UNIVERSITY OF ABERDEEN

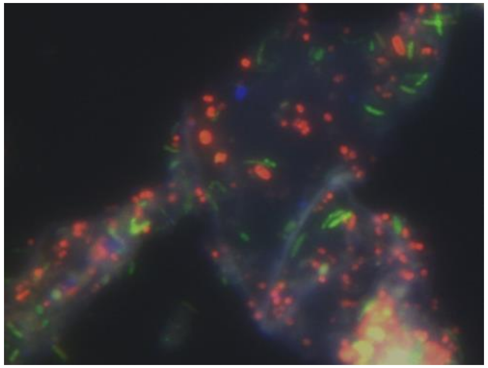
Rowett Institute of Nutrition and Health
University of Aberdeen

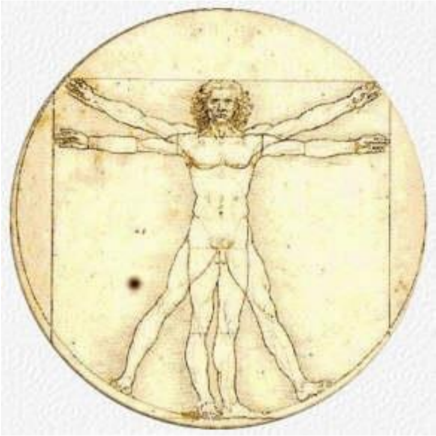
Diet, intestinal microbial communities and host health

Alan Walker

Rowett Institute of Nutrition and Health,
University of Aberdeen

8/9/15

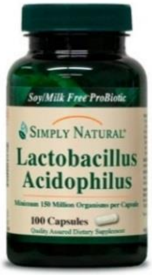




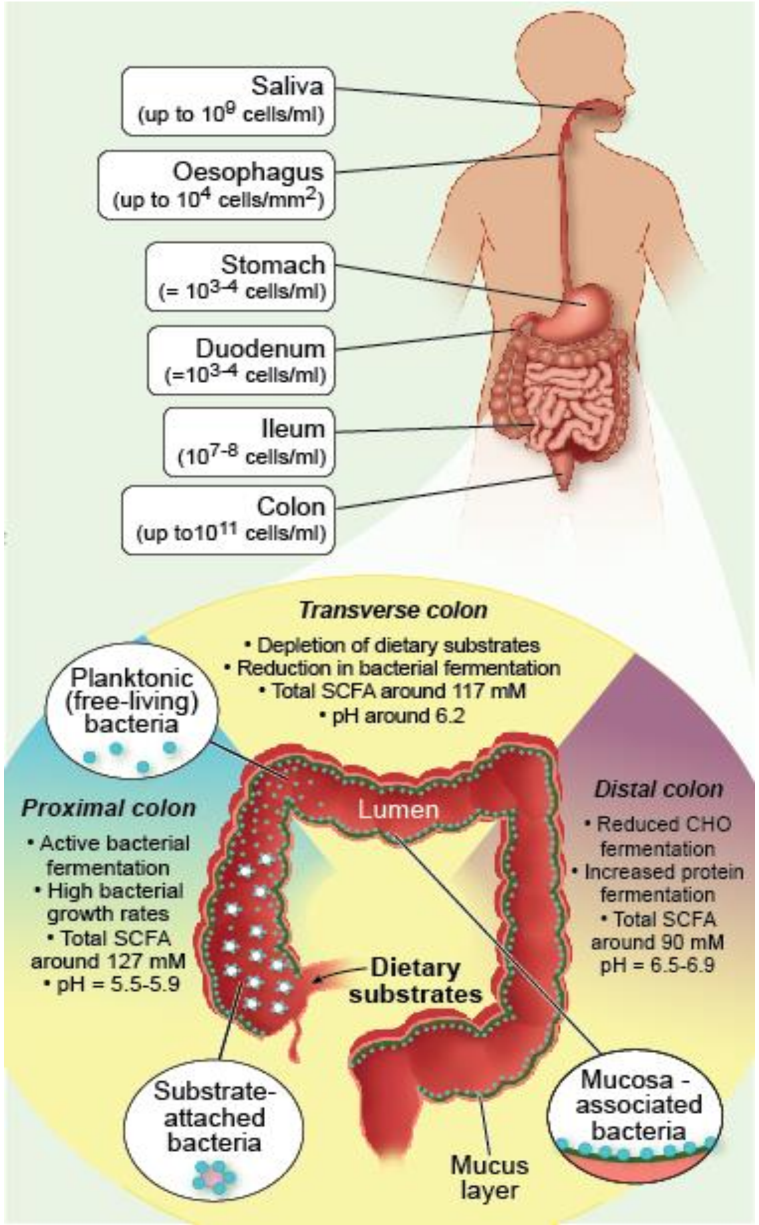
NuGO

The human intestinal microbiota

- **Human large intestine hosts an enormous number of microbes ("microbiota")**
  - 100,000,000,000,000 (**10^{14}**) bacterial cells
  - Greater than the number of human cells
- **Thousands of different species colonise**

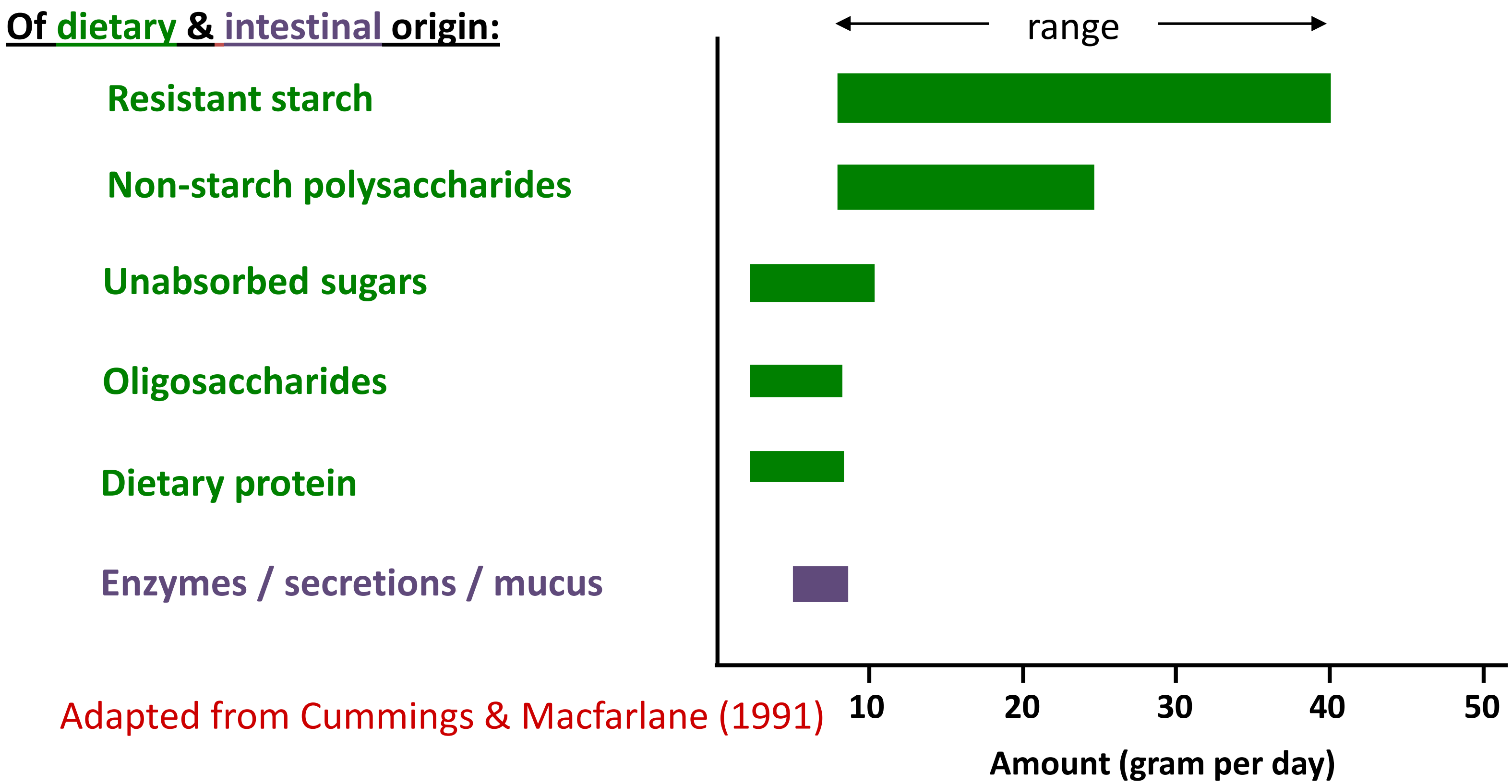


  - Most are strict anaerobes
  - Each host have a unique and largely stable microbiota
- **The cumulative "microbiome" of these cells contains 400x more unique genes than the human genome**
  - est. 8 million vs ~20-25,000
- **Plays a number of key roles in maintaining host health**
  - Enhances resistance against infection
  - Immune system development/maintenance
  - Beneficial compound production
  - Breakdown dietary fibre



Lawley & Walker (2013) *Immunology* **138**, 1-11

Principal substrates available for utilisation by intestinal microbes

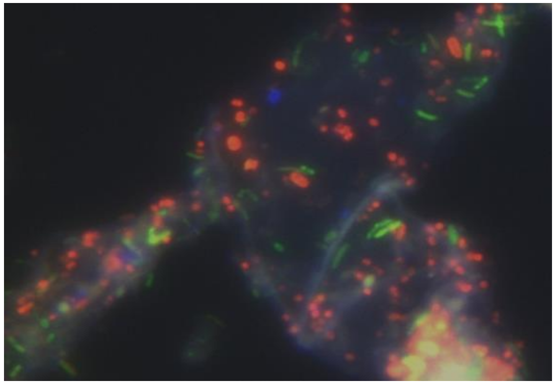


Adapted from Cummings & Macfarlane (1991)

Digestibilities for plant cell wall polysaccharides – 7 subjects (Slavin *et al* J. Nut 1981)

Pure cellulose (Solka Flok)	minimal
Cellulose (in normal diets)	69.7% (+/-10.7)
Hemicellulose	71.7% (+/- 5.4)

