MICROBA

Managing metabolic health through the gut microbiome

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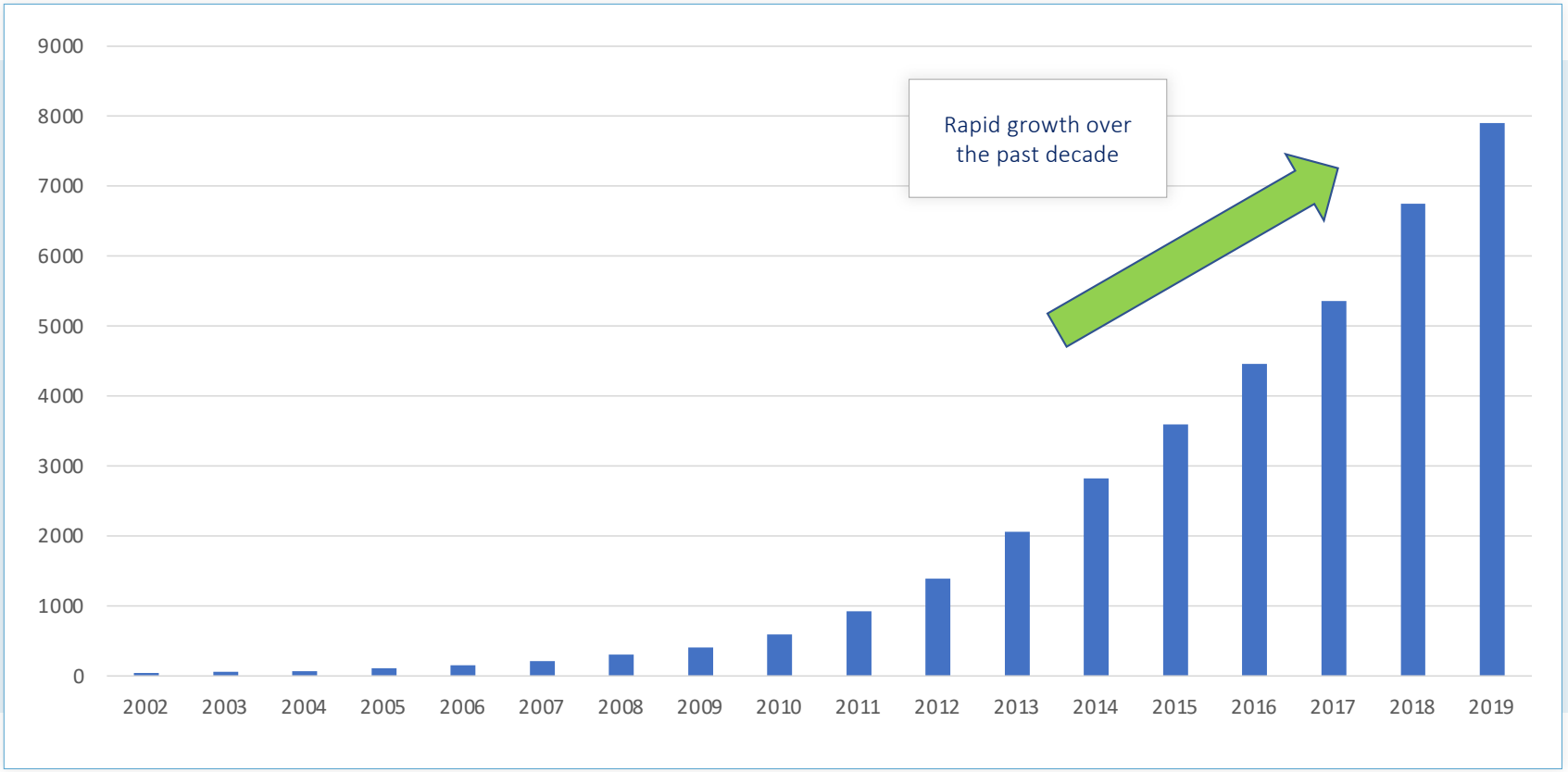
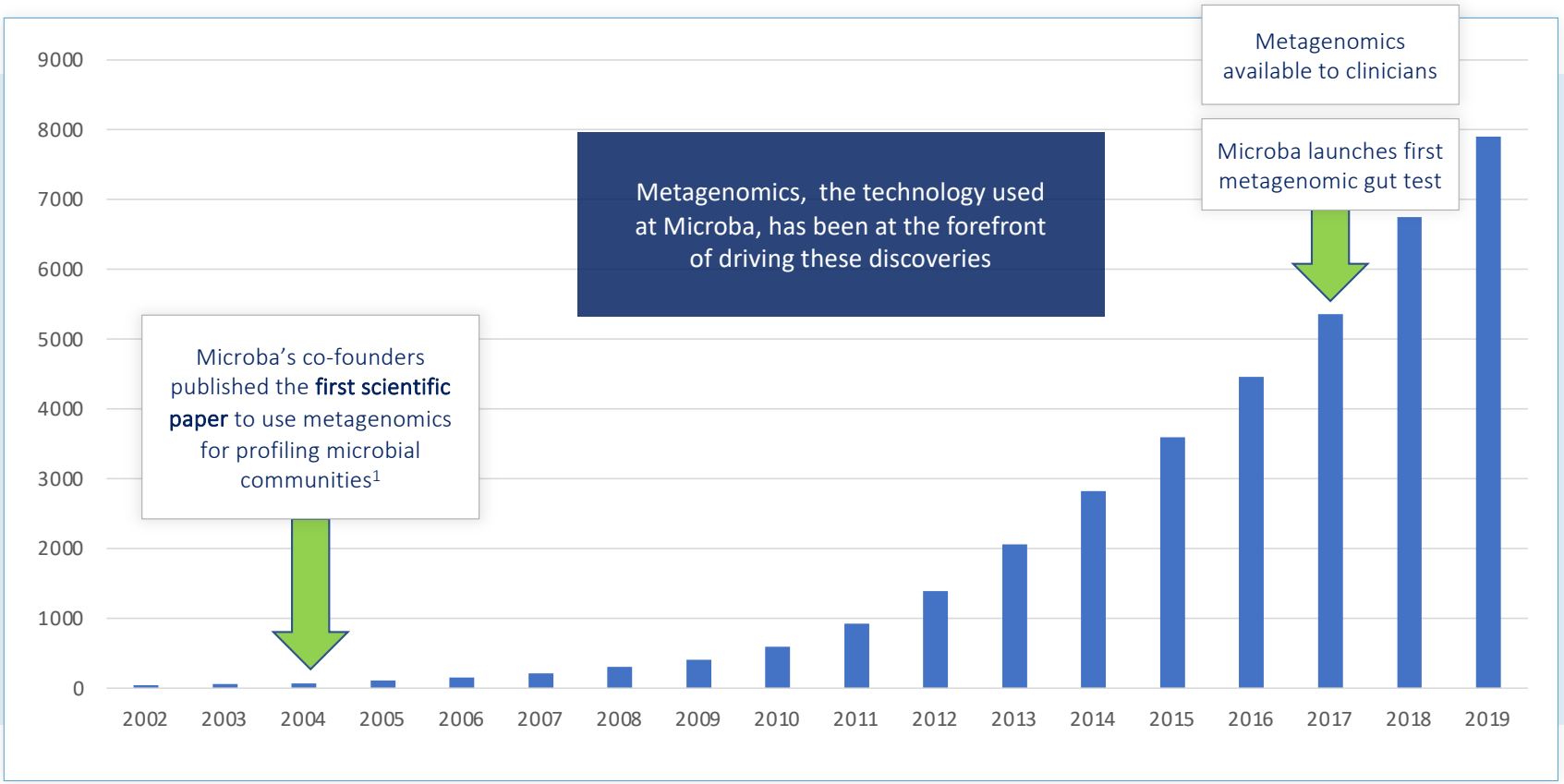
Global metabolic disease epidemic

CVD accounts for 31% deaths	39% overweight	13% obese
24% NAFLD	9.5% diabetes	3.4% PCOS

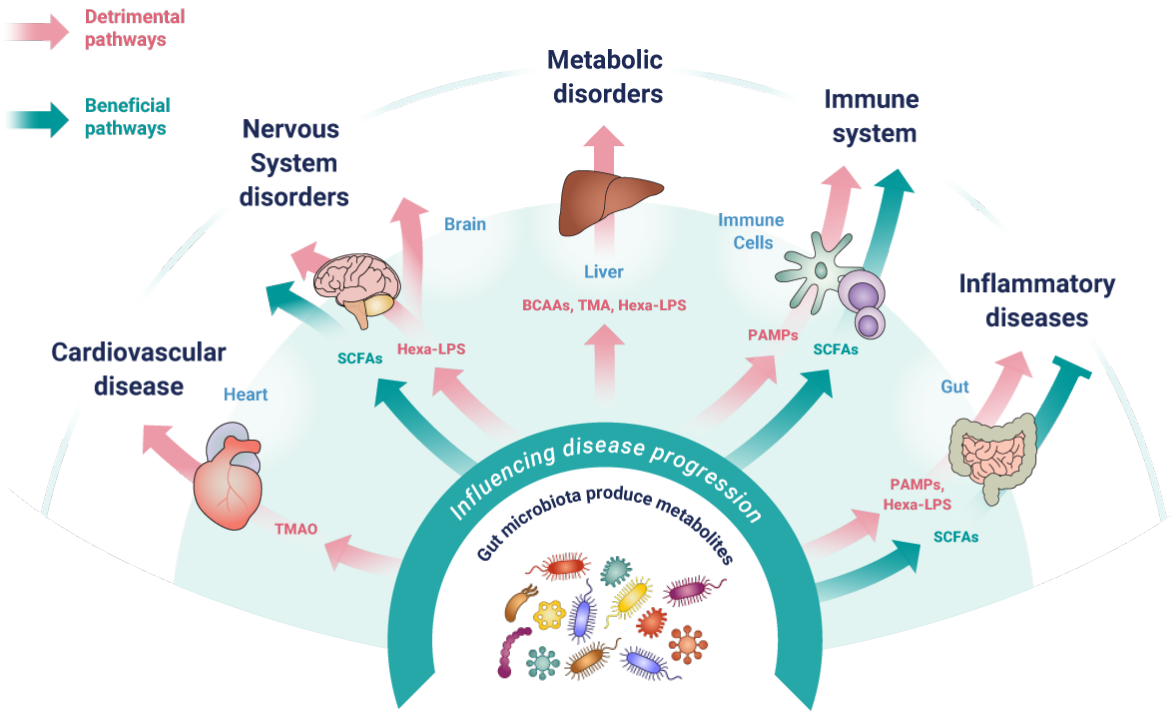
Extensive research exploring the microbiome in metabolic disease



