The Microbiome, Diet and Health: Assessing Gaps in Science and Innovation

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New foods and dietary guidelines must target the gut microbiota: the clinical prospective

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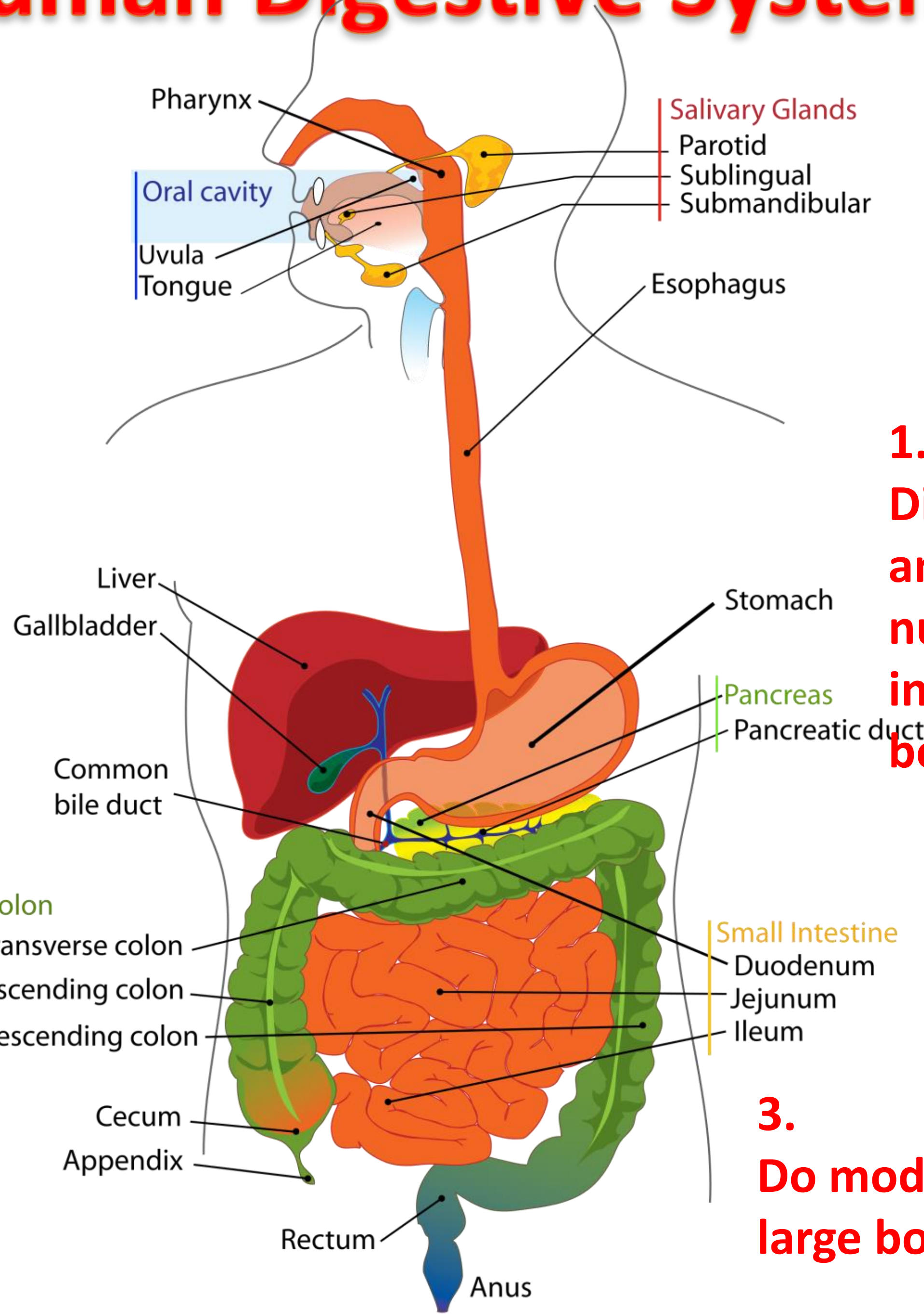
Human Digestive System



1. Digestion of foods and absorption of nutrients takes place in stomach and small bowel in only 2-3 h.

2. The "waste" is then stored for 2 days in the large bowel.

3. Do modern humans need a large bowel?

Gut Microbiota and Bowel Motor Function

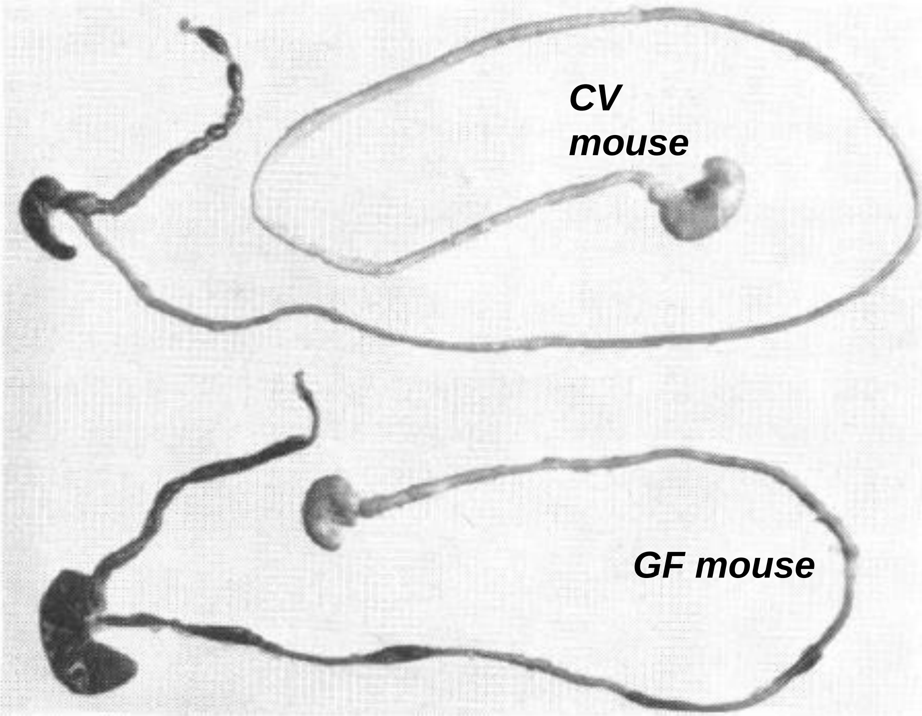


FIG. 1. *Gastrointestinal tract of conventional (above) and germ-free mice fed an aqueous carmine suspension via intragastric tube 6 hr prior to sacrifice. The small intestine of the germ-free animal contains a greater residual amount of dye than does its conventional counterpart. The distended cecum, characteristic of the germ-free mouse, is evident at the left.*

CV mouse

GF mouse

Abrams and Bishop, *J Bacteriol* 1966

IMPACT OF THE MICROBIOTA ON HOST ANATOMY AND PHYSIOLOGY

GERM FREE versus CONVENTIONAL MICROBIOTA

Reduced:

Organ weight (heart, liver, lungs)

Cardiac output

Oxygen consumption

Increased:

Food intake

Nutrition, Growth & Development

Reduced:

Mesenteric and systemic lymph nodes

Mucosa-associated lymphoid tissue

Serum immunoglobulin levels

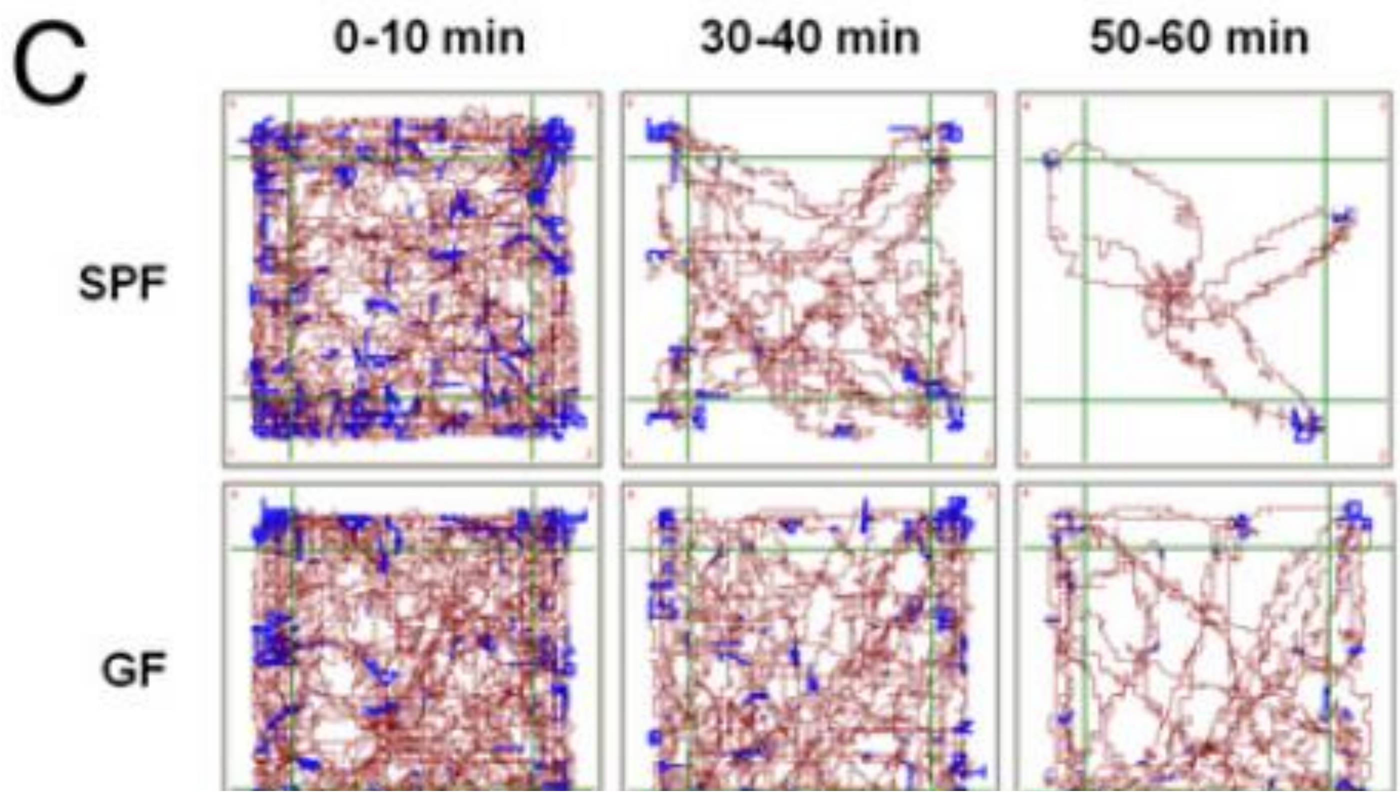
Increased:

Susceptibility to infection

Immunity

Wostmann, Annu Rev Nutr 1981

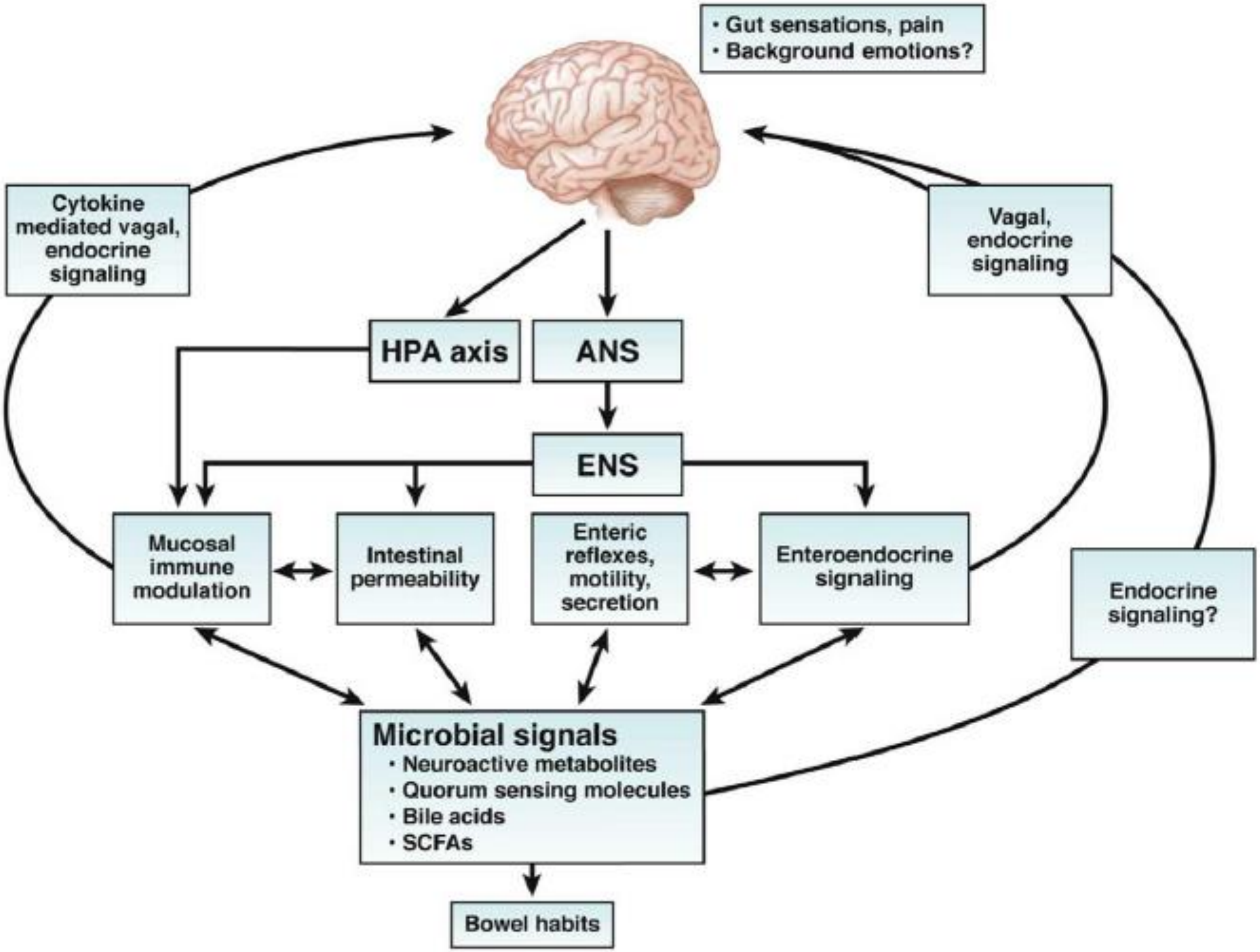
MICROBIOTA AND BEHAVIOR



Legacy of natural behaviour through the microbiome?

