



Ameliorating the gut microbiome for longevity and healthy ageing

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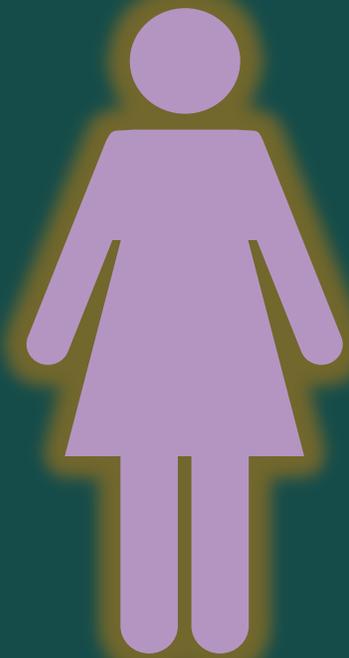



In the next 20 minutes

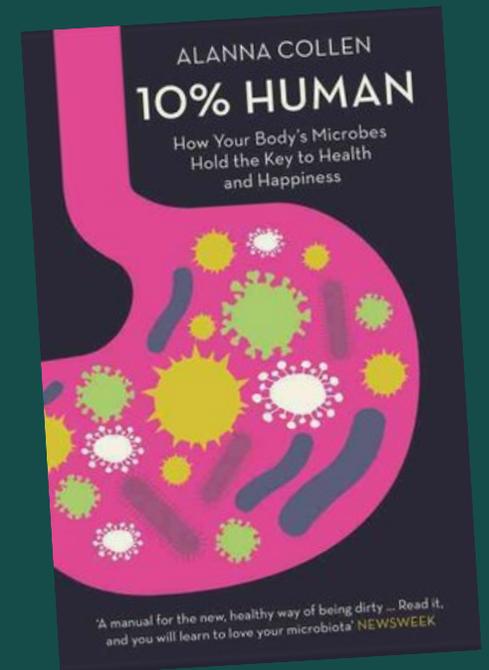
- The human microbiome
- The ageing gut microbiome
- Modifying the microbiome
- Preventing and treating diseases of old age through the gut