Metagenomics has enabled new discoveries



Metagenomics measures the potential to influence human health

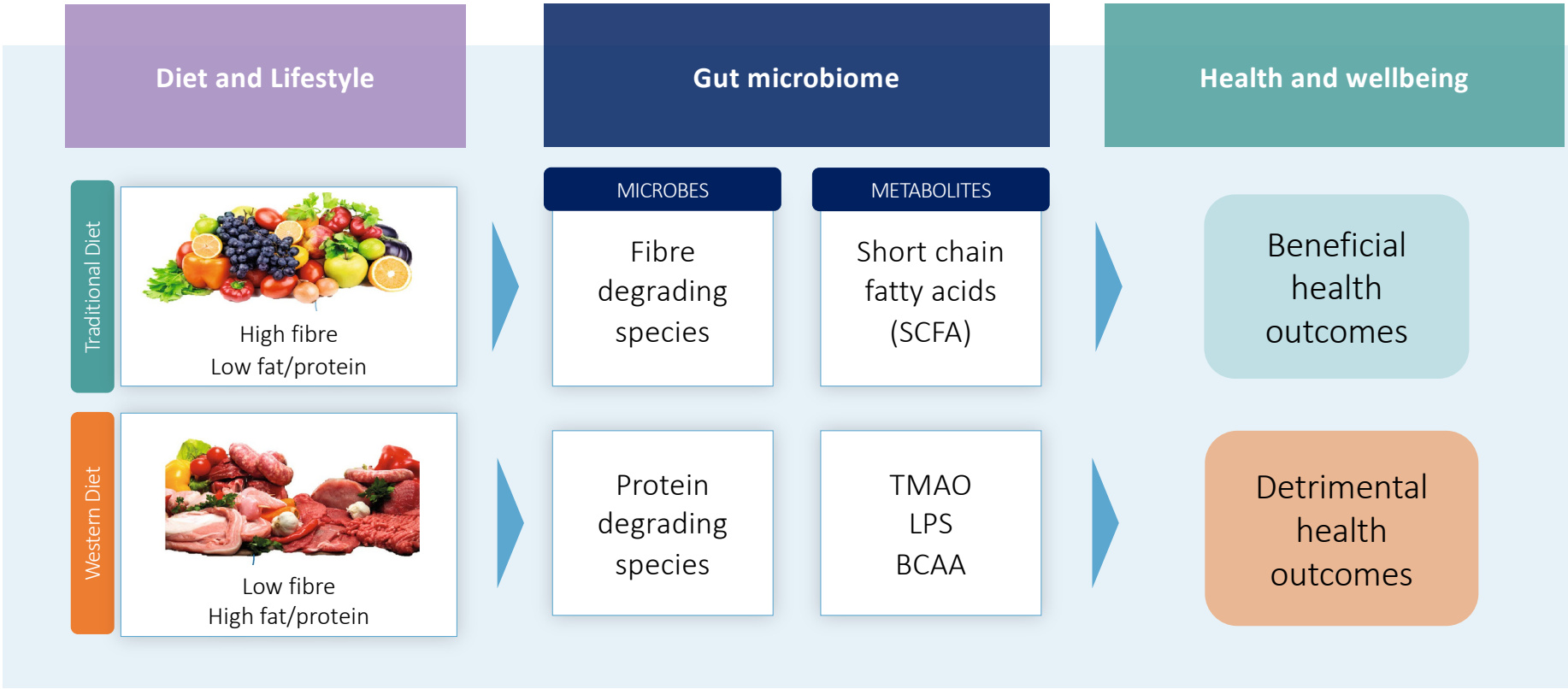


Accurate measurement of the potential of the microbiome to produce metabolites offers an opportunity to improve health.

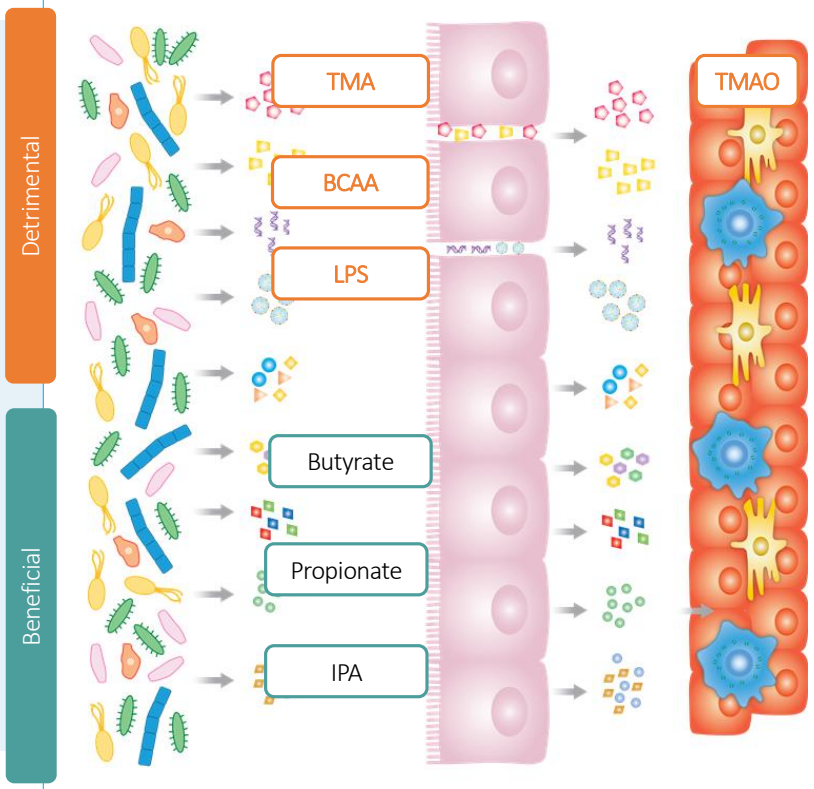
The microbes living in our gut produce thousands of compounds which act systemically throughout the entire body in ways which can be detrimental and beneficial to health.

Metagenomics provides information about the functions the organisms can perform – including which compounds they can break down and metabolites they can produce.

Diet significantly influences the microbiome and microbial metabolites



Key metabolites associated with metabolic health



Changes in the gut microbiome are seen across the spectrum of metabolic health conditions.

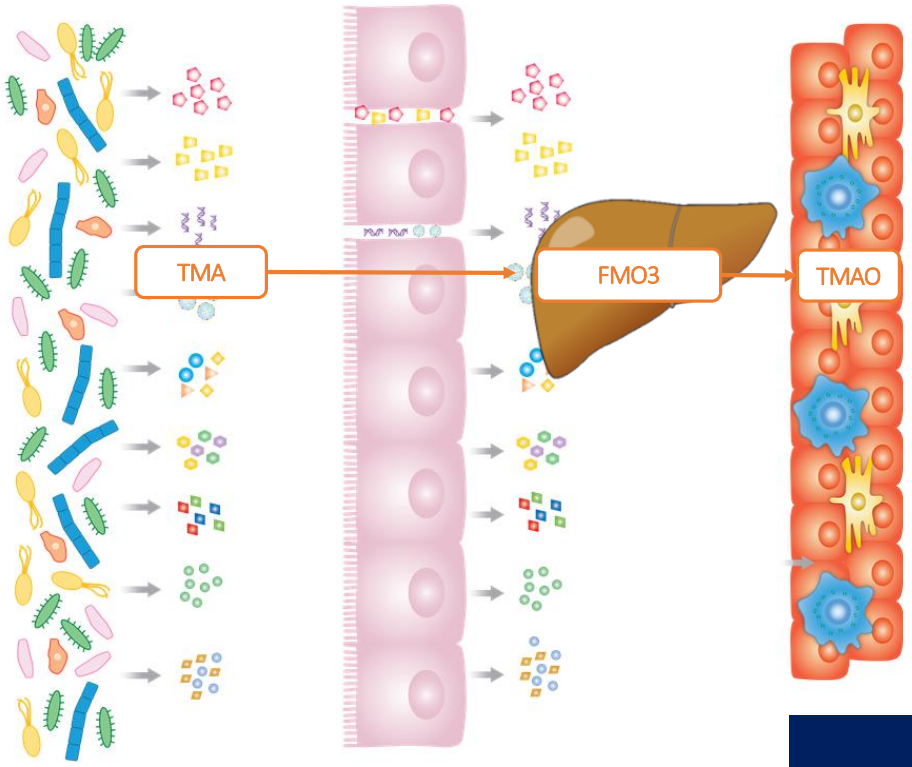
Thrombosis, inflammation, dyslipidaemia and insulin resistance, which occur as part of metabolic disease, are all influenced by metabolites produced in the gut microbiome.

Understanding these pathways, alongside accurate measurement of the microbiome, allows us to optimise metabolic health through microbiome focused interventions.

Part 1

Microbial Metabolites:
Trimethylamine

The role of TMA in driving metabolic disease



- Inflammation
- Atherosclerosis
- Platelet aggregation
- Blood glucose control

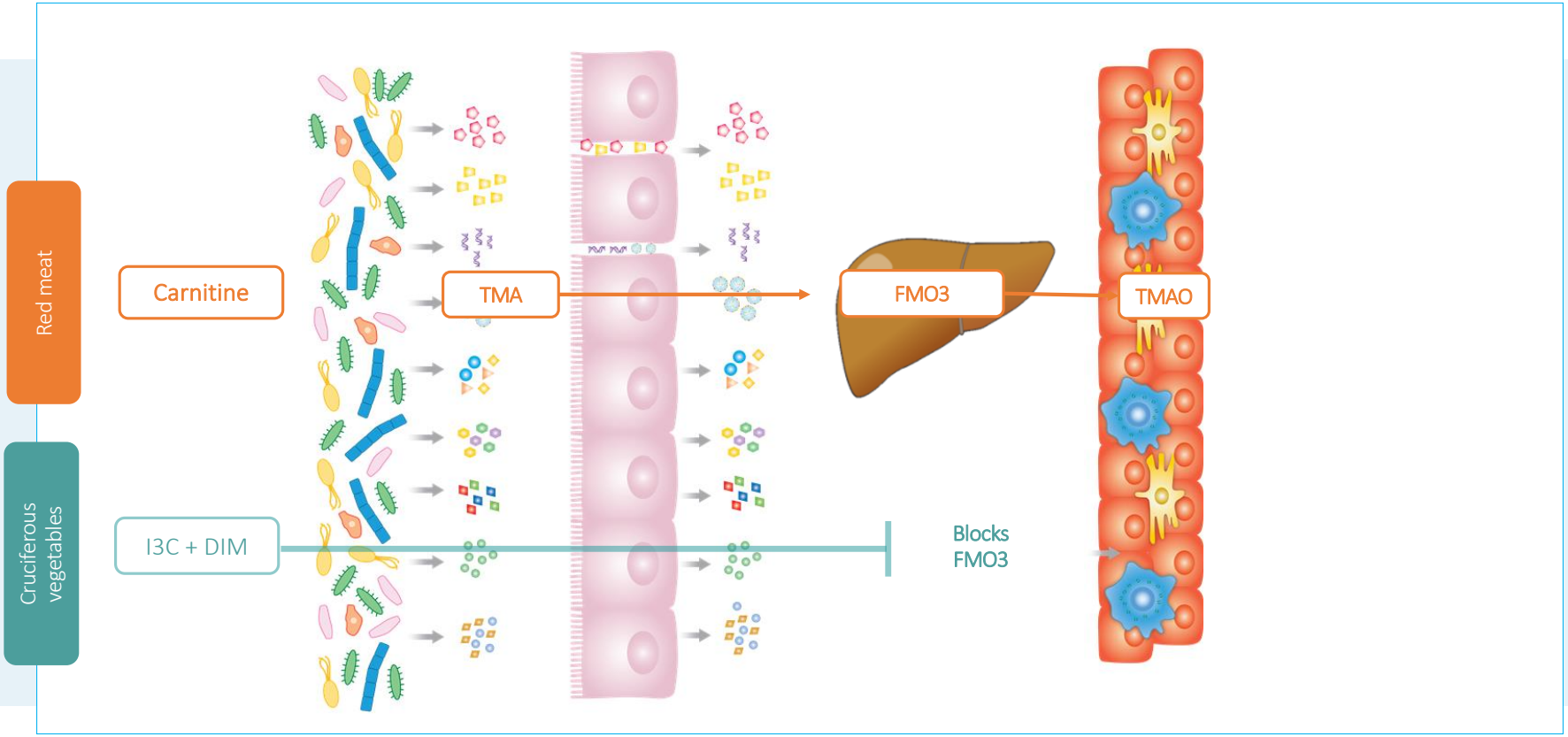
Blood TMAO levels predict health outcomes