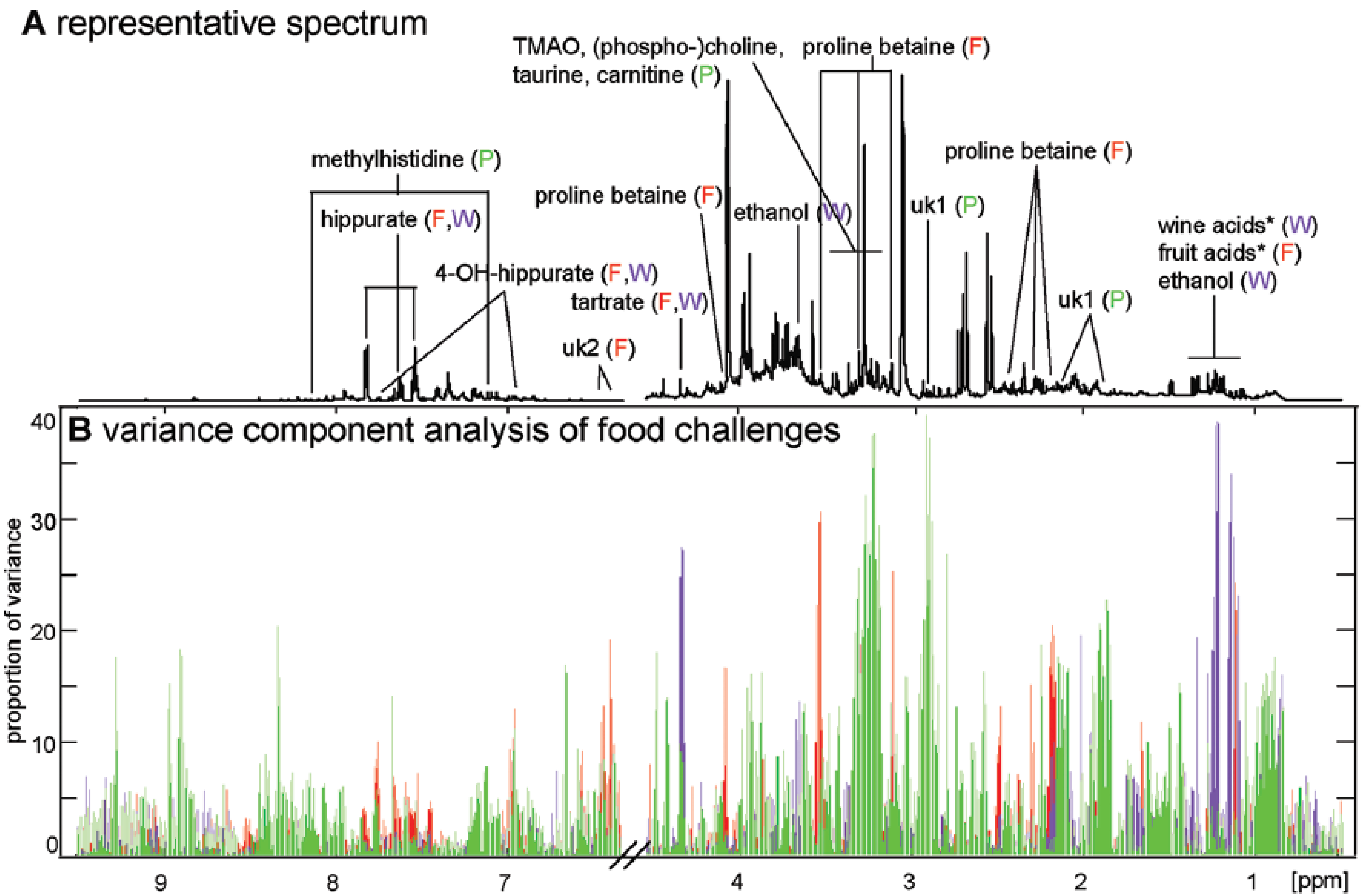
Diaz Heijtz et al. PNAS 2011

Brain-Gut Microbial interactions



Mayer et al, Gastroenterology 2014

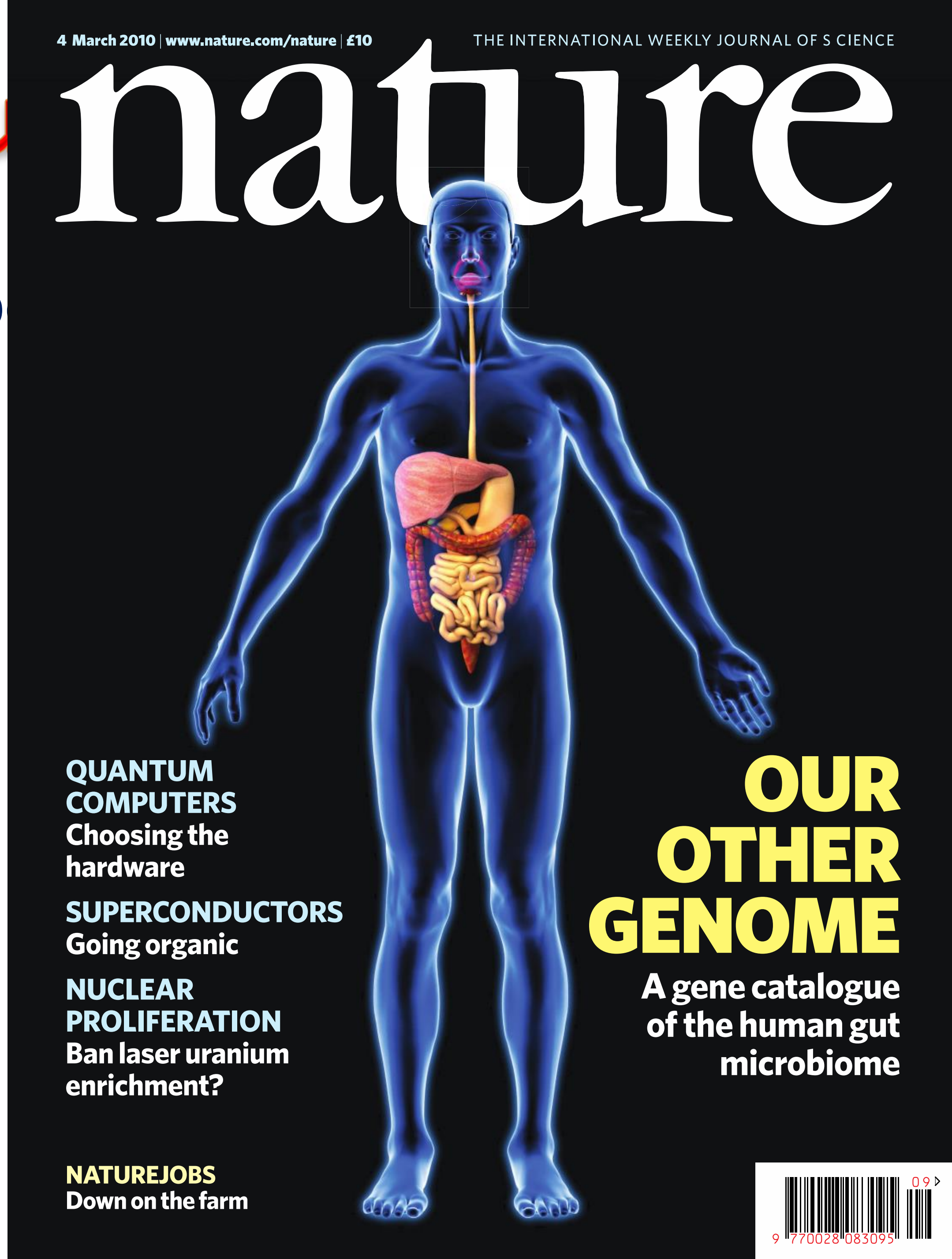
Microbiota Impact on Human Metabolic Phenotype