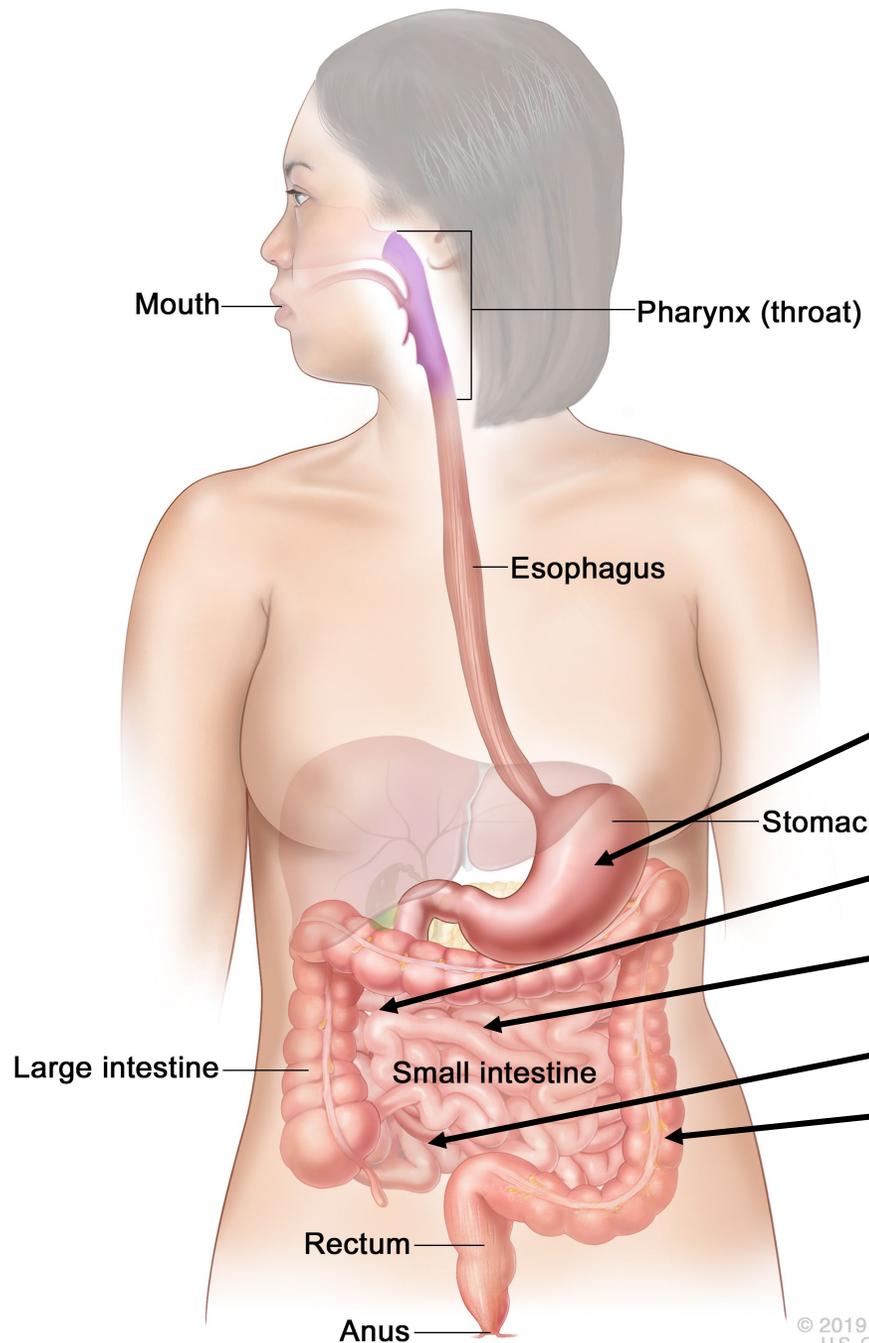
We are only 1% human



- The human body is home to trillions of bacteria, viruses, fungi, archaea, and protozoa
- Bacteria code for 100-fold more unique genes than humans
- Microbiota = microbiome?
- Coexist in a mostly symbiotic relationship



