Challenges and Controversies of manipulating the Microbiome

The role of pre- and probiotics

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2016

Overview

The Microbiome - definition and development
- in health and disease

Challenges in evaluating the microbiome

Dysbiosis and spectrum of associated diseases

Manipulation of the microbiome

Effects of pre- and probiotics on microbiome:
- in health
- in IBS

Gut Microbiota in ‘Health’

1000 species, >7000 strains (biodiversity)

10 bacteria:1 human cell

>99% anaerobic

Individualised, stable enterotype

‘Core microbiome’

Microbiome gradient

Stomach

10^{1-2}

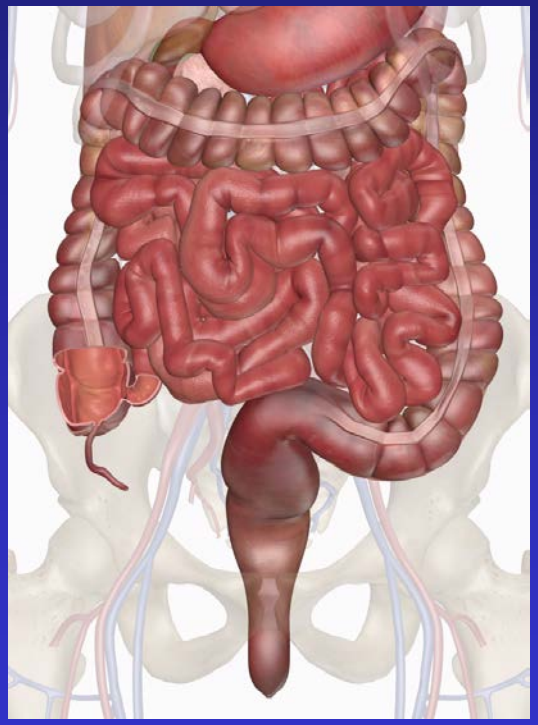
Lactobacilli
Streptococci
Proteobacteria
(H.Pylori)

Small Bowel

10^{4} Jej

10^{7} ileum

Lactobacilli
Streptococci



Large Bowel

10^{9-12}

Enterobacter
S. Faecalis
Bacteroides
Bifidobacteria
Lactobacilli
Clostridia
Peptostreptococcus

Microbiome development

Maternal microbiome

Antibiotics

Mode of delivery at birth

Infections early in life

Breast vs formula feeding

Siblings

Nutritional status

Pets

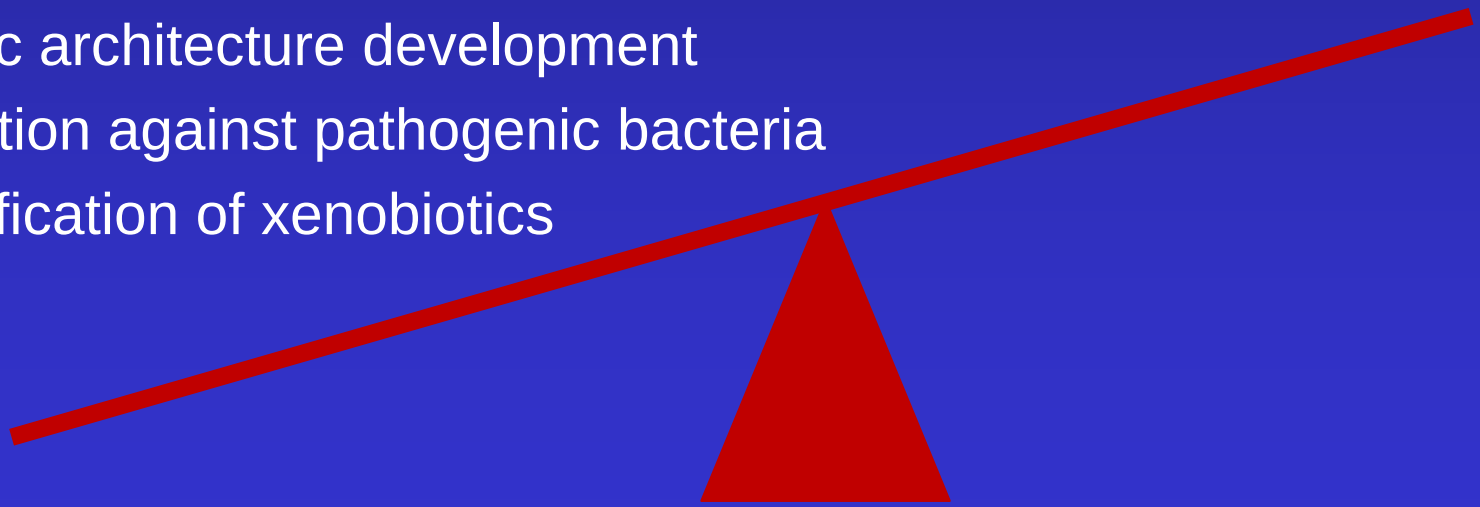
Early years environment

Role of microbiome

Bile acid metabolism
Vitamin synthesis
Brain-gut functioning
Digestion of complex CH2O
Immune system development
Colonic architecture development
Protection against pathogenic bacteria
Detoxification of xenobiotics