Heinzmann et al, J Proteome Res 2012

The Hu atabase

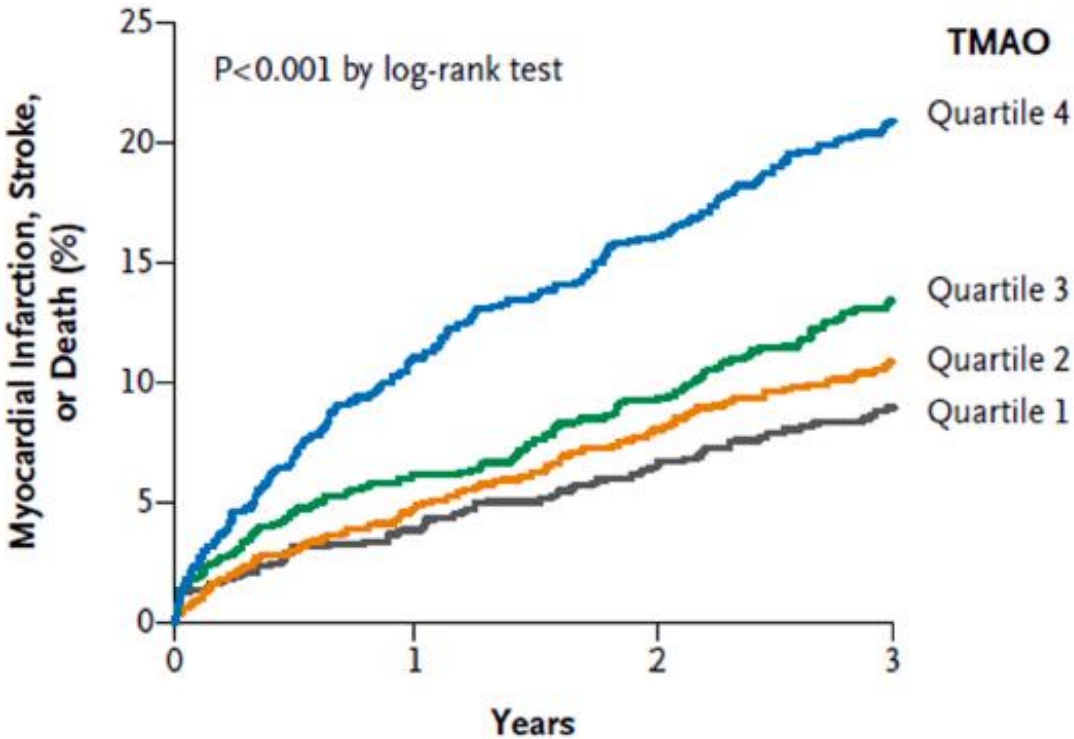
Numb an Fluids



Fluid	% Microbial origin
All fluids	3,4
Blood	4,5
Urine	5,8
Saliva	4,8
CSF	8,2

vw.hmdb.ca

Intestinal Microbial Metabolism of Phosphatidylcholine and Cardiovascular Risk



No. at Risk

Quartile 1	1001	933	869	827
Quartile 2	998	940	884	843
Quartile 3	1003	938	888	835
Quartile 4	1005	913	849	791

Tang et al, NEJM 2013

Microbial metabolites of dietary lignans: potential for disease risk reduction

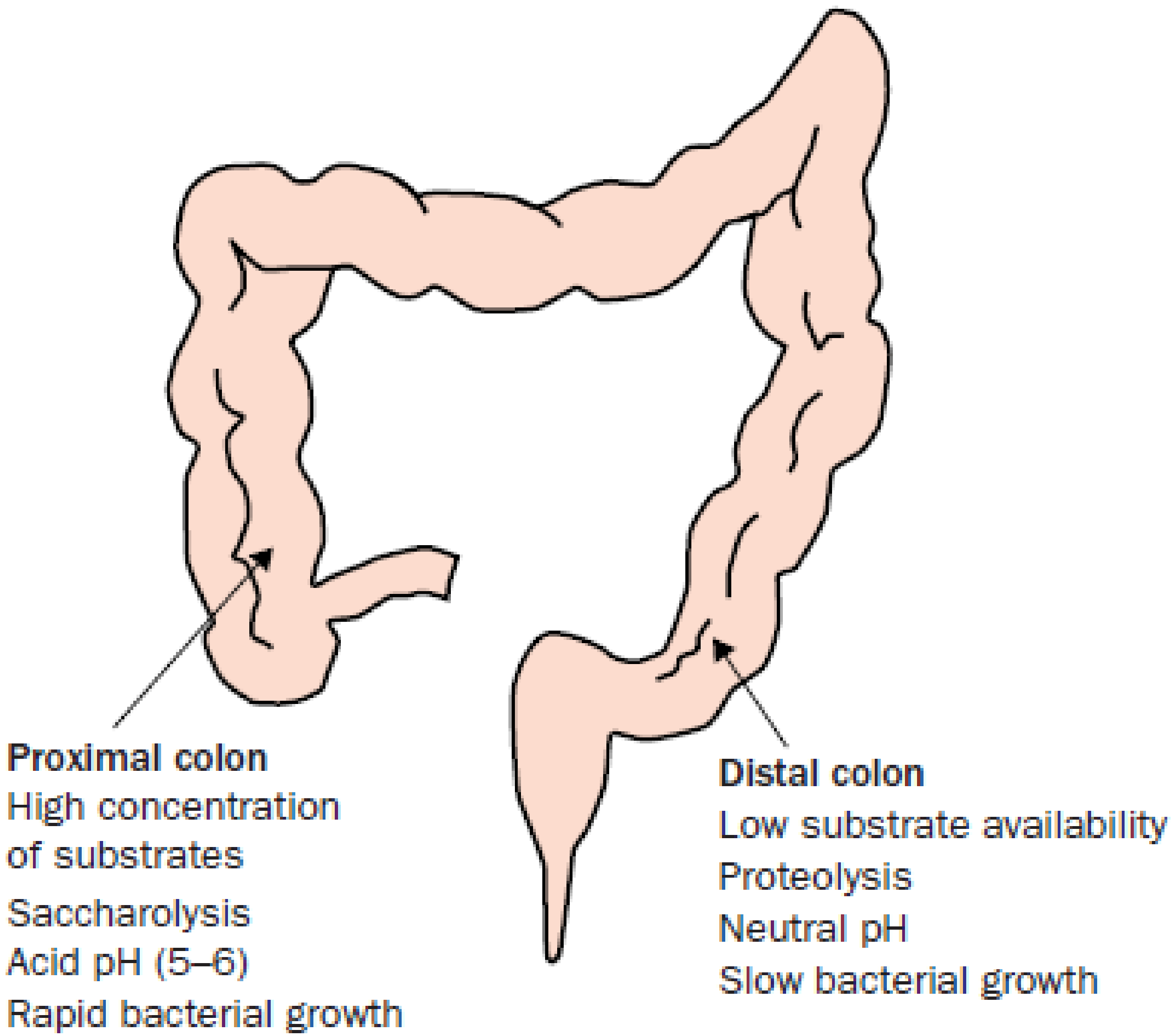
Hu Y, et al. A Prospective Investigation of the Association Between Urinary Excretion of Dietary Lignan Metabolites and Weight Change in US Women. Am J Epidemiol. 2015 Sep 15;182(6):503-11.

Struja T, et al. The association between urinary phytoestrogen excretion and components of the metabolic syndrome in NHANES. Eur J Nutr. 2014 Sep;53(6):1371-81.

Seibold P, et al. Enterolactone concentrations and prognosis after postmenopausal breast cancer: assessment of effect modification and meta-analysis. Int J Cancer. 2014 Aug 15;135(4):923-33.

Richard A, et al. Urinary phytoestrogens and depression in perimenopausal US women: NHANES 2005-2008. J Affect Disord. 2014 Mar;156:200-5.