Digestive Tract



The gut microbiome

Stomach: 10^1 bacteria/g content

Duodenum: 10^3 /g content

Jejunum: 10^4 /g content

Ileum: 10^7 /g content

Colon: up to 10^{11-13} /g content, 500 - 1000 different species

We age with them

SCIENTIFIC REPORTS

nature research

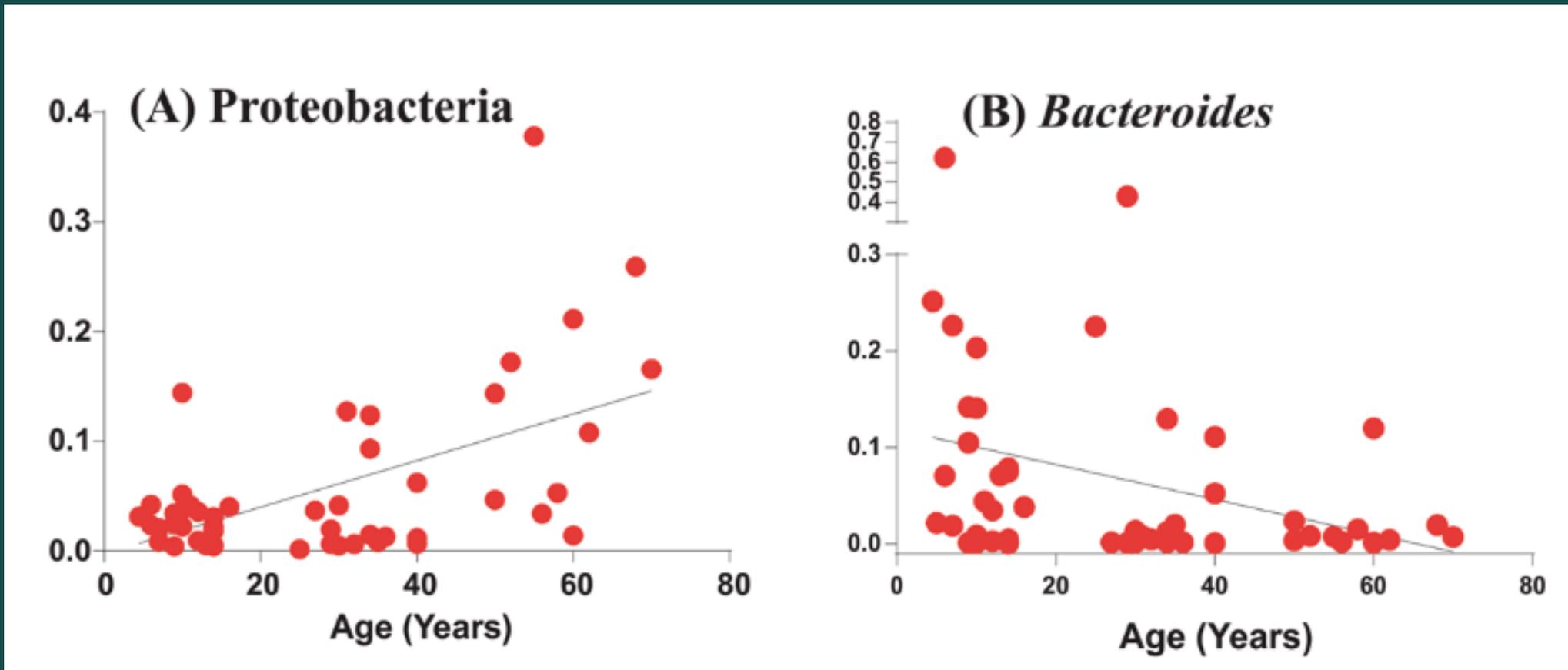
OPEN Gut, oral and skin microbiome of Indian patrilineal families reveal perceptible association with age

Diptaraj S. Chaudhari^{1,3,7}, Dhiraj P. Dhotre^{1,7*}, Dhiraj M. Agarwal², Akshay H. Gaikar^{1,2}, Devika Bhalerao², Parmeshwar Jadhav², Dattatray Mongad¹, Himangi Lubree², Vilas P. Sinkar¹, Ulhas K. Patil^{3,6}, Sundeep Salvi⁶, Ashish Bavdekar⁵, Sanjay K. Juvekar² & Yogesh S. Shouche^{1*}

The human microbiome plays a key role in maintaining host homeostasis and is influenced by age, geography, diet, and other factors. Traditionally, India has an established convention of extended family arrangements wherein three or more generations, bound by genetic relatedness, stay in the same household. In the present study, we have utilized this unique family arrangement to understand the association of age with the microbiome. **We characterized stool, oral and skin microbiome of 54 healthy individuals from six joint families by 16S rRNA gene-based metagenomics.** In total, 69 (1.03%), 293 (2.68%) and 190 (8.66%) differentially abundant OTUs were detected across three generations in the gut, skin and oral microbiome, respectively. Age-associated changes in the gut and oral microbiome of patrilineal families showed **positive correlations in the abundance of phyla Proteobacteria and Fusobacteria, respectively.** Genera *Treponema* and *Fusobacterium* showed a positive correlation with age while *Granulicatella* and *Streptococcus* showed a negative correlation with age in the oral microbiome. Members of genus *Prevotella* illustrated high abundance and prevalence as a core OTUs in the gut and oral microbiome. In conclusion, this study highlights that precise and perceptible association of age with microbiome can be drawn when other causal factors are kept constant.