Meta-analysis of serum TMAO levels and health outcomes

47% increase in all cause mortality risk *Farhangi, 2020*	*62% increase in major adverse cardiovascular events* *Heianza et al, 2017*	*89% increase in diabetes risk* *Zhuang et al, 2019*
20 studies 30,286 subjects	16 studies 19,256 subjects	12 studies 15,314 subjects
12% increase in hypertension risk *Ge et al, 2020*	*0.27mg/l increase in CRP as a marker of inflammation* *Farhangi + Vajdi, 2020*	*0.56kg/m2 increase in BMI as a measure of obesity* *Dehghan et al, 2020*
8 studies 19,256 subjects	16 studies 13,783 subjects	12 studies 17,628 subjects

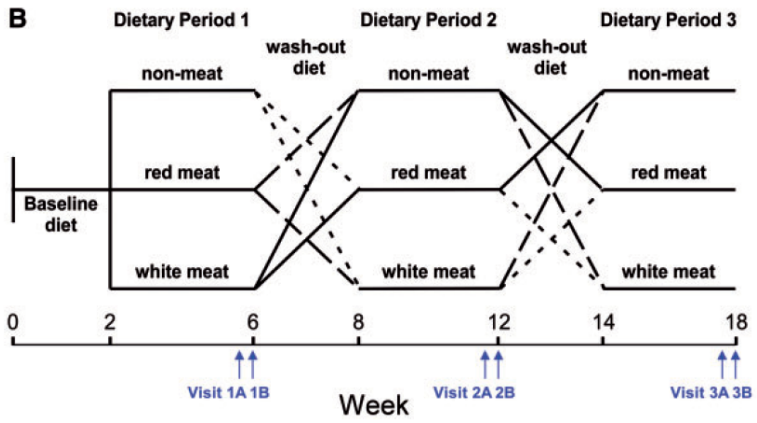
Highest versus lowest blood TMAO levels was associated with significant increased risk of metabolic disease

Dietary interventions for reducing plasma TMAO levels



Red meat increases plasma TMAO levels

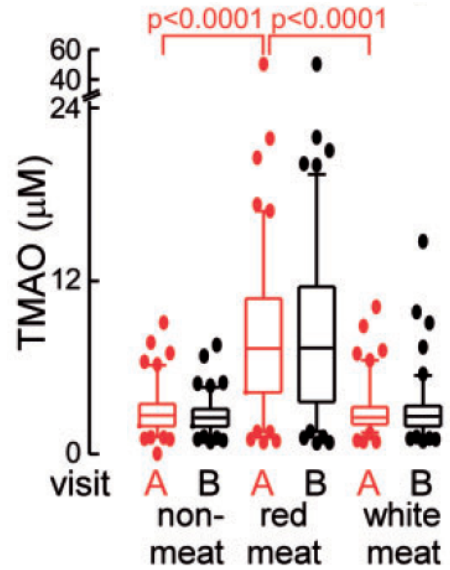
Randomised 2 arm (high or low saturated fat) crossover design comparing red meat, white meat and non-meat diet interventions on fasting TMAO levels



After consuming a 2 week baseline diet 113 subjects were assigned to 3 experimental diets providing 12% energy from red meat, white meat or non-meat for 4 weeks, each separted by 2 to 7 week washout period

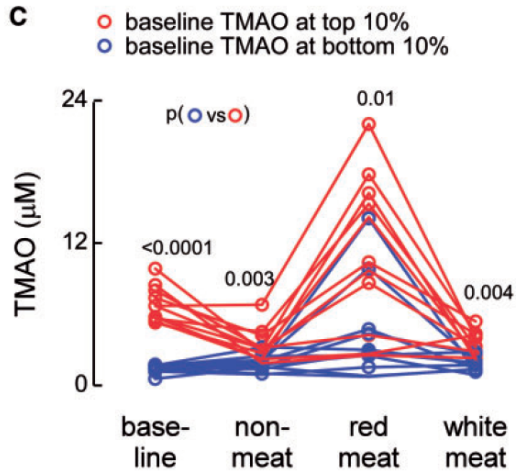
Wang et al 2019 doi:10.1093/eurheartj/ehy799

Red meat increases plasma TMAO levels



On average red meat intervention increased TMAO levels 3 fold.

Equivalent to 4.6% increase in relative risk of all-cause mortality



Response was variable with some showing a 10 fold increase on red meat diet

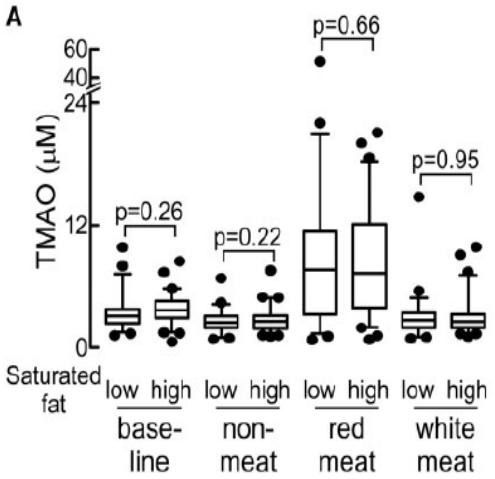
Higher TMAO levels on baseline diet associated with larger elevations in TMAO during red meat intervention

Red meat diet increased blood TMAO levels but response was highly individual

Wang et al 2019 doi:10.1093/eurheartj/ehy799

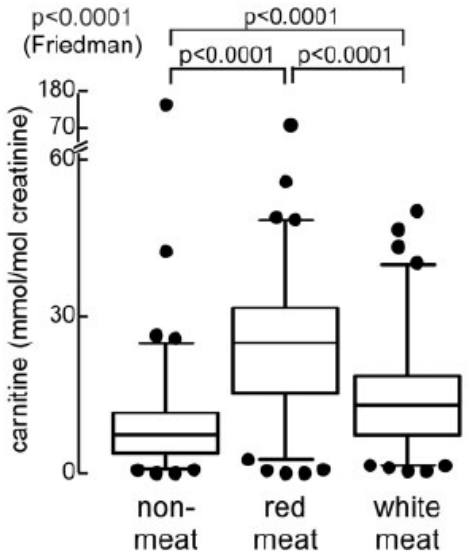
Examining how red meat drives microbial TMA production

Saturated fat levels did not influence TMAO levels

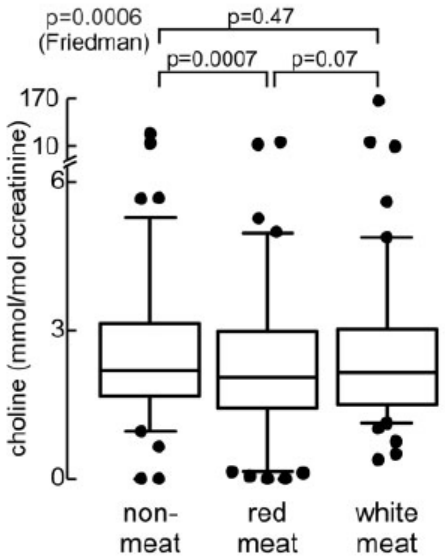


Comparison of low and saturated fat arms of diet

Increased carnitine derived metabolites from red meat diet



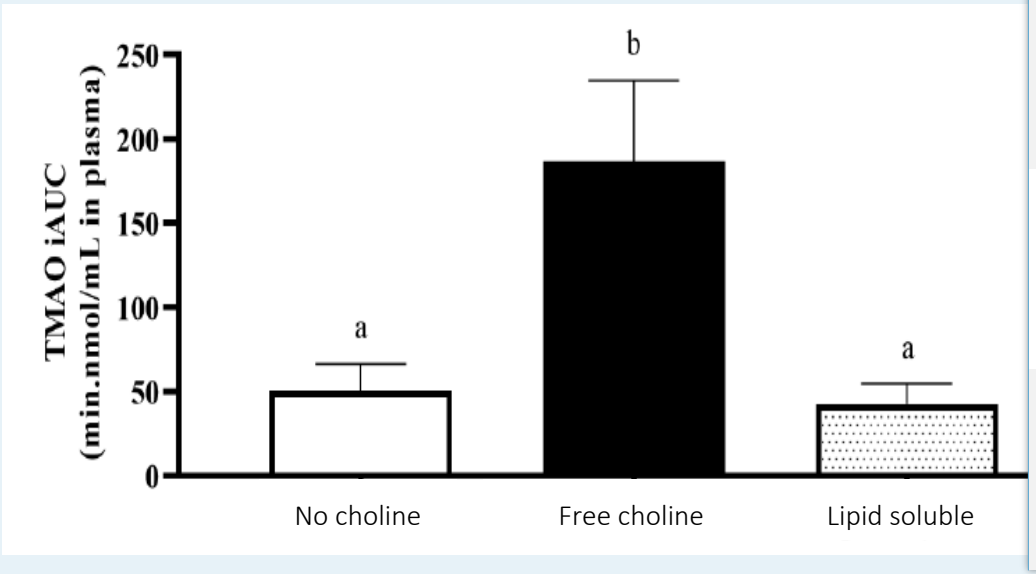
No change in choline derived metabolites from red meat diet



Carnitine in red meat drives microbial TMA production

Wang et al 2019 doi:10.1093/eurheartj/ehy799

The form of choline influences microbial TMA production



- Microbes were able to convert free choline into TMA, leading to increased TMAO in the blood
- Lipid soluble choline is well absorbed in the small intestine and does not reach the microbiome
- Most choline in food is lipid soluble, so does not reach the microbiome

Most choline in food is lipid soluble so does not drive microbial TMA production

Cho et al. Nutrients 2020, 12, 2220; doi:10.3390/nu12082220

Explaining the research about eggs and TMAO

Whole egg consumption increases plasma choline and betaine without affecting TMAO levels or gut microbiome in overweight postmenopausal women

Zhu, Chenghao & Sawrey-Kubicek, Lisa & Bardagjy, Allison & Houts, Hannah & Tang, Xinyu & Sacchi, Romina & Randolph, Jody & Steinberg, Francene & Zivkovic, Angela.

Nutrition Research 2020

Compared to an Oatmeal Breakfast, Two Eggs/Day Increased Plasma Carotenoids and Choline without Increasing Trimethyl Amine N -Oxide Concentrations

Amanda Missimer, Maria Luz Fernandez, Diana M. DiMarco, Gregory H. Norris, Christopher N. Blesso, Ana Gabriela Murillo, Marcela Vergara-Jimenez, Bruno S. Lemos, Isabel Medina-Vera, Olga V. Malysheva & Marie A. Caudill

Journal of the American College of Nutrition., 2018

Effects of Egg Consumption and Choline Supplementation on Plasma Choline and Trimethylamine-N-Oxide in a Young Population

Lemos BS, Medina-Vera I, Malysheva OV, Caudill MA, Fernandez ML.