Fibre utilisation by gut microbes



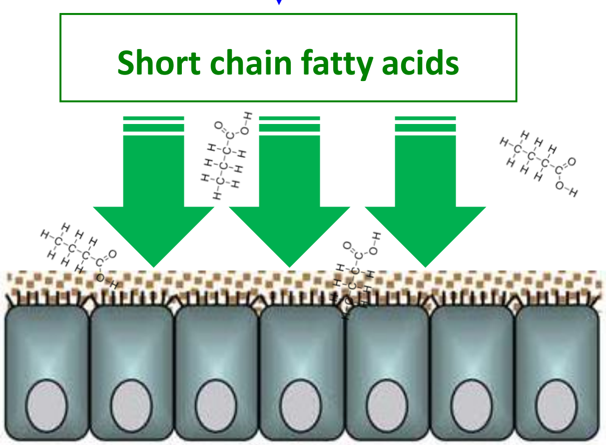
complex polysaccharides

↓ *Polysaccharide degraders*

oligo-, mono-saccharides

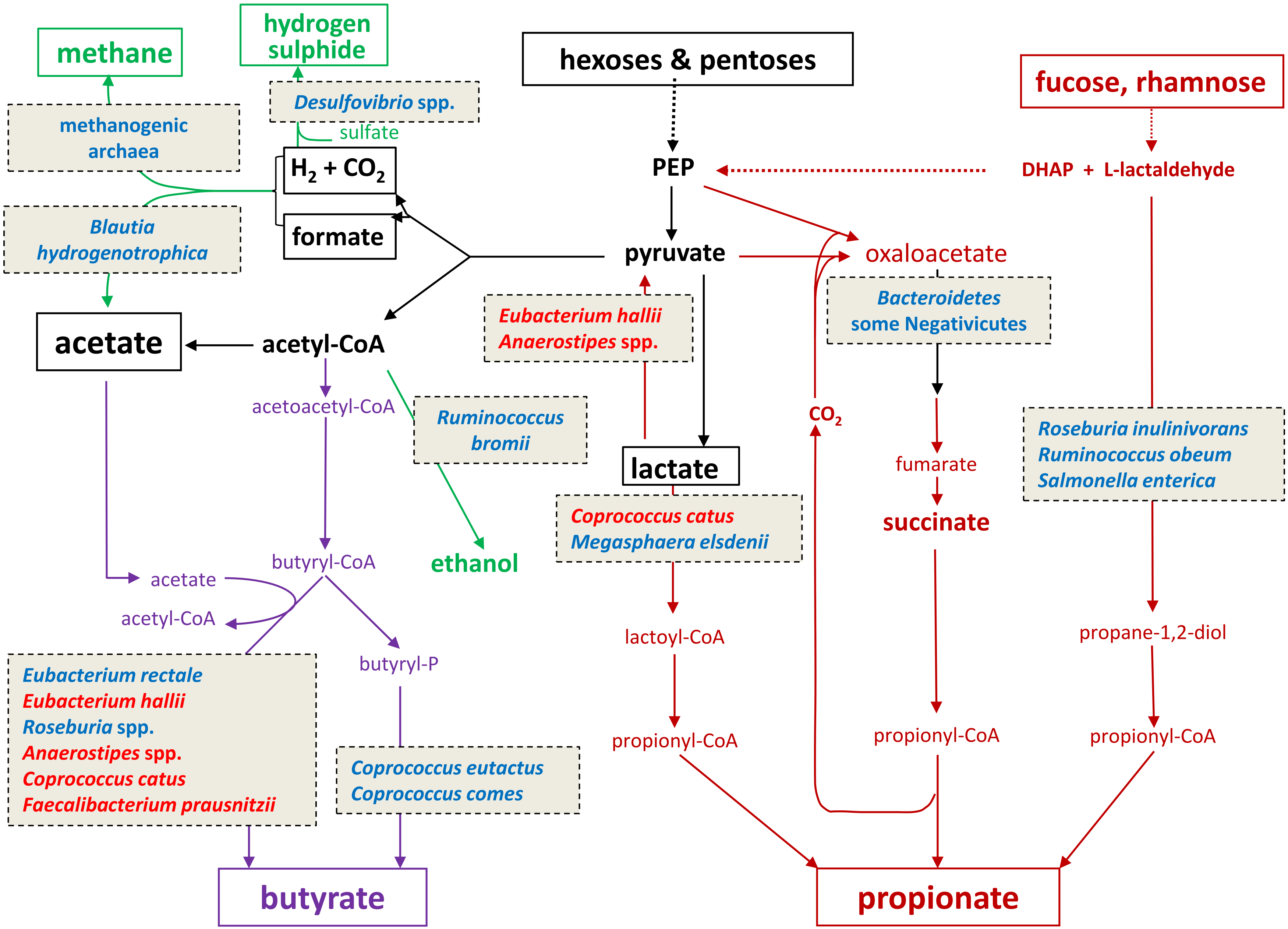
saccharolytic bacteria

↓ *Anaerobic fermentation*



- Metabolise dietary components that escape digestion by human enzymes
  - Endows host with degradative capabilities they have not needed to evolve themselves
- Vitamin production
  - K, riboflavin (B_2), biotin (B_7), folic acid (B_9), cobalamin (B_{12})
- Release of phytochemicals
  - Phenolic compounds etc
- Primary end products are short chain fatty acids
  - Acetate (C2), propionate (C3) and butyrate (C4)
- SCFAs are symbiotic compounds
  - Gut epithelial cells grow on products of bacterial metabolism
  - Derive up to 70% of energy needs from bacterially-produced butyrate
  - Increases energy yield from diet (5 to 10% of caloric intake per day)

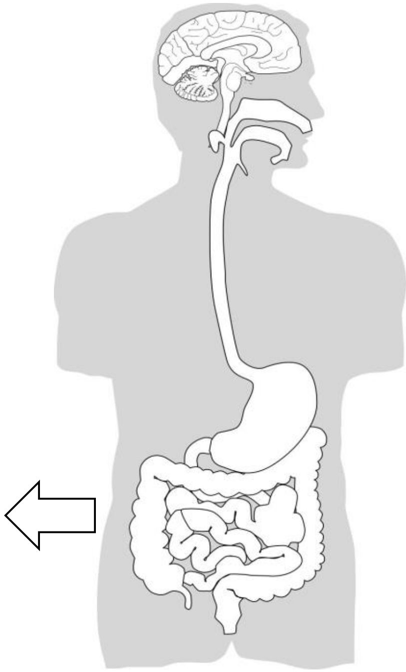
Major fermentation pathways

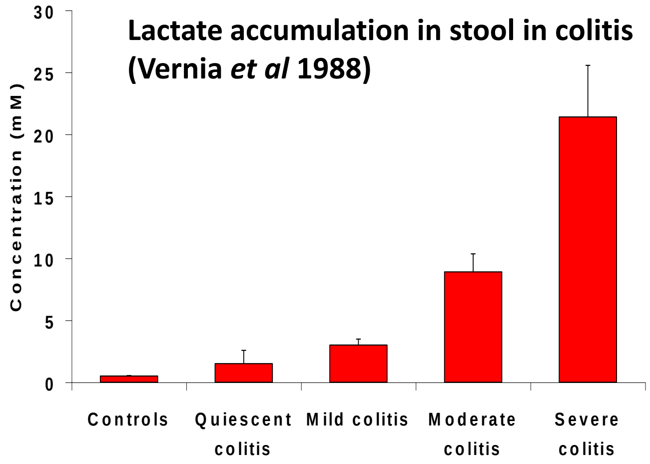


Adapted from Louis *et al.*, *Nat Rev Microbiol* (2014)

Impact of gut bacterial short chain fatty acids on the host

- Inhibition of histone deacetylase *(butyrate, propionate)*
- Altered mucosal gene expression, cell differentiation
- Protection against colorectal cancer, colitis *(butyrate)*
- Energy source for the colonic epithelium *(butyrate)*
- Anti-inflammatory effects (including stimulation of Tregs)
- Suppression of colitogenic pathogens *(acetate)*
- Stimulation of host receptors (FFAR2, FFAR3, GPR109)
- Influence on gut hormones (e.g. GLP-1, PYY) and satiety
- Influences upon gut transit, gut barrier function
- Peripheral energy supply, lipogenesis *(acetate)*
- Promote intestinal gluconeogenesis *(butyrate, propionate)*





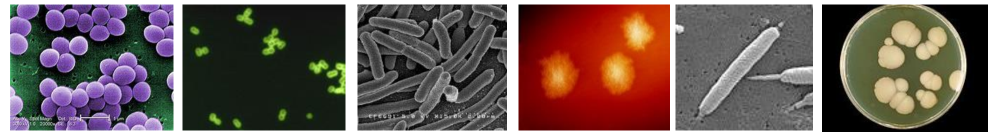
Lactate accumulation shown to be due mainly to reduced lactate utilization by other bacteria at pH 5.2 (^{13}C lactate)

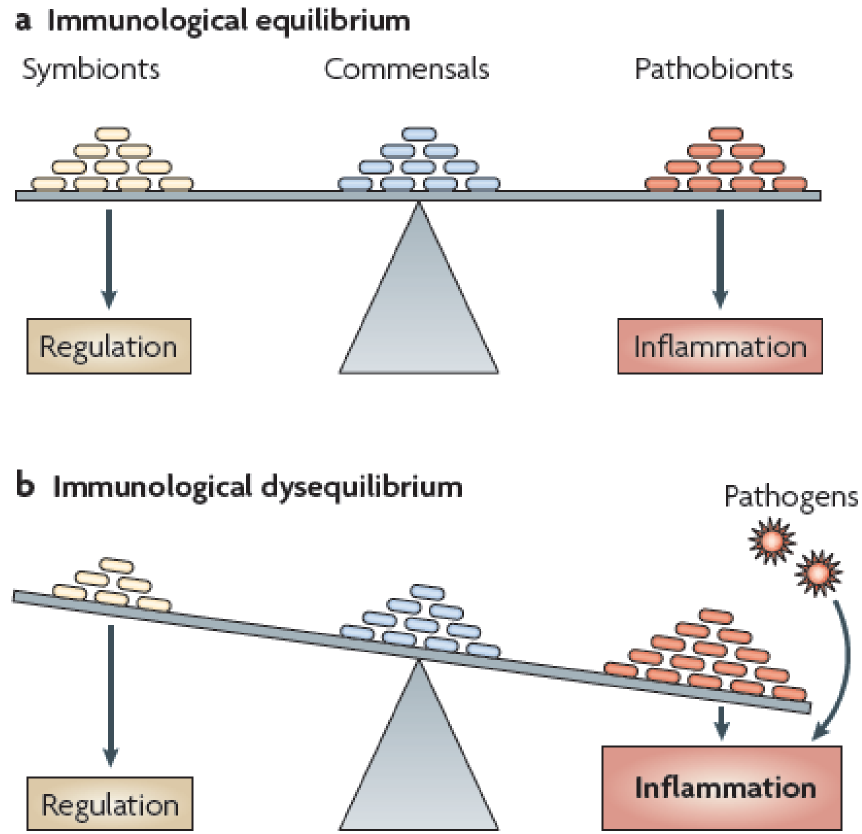
Belenguer, A. *et al* (2007) *A.E.M.* **73**, 6526-6533.

Host-associated microbes in disease

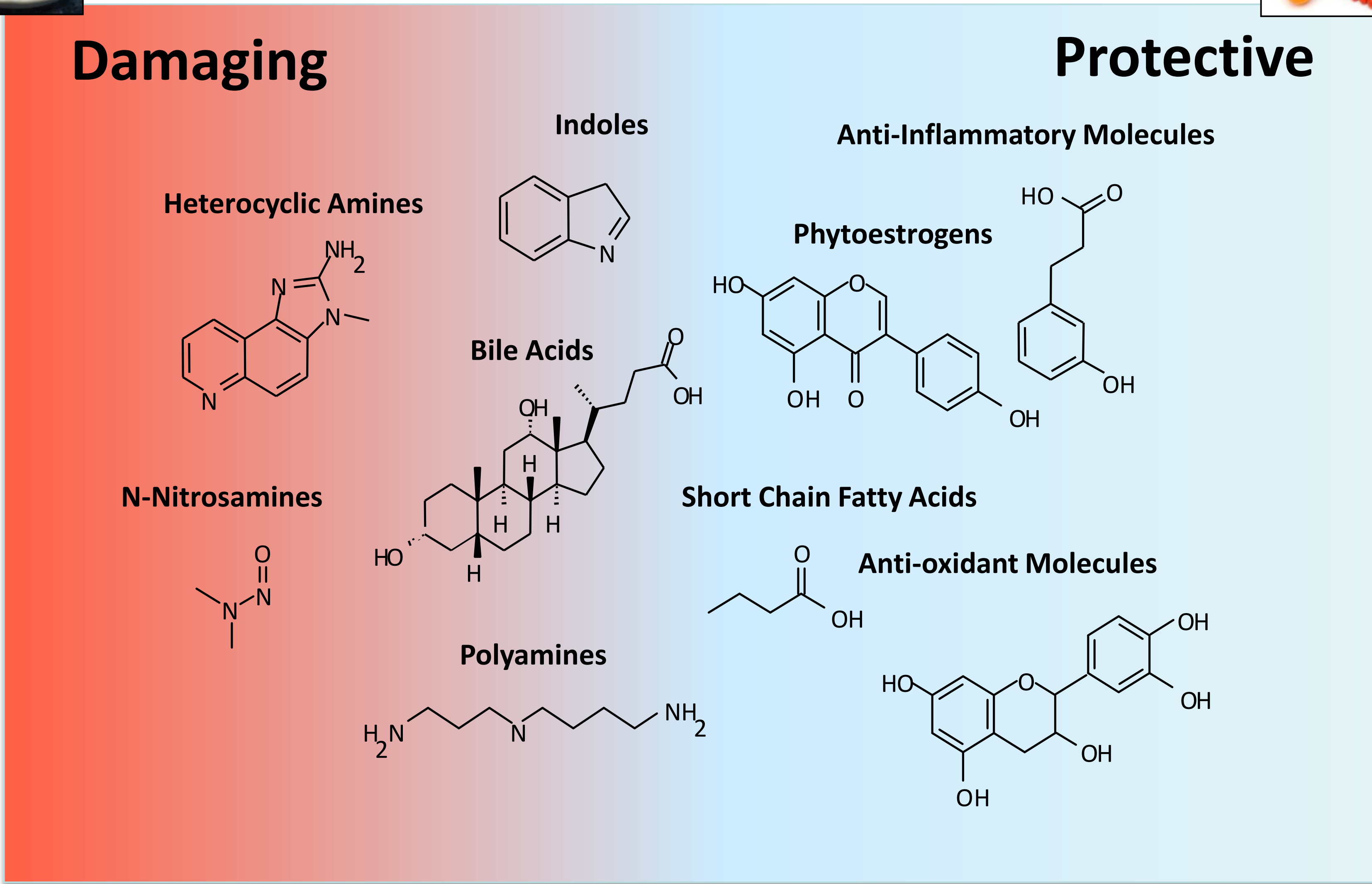
- Many diseases are caused by microbes that normally live asymptomatically on the host
  - e.g. *Staphylococcus aureus* (MRSA), Strep throat, gingivitis, acne, meningitis, pneumonia, *C. difficile* diarrhoea, thrush, UTIs, gastric cancer (*Helicobacter pylori*).