- Gut microbiome composition changes over the lifetime
- ↑ phylum Proteobacteria with increasing age
- ↓ genus Bacteroides with increasing age

Relative abundance of Proteobacteria and Bacteroides with age



(Chaudhari, Dhotre et al. 2020)

Alterations in pharmacokinetics



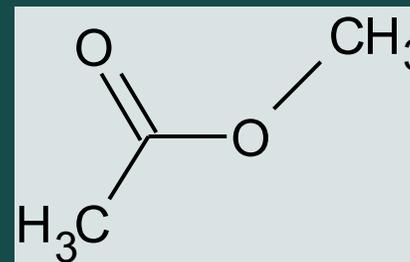
Proteobacteria

- Inactivate antineoplastic drugs
capecitabine, doxifluridine, and
trifluridine
- Degrade tinidazole, entacapone,
enalapril, artemisinin

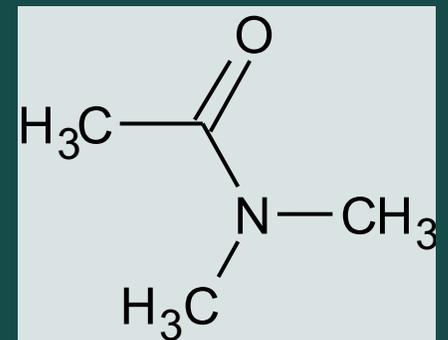
Bacteroides

- Activate the laxative lactulose
- Degrade ramipril, budesonide,
famciclovir, clopidogrel,
fluoxetine, diclofenac,
indomethacin, irinotecan

