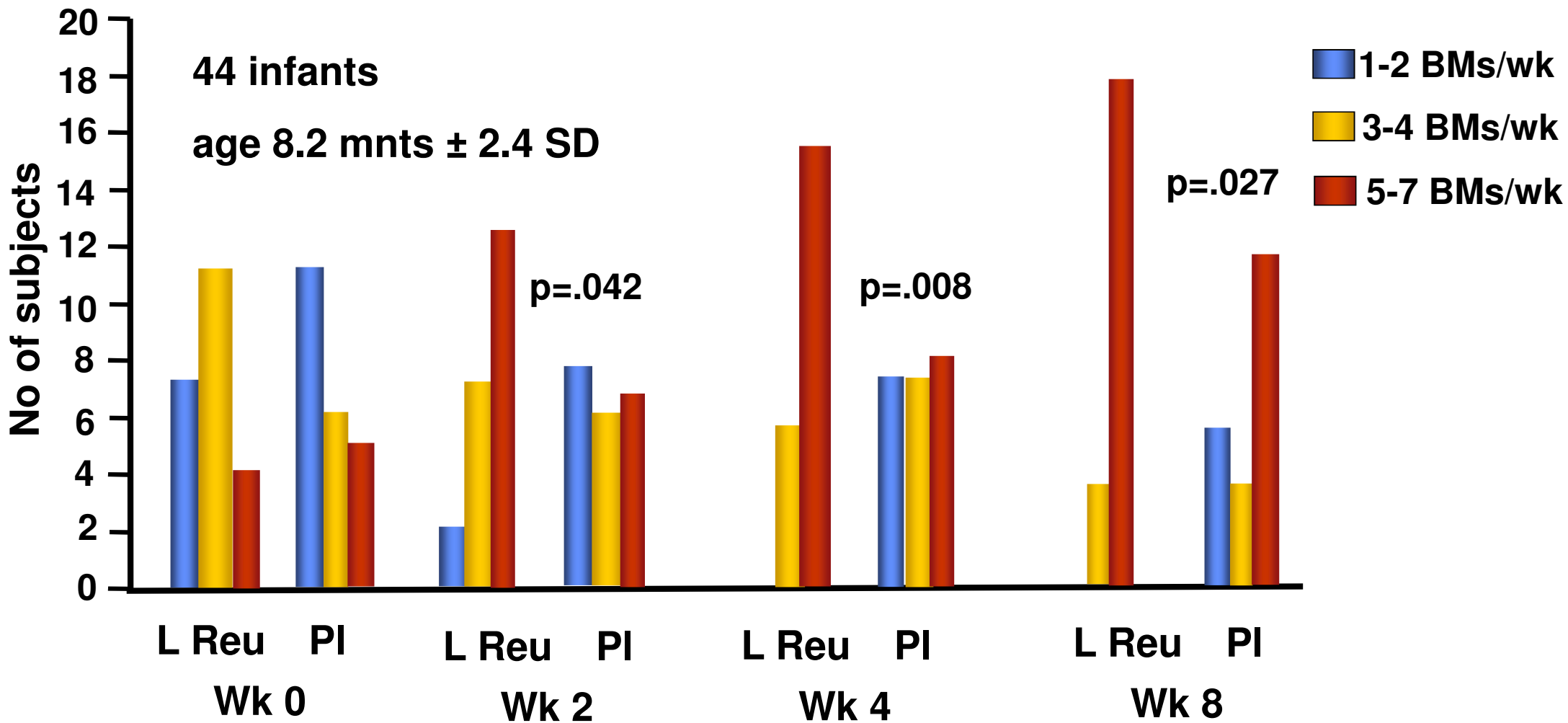


Results

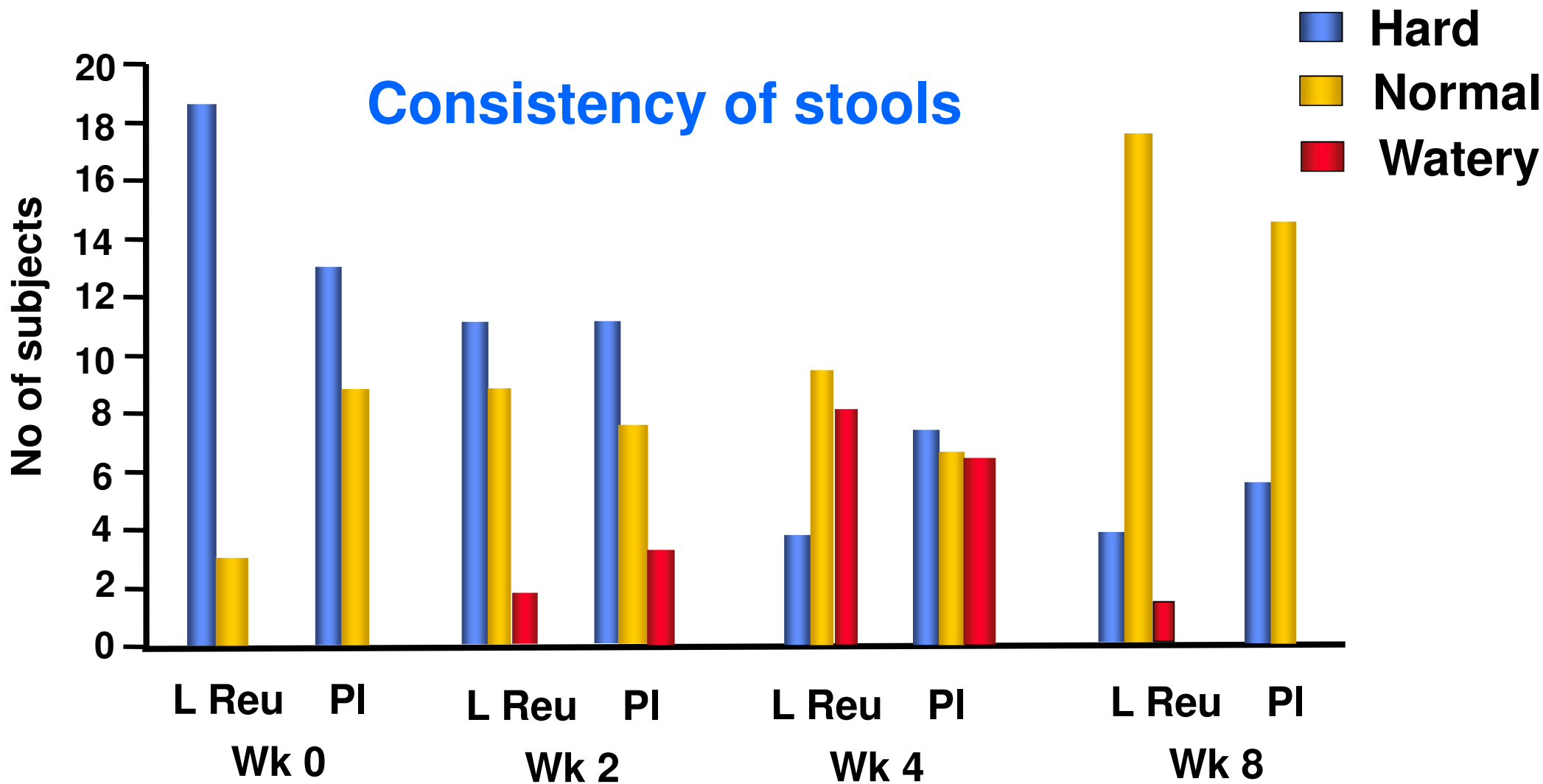
N = 126



Lactobacillus Reuteri and constipation: DBRPCT

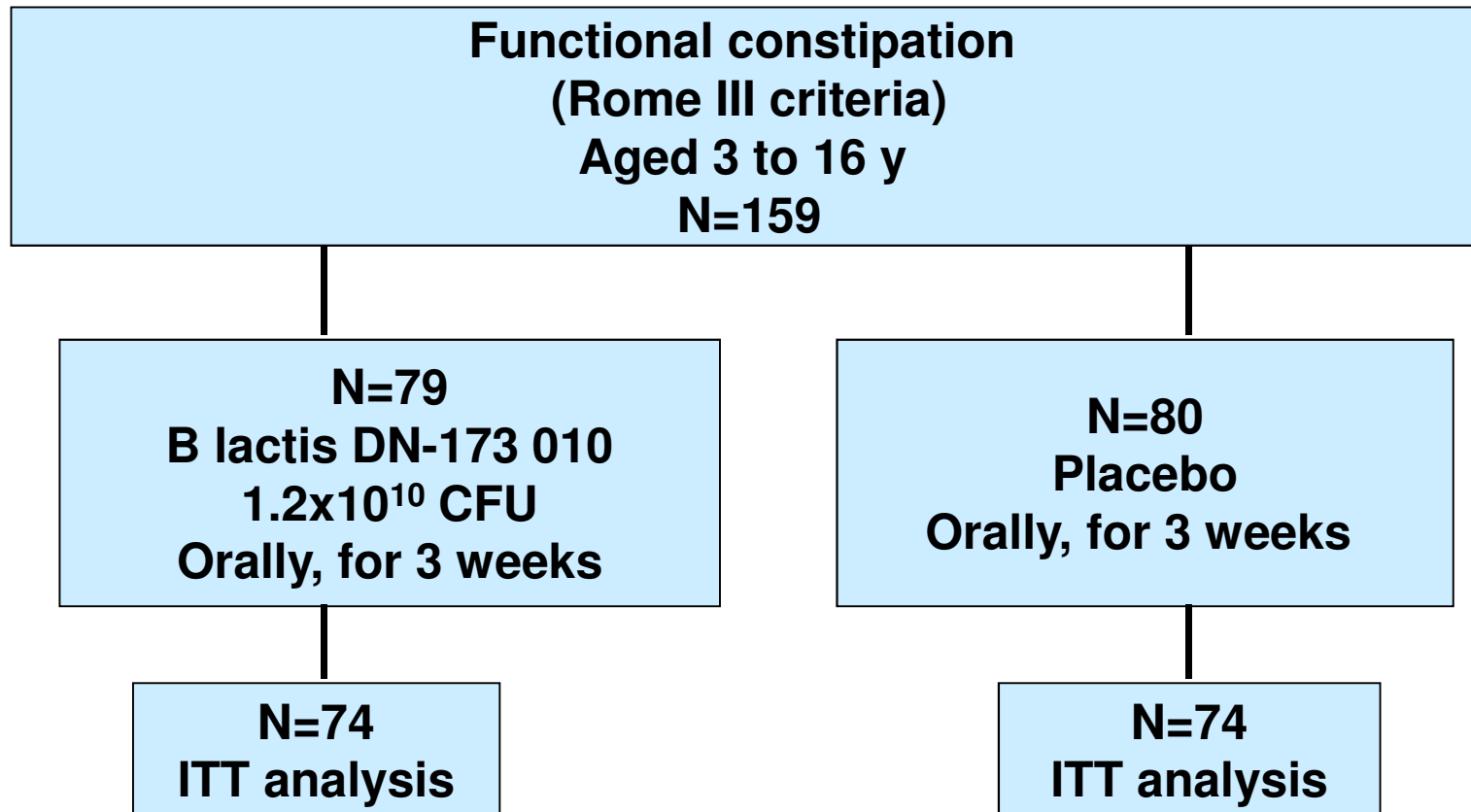


Lactobacillus Reuteri and constipation: DBRPCT



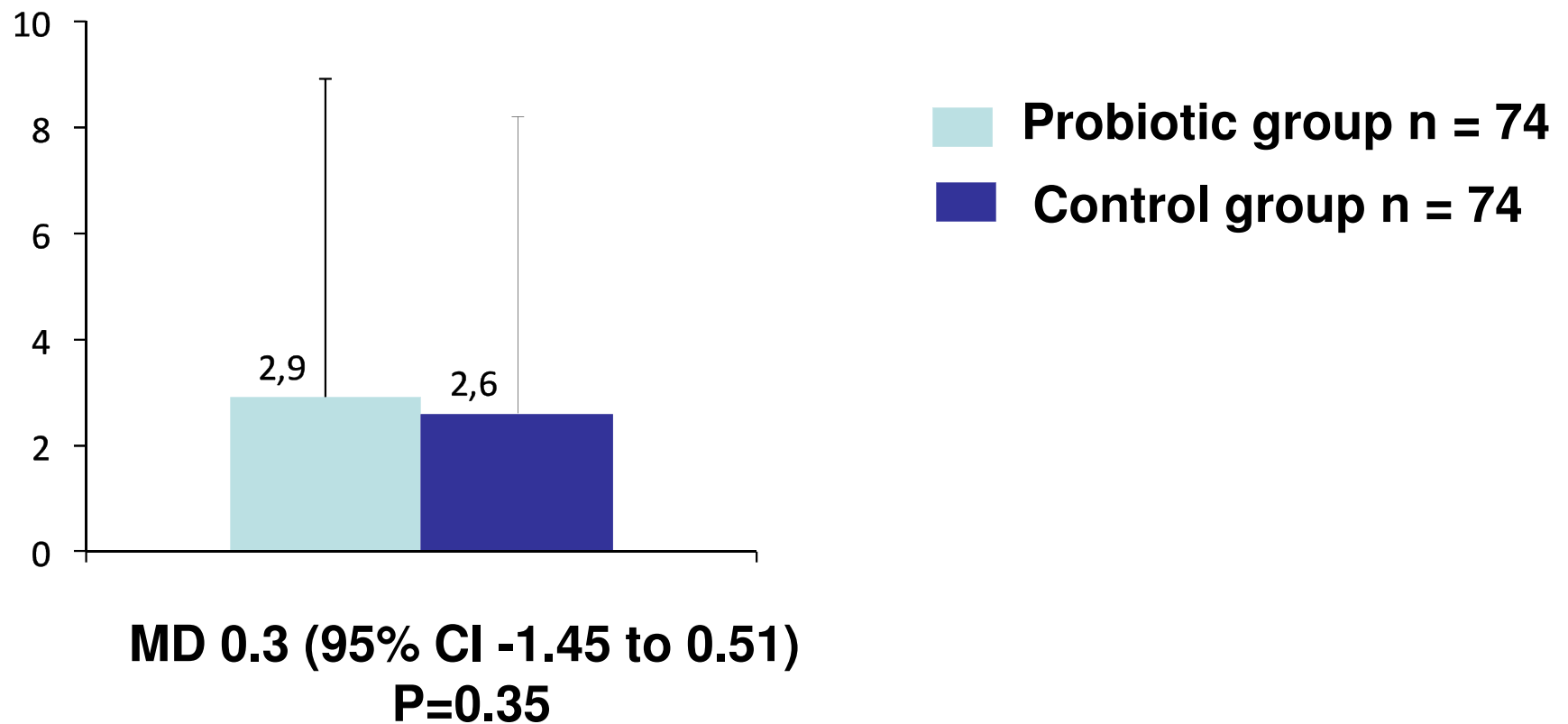
Functional constipation in children

B lactis DN 173010



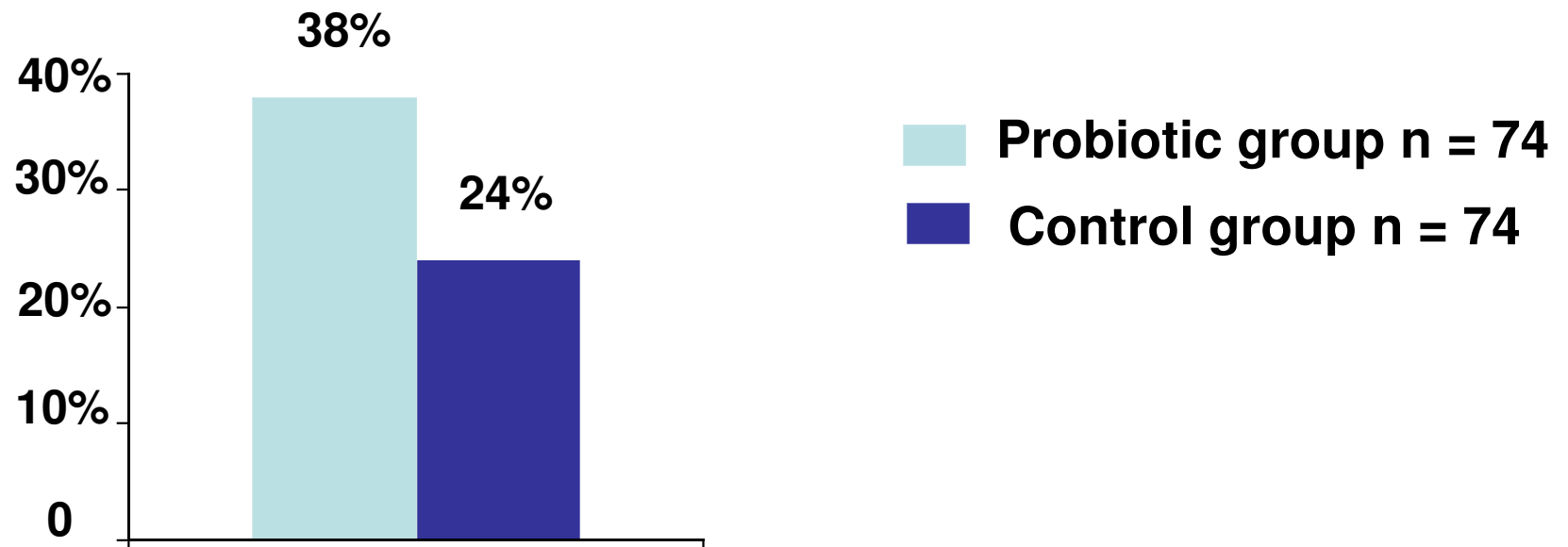
Primary outcome