- A general imbalance ("dysbiosis") in microbiota composition has been implicated in many disorders
  - e.g. Inflammatory bowel diseases, bowel cancer, irritable bowel syndrome, diabetes, liver disease, allergies, atherosclerosis





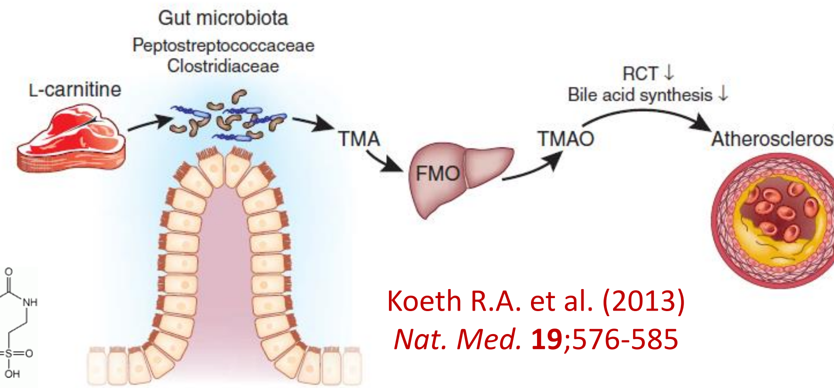
Impact of microbially derived metabolites on the host



The “Western” diet, microbiota and host health

High-protein, reduced-carbohydrate weight-loss diets promote metabolite profiles likely to be detrimental to colonic health[1–4]

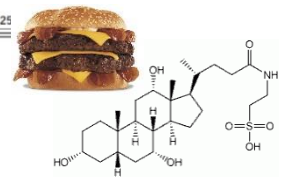
Wendy R Russell, Silvia W Gratz, Sylvia H Duncan, Grietje Holtrop, Jennifer Ince, Lorraine Scobbie, Garry Duncan, Alexandra M Johnstone, Gerald E Lobley, R John Wallace, Garry G Duthie, and Harry J Flint



Koeth R.A. et al. (2013)
Nat. Med. **19**;576-585

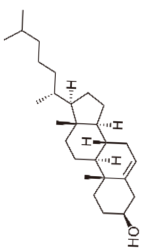
LETTER

doi:10.1038/nature11225



Dietary-fat-induced taurocholic acid promotes pathobiont expansion and colitis in *Il10*$^{-/-}$ mice

Suzanne Devkota[1], Yunwei Wang[1], Mark W. Musch[1], Vanessa Leone[1], Hannah Fehlner-Peach[1], Anuradha Nadimpalli[1], Dionysios A. Antonopoulos[2], Bana Jabri[1] & Eugene B. Chang[1]



nature COMMUNICATIONS

ARTICLE

Received 23 Jun 2014 | Accepted 14 Nov 2014 | Published 23 Dec 2014 DOI: 10.1038/ncomms6864 OPEN

Dietary cholesterol directly induces acute inflammasome-dependent intestinal inflammation

Fränze Progatzky[1], Navjyot J. Sangha[1], Nagisa Yoshida[1], Marie McBrien[1], Jackie Cheung[1], Alice Shia[1,2], James Scott[2], Julian R. Marchesi[3,4,5,6], Jonathan R. Lamb[1], Laurence Bugeon[1,*] & Margaret J. Dallman[1,*]

ARTICLE

doi:10.1038/nature13793

Artificial sweeteners induce glucose intolerance by altering the gut microbiota

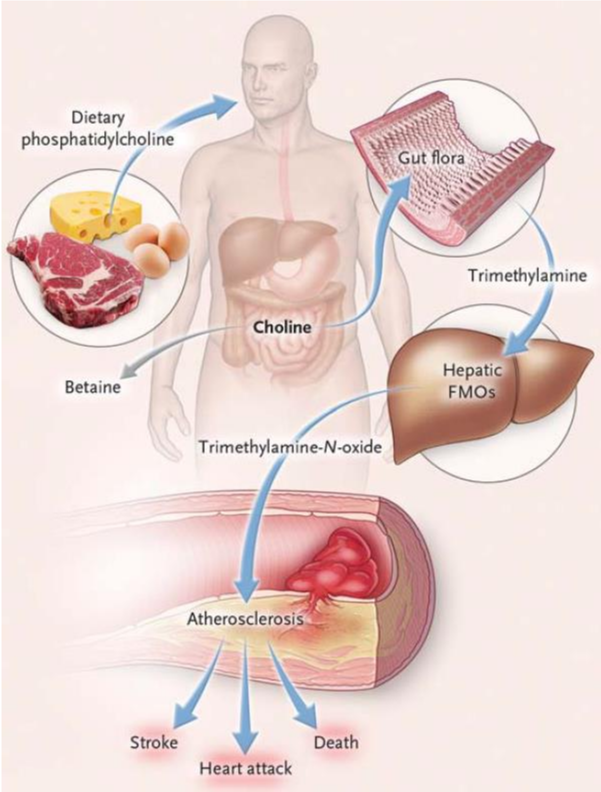
Jotham Suez[1], Tal Korem[2*], David Zeevi[2*], Gili Zilberman-Schapira[1*], Christoph A. Thaiss[1], Ori Maza[1], David Israeli[3], Niv Zmora[4,5,6], Shlomit Gilad[7], Adina Weinberger[2], Yael Kuperman[8], Alon Harmelin[8], Ilana Kolodkin-Gal[9], Hagit Shapiro[1], Zamir Halpern[5,6], Eran Segal[2] & Eran Elinav[1]

LETTER

doi:10.1038/nature14232

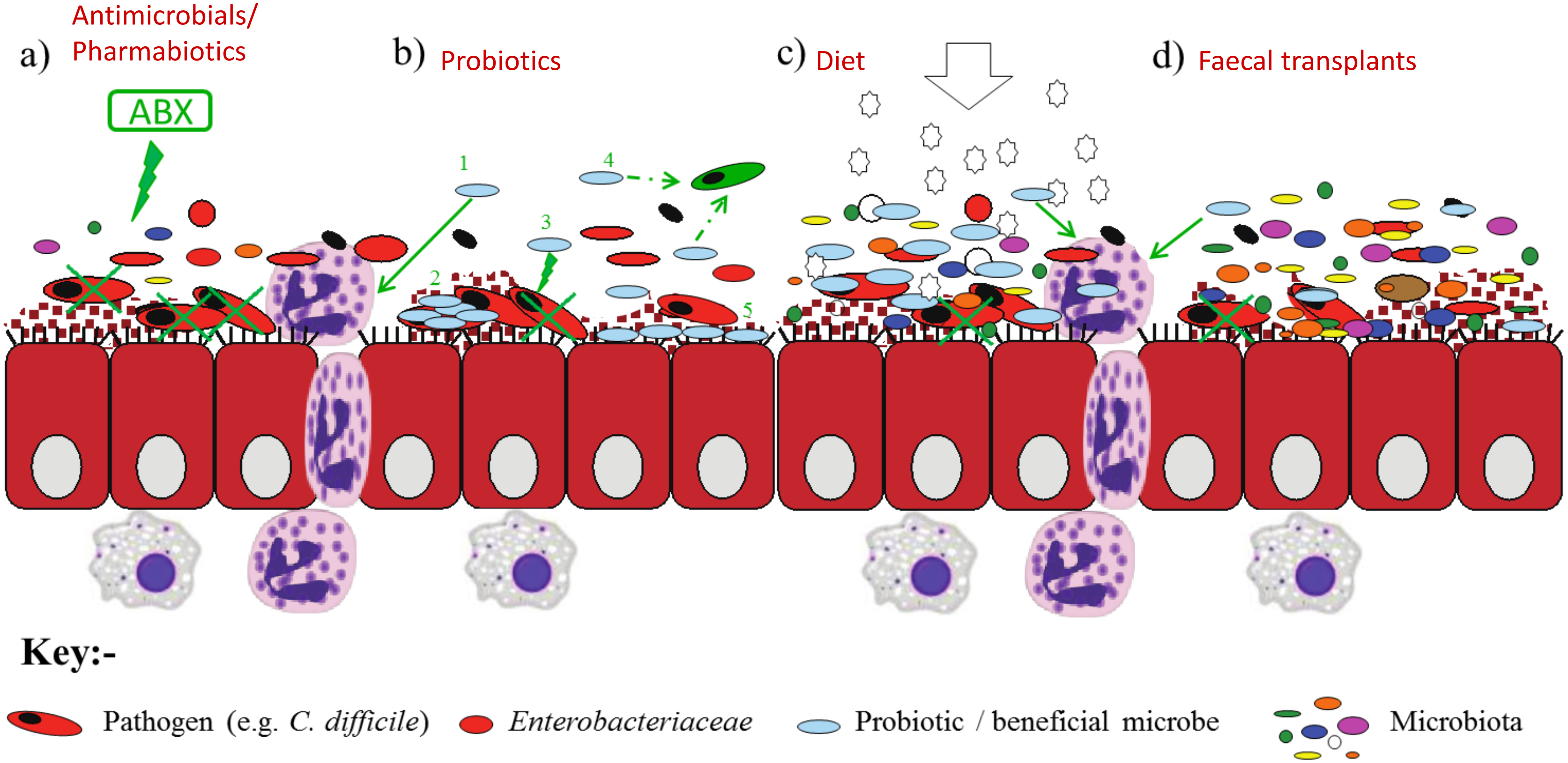
Dietary emulsifiers impact the mouse gut microbiota promoting colitis and metabolic syndrome

Benoit Chassaing[1], Omry Koren[2], Julia K. Goodrich[3], Angela C. Poole[3], Shanthi Srinivasan[4], Ruth E. Ley[3] & Andrew T. Gewirtz[1]



Tang W.H. *et al.* (2013) *NEJM* **368**; 1575-1584

Altering the intestinal microbiota



- The aim of all of these approaches is to shift the composition of the microbiota to a more beneficial state
  - Is targeted manipulation possible via alterations in host diet?

Walker & Lawley (2013) *Pharmacol. Res.* **69**:75-86.

Short- v long-term impacts of diet on the intestinal microbiota

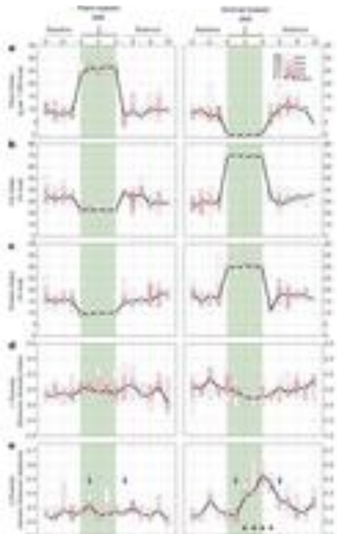
LETTER

doi:10.1038/nature12820

Diet rapidly and reproducibly alters the human gut microbiome

Lawrence A. David[1,2]†, Corinne F. Maurice[1], Rachel N. Carmody[1], David B. Gootenberg[1], Julie E. Button[1], Benjamin E. Wolfe[1], Alisha V. Ling[3], A. Sloan Devlin[4], Yug Varma[4], Michael A. Fischbach[4], Sudha B. Biddinger[3], Rachel J. Dutton[1] & Peter J. Turnbaugh[1]

Figure 1: Short-term diet alters the gut microbiota.



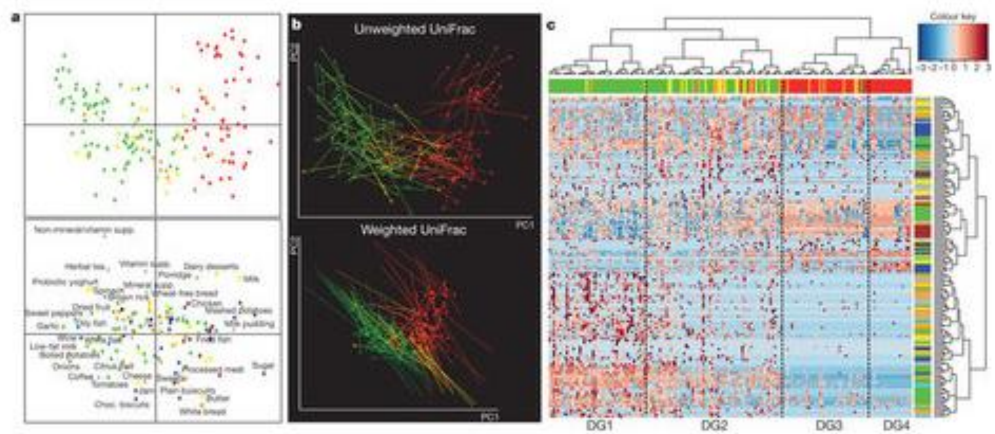
ARTICLE

doi:10.1038/nature11319

Gut microbiota composition correlates with diet and health in the elderly

Marcus J. Claesson[1,2]*, Ian B. Jeffery[1,2]*, Susana Conde[3], Susan E. Power[1], Eibhlís M. O'Connor[1,2], Siobhán Cusack[1], Hugh M. B. Harris[1], Mairead Coakley[4], Bhuvaneswari Lakshminarayanan[4], Orla O'Sullivan[4], Gerald F. Fitzgerald[1,2], Jennifer Deane[1], Michael O'Connor[5,6], Norma Harnedy[5,6], Kieran O'Connor[6,7,8], Denis O'Mahony[5,6,8], Douwe van Sinderen[1,2], Martina Wallace[9], Lorraine Brennan[9], Catherine Stanton[2,4], Julian R. Marchesi[10], Anthony P. Fitzgerald[3,11], Fergus Shanahan[2,12], Colin Hill[1,2], R. Paul Ross[2,4] & Paul W. O'Toole[1,2]

Figure 2: **Dietary patterns in community location correlate with separations based on microbiota composition.**



- Short term dietary regimes can result in reproducible *but limited* microbiota response
- Changes in long-term dietary patterns illicit extensive changes in microbiota composition

Disappearing human microbiota?