Physiological Role of the Human Colon



Guarner & Malagelada, Lancet 2003

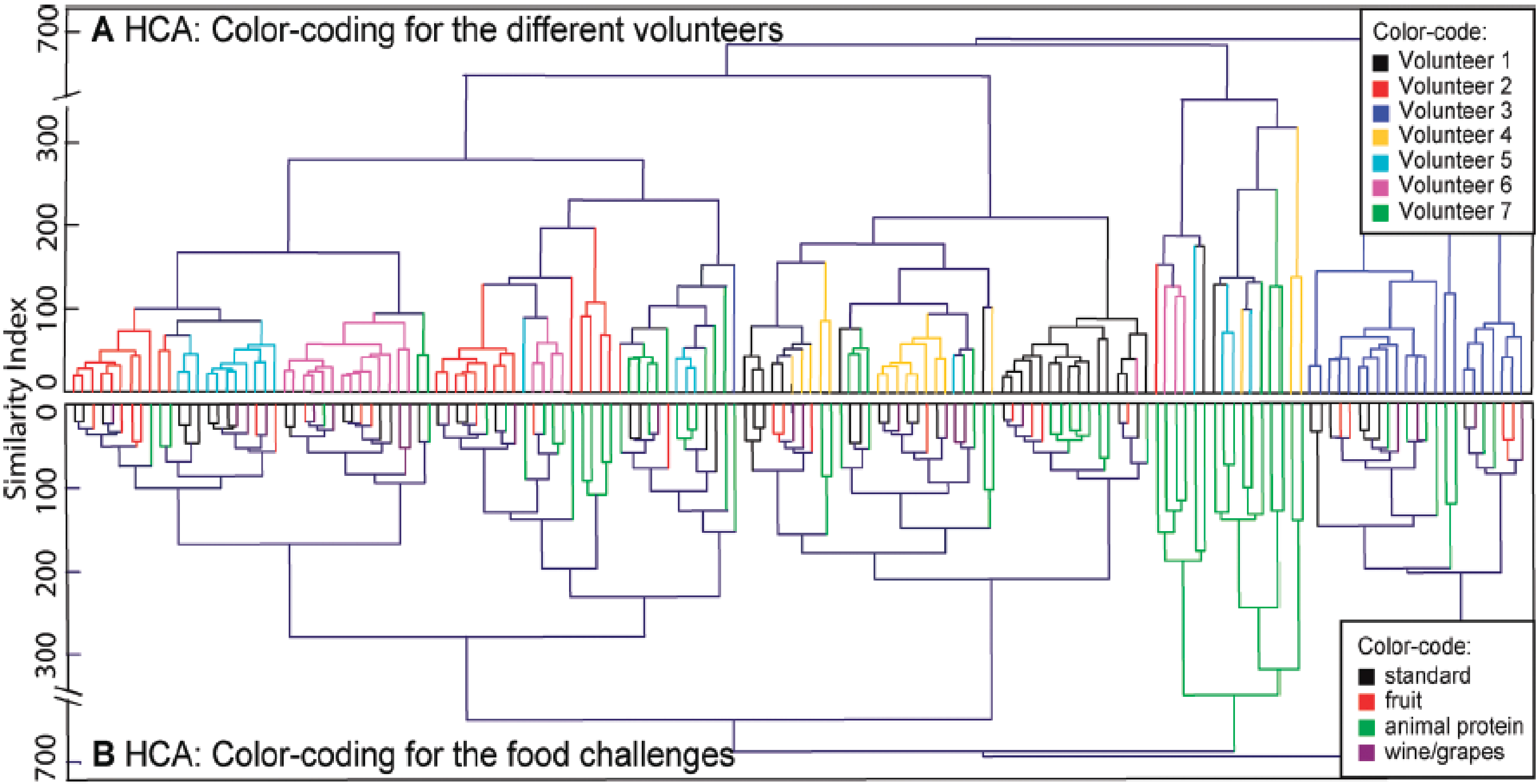
Fermentable substrates that reach the Human Colon

Substrate	Component	Amount ($g\ day^{-1}$)
Carbohydrates	Resistant starch	5–35
	Non-digestible polysaccharides	10–25
	Oligosaccharides (e.g. fructo- or gluco-oligosaccharides, inulin)	2–8
	Monosaccharides (e.g. sugars, sugar alcohols)	2–5
	Mucins	3–5
	Synthetic carbohydrates (e.g. lactulose, polydextrose, modified cellulose)	Variable
Protein	Of dietary origin	1–12
	Of endogenous origin (e.g. pancreatic enzymes and other secretions)	4–8
	Desquamated epithelial cells	30–50
Other	Non-protein nitrogen (e.g. urea, nitrate)	~0.5
	Organic acids, lipids, bacterial recycling	Unknown

[a]Based on Refs [19,65–67].