The change in stool frequency from baseline to after 3 wk of product consumption



Secondary outcome Success rate

≥ 3 BM per wk and < 1 fecal incontinence episodes in 2 wk



RR 1.6 (95% CI 0.97 to 2.7)
P=0.06

Probiotics for functional constipation

RCTs in children - summary

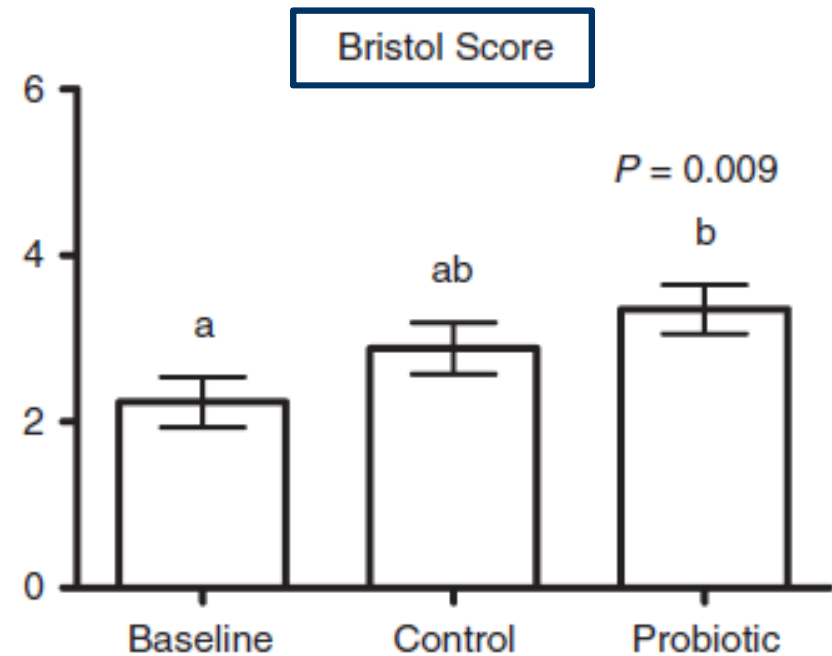
Reference	Probiotic	Constipation	N	Effect
Banaszkiewicz & Szajewska 2005	LGG	<3 BM per wk for at least 12 wk	60	NS
Bu et al. 2007	L casei rhamnosus Lcr35	<3 BM per wk for >2 mo	27	√ (?)
Coccorullo et al. 2010	L reuteri DSM 17938	Rome III criteria	44	√
Tabbers et al. 2011	B lactis DN 173010	Rome III criteria	160	NS
Guerra et al. 2011	B longum	Rome III criteria	59	√

Total

350

Promising foods....

- 20 pts consumed 180 g per day of ordinary artichokes or artichokes enriched with *L. paracasei* IMPC 2.1 for 15 days (daily dose of 2×10^{10} CFU)