Journal of the American College of Nutrition., 2018

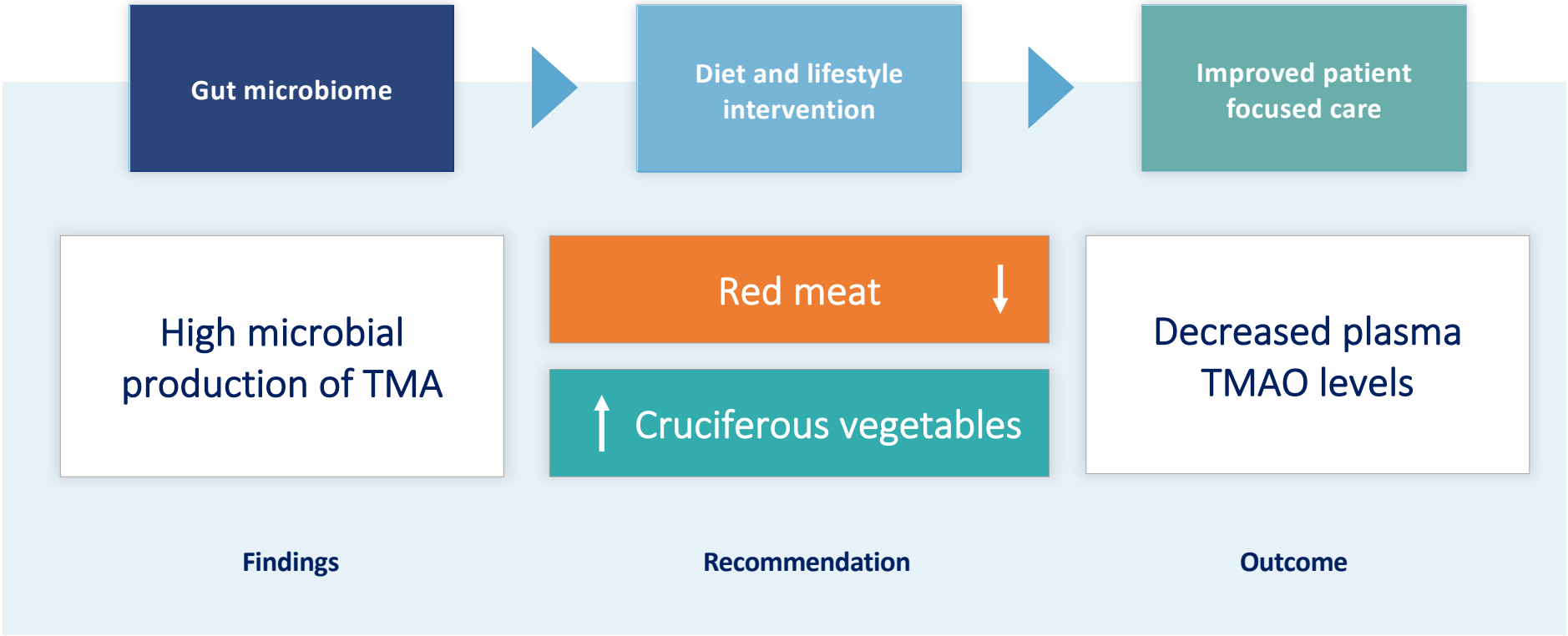
Intake of up to 3 Eggs/Day Increases HDL Cholesterol and Plasma Choline While Plasma Trimethylamine-N-oxide is Unchanged in a Healthy Population

Diana M. DiMarco Amanda Missimer Ana Gabriela Murillo Bruno S. Lemos Olga V. Malysheva Marie A. Caudill Christopher N. Blesso Maria Luz Fernandez

Lipids, 2017

Eggs do not increase microbial TMA production because the choline is lipid soluble

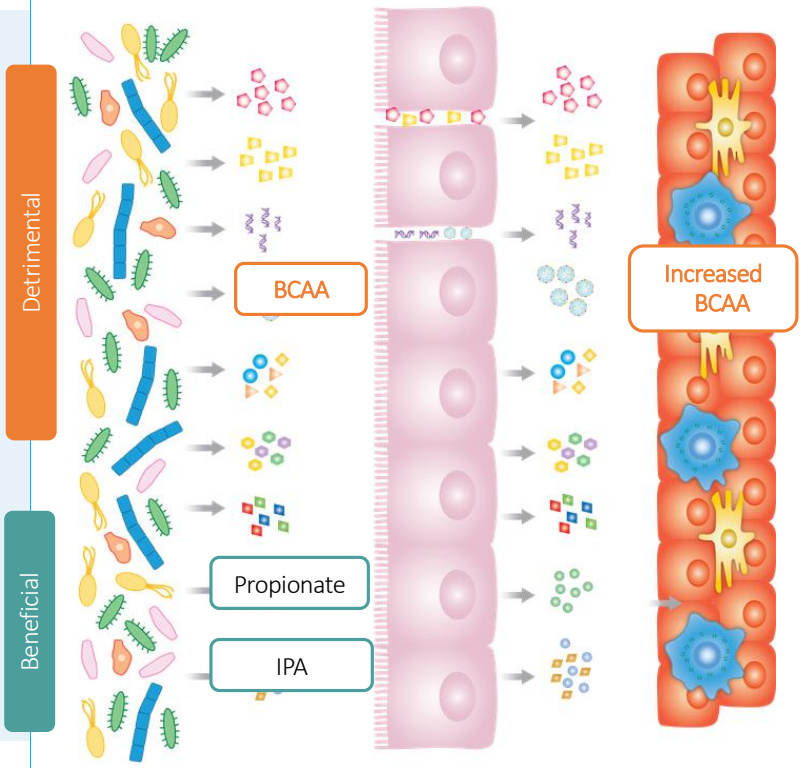
Improving health outcomes through microbial production of TMA



Part 2

Microbial Metabolites:
Branched Chain Amino Acids

The role of microbial metabolites in blood glucose control

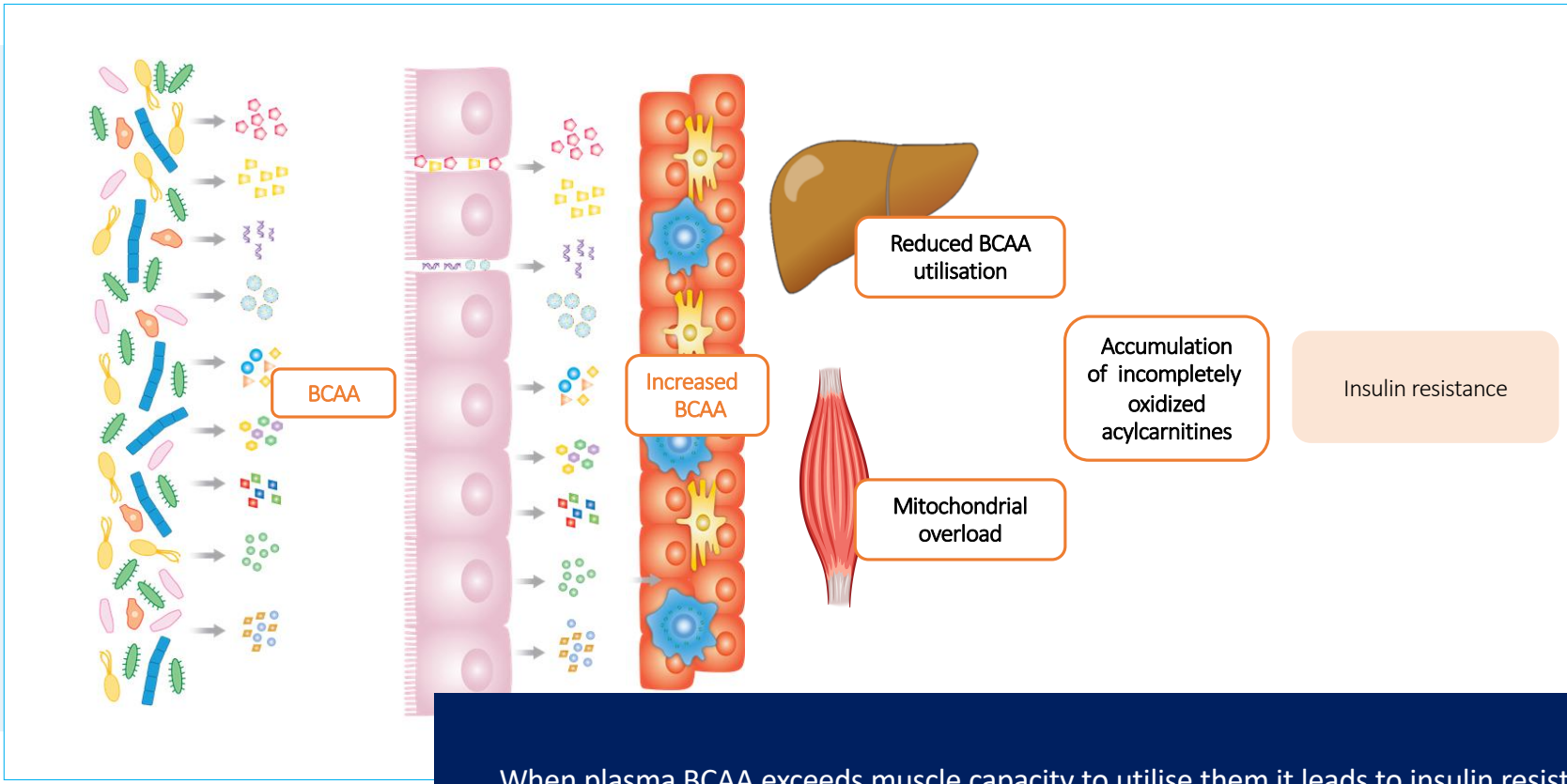


Insulin resistance

Regulates blood glucose

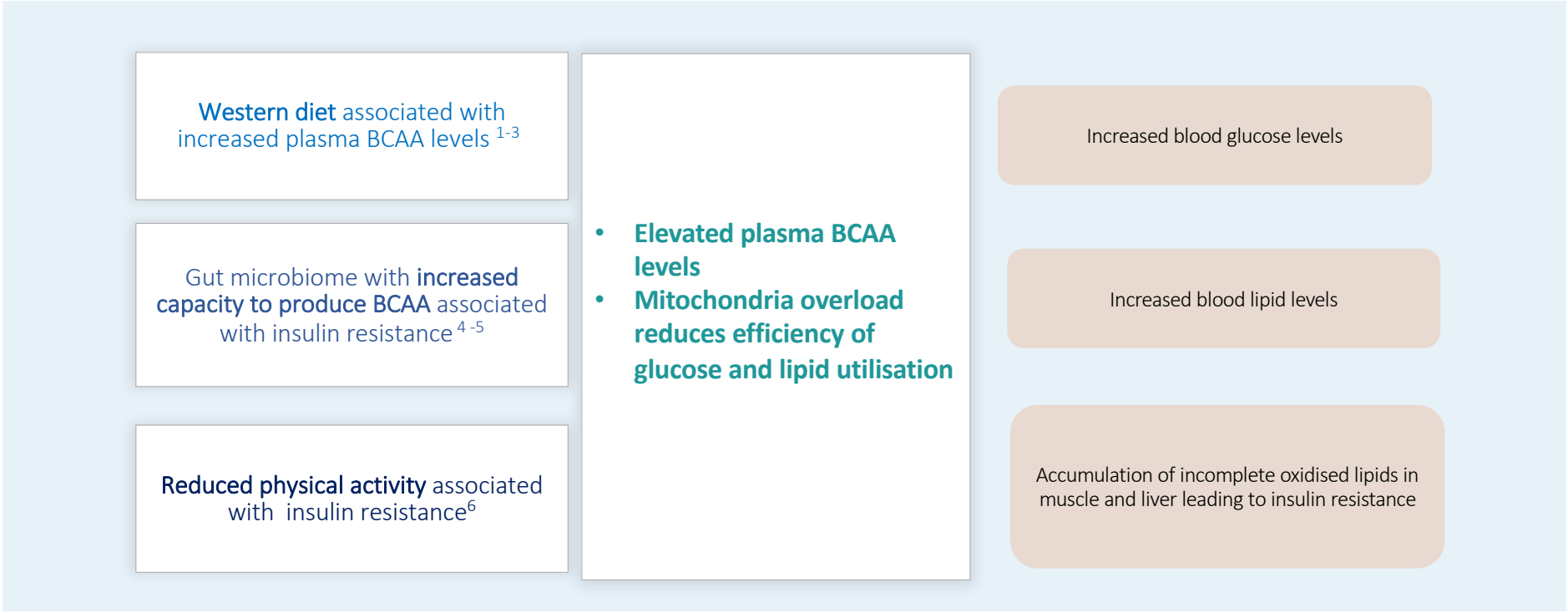
Elevated plasma levels of branch chain amino acids have been associated with up to a 5 fold risk for future development of diabetes