- Have host behavioural changes in the urbanisation era introduced changes in microbiota composition?

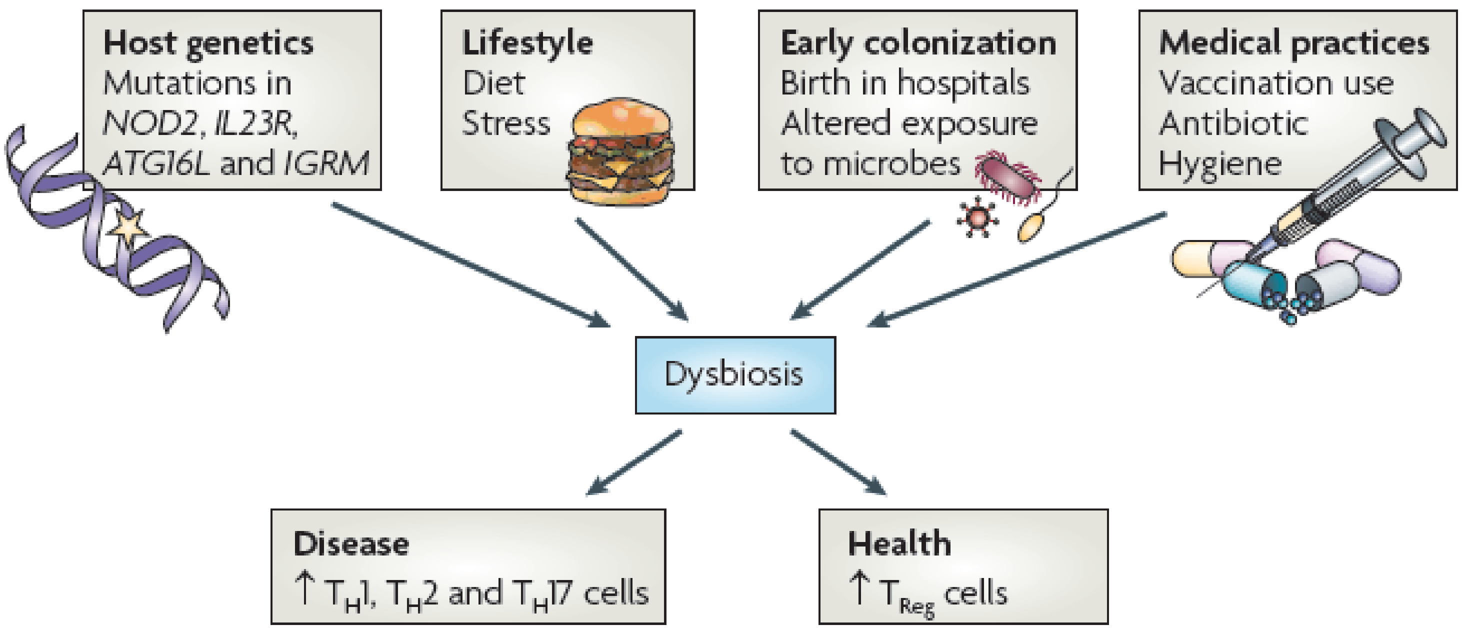
ESSAY

What are the consequences of the disappearing human microbiota?

Martin J. Blaser and Stanley Falkow

The 'disappearing microbiota' hypothesis [...] suggests [...] developments over the past century [...] contributed to a shift in the [...] species and types of microorganism in the gut

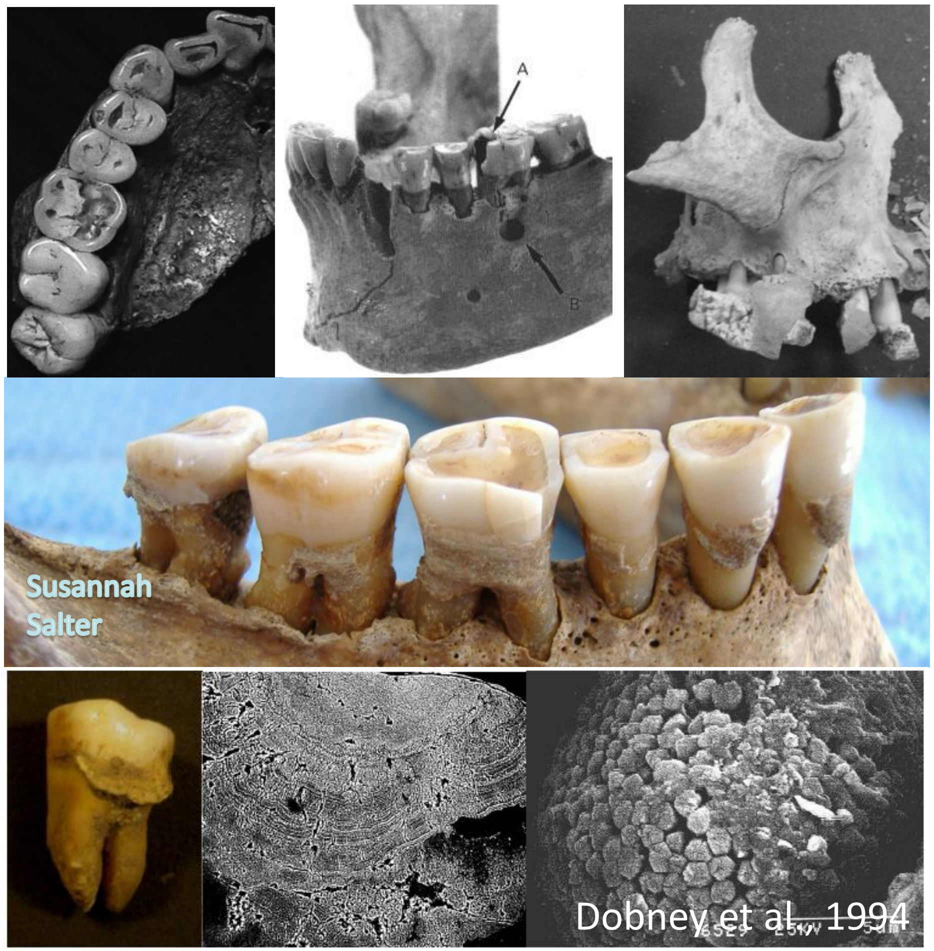
Hunter (2012) *EMBO reports*.**13**, 498–500



Round & Mazmanian (2009) *Nat. Rev. Immun.* **9**;313

Link between diet, oral microbiota and health

Hunter-gatherer | Neolithic agriculturist | Medieval agriculturist



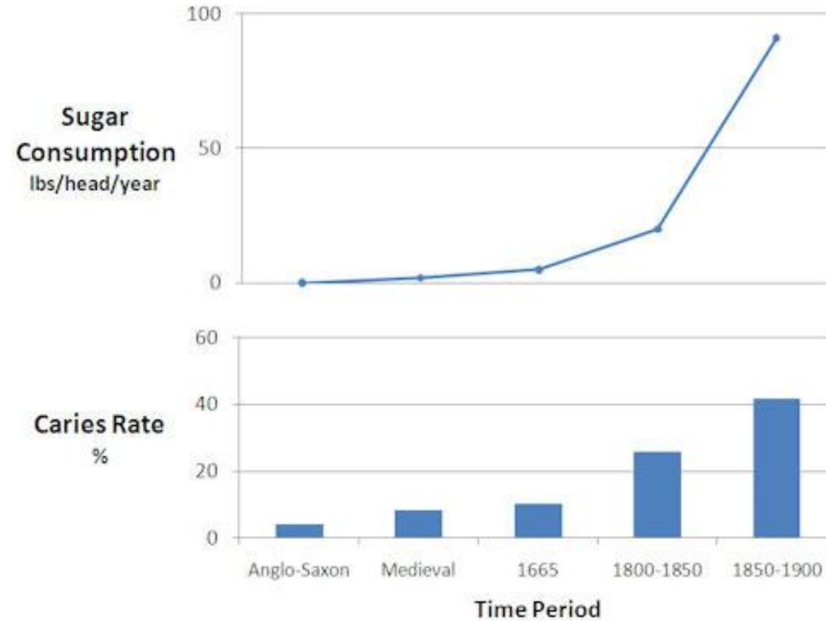
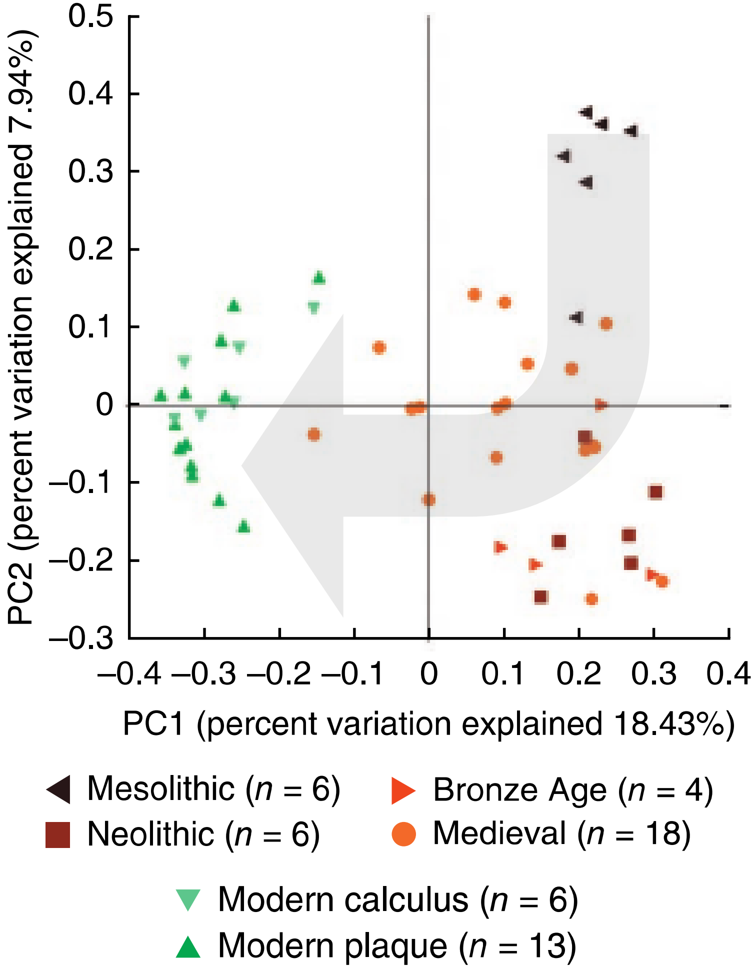