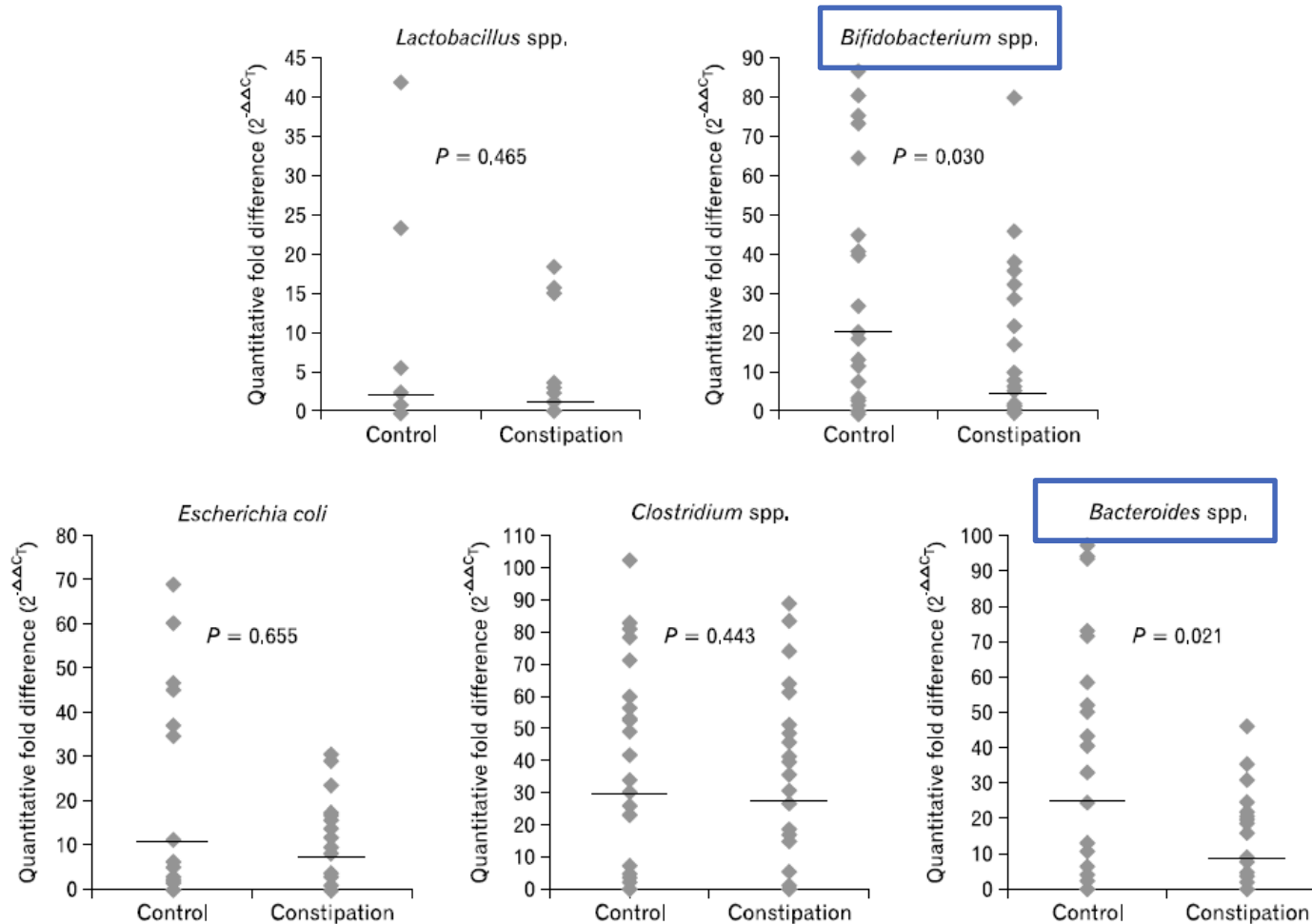


Riezzo G, et al. Aliment Pharmacol Ther 2013

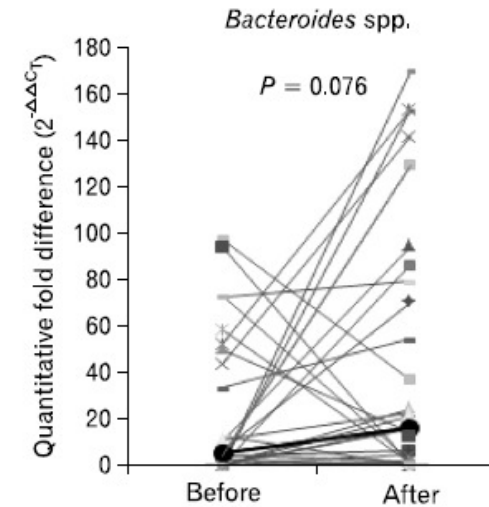
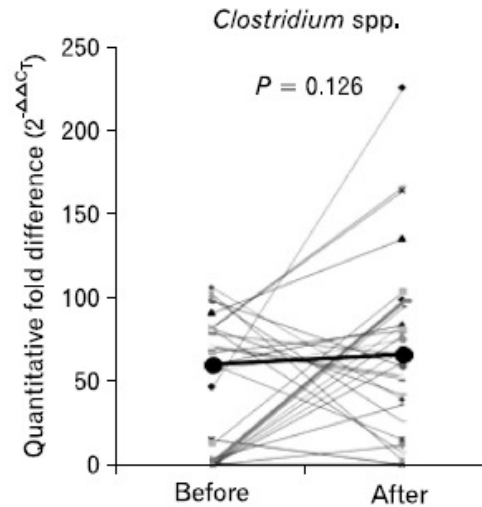
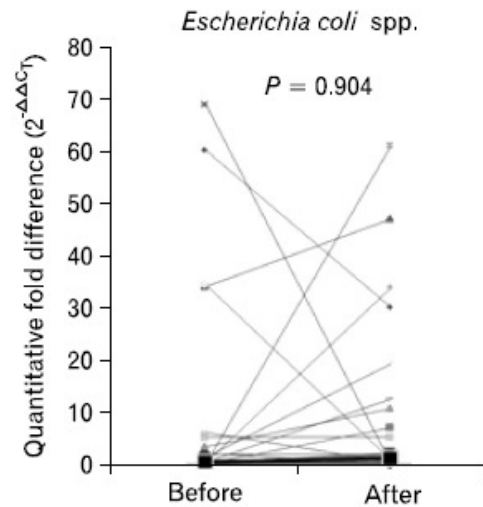
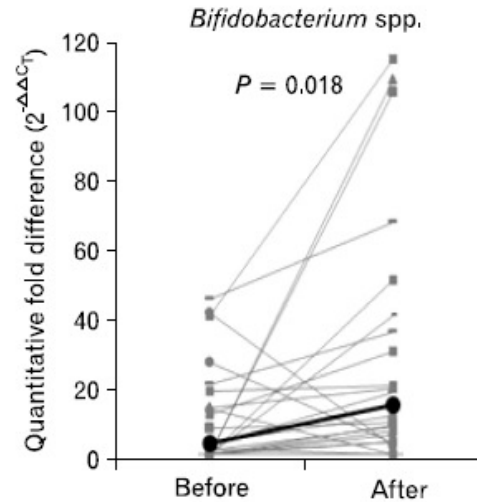
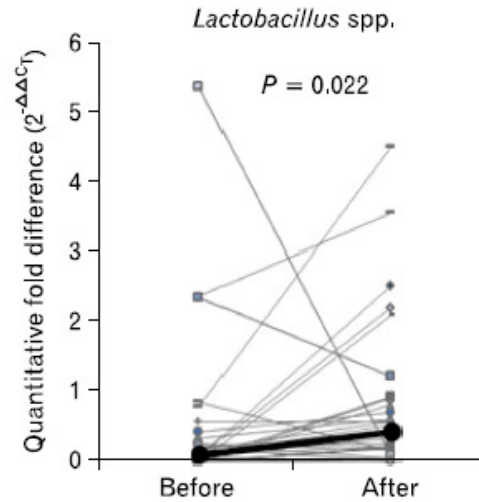
Change of Fecal Flora and Effectiveness of the Short-term VSL#3 Probiotic Treatment in Patients With Functional Constipation

- 30 pts fulfilling Rome III criteria for FC and 30 controls were enrolled
- Fecal samples were obtained before and after VSL#3 intake (one sachet twice daily for 2 weeks)
 - VSL#3 sachet contains 450 billion lyophilized bacteria: *Bifidobacterium* (*B. longum*, *B. infantis* and *B. breve*); *Lactobacillus* (*L. acidophilus*, *L. casei*, *L. bulgaricus*, and *L. plantarum*); and *Streptococcus thermophilus*
- Flora examined by quantitative real-time polymerase reaction