Esters

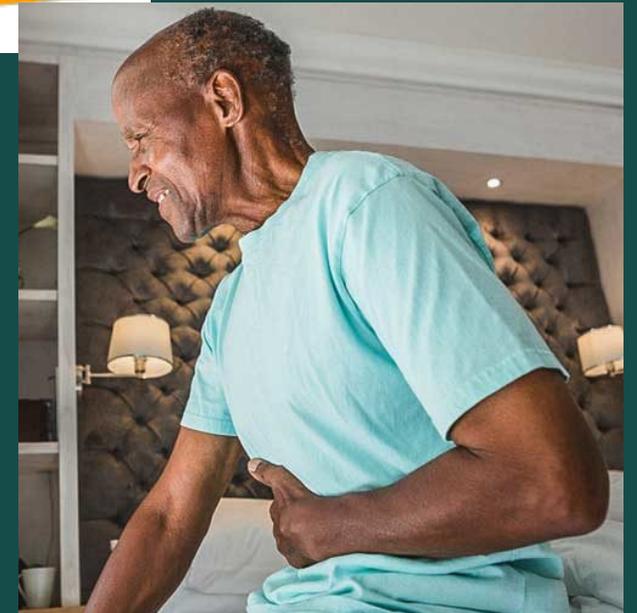


Amides

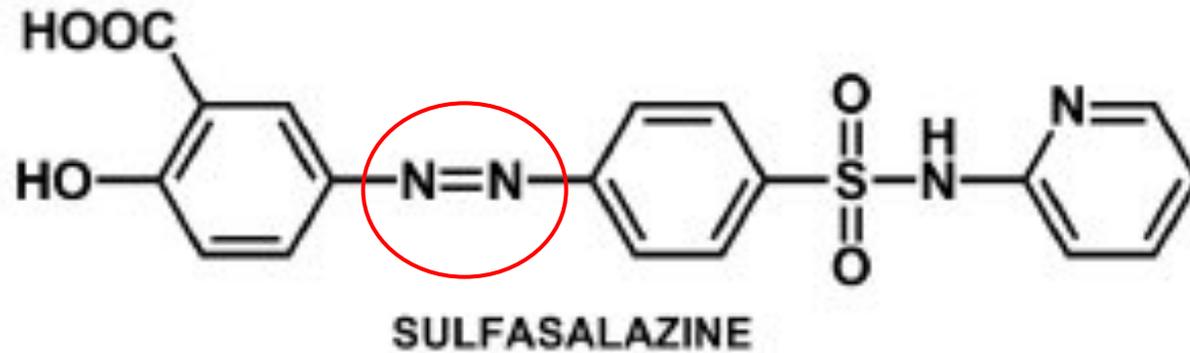


Sulfasalazine vs. Proteobacteria

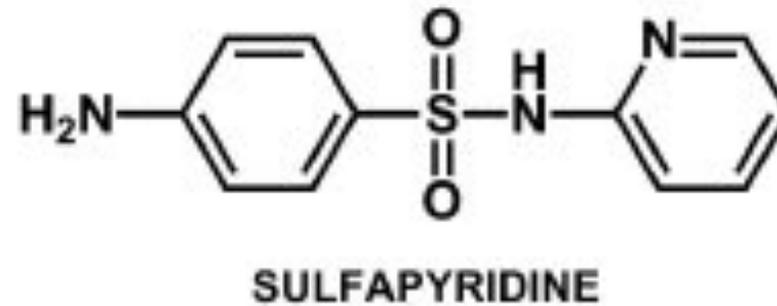
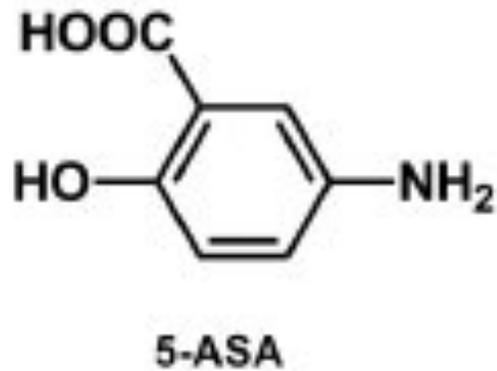
- Indicated for inflammatory bowel disease, up to 8 g orally per day
- Metabolised by Proteobacteria in the colon to the active compounds sulfapyridine and mesalazine (5-ASA)
- $T_{1/2}$ and C_{SS} are increased in the elderly (Taggart et al., 1992)



Sulfasalazine vs. Proteobacteria



↓
AZOREDUCTASES



↑
Age

↑
Proteobacteria in colon

↑
Azoreductases

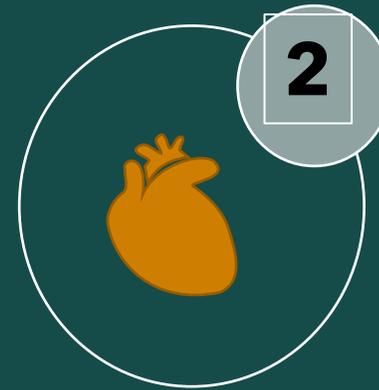
↑
Drug activation

Chronic disease: an unavoidable fact of life?



Dementia

1 in 6 people
over 80 in the UK
have dementia
(Age Concern)



Metabolic syndrome

1 in 3 people over
50 in the UK are
estimated to have
metabolic syndrome
(NHS)

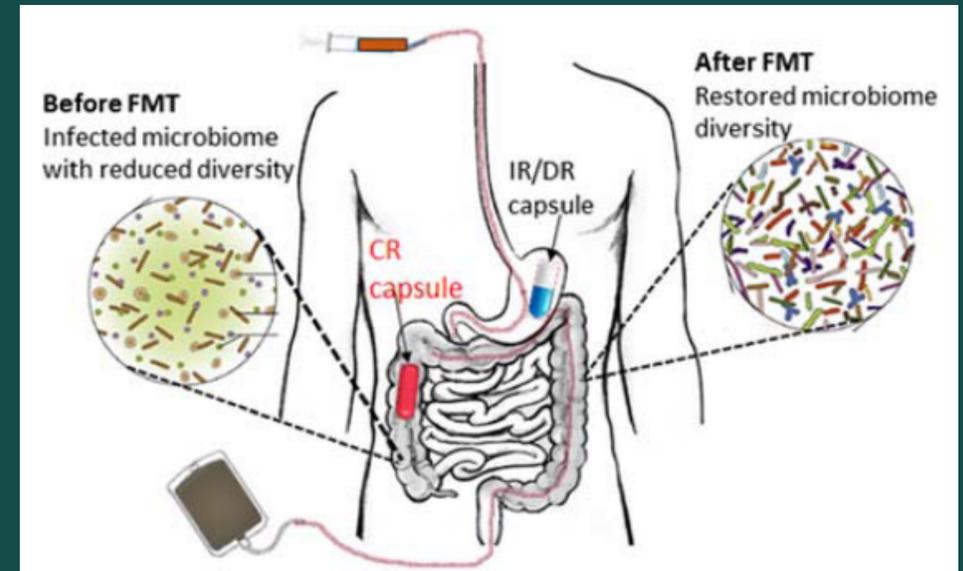
Microbiome medicine



Method	Definition	Example
Probiotics	Live microorganisms, which when administered in adequate amounts, confer a health benefit on the host	Faecal microbiota transplant for treatment of <i>C. difficile</i> infection
Prebiotics	A substrate that is selectively utilised by host microorganisms conferring a health benefit	Plant-based starches resistant to human digestion
Entities altering the microbiome microenvironment	Small molecules and biopharmaceuticals that promote the growth of beneficial microbiota or dissuade the growth of pathogens	Inulin-propionate ester for improvement of obesity