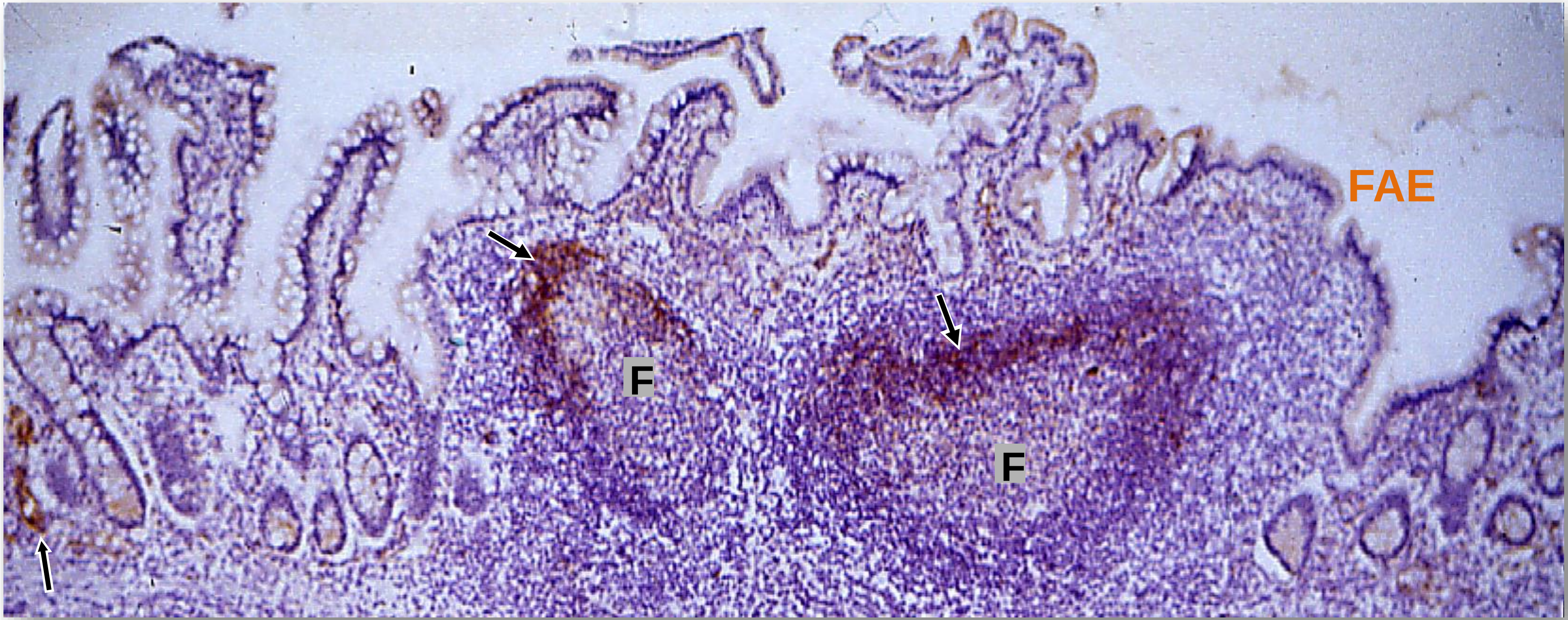
Egert et al, Trends Microbiol 2006

Diet and Microbiota



Heinzmann et al, J Proteome Res 2012

Induction of the Immune System

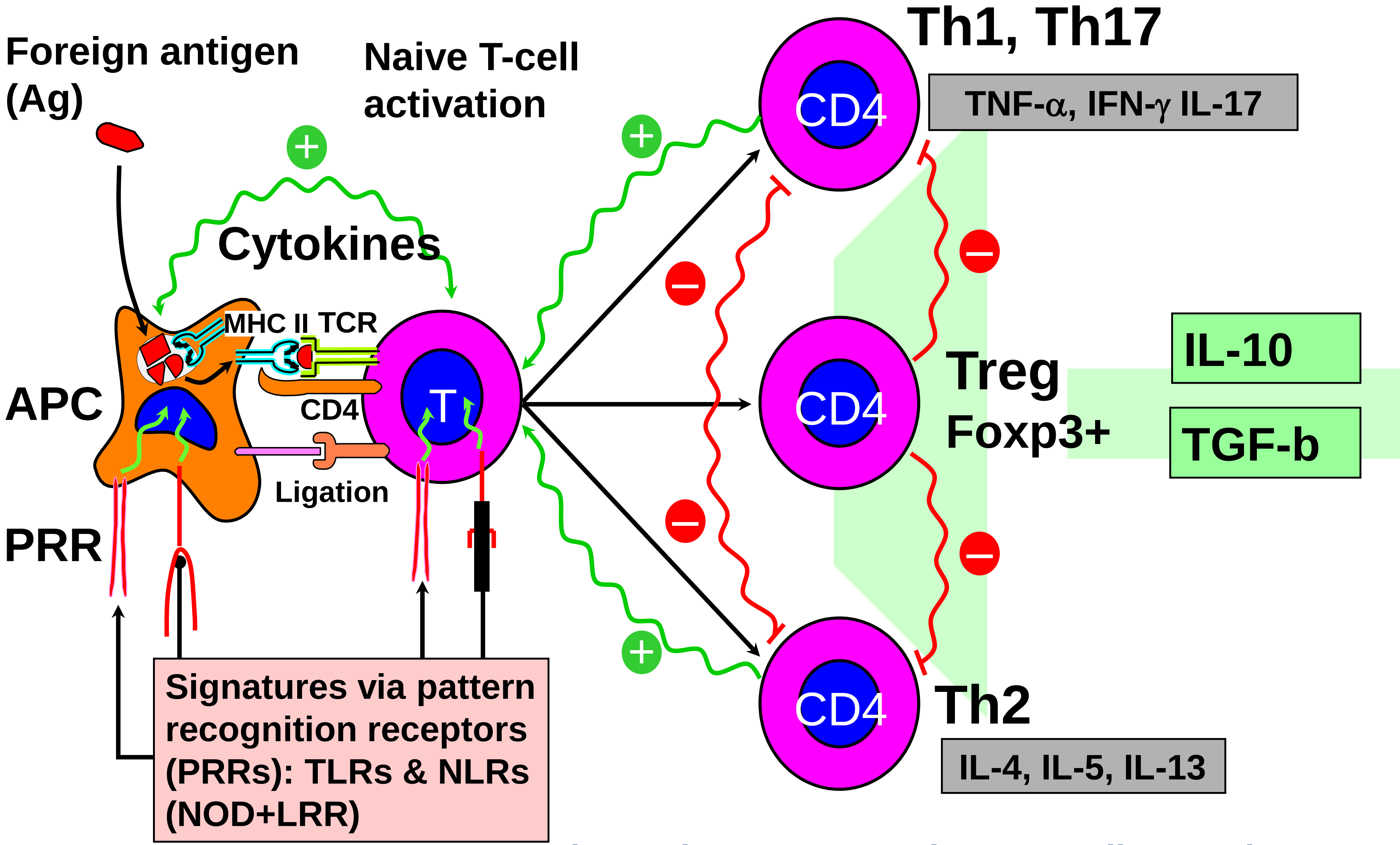


Gut-Associated Lymphoid Tissue structures are strategically situated in relation to the greatest concentration of microbiota

- **Peyer's patches:**
  distal ileum (nos. 100-250)
- **Isolated lymphoid follicles (ILFs):**
  large bowel (nos. ~ 30 000)

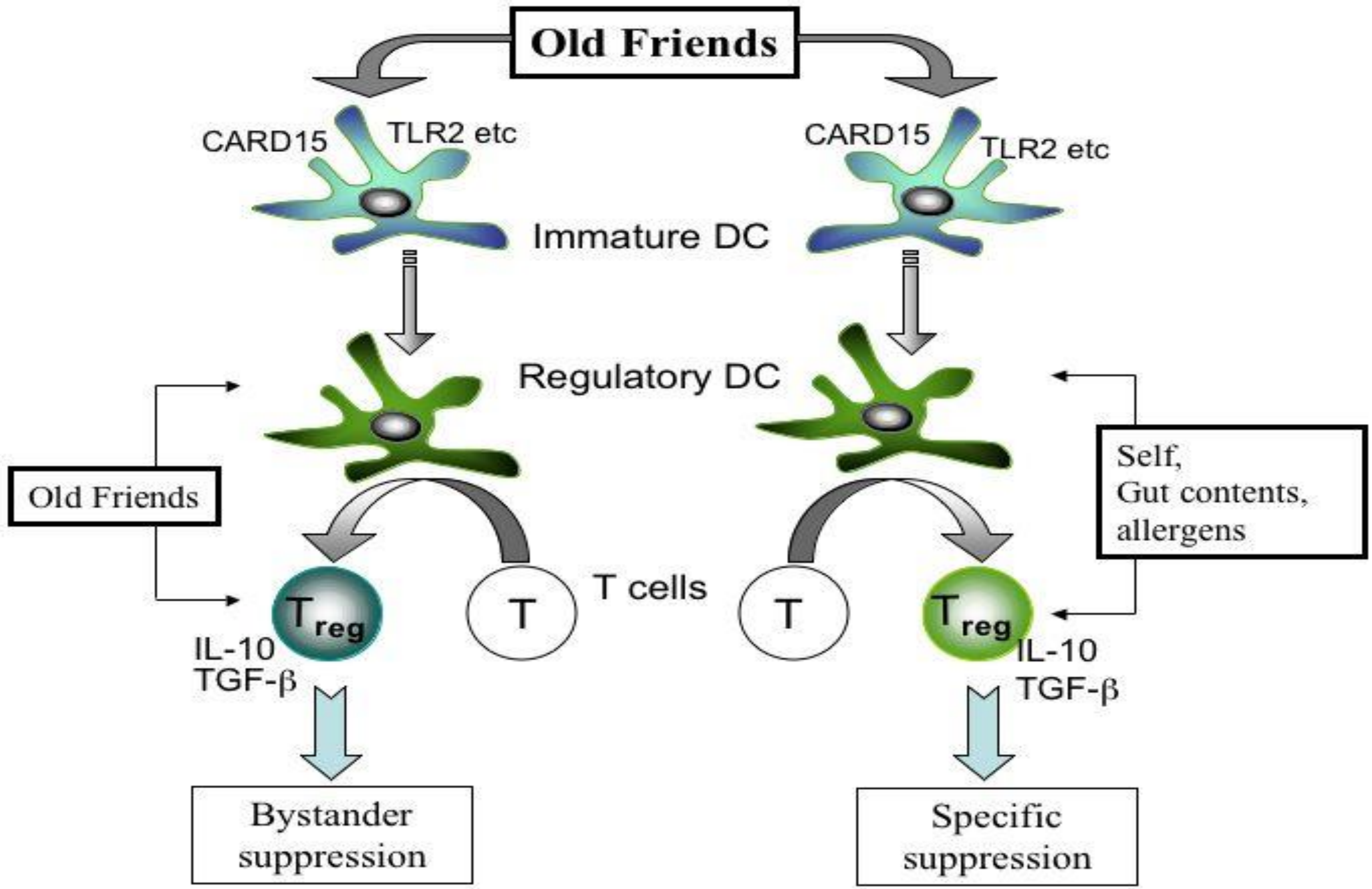
Brandtzaeg, Immunological Investigations 2010

Decision making in the adaptive (acquired) immune system is instructed by the microbial impact on APCs and T cells