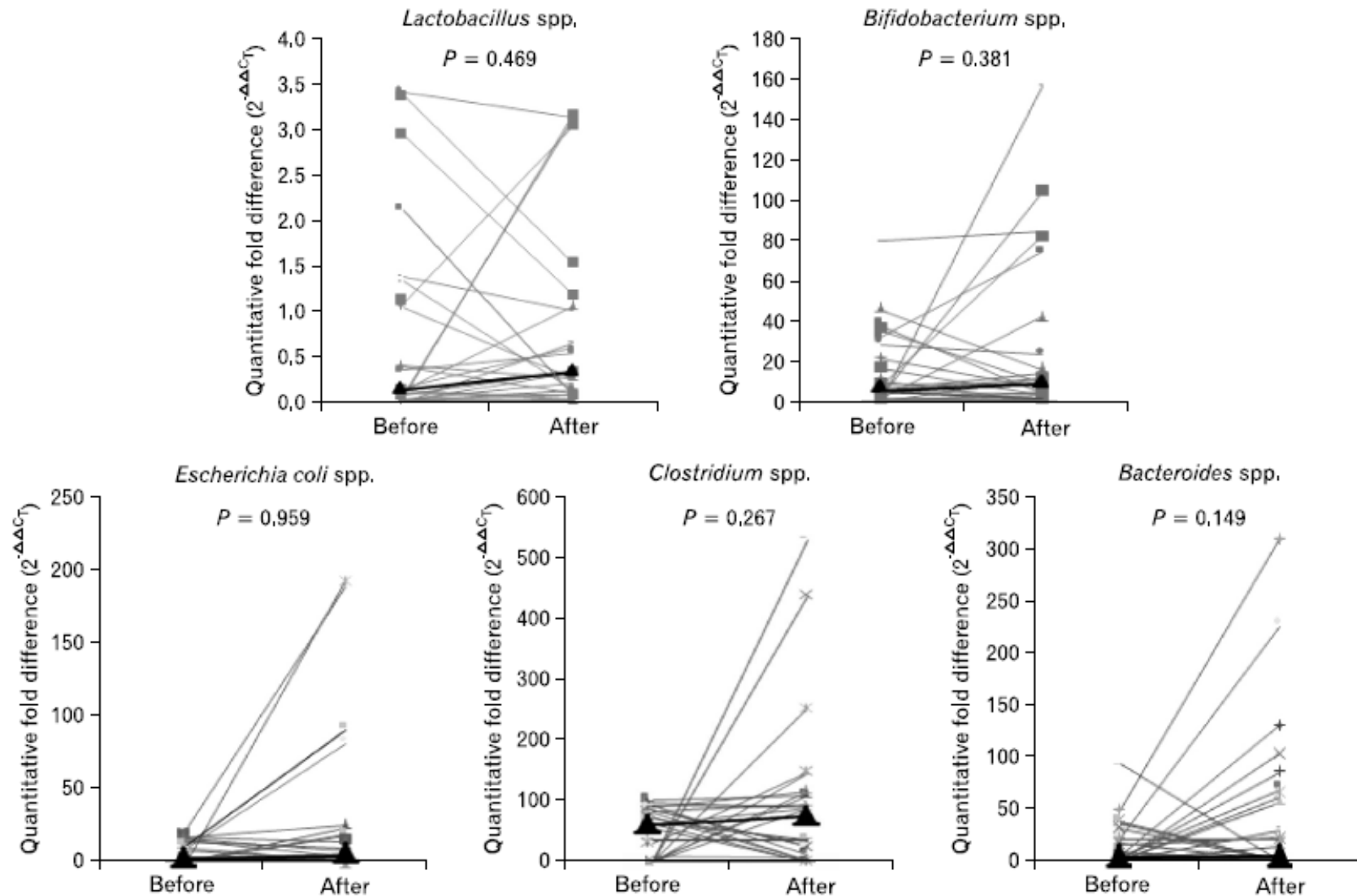
Comparison of fold differences in concentrations of gut flora between functional constipation patients and controls



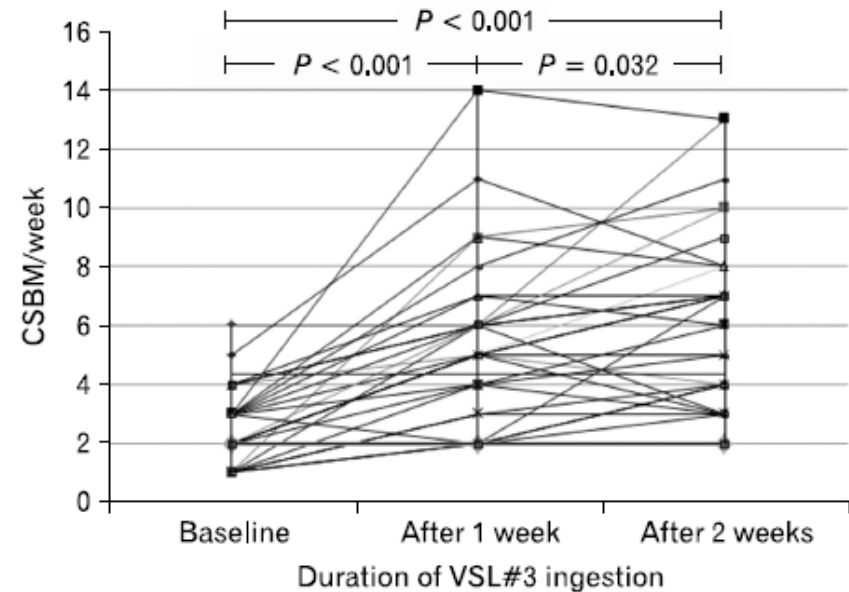
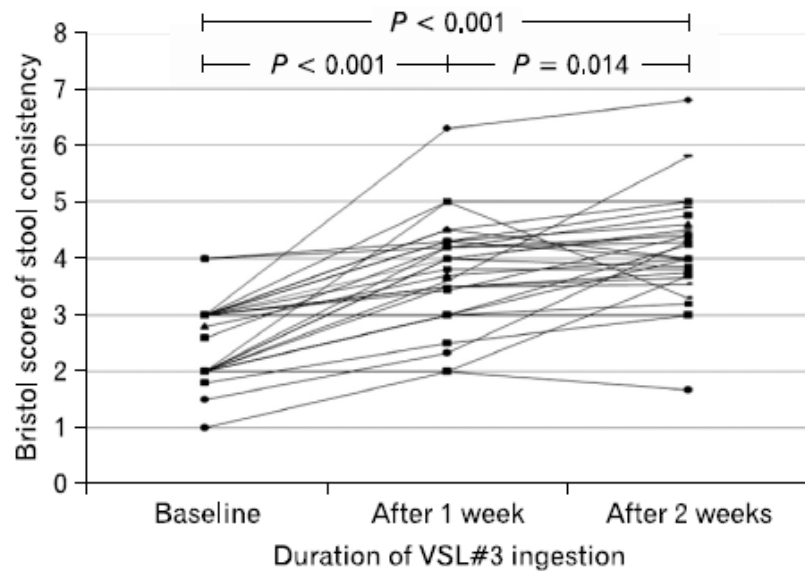
Fold differences in each bacterial gene expression; healthy controls