Elevated levels of BCAA precede the development of insulin resistance



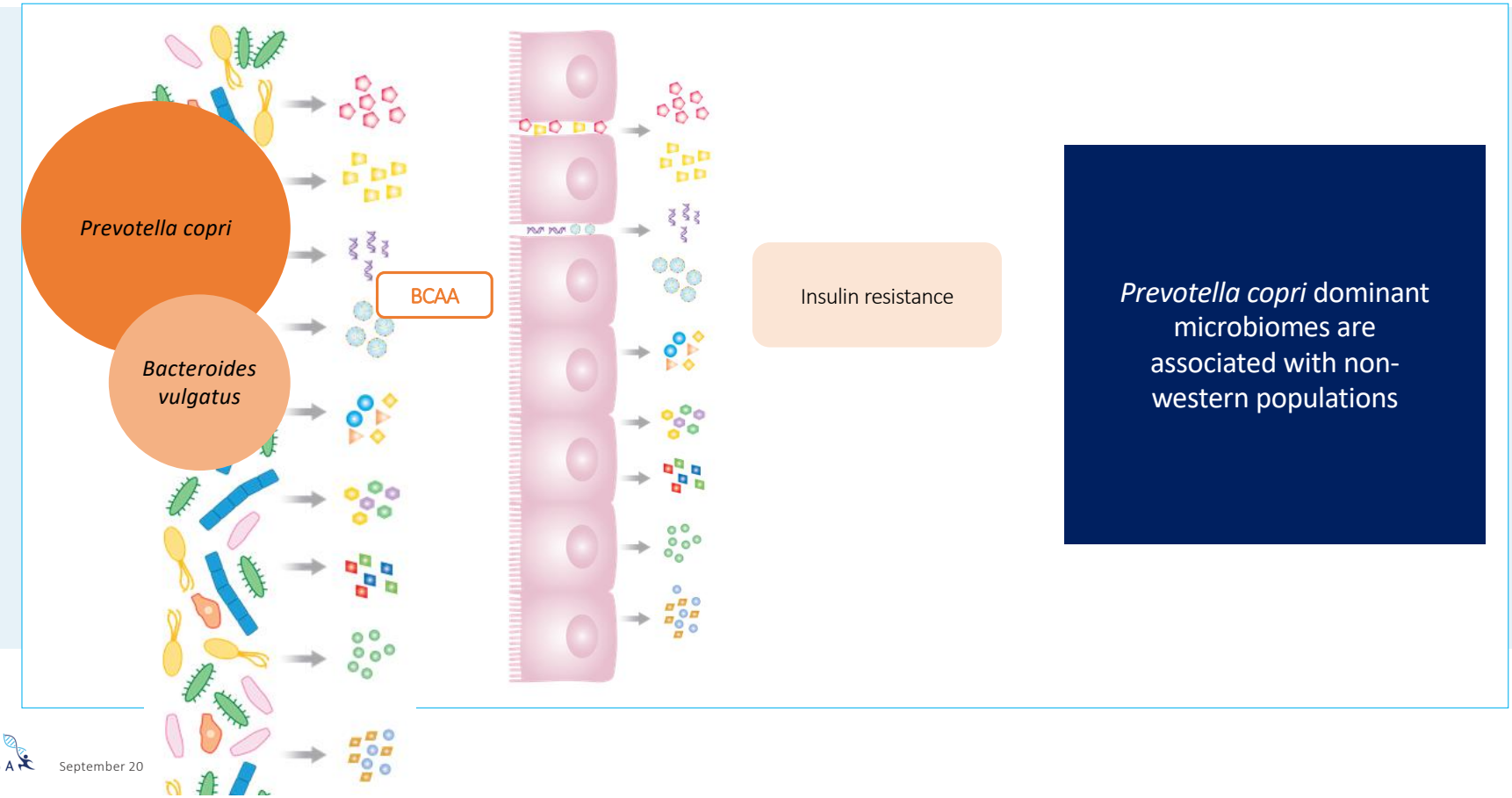
When plasma BCAA exceeds muscle capacity to utilise them it leads to insulin resistance

A western diet and lifestyle increase plasma BCAA levels

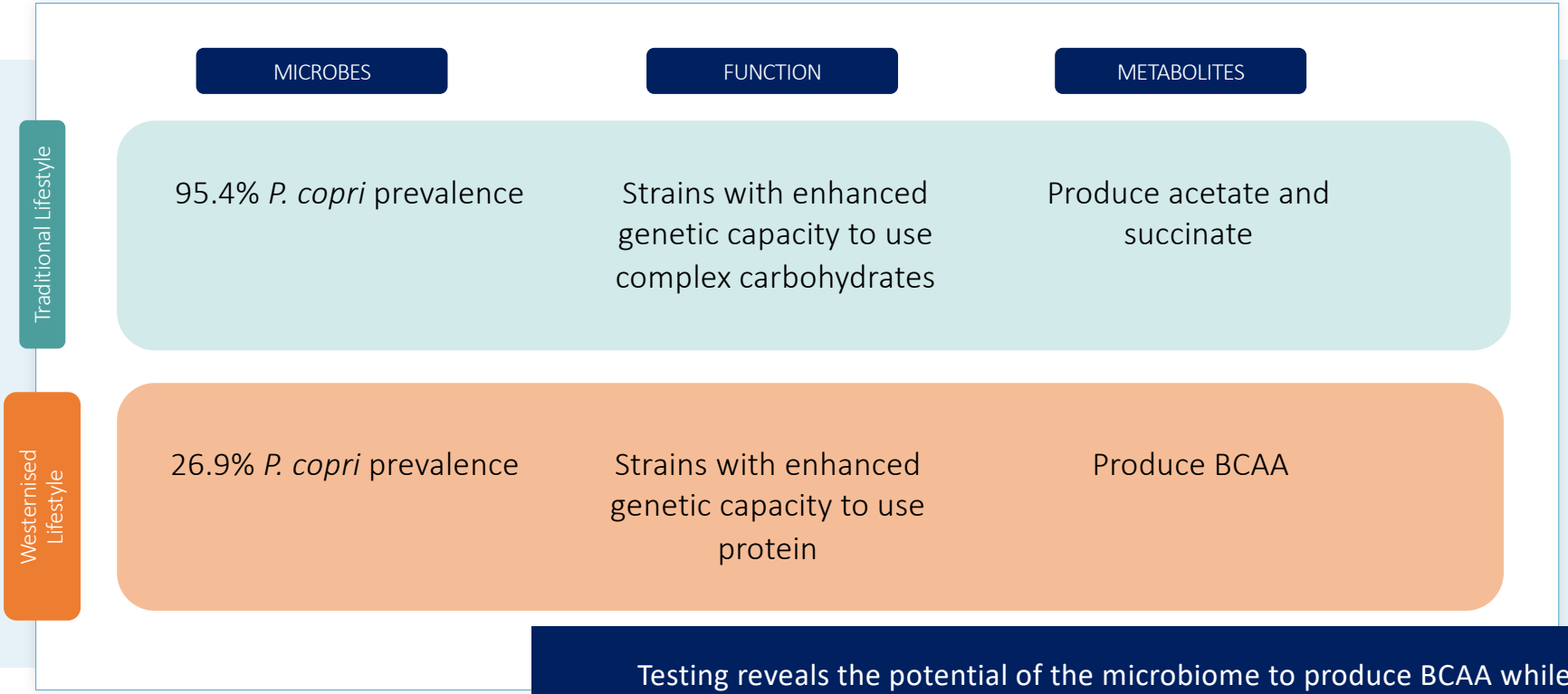


1. Merz et al, 2018, doi:10.3390/nu10050623
2. Dhakan et al, 2019 doi: 10.1093/gigascience/giz004
3. DeFilippis et al, 2019 doi.org/10.1016/j.chom.2019.01.004
4. Wu et al, 2020 doi.org/10.1016/j.cmet.2020.06.011
5. Pederson et al Nature 2016 doi:10.1038/nature18646
6.Shou, Chen and Xiao, 2019 *J Nutr Sci Vitaminol*, **65**, 383–389