Faecal Microbiota Transplant (FMT)

- 13,286 cases of *Clostridium difficile* infection in England (2017-2018)
- 80% of *C. difficile* deaths occur in people aged over 65 (Balsells, Shi et al. 2019)
- Mean recurrence rate of 20% for *C. difficile* treated with first-line therapies (metronidazole/vancomycin)
- FMT has a 92% success rate in rectifying treatment-resistant *C. difficile*
- Focus in recent years to develop oral dosage forms for FMT (Fadda 2020)



Dementia and the gut microbiome

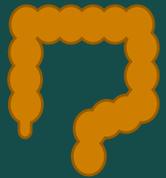


1 in 6

1 in 6 people over 80 in the UK have dementia



Bacteroides prevalence has been associated with all types of dementia (Saji et al., 2019)



The gut microbiome is known to modulate host brain function via the microbiome-gut-brain axis



Overall faecal microbial diversity in Alzheimer's disease (Liu et al., 2019)



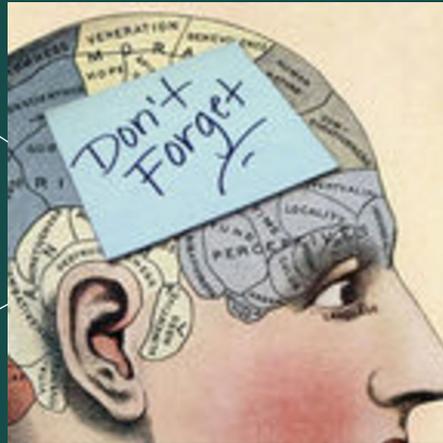
Disruption of the neuro-inflammatory system may be caused by microbiota, leading to deposition of amyloid β in the brain



Microbiome medicine for dementia



Lactobacilli



Cheese



Bifidobacteria



Dairy-based kefir

Metabolic syndrome and the gut microbiome



1 in 3

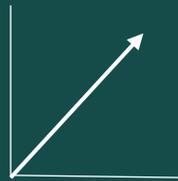
1 in 3 people over 50 in the UK have metabolic syndrome



Metabolic syndrome is an umbrella term for combined type 2 diabetes mellitus, hypertension, and obesity



An increased Firmicutes/Bacteroidetes ratio is often associated with obesity



Escherichia Shigella has been found to positively correlate with elevated BMI and blood glucose, whereas *Fusobacterium* and *Bacillus* are found to correlate with higher insulin levels (Gao et al., 2018)