Role of Host

Habitat
Nutrient source



Dysbiosis: spectrum of disease association

Disorders of mood

Neurological conditions

Cancer

Obesity

Diabetes

Inflammatory bowel disease

Atherosclerosis

Enteric infection

Hepatic encephalopathy

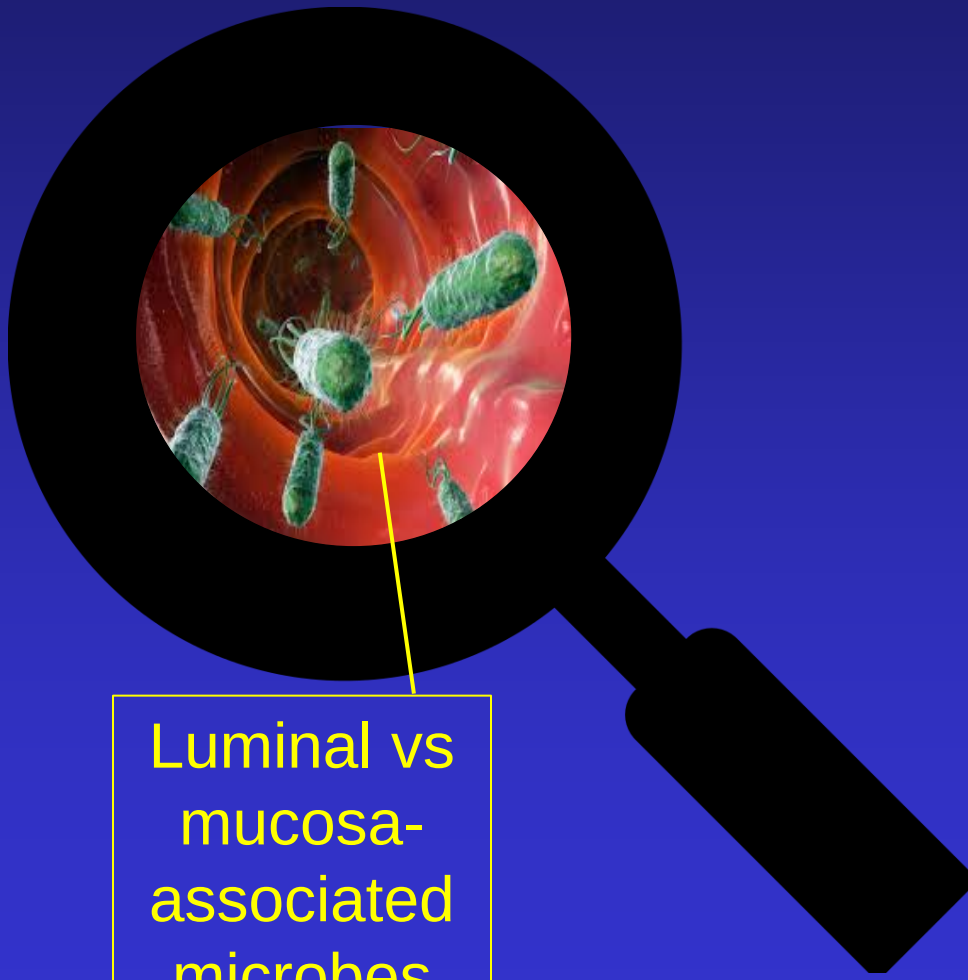
Irritable bowel syndrome

Allergy

Auto-immune diseases

Challenges in microbiome profiling

Bacterial gradient, diversity along the gut



Luminal vs mucosa-associated microbes

Microbiome profiling

: culture of organisms

: laborious

: inability to ID majority of bacteria

Microbiome profiling

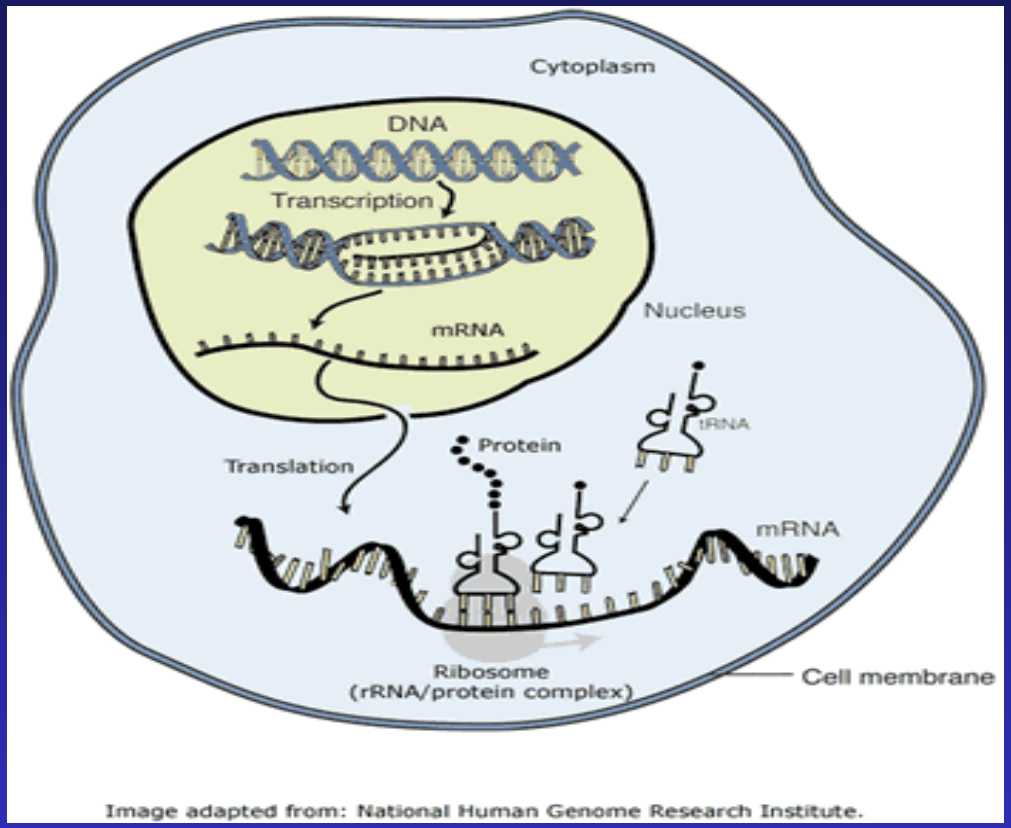


Image adapted from: National Human Genome Research Institute.

DNA
-genomics

mRNA
- transcriptomics

Protein
- proteomics

Metabolic products
-metabolomics

Challenges and Controversies in manipulating the Microbiome

Defining a ‘normal ’ microbiome

Proving that the intervention influences the microbiome

Practicalities of delivering an intervention

Acceptability of the intervention

Are the effects sustained?

Adverse effects?

Manipulation of the Microbiome