Prevotella copri dominant microbiome have a high capacity to produce BCAAs



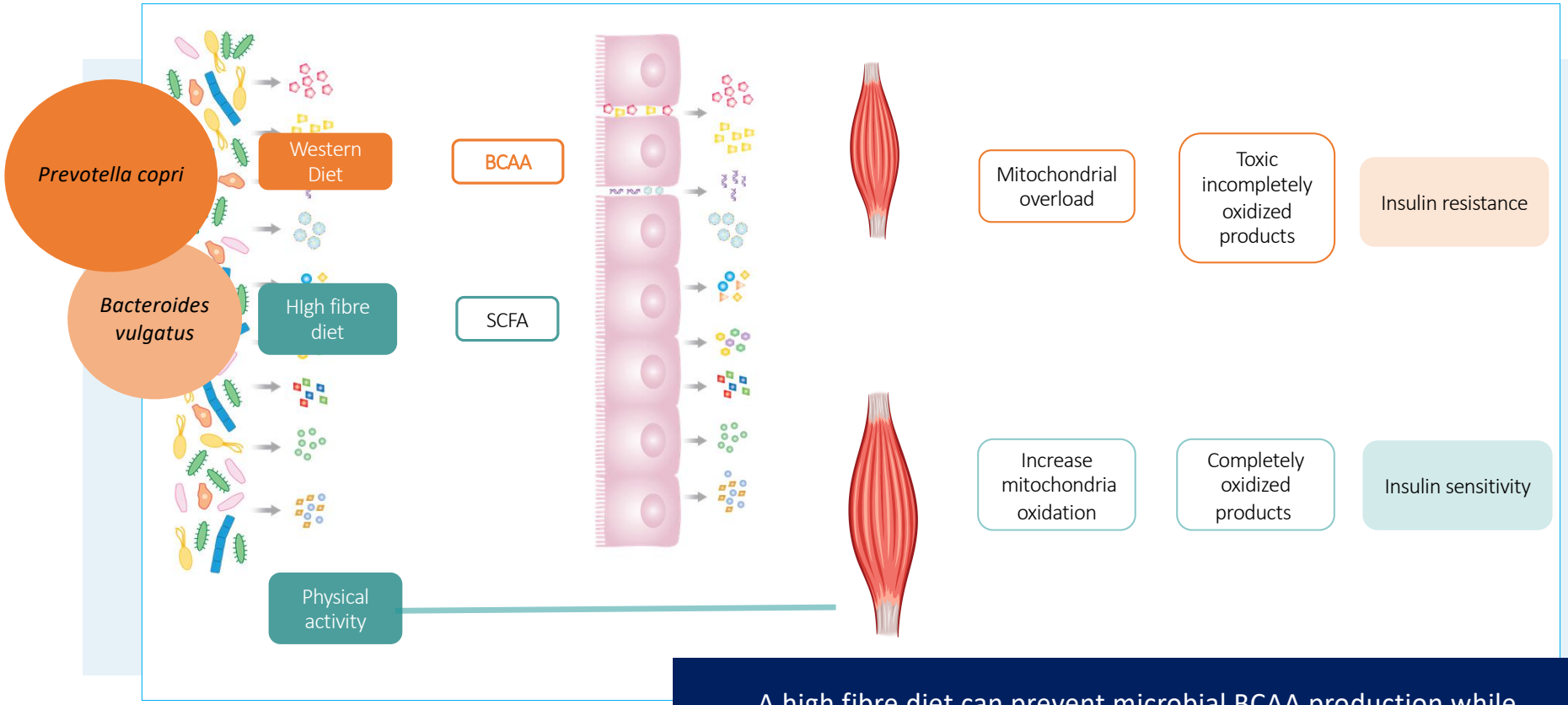
The *Prevotella copri* paradox



Testing reveals the potential of the microbiome to produce BCAA while the diet influences whether they are actually produced or not

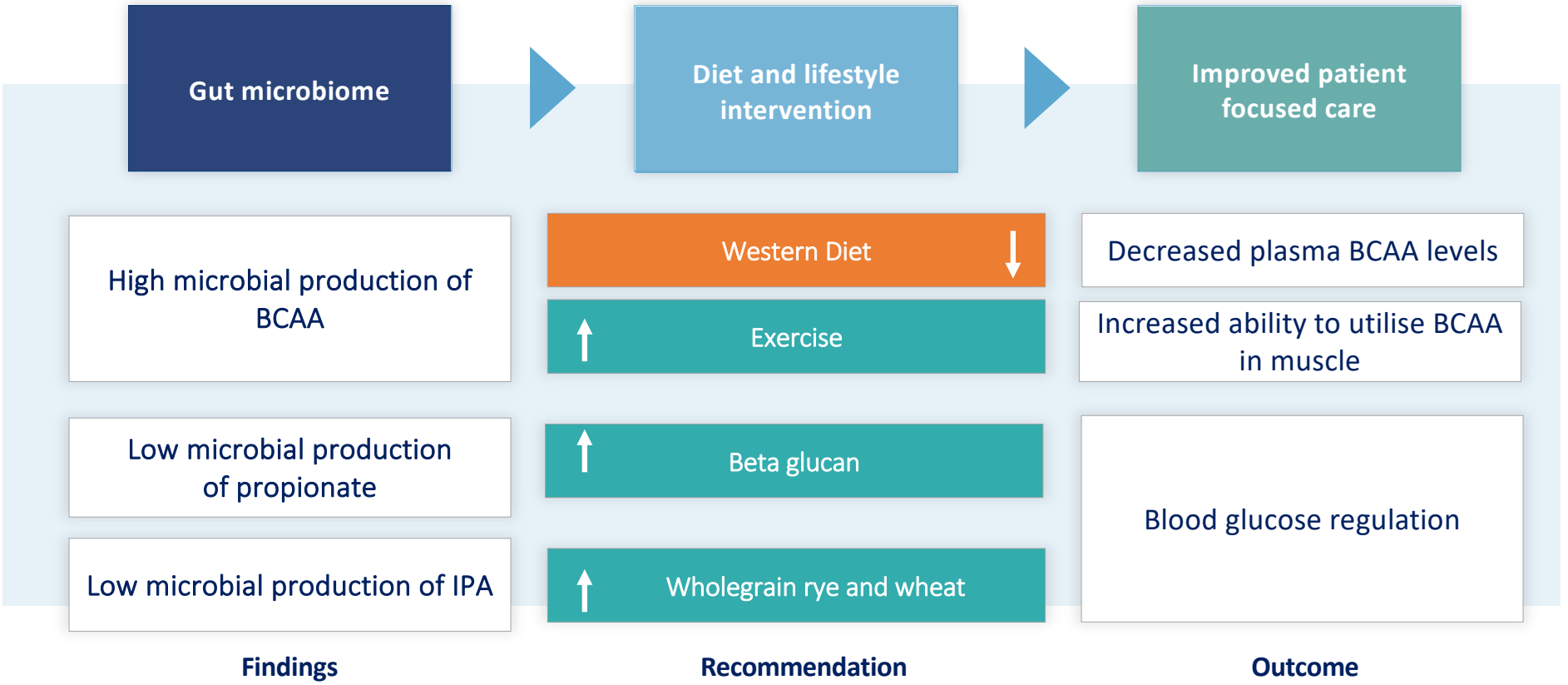
Tett et al 2019 https://doi.org/10.1016/j.chom.2019.08.018

Prevotella copri dominant microbiomes evolved with non-western diet and lifestyle



A high fibre diet can prevent microbial BCAA production while physical activity increases muscle capacity to utilise BCAAs

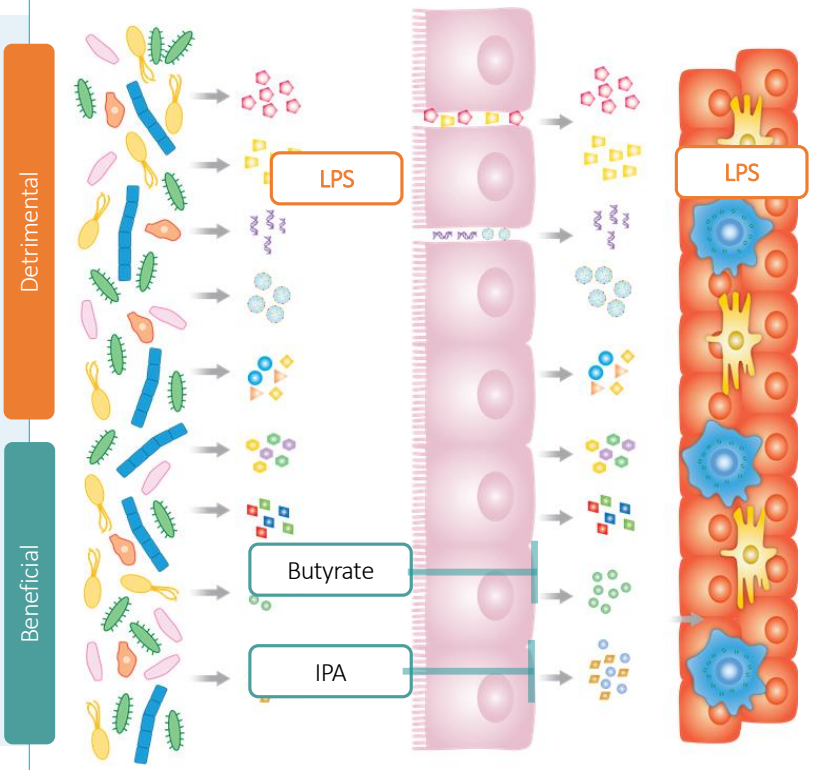
Improving health outcomes through microbial production of BCAA