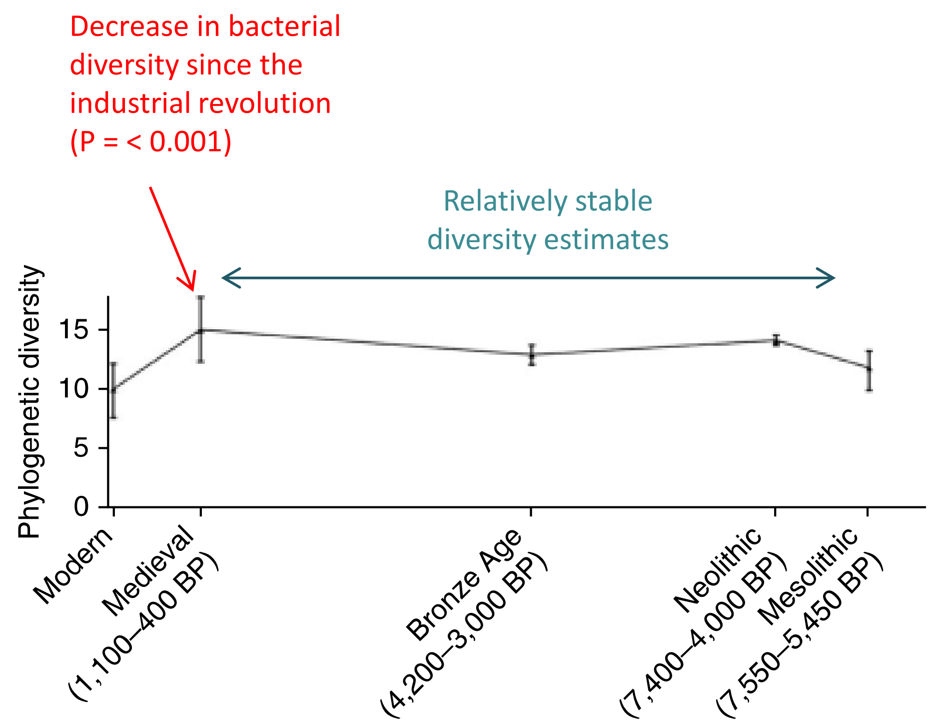
Image: Dr Jo Buckburry (re-plotted from Moore and Corbett 1978)
http://www.leeds.ac.uk/yawya/bioarchaeology/Dental%20disease.html

- Calcified plaque – one of the only preserved records of bacteria
- Densely colonised by oral microbiota

- Increased caries rate in skeletal records is linked to increased consumption of carbohydrates
- Unknown whether or not these changes were accompanied by shifts in microbiota composition

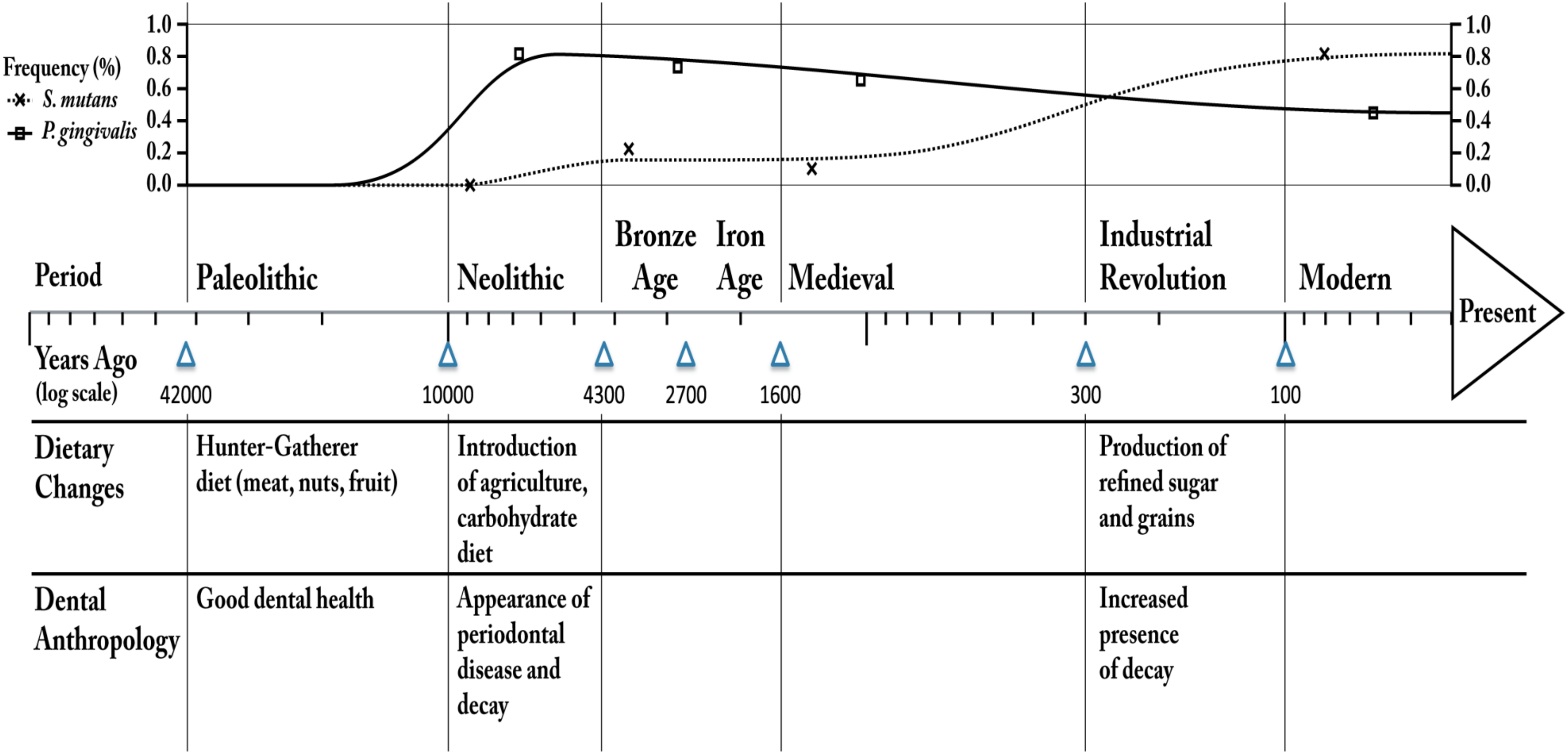
Oral microbiota changes through history





- Non-pathogenic *Ruminococcaceae* associated with hunter-gatherers
- Decay-associated *Veillonellaceae* increase post-farming

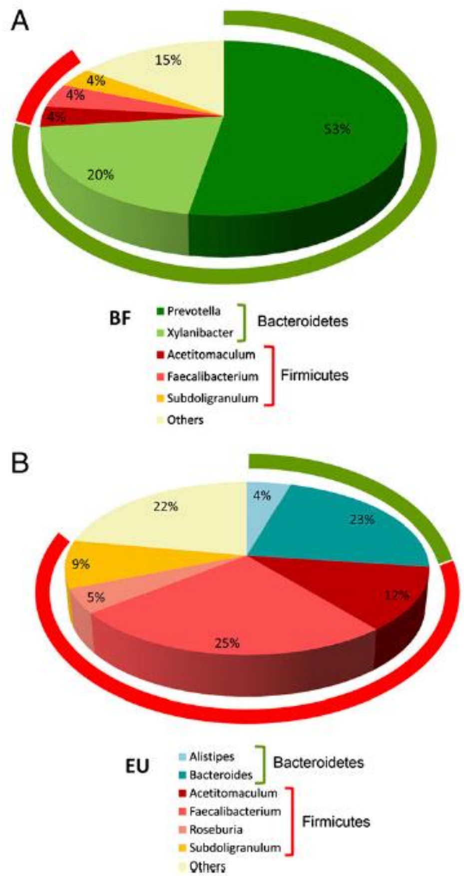
Changes in predominant oral pathogens as a result of diet and culture



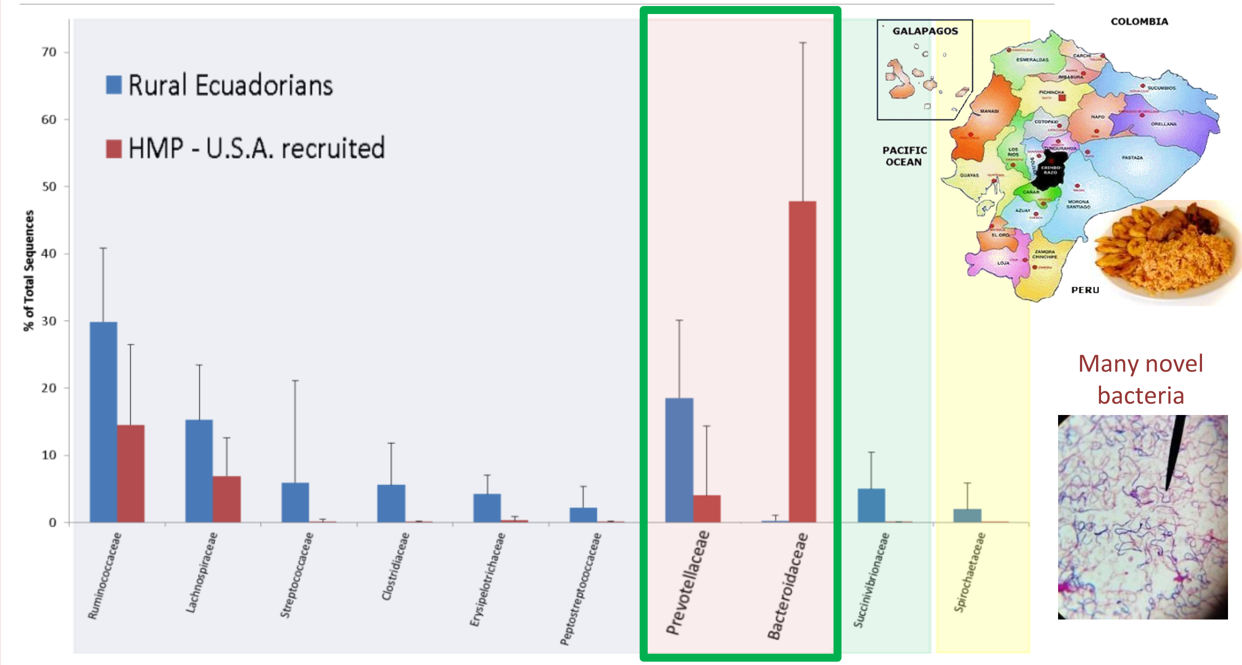
- These pathogens do not appear to be prominent in hunter-gatherers
- *Streptococcus mutans* became dominant relatively recently
- Shifts correlate with human behavioural changes (e.g. diet)

Regional variations in gut microbiota composition

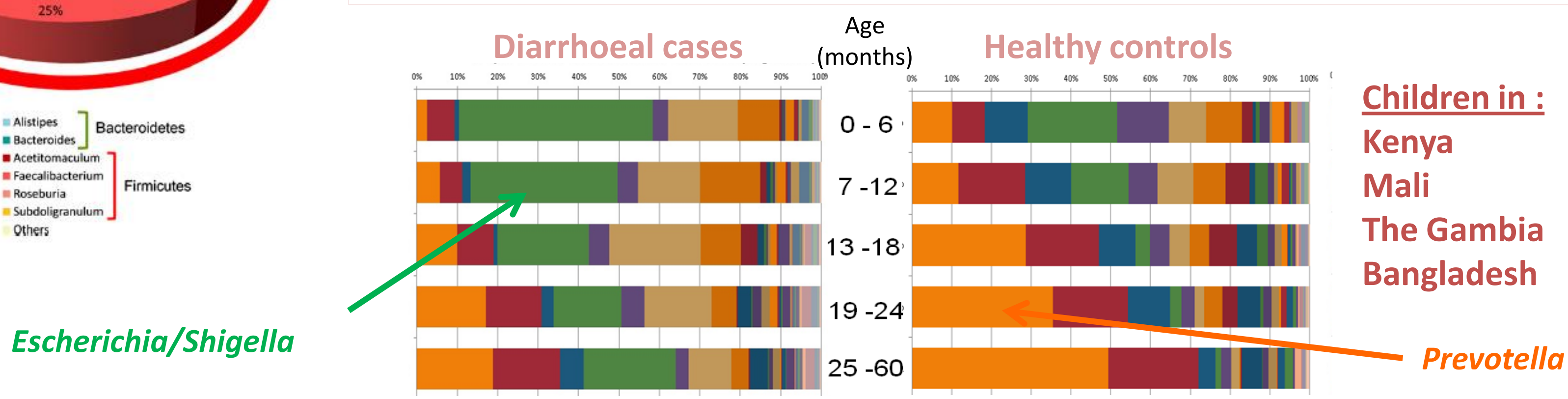
- We may need to reconsider what we think of as a normal "healthy" intestinal microbiota



De Filippo *et al. PNAS* (2010)