Diet

Pre- and Probiotics

Antibiotics

Faecal transplantation

Probiotics: contain live organisms that exert a potential health benefit on the host

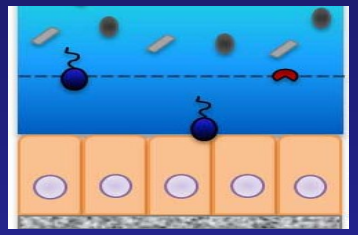
Prebiotics: dietary substances that selectively promote the growth / activity of beneficial gut bacteria

Symbiotics: contain a synergistic combination of prebiotics and probiotics

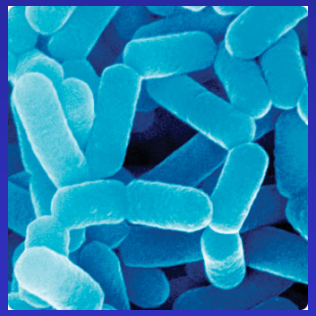
Probiotics

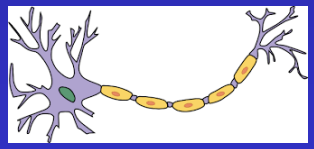
Probiotics: Mechanisms of action

1) Action on pathogenic bacteria
- competition for nutrients
- prevention of binding / invasion
- produce antibacterial molecules



2) Barrier function
- enhanced mucus layer





3) Brain-Gut Axis
-effects on pain perception

4) Immune effects
- ↑anti-inflammatory
- ↓pro-inflammatory cytokines

Probiotic Formulations

Lactobacillus

Bifidobacterium

Non-pathogenic: E-coli (eg *E. Nissle*)

: Streptococci (eg *S. Salivarius*)

: Yeasts (eg *S. Boulardii*)

Capsules, sachets, yoghurts, fermented milks, fruit drinks

Do probiotics alter the microbiome in Health?