Part 2

Microbial Metabolites:
Lipopolysaccharides

The role of microbial metabolites in inflammation

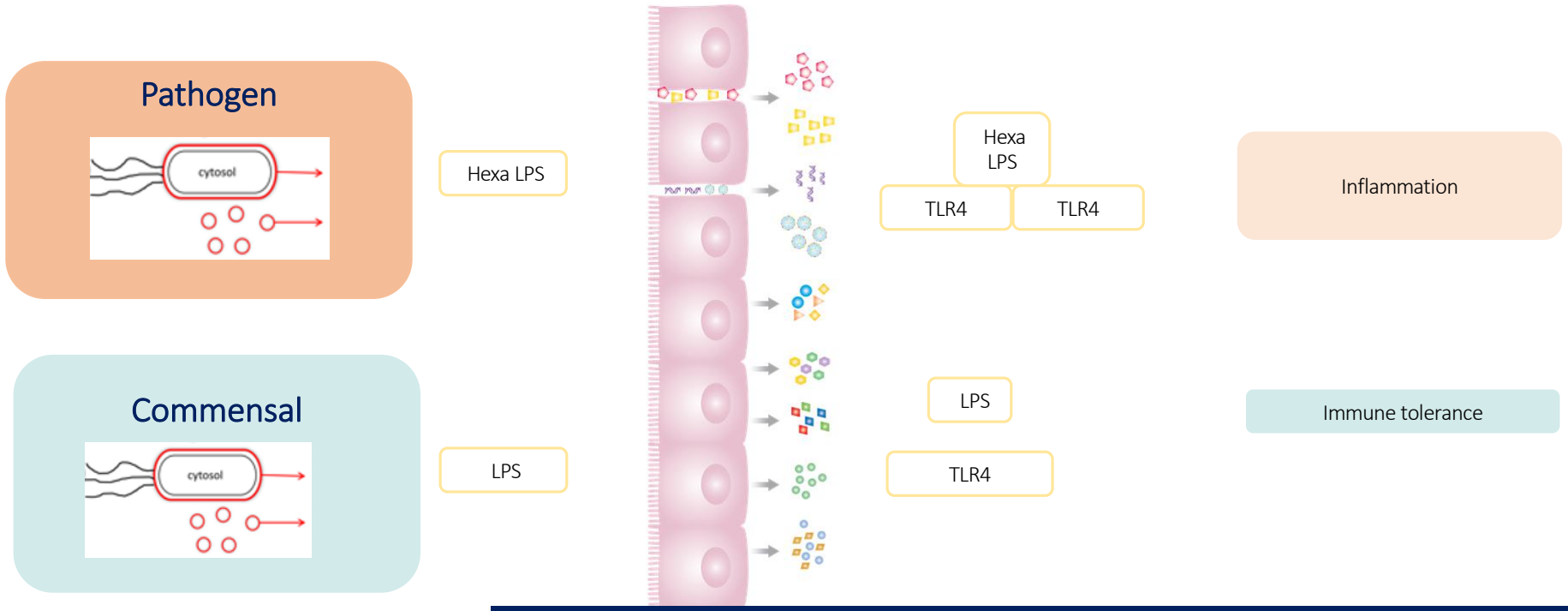


Inflammation

Protects gut barrier and reduces inflammation

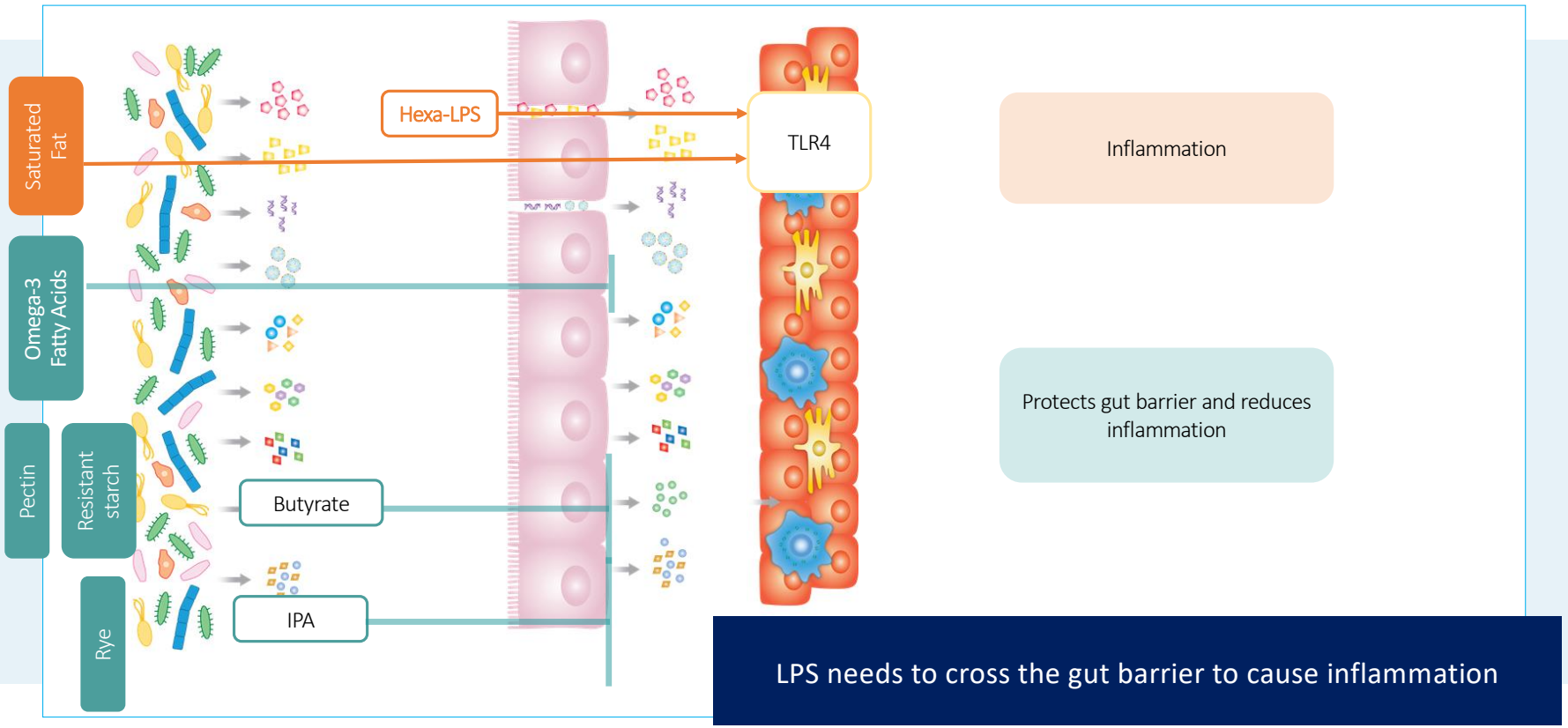
Higher blood LPS levels seen in people with obesity, type 2 diabetes, and non-alcoholic fatty liver disease and Alzheimer's disease.

LPS in the blood interacts with the immune system

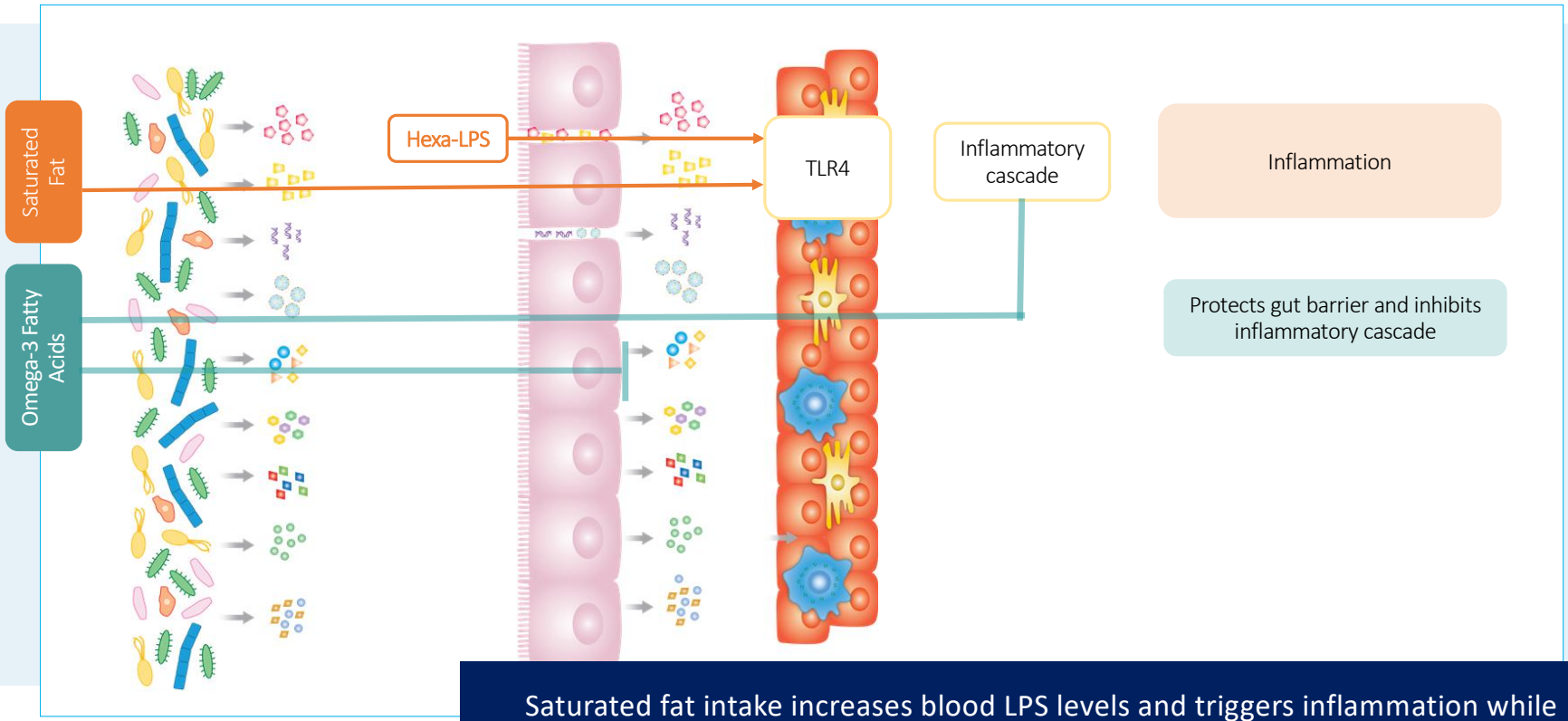


Toll Like Receptors (TLR) on immune cells recognize bacterial LPS to distinguish between invading pathogen and harmless commensals.

Diet influences blood LPS levels via microbiome

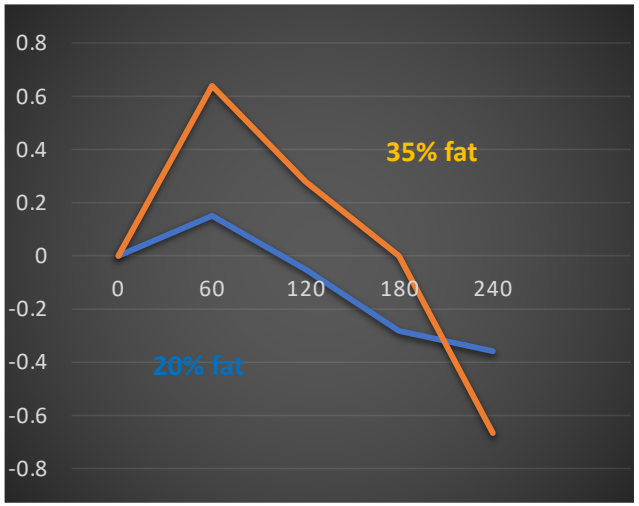


Source of dietary fat influences how much LPS crosses the gut barrier

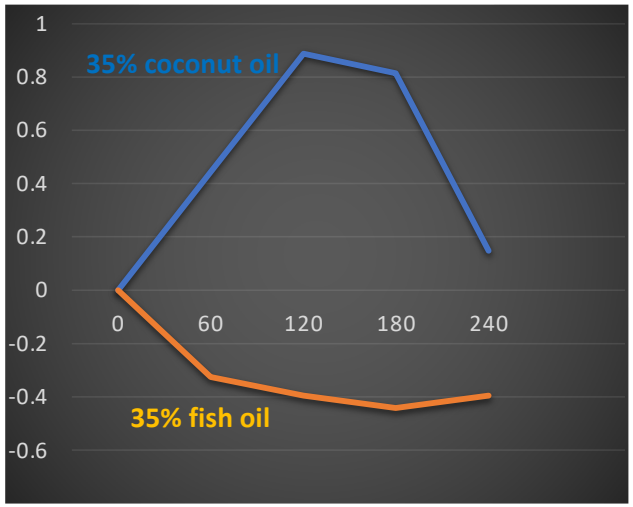


Saturated fat intake increases blood LPS levels and triggers inflammation while omega 3 fatty acids decreases blood LPS levels and prevents inflammation.

Controlled feeding trial showed **fat quality but not fat quantity** influences postprandial LPS levels.



No difference in LPS levels between low fat and high fat meals ($p > 0.05$)



Saturated fat increased and omega 3 fat decreased LPS levels ($p < 0.05$)

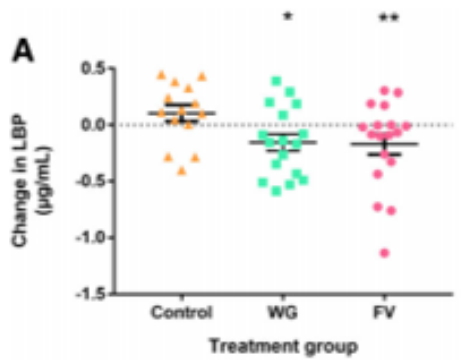
Long term dietary patterns rich in fish were associated with lower plasma LPS levels in a cohort of 668 individuals with type 1 diabetes.

Aloha *et al*, 2017
DOI:10.1038/s41598-017-06885-7

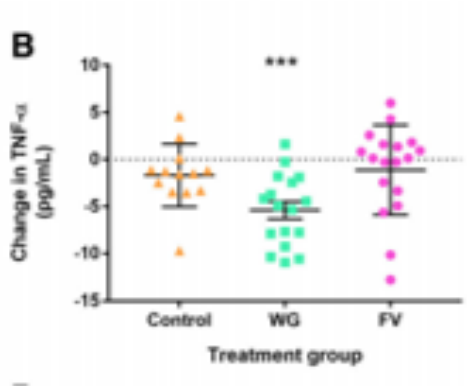
Lyte *et al*, 2016 DOI 10.1186/s12944-016-0357-6

Fibre protects the gut barrier and prevents LPS from entering the blood and stimulating the immune system

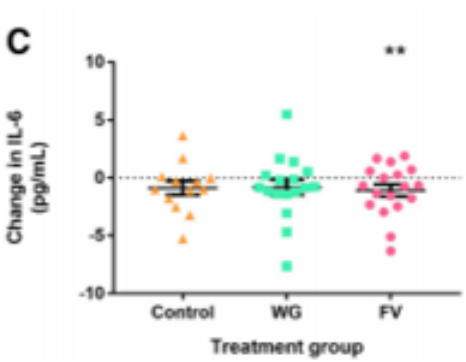
Dietary intervention study showed consuming 3 serves fruits and vegetables or 3 serves wholegrains per day reduced blood LPS levels and inflammation.