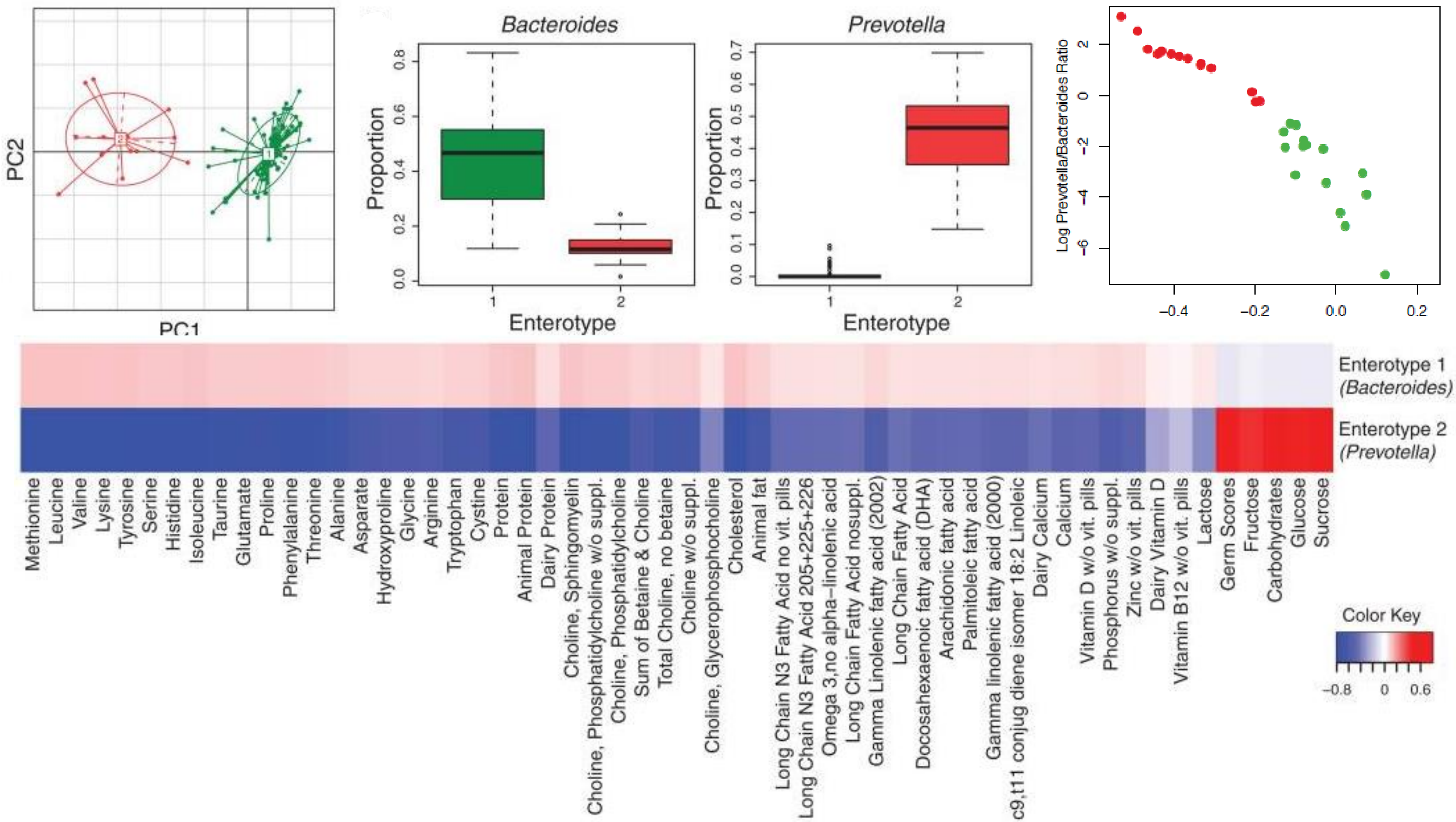
[Cooper, P. *et al.*, (2013) *PLOS ONE* **8**,e76573]



Children in :
Kenya
Mali
The Gambia
Bangladesh

Links between host diet and microbiota structure

- Microbiota structures are associated with long term dietary consumption patterns



Wu *et al*. (2011) *Science* **334**;105-8

Links between host diet and microbiota activity

- O'Keefe *et al* performed 2-week food exchanges
- African Americans were fed a high-fibre, low-fat African-style diet and rural Africans a high-fat, low-fibre western-style diet
- Resulted in measurable changes in health biomarkers
  - ↑ butyrogenesis, ↓ secondary bile acid synthesis in the African Americans

nature COMMUNICATIONS

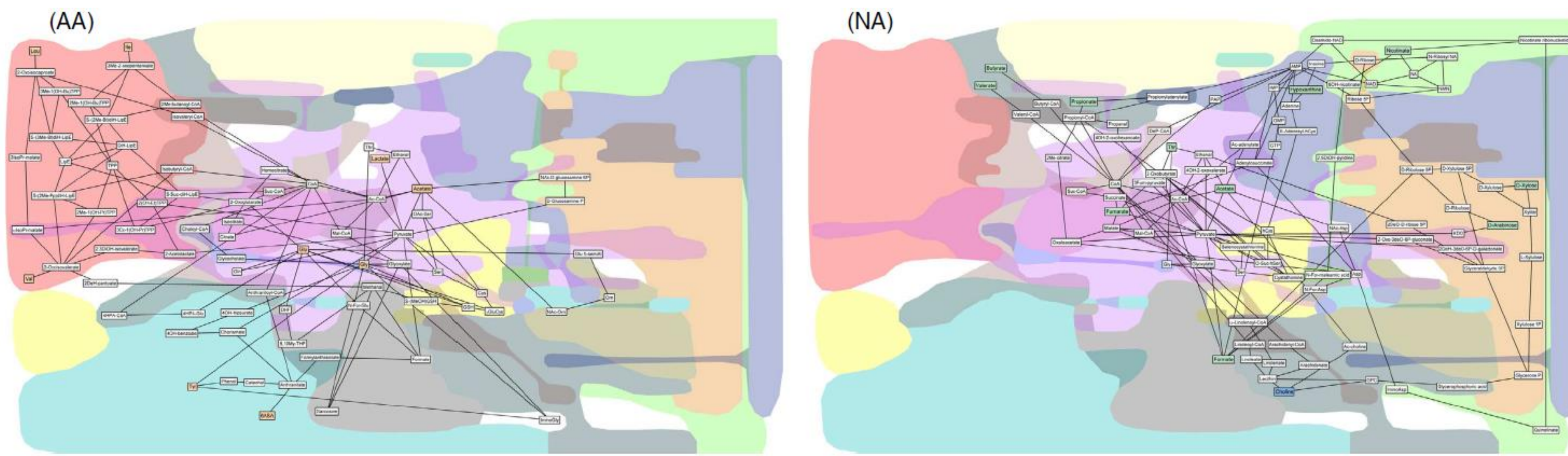
ARTICLE

Received 23 May 2014 | Accepted 20 Jan 2015 | Published 28 Apr 2015

DOI: 10.1038/ncomms7342

Fat, fibre and cancer risk in African Americans and rural Africans

Stephen J.D. O'Keefe[1], Jia V. Li[2], Leo Lahti[3,4], Junhai Ou[1], Franck Carbonero[5,†], Khaled Mohammed[1], Joram M. Posma[2], James Kinross[2], Elaine Wahl[1], Elizabeth Ruder[6], Kishore Vipperla[1], Vasudevan Naidoo[7], Lungile Mtshali[7], Sebastian Tims[3], Philippe G.B. Puylaert[3], James DeLany[8], Alyssa Krasinskas[9], Ann C. Benefiel[5], Hatem O. Kaseb[1], Keith Newton[7], Jeremy K. Nicholson[2], Willem M. de Vos[3,4,10], H. Rex Gaskins[5] & Erwin G. Zoetendal[3]

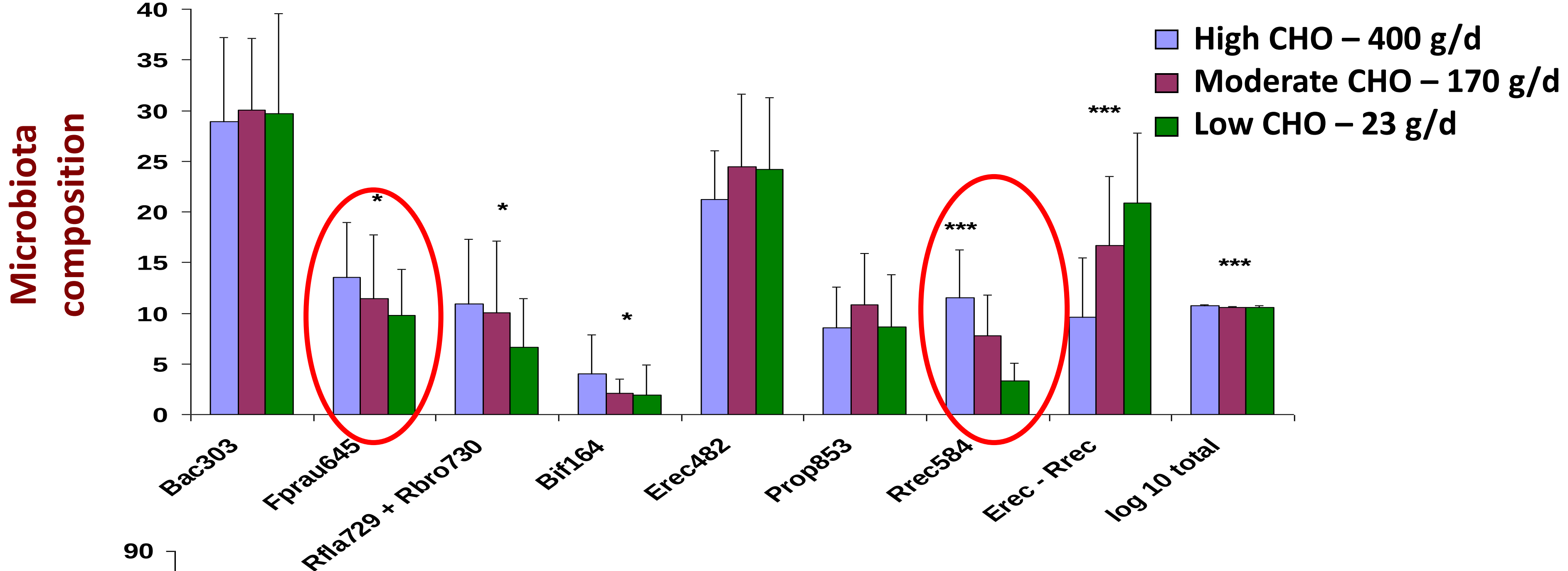


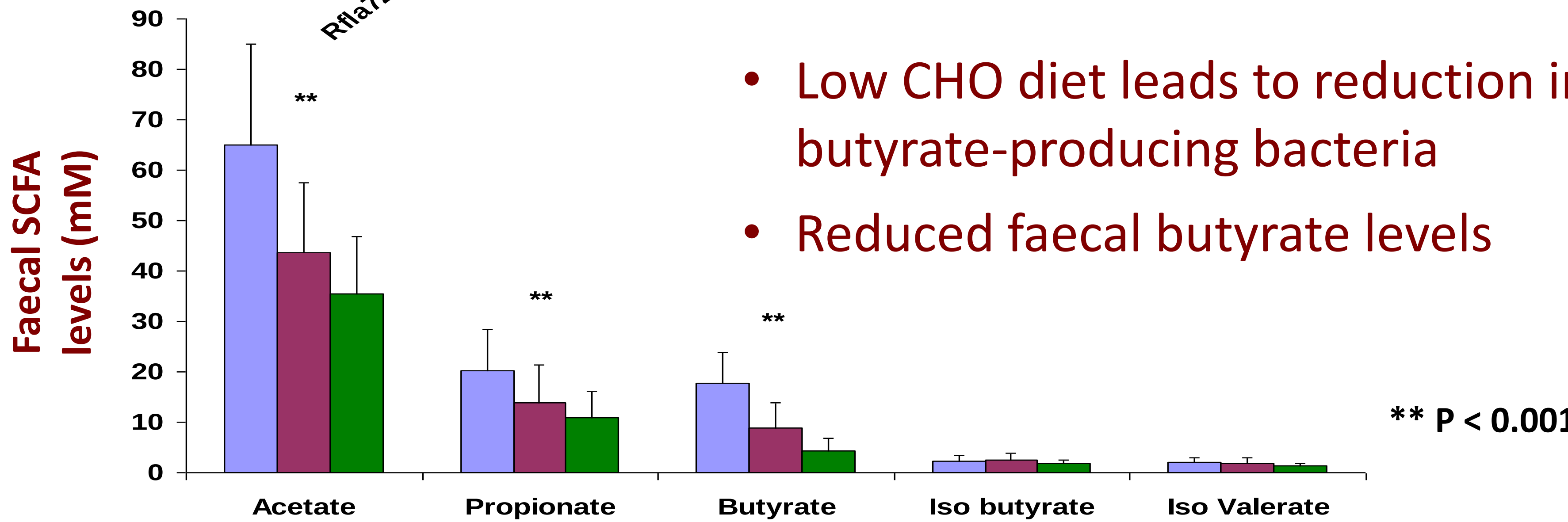
Pathways: Tricarboxylic acid (TCA) cycle | TCA anaplerotic metabolism | Aromatic and indole compounds | Lipid and fatty acid related metabolism | Bile acid metabolism | Branch-chain amino acid metabolism | Nicotinamide metabolism | Coenzyme A metabolism | Purine and pyrimidine metabolism | Glycolysis and amino sugar metabolism | 1-carbon and related metabolism | Sulphur metabolism | Urea cycle and related metabolites | Lysine metabolism