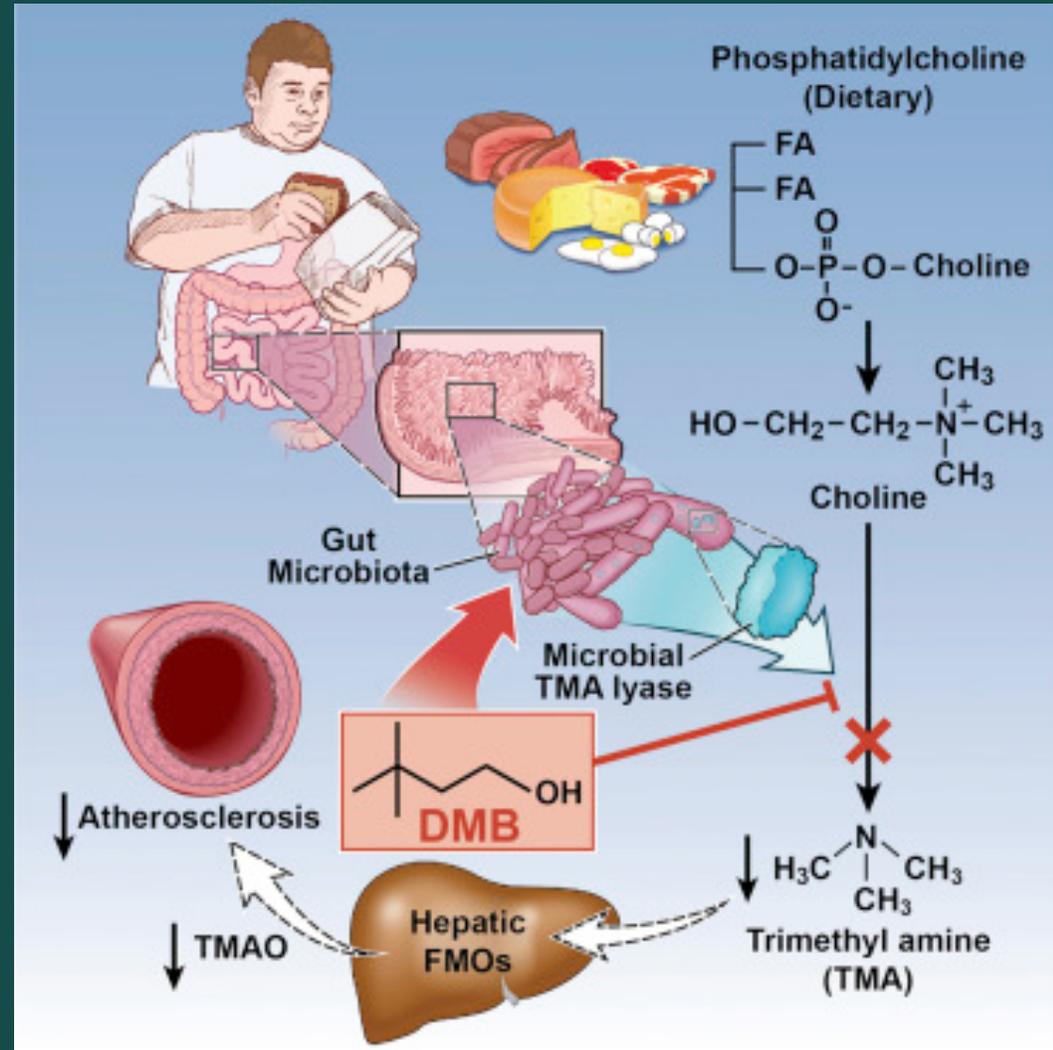
Dietary phosphatidylcholine metabolism by gut bacteria is correlated with atherosclerosis, platelet hyperactivity, and thrombosis (Ahmadmehrabi and Tang 2017)

Microbiome medicine for metabolic disease



- A high fibre diet with acetate supplementation has been reported to improve gut dysbiosis, lower blood pressure, reduce cardiac fibrosis and improve left ventricular hypertrophy in mice (Marques, Nelson et al. 2017)
- FMT has improved insulin sensitivity in humans (Vrieze, Van Nood et al. 2012)
- Inulin-propionate ester has been used in several human clinical trials for metabolic disease, and has been shown to improve non-alcoholic fatty liver disease, reduce weight gain, protect insulin sensitivity, and control appetite in obese individuals (Byrne, Chambers et al. 2019).
- A small molecule (DMB) has been developed to block phosphatidylcholine metabolism, treating atherosclerosis and heart failure in mice (Wang, Kong et al. 2020)

Blocking harmful phosphatidylcholine metabolism



Summary

- Many aspects of human health are reliant on a symbiotic microbiome relationship
- Dysbiosis can lead to disease and alterations in drug pharmacokinetics
- The human microbiome alters as the host ages, potentially leading to dysbiosis
- Many age-related diseases may be prevented and treated using microbiome medicine



~~Multiple sclerosis~~

~~Diverticulitis~~

~~Dementia~~

~~Stroke~~

~~Colon cancer~~

~~Metabolic disease~~

~~Kidney failure~~

~~Parkinson's~~

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