Kristensen, *Genome Medicine;* 2016

Systematic review

- 7 RCTs identified
- only 1 study [Ferrario] showed alteration in β-diversity of microbiome after lactobacilli supplementation

Prebiotics

Prebiotics

Dietary substance

Resistant to : gastric acid

: digestion / absorption

Fermented by gut microflora

SCFAs, lactic acid production

Inexpensive; favourable safety profile

[Roberfroid]

Proliferation of beneficial bacteria

Enhanced immune functioning

↑Stool pH
↑Stool SCFAs

Improved lipid profile

Reduced colon cancer risk

↑dietary Ca, Fe, Mg absorption

↓calorie intake

↑ stool output

Effect of prebiotics on the microbiome in Health

Ramnani *et al* Journal of Nutritional Science, 2015

RCT; n=38

Crossover study 5g agave extract vs placebo

Faecal bacterial numbers (log10 cells/g faeces) assessed

	Baseline	Prebiotic	P value
Lactobacilli	7.3	7.7	<0.001
Bifidobacteria	9.2	9.6	<0.01

Side effects of bloating, flatulence noted

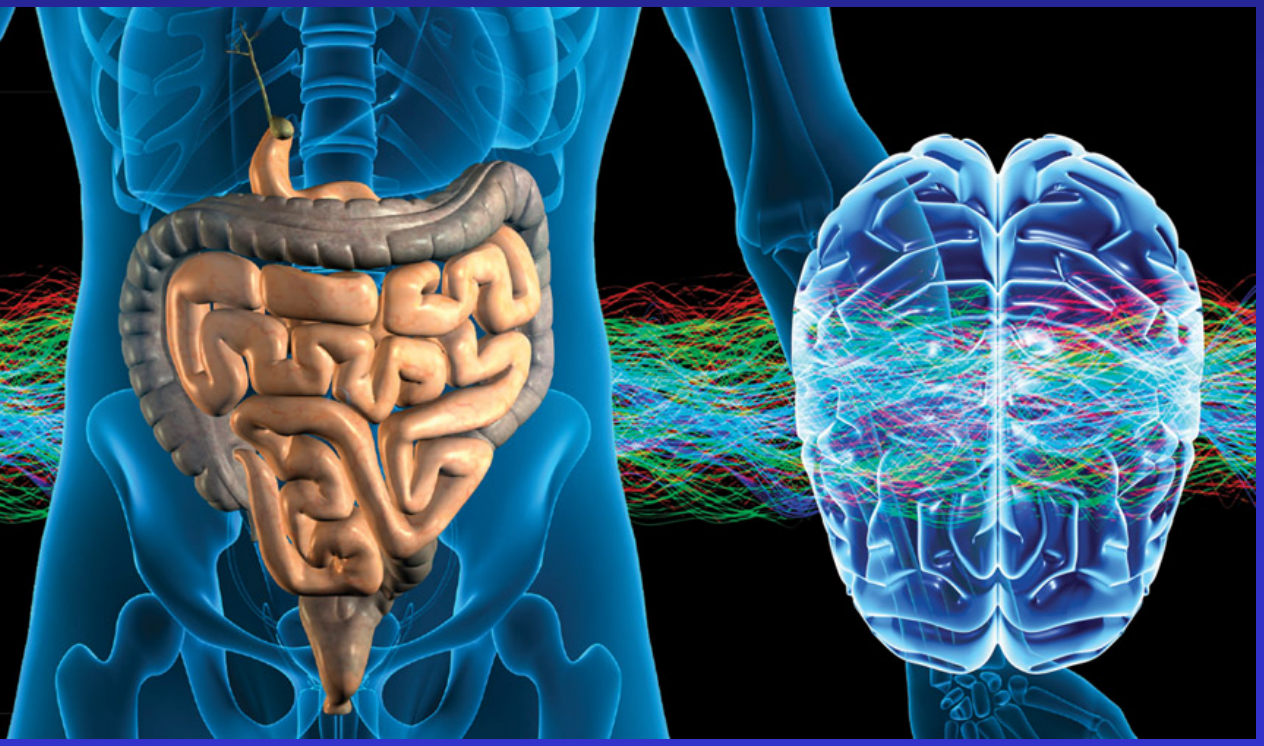
No effect on stool frequency

Prebiotics and Probiotics in IBS

Pathogenesis of IBS

1) Luminal factors
Dietary factors
Enteric infection
Dysbiosis

2) Within gut wall
Dysmotility
Hypersensitivity
Low grade inflammation



3) Abnormal processing
Genetics
Brain-gut interaction
Psychological factors
Coping skills