Metabolites: Higher after African diet | Higher after African-American diet | Higher in African home environment | Higher in African-American home environment | Higher in urine after African-American diet, higher in faeces after African diet

O'Keefe *et al*., *Nat. Commun.* (2014), **6**:6342

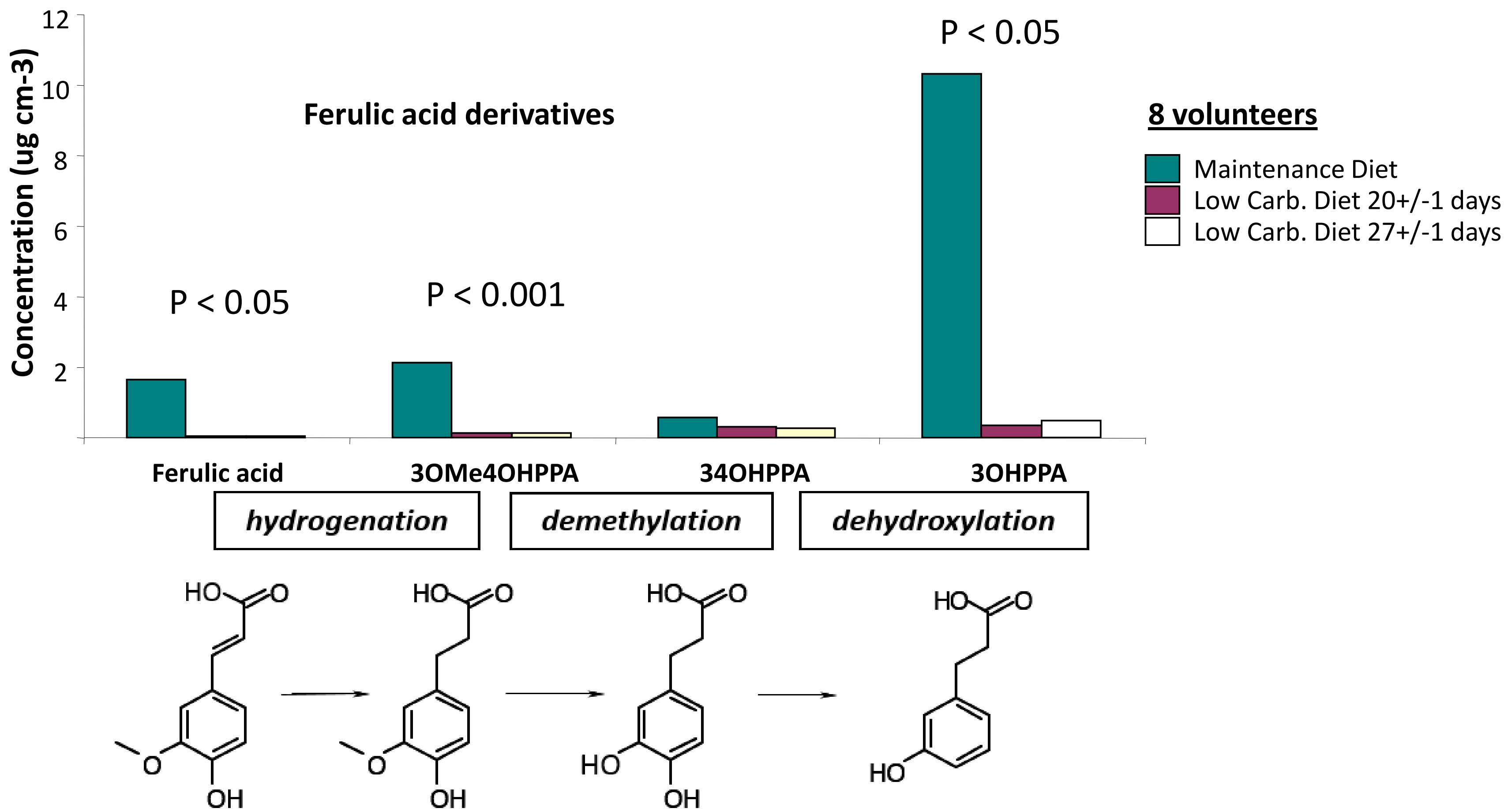
Impact of low carbohydrate weight loss diets





- Low CHO diet leads to reduction in butyrate-producing bacteria
- Reduced faecal butyrate levels

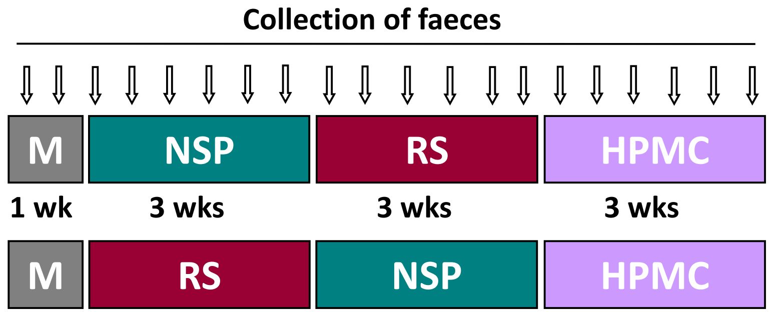
Major fibre derived phenolics in faecal samples



- Low carbohydrate, high protein intake resulted in reduced concentrations of potentially cancer–protective plant phenolic derivatives

Resistant starch vs non-starch polysaccharide diet

14 obese male volunteers with metabolic syndrome (mean age 54 years, mean BMI 39.4 kg/m²)



Mean dietary intake [g/d]:

Diet	CHO	Starch	RS	NSP	Protein	Fat
M	427	230	5	28	103	126
NSP	427	138	2	42	102	136
RS	434	275	26	13	109	127
HPMC	201	110	3	22	144	63

Weight maintenance (M, NSP, RS)

Weight loss (HPMC)

CHO: carbohydrate

M: Weight maintenance, mixed diet (55% energy from carbohydrates)

NSP : High non-starch polysaccharides (added bran), low RS

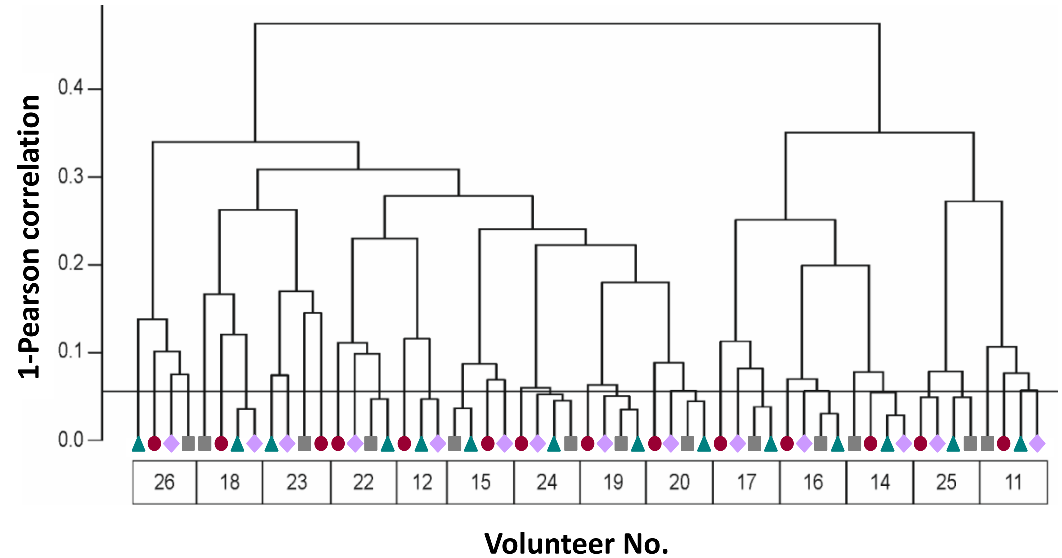
RS: High resistant starch (Type III), reduced NSP

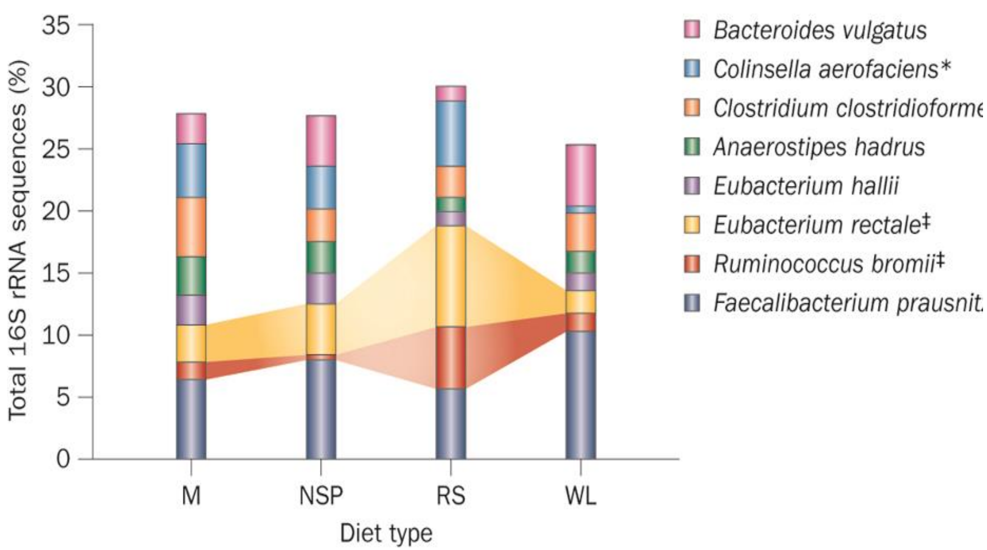
HPMC: Reduced calorie intake. Increased % protein, moderate carbohydrate

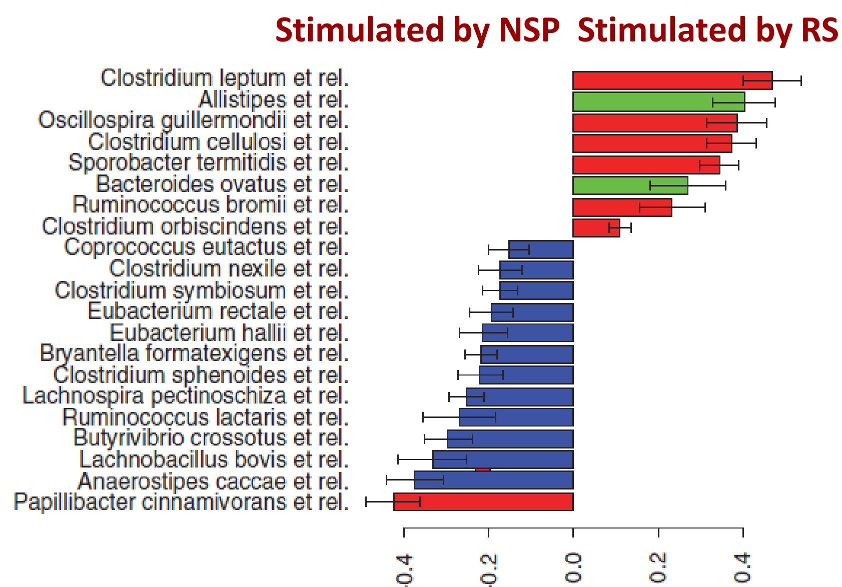
Walker AW. *et al* (2011) *ISME J* 5, 220-230

Resistant starch vs non-starch polysaccharide diet

- Samples cluster by donor, not by diet
- Sub-group of bacteria are highly responsive to both the NSP and RS-enriched diets
  - More *Ruminococcaceae* species increase with RS
  - More *Lachnospiraceae* species increase with NSP