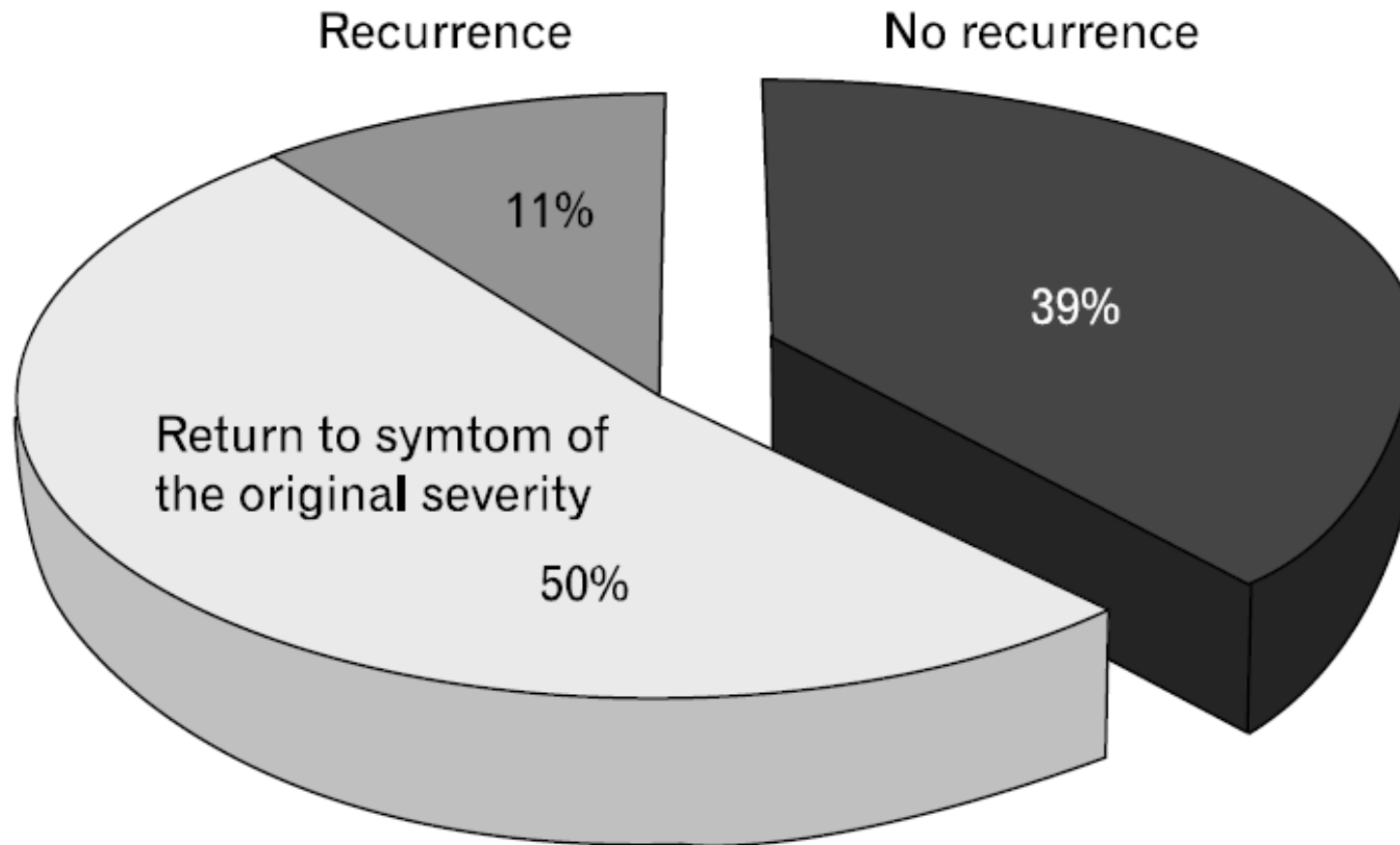
Fold differences in each bacterial gene expression; constipated patients



Bristol stool scale and mean complete spontaneous bowel movement before and after VSL#3