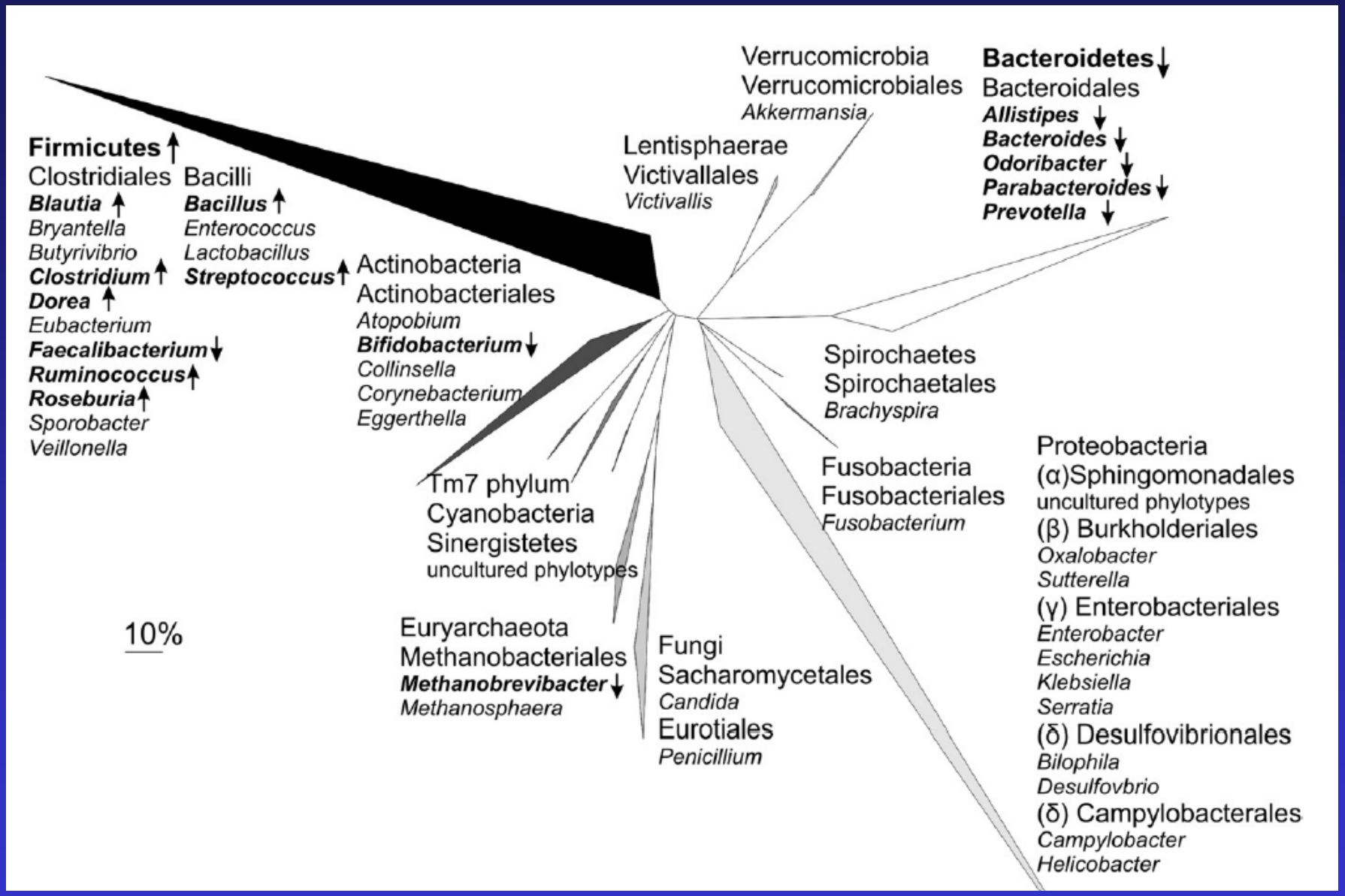
Dysbiosis and IBS: What's the evidence?

1) ↑ firmicutes:bacteroidetes [Sundin][Jeffery][Rajilic-Stojanovic]
   ↓ actinobacter/ bifidobacteria [Malinen][Parkes][Kerckhoffs]
   ↓ lactobacillus in IBS-D vs IBS-C [Malinen]

2) IBS common after enteritis [Thabane], antibiotics [Villarreal]

3) Microbiota influences gut contractility [Quigley]

4) Transfer of stool from IBS donor into germ free rats induces visceral hypersensitivity [Crouzet]



Rajilic-Stojanovic *et al*; Gastroenterology, 2011

Combination:

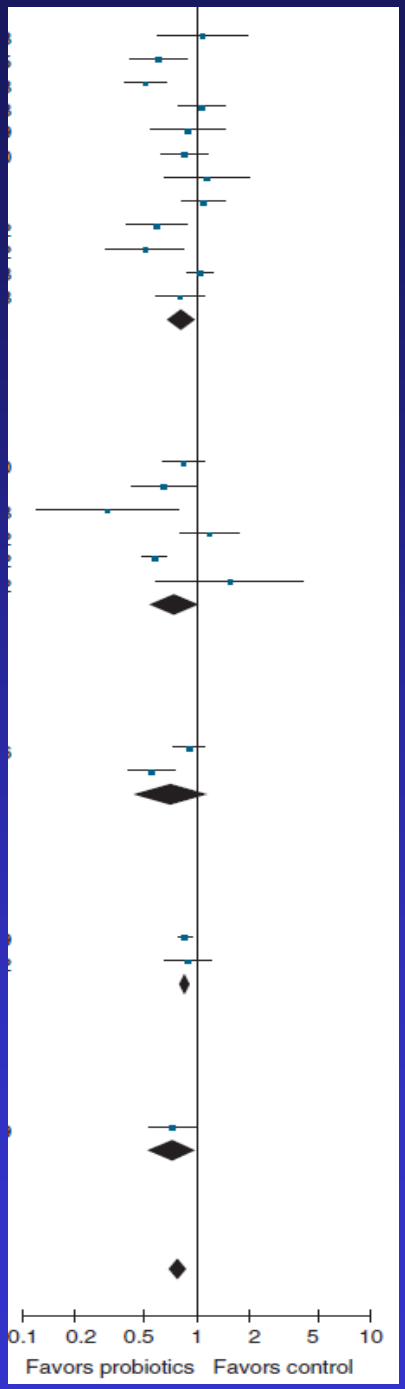
Lactobacillus:

Bifidobacteria:

E. Coli:

Saccharomyces:

Total:



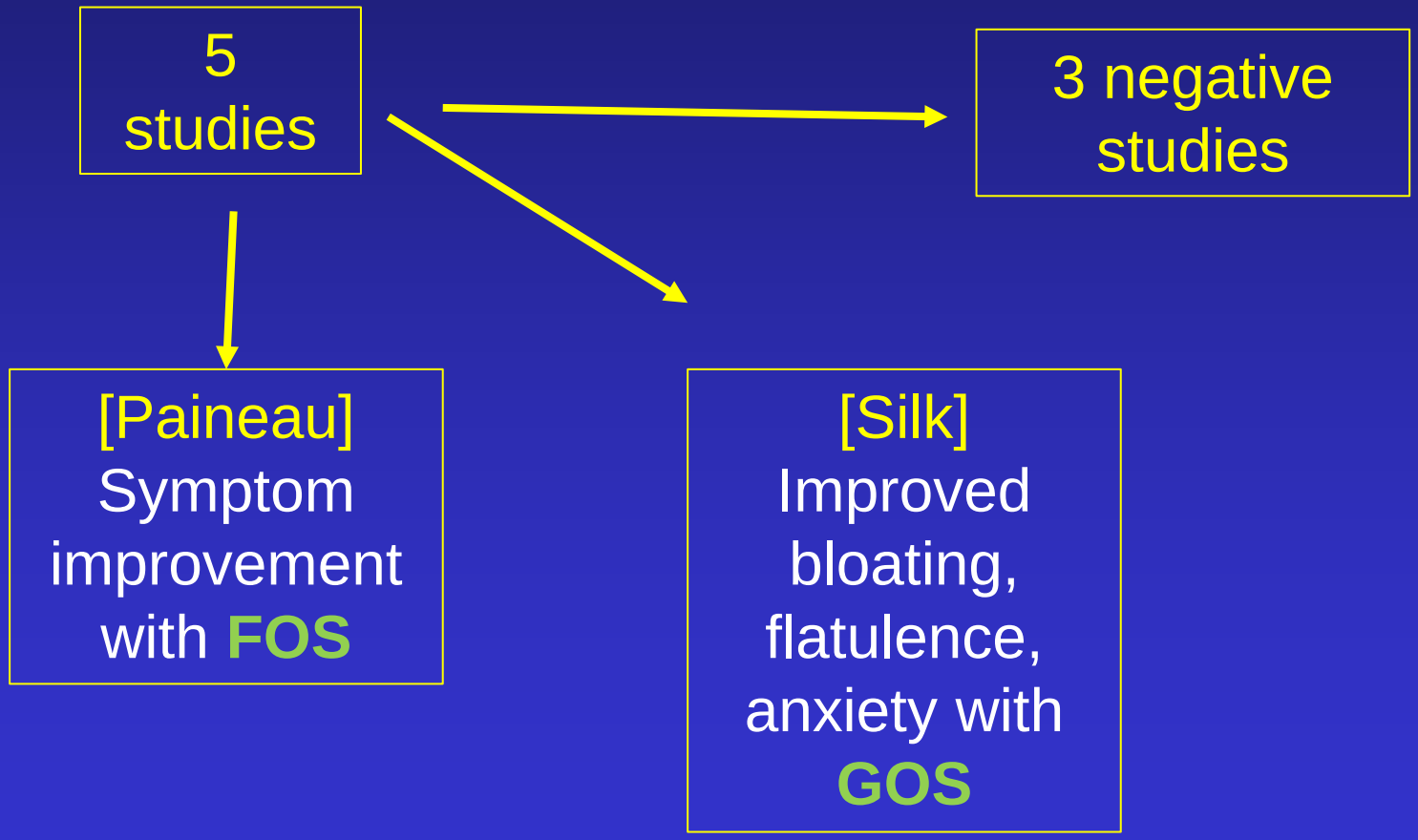
Effect of Probiotics on persistence of IBS symptoms