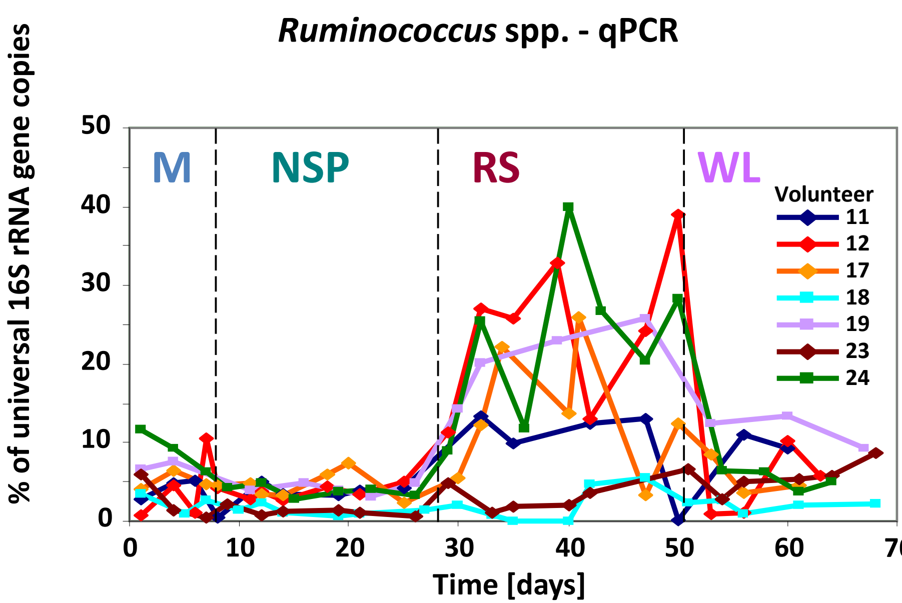


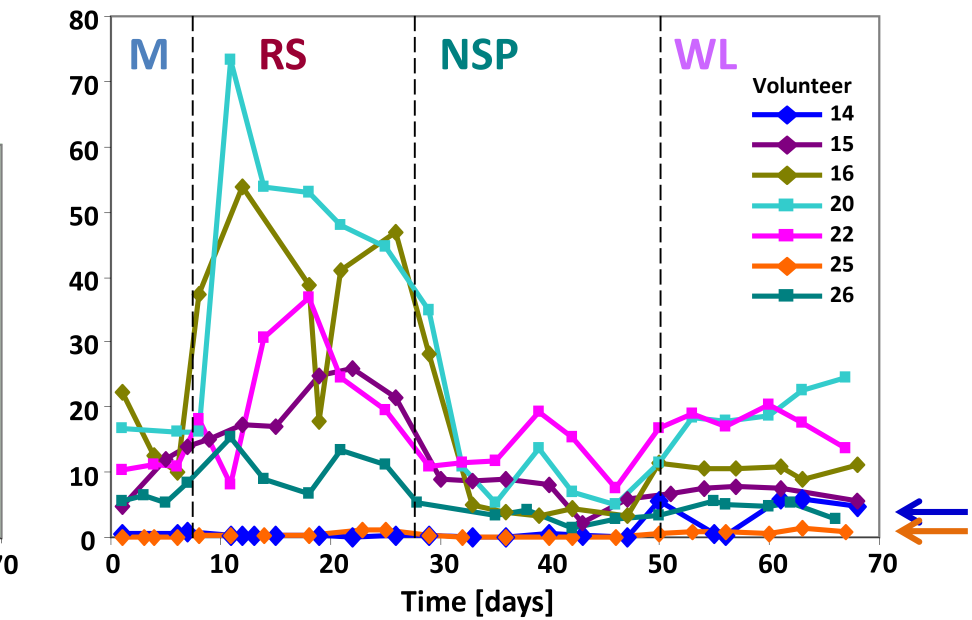




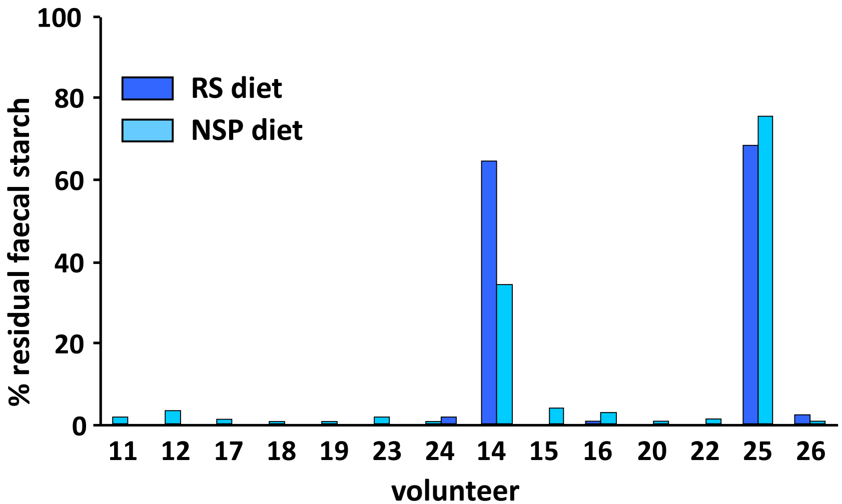
Salonen, A. *et al* (2014) *ISME J* **8**, 2218-30.

Keystone species within the microbiota

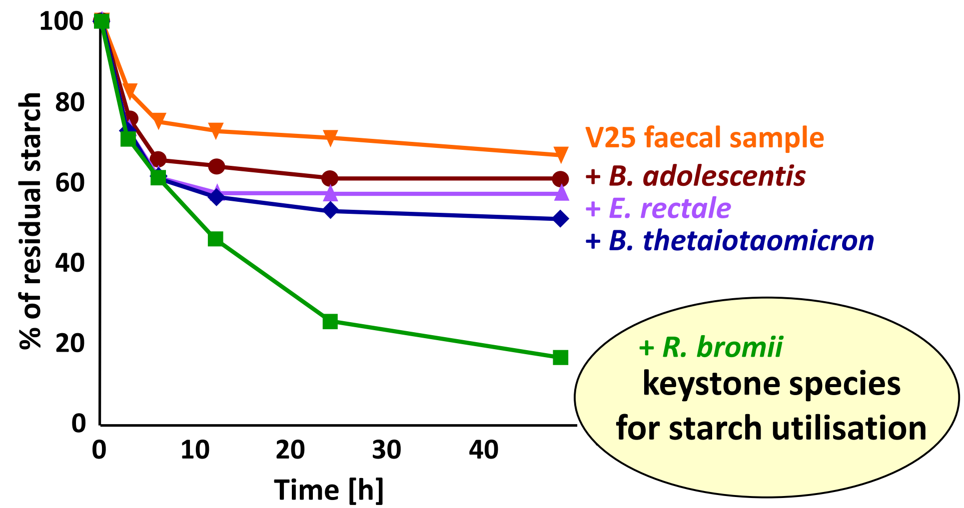




Residual faecal starch in volunteers



Volunteer 25 *in vitro* faecal starch utilisation

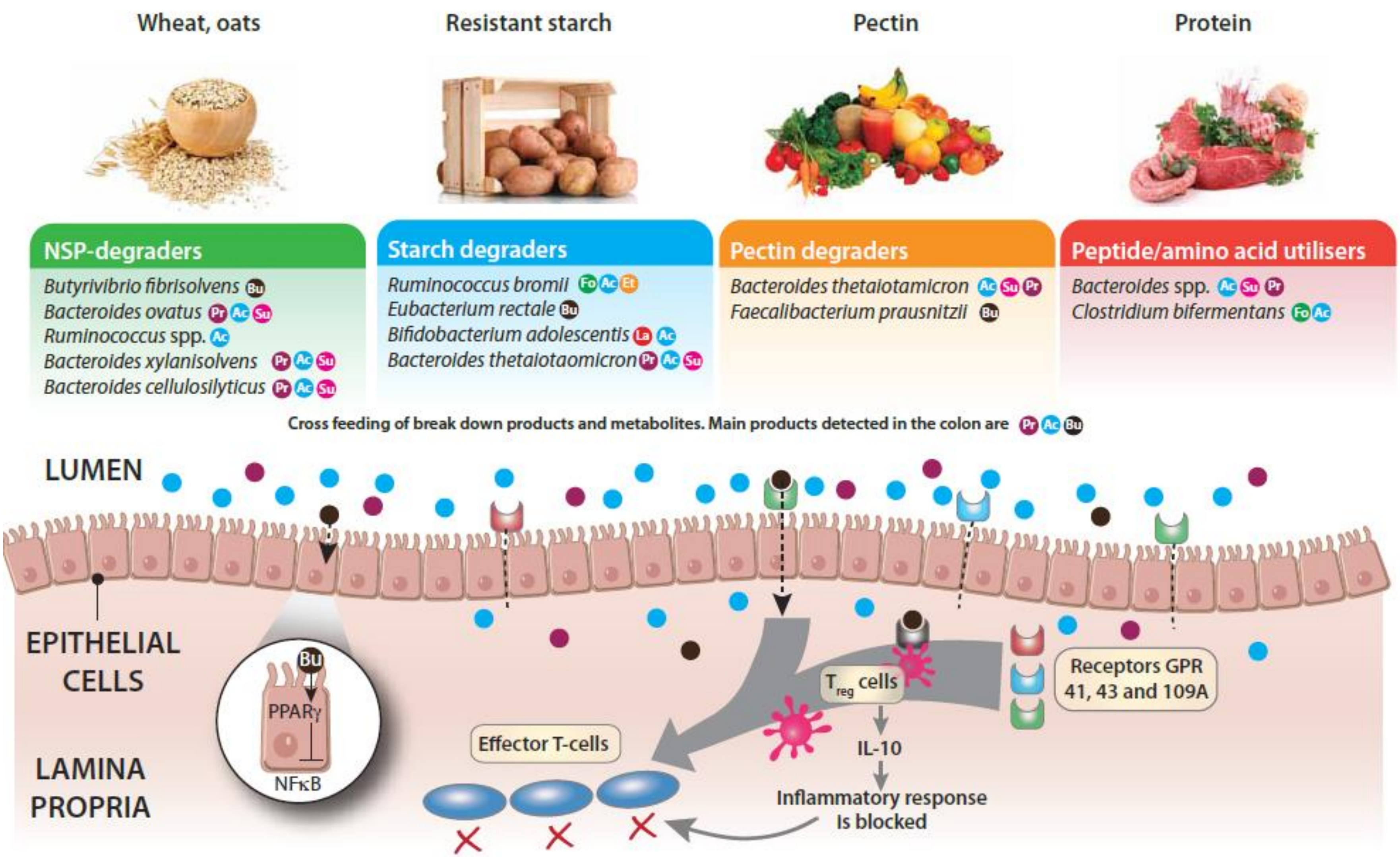


UNIVERSITY OF ABERDEEN

Rowett Institute of Nutrition and Health

Walker *et al. ISME J* (2011); Ze *et al. ISME J* (2012)

Links between diet, microbiota and health



Conclusions

- **Long-term dietary patterns have significant impacts on both intestinal microbiota composition and activity**
  - Fibre consumption appears to be a major driver
- **Microbiota composition and activity are strongly correlated with markers of host health/disease**
  - Mechanistic studies now starting to emerge that link diet/microbiota/health
- **Specific bacterial groups/species respond strongly to dietary change, but there is inter-individual variation in the groups that respond**
- **Many gut bacteria appear to be nutritionally specialised; these species are likely to show the greatest responses to dietary manipulation**
  - 'Keystone' species may determine the ability to ferment insoluble substrates
- **Implications for therapeutic dietary intervention:**
  - The response may depend on the underlying microbiota composition of a given individual
  - Need continued and improved characterisation of the microbiota in order to predict responses to dietary manipulation

Contact : alan.walker@abdn.ac.uk

Interplay between diet and microbiota on gut health

↑ Protection against colorectal cancer and colitis

Interplay between diet and microbiota

↓ Exposure to metabolites and bacteria that promote disease

Nutrient supply to mucosa

Barrier against infection

Release of phytochemicals

phenols, amines, indoles, N-nitroso compounds, H_2S, amines, bile acids, faecapentaenes, heme

Fermentable carbohydrates:

↑ supply of short chain fatty acids

↑ phytochemicals in colon

↓ colonic pH

Acknowledgements

Rowett Institute of Nutrition and Health/University of Aberdeen

Microbiology Group

Harry Flint
Sylvia Duncan
Gillian Donachie
Petra Louis
Jennifer Ince
Lucy Webster
Xiaolei Ze
Aurore Bergerat
Freda McIntosh
Karen Scott
Jenny Martin

David Brown *(Analytical Chem)*
Wendy Russell *(Mol Nutr)*
Alex Johnstone *(OMH)*
Gerald Lobley *(OMH)*
Sylvia Stephen *(HNU)*
Grietje Holtrop *(BioSS)*

University of Aberdeen

Keith Dobney

wellcome trust sanger institute

Pathogen Genomics Group

Julian Parkhill
Paul Scott

Bacterial Pathogenesis Group

Trevor Lawley
Mark Stares

Core Sequencing Teams

Carol Churcher
David Harris
Richard Rance

All other members of the Sanger Institute's sequencing teams

University of Modena and Reggio Emilia

Maddalena Rossi
Andrea Quartieri

University of Adelaide

Alan Cooper
Christina Adler
Laura Weyrich
John Kaidonis
Wolfgang Haak
Corey Bradshaw
Grant Townsend

University of Warsaw

Arkadiusz Sołtysiak

Johannes Gutenberg University of Mainz

Kurt Alt

St. George's, University of London

Phil Cooper

U. Maryland

Colin Stine
Mihai Pop

Funding Sources: wellcome trust; MRC Medical Research Council; The Scottish Government Riaghaltas na h-Alba; RESAS Rural & Environment Science & Analytical Services