Wholegrain and fruit and veg intervention decreased blood LBP level.



Wholegrain intervention decreased TNF-α inflammation marker

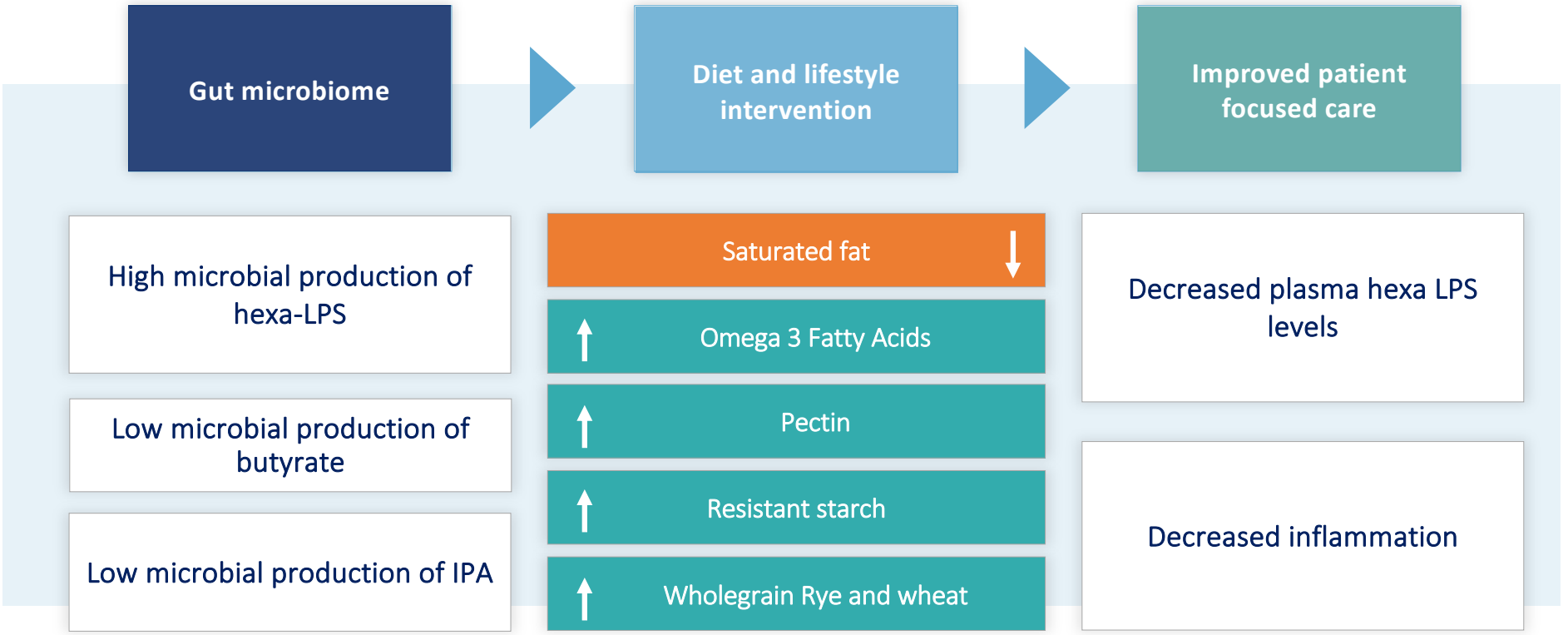


Fruit and veg intervention decreased IL-6 inflammation marker

Both wholegrains and fruits and vegetables are important for reducing inflammation

Kopf *et al*. 2018 doi.org/10.1186/s12937-018-0381-7

Improving health outcomes through microbial production of LPS



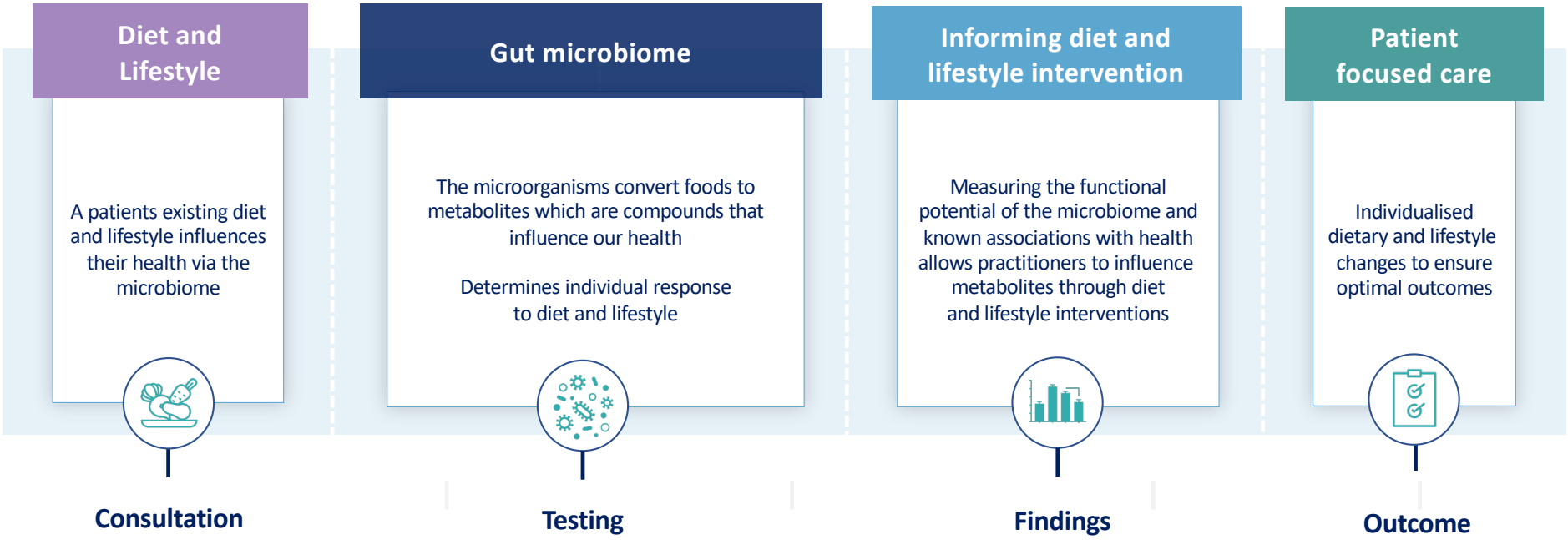
MICROBA

Testing the gut microbiome in dietetic practice

Anita Tait APD

Dr Paula Smith-Brown APD PhD

Measuring and influencing the microbiome to provide patient focused care



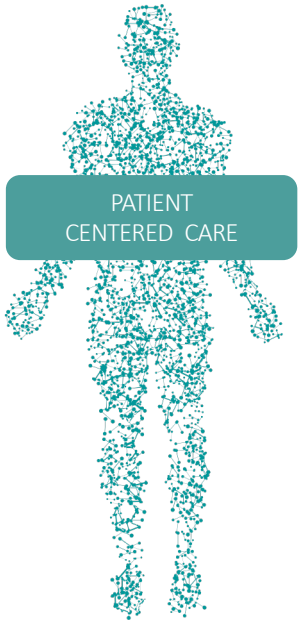
Accurate measurement of the microorganisms in the gut and their functional potential **offers an opportunity to develop patient focused** dietary interventions to improve metabolic health.

The benefits of microbiome testing in health management

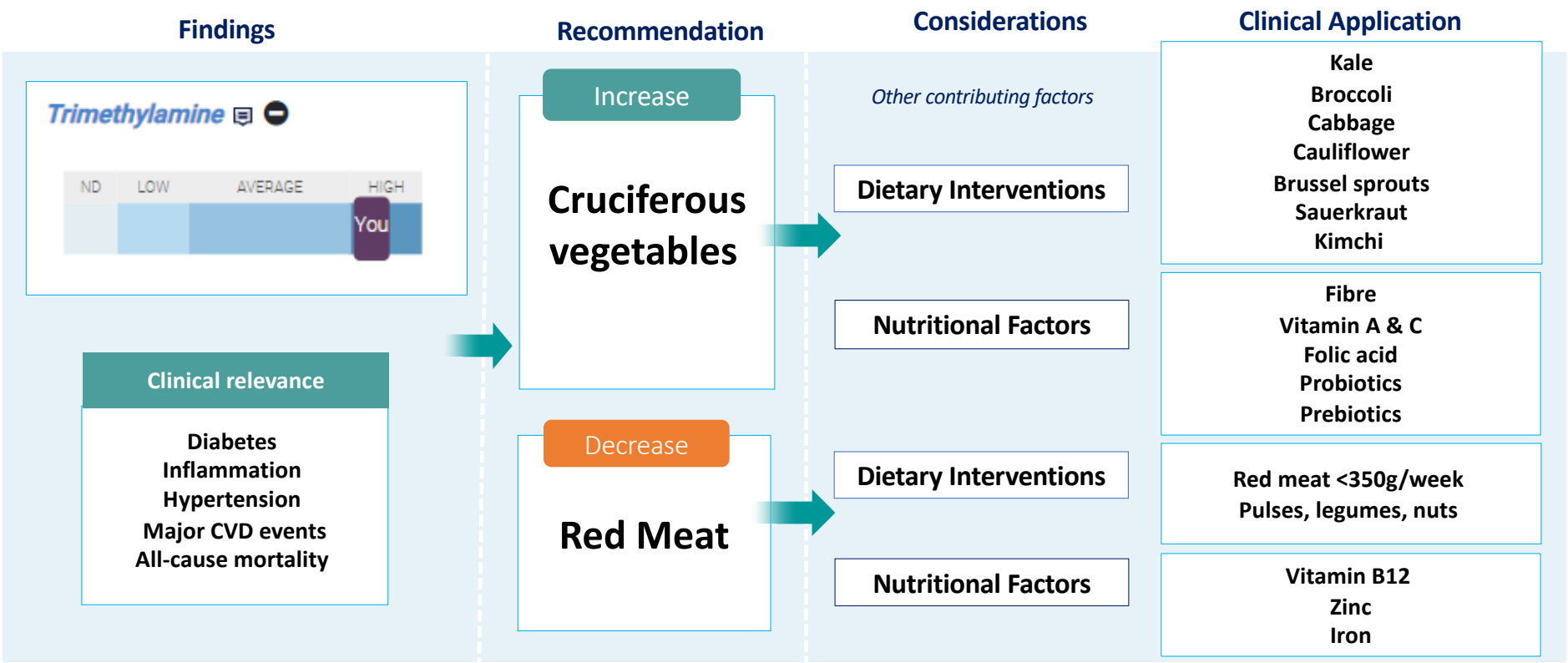
Interventions focused on