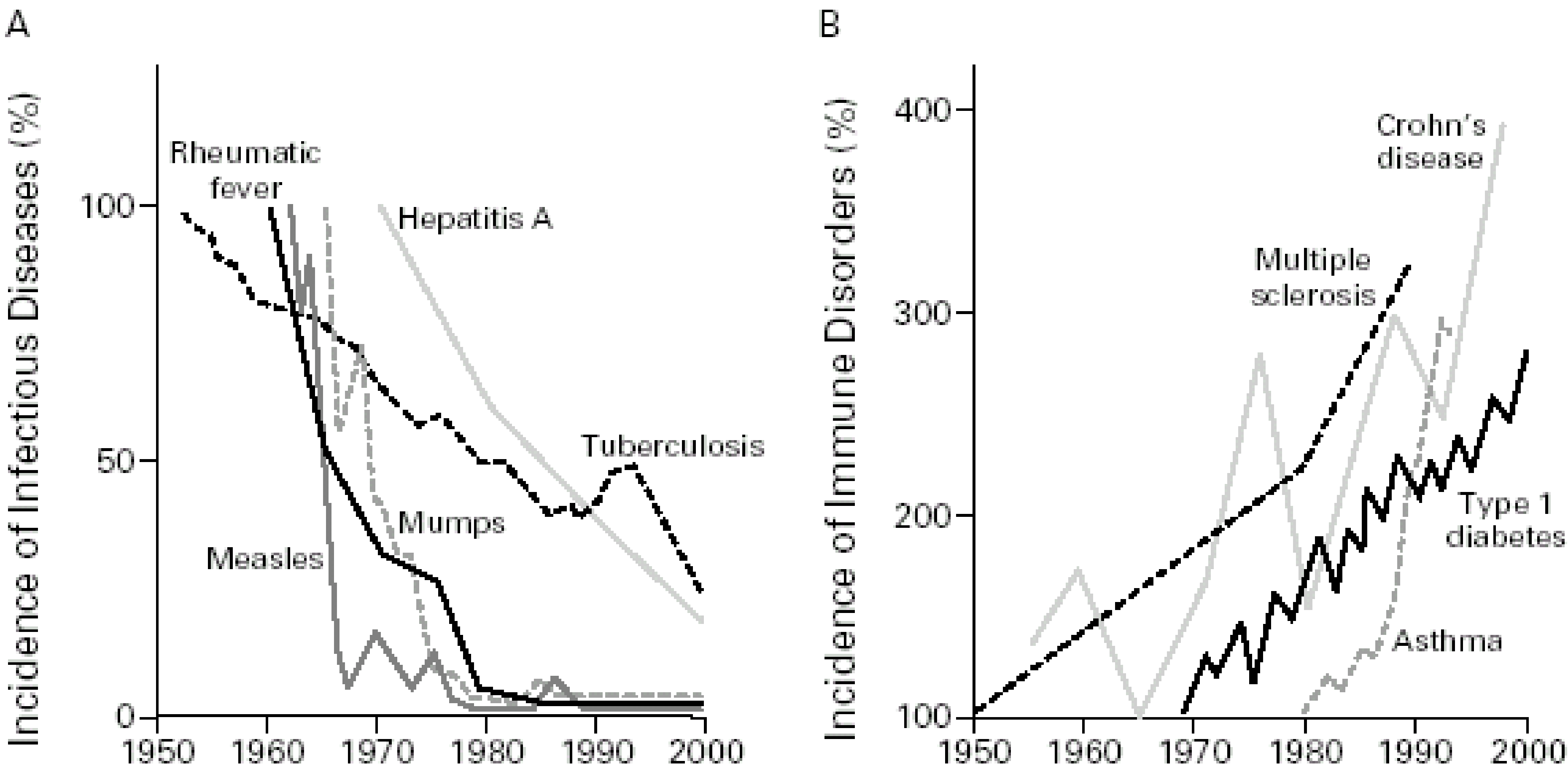
By Per Brandtzaeg in Guarner et al, Nature Clin Practice 2006

THE 'OLD FRIENDS' HYPOTHESIS



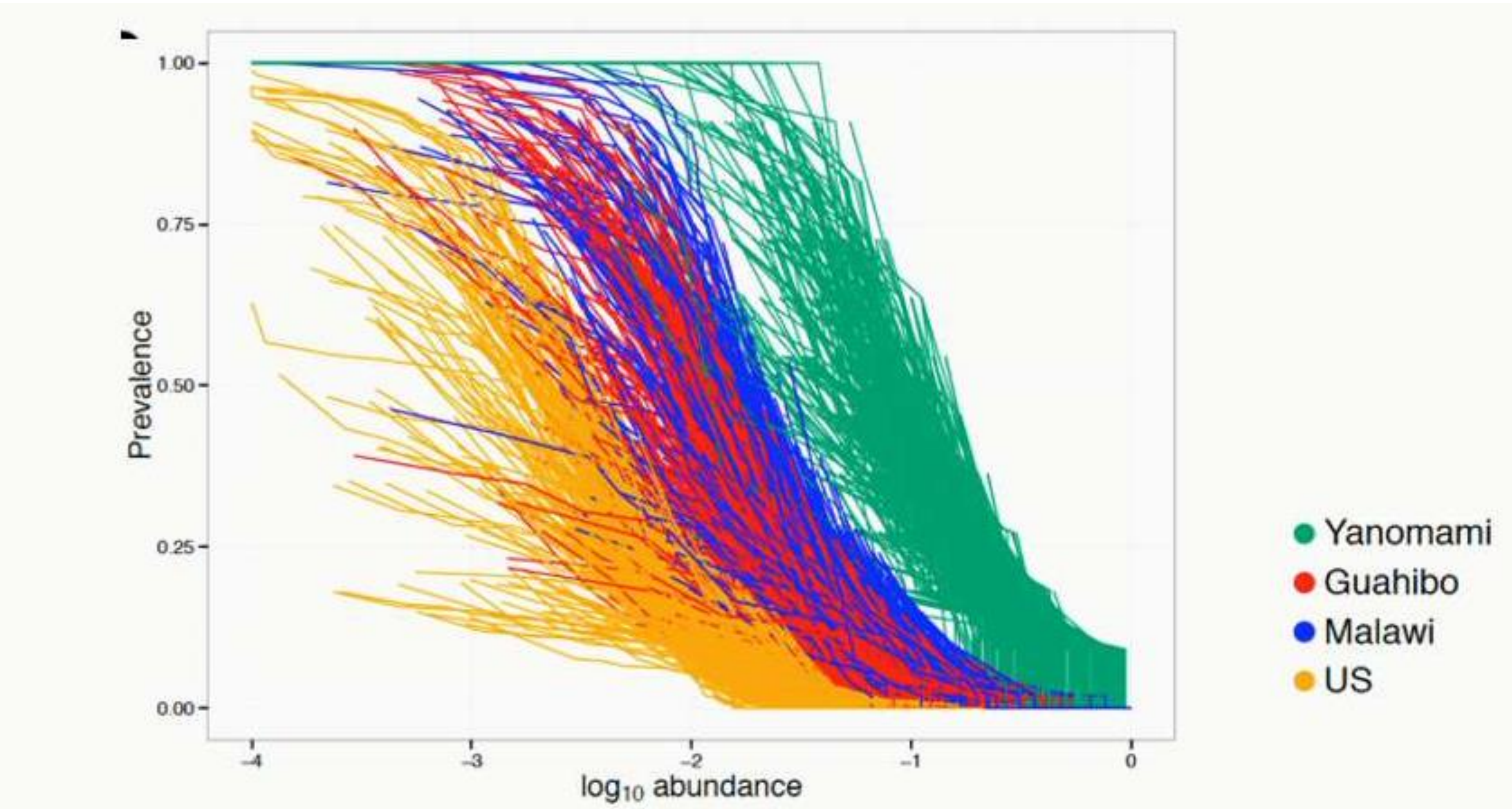
By Graham Rook in Guarner et al, Nature Clin Practice 2006

INVERSE RELATION BETWEEN THE INCIDENCE OF INFECTIOUS DISEASES AND IMMUNE DISORDERS



Bach JF, N Eng J Med 2002

Prevalence/abundance curves of individual bacteria in human groups with different degree of Westernization



Clemente et al, Science Advances 2015

Gut Microbiota Dysbiosis and Disease

Disorders linked to altered composition of the gut microbiota:

- Nutrition-related disorders (obesity, type 2 diabetes and the metabolic syndrome)

Dysbiosis

An imbalance of the normal structure and function of the microbiota

- Functional bowel disorders
- Systemic complications of decompensated liver disease
- Colo-rectal cancer
- Certain allergies
- Certain mental and neuro-developmental conditions, such as autism spectrum disorders