After the VSL#3 ingestion period ended

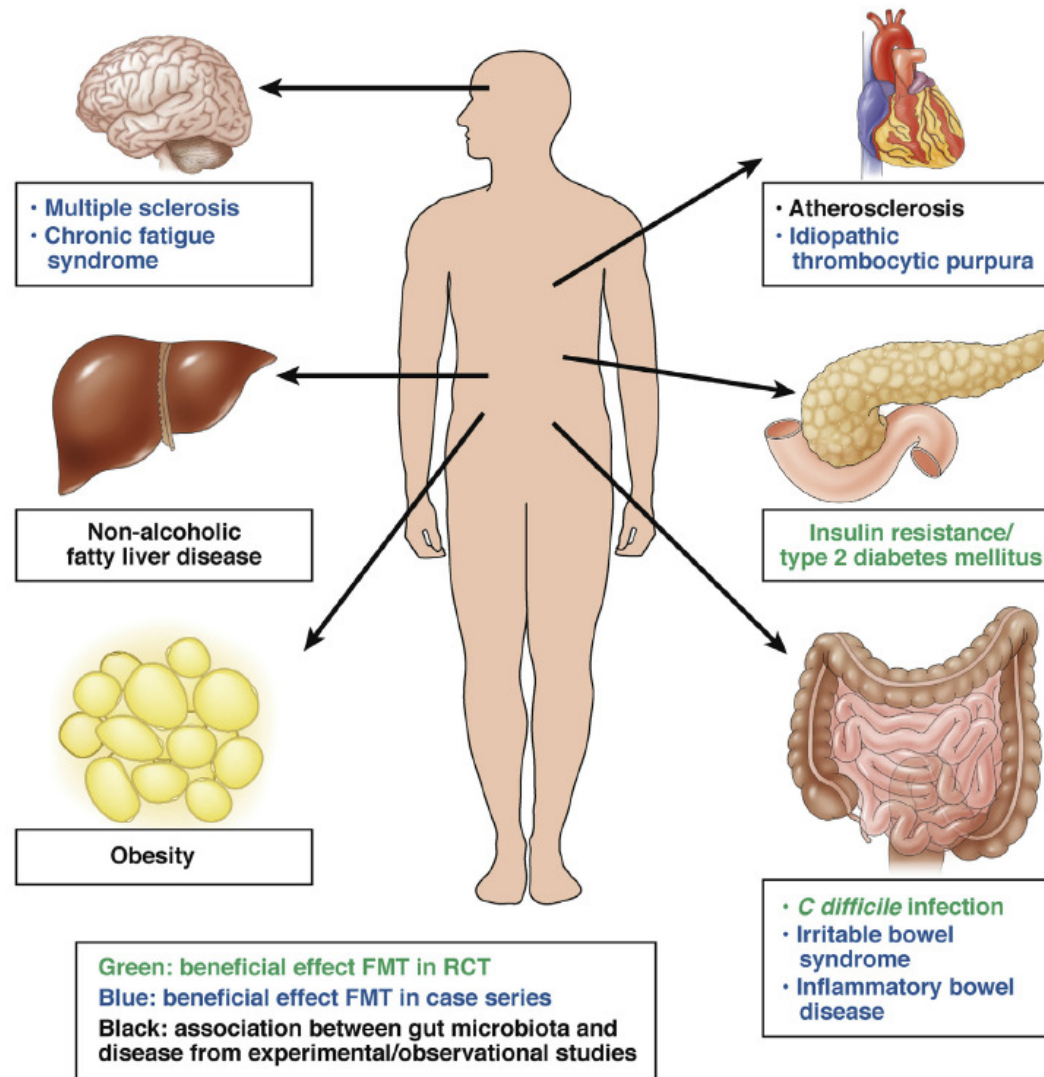


Role of Synbiotics in the Treatment of Childhood Constipation: A Double-Blind Randomized Placebo Controlled Trial

- 102 children, 4-12 yrs of age, Rome III criteria
- Group A, received 1.5 ml/kg/day oral liquid paraffin +placebo
- Group B, 1 sachet synbiotic/day + placebo
- Group C, 1.5 ml/kg/day oral liquid paraffin + 1 sachet synbiotic/day
- Protexin CO, UK 1x10⁹ CFU/1 sachet:
 - Combination of probiotic strains: *L. casei*, *L. rhamnosus*, *S. thermophilus*, *B. breve*, *L. acidophilus*, *B. infantis* and fructooligosaccharide as prebiotic

Characteristic	Liquid paraffin + Placebo	Synbiotics + Placebo	Liquid paraffin + Synbiotics	P value
No of patients at randomization (%)	29 (29.9)	31 (32.0)	37 (38.1)	--
No. of encopresis per week pretreatment (\pmSD)	2.34 (\pm 4.9)	2.68 (\pm 4.7)	0.92 (\pm 2.9)	0.208
No. of Encopresis per week after treatment (\pmSD)	0.24 (\pm 1.3)	0.06 (\pm 0.25)	0.0 (\pm 0.0)	0.317
No. of patients with abdominal pain pretreatment (%)	17 (58.6)	21 (67.6)	24 (64.9)	0.754
No. of patients with abdominal pain after treatment (%)	4 (13.8)	2 (6.5)	5 (13.5)	0.582
No. of patients with side effects (seepage) (%)	18 (62.1)	0 (0)	21 (56.8)	< 0.001
No. of patients with successful treatment (%)	24/29 (82.8)	22/31 (71.0)	28/37 (75.7)	0.559

Therapeutic Potential of Fecal Microbiota Transplantation



Treatment of Slow Transit Constipation With Fecal Microbiota Transplantation; A Pilot Study

- **20 pts, Rome III-constipation not responsive to conventional treatment including biofeedback training**
- **Received FMT on 3 consecutive days through nasojejunal tube and followed up for 12 weeks after treatment**

Treatment of Slow Transit Constipation With Fecal Microbiota Transplantation; A Pilot Study

Clinical remission rate (%)	1 wk	66.7% (16/24)
	2 wk	62.5% (15/24)
	4 wk	62.5% (15/24)
	8 wk	50% (12/24)
	12 wk	37.5% (9/24)
	Stool consistency score‡	Pre-FMT
1 wk		3.1 ± 0.6*
2 wk		3.8 ± 1.1*
4 wk		3.6 ± 2.1*
8 wk		3.5 ± 2.3*
12 wk		3.1 ± 2.4*
No. bowel movement per week‡		Pre-FMT
	1 wk	3.1 ± 2.2*
	2 wk	4.1 ± 2.0*
	4 wk	4.7 ± 2.2*
	8 wk	4.5 ± 1.4*
	12 wk	4.1 ± 2.6*

Treatment of Slow Transit Constipation With Fecal Microbiota Transplantation; A Pilot Study

- **Adverse effects; diarrhea, bloating, abdominal pain**

Summary & Conclusions

- **Knowledge is lacking regarding the microbiota composition of children with constipation**
- **The addition of prebiotics/probiotics in infant formula is safe and softens stool**
- **Inulin seems to be effective in adults with constipation, trials in children with constipation are lacking**
- **Inconsistent data exist regarding the efficacy of probiotics in children with constipation**
- **Future studies to determine whether therapeutic strategies aimed at restoration of observed microbial dysbalance are beneficial**