Ford *et al* 2014

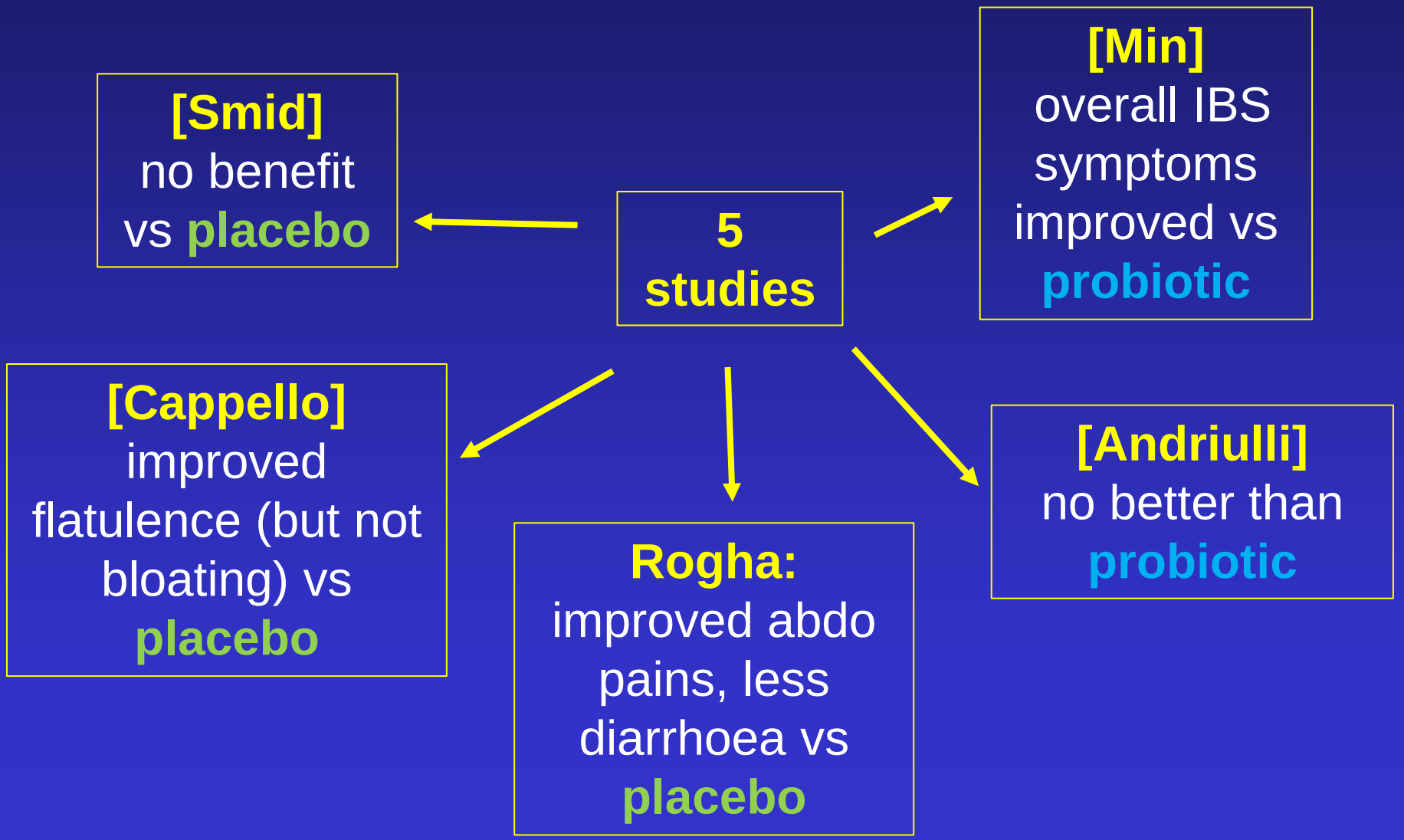
0.79 [0.70, 0.89]