Common Traits of Dysbiosis

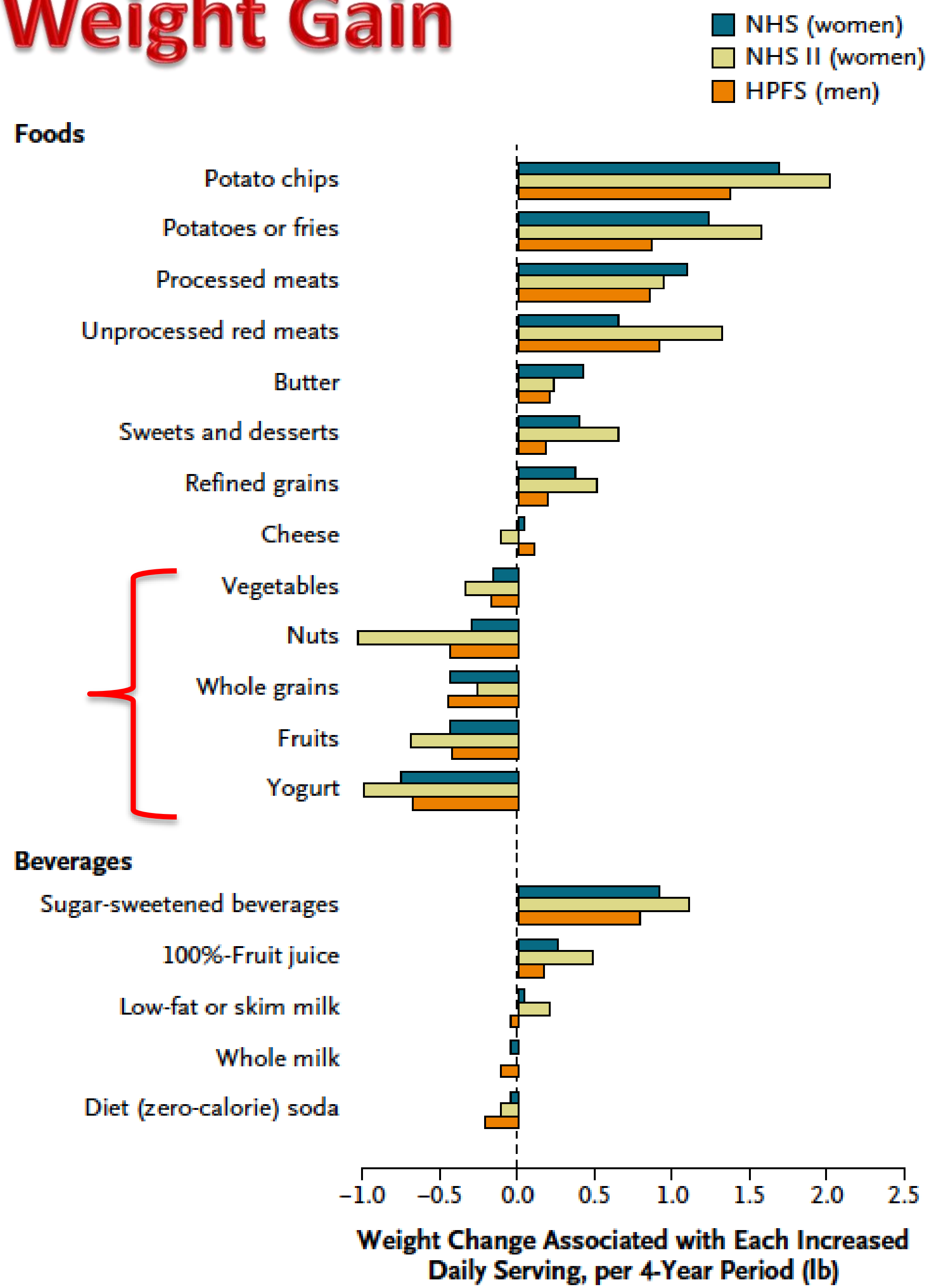
- Reduction of SCFA producing bacteria (butyrate producers such as Faecalibacterium, Roseburia, Lachnospiraceae, Eubacterium, Subdoligranulum).
- Increased mucus degradation potential by abnormal mucin degraders that displace Akkermansia.
- Reduced hydrogen and methane production potential combined with increased hydrogen sulphide formation potential. Hydrogen sulphide is toxic for the epithelium.
- Increase in abundance of bacteria with LPS endotoxins (Proteobacteria) that can drive inflammation.
- Increased potential to manage oxidative stress, i.e. microbes become able to proliferate in close vicinity to the epithelium.

Le Chatellier et al, Nature 2013

Diet and Long-Term Weight Gain

- Prospective observational study involving three separate cohorts that included 120,877 women and men who were free of chronic diseases and not obese at baseline.
- Follow-up period from 1986 to 2006.

Feeding the gut microbiota proved very beneficial!



Mozaffarian et al, NEJM 2011

Meta analysis for GI disease

PLoS one

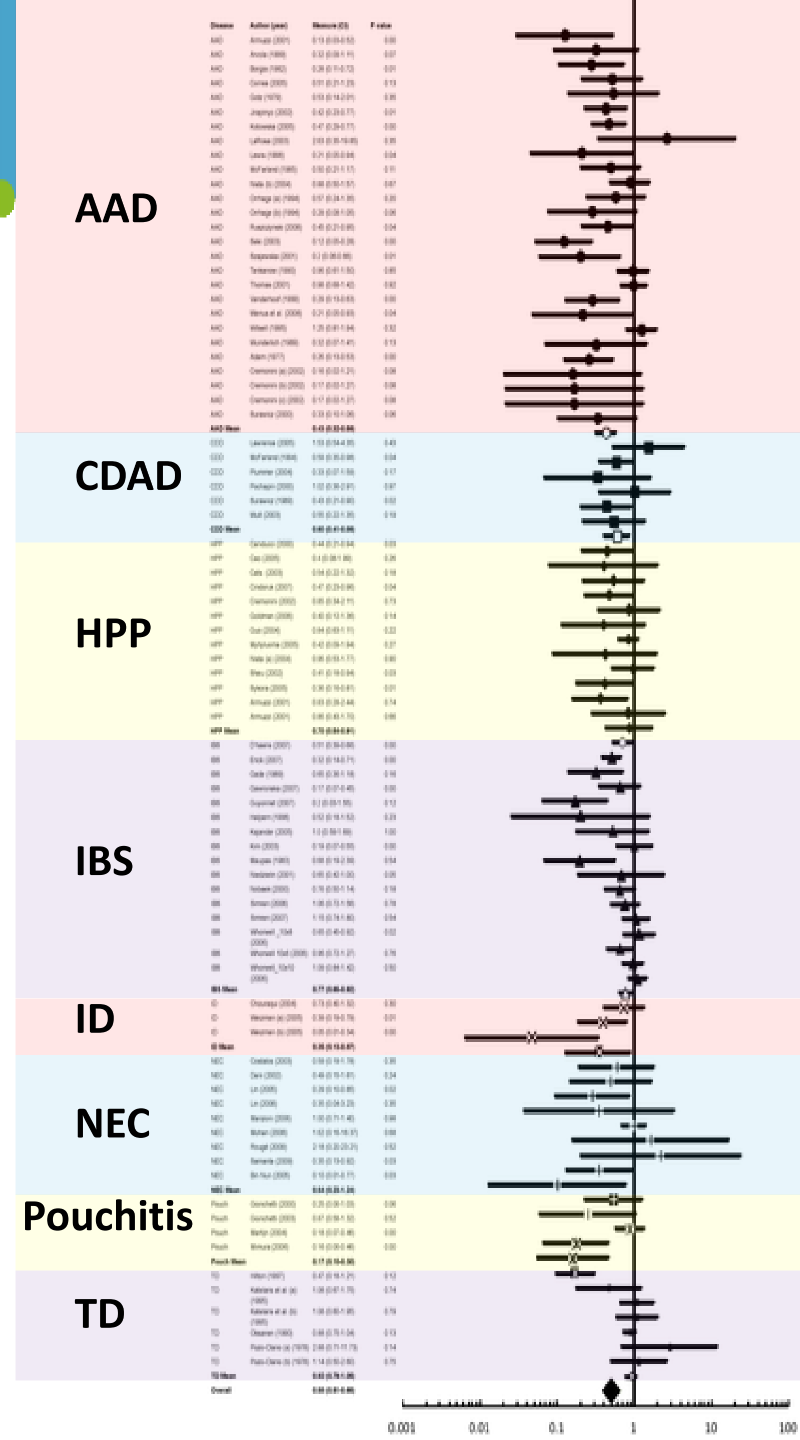
A Meta-Analysis of Probiotic Efficacy for Gastrointestinal Diseases

Marina L. Ritchie*, Tamara N. Romanuk

Department of Biology, Dalhousie University, Halifax, Nova Scotia, Canada

April 2012 | Volume 7 | Issue 4 | e34938

In conclusion, our meta-analysis containing 74 studies, 84 trials and 10,351 patients shows that in general, probiotics are beneficial in treatment and prevention of GI diseases.



Prevention and Treatment of Dysbiosis

Current strategies:

- Prebiotics and diet may increase diversity
- Screen probiotic organisms for properties and use them in disease
- Study the microbiota in disease and “replace” what is missing
- Study a clinically beneficial outcome (e.g. faecal transplant) and reverse engineer