Prebiotics in IBS

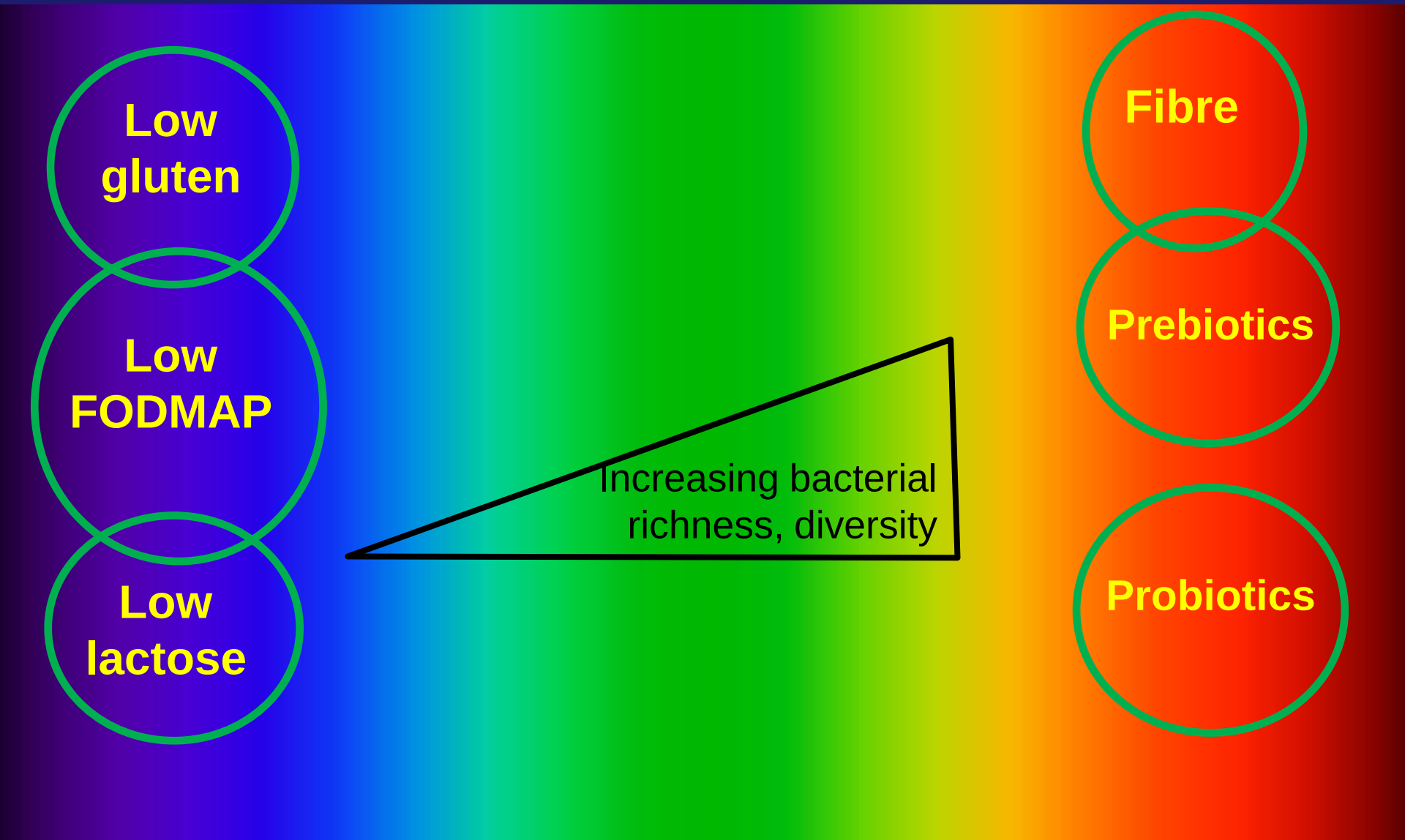
Distrutti *et al* 2016



RCTs of Symbiotics in IBS



Paradox of IBS Dietary Interventions



Conclusions

Microbiome plays a vital role in gut homeostasis

Complex physiological environment, still poorly understood / characterised

Dysbiosis is associated with various diseases and may be a potential therapeutic target

Challenges, controversies remain regarding the effects of manipulation of the microbiome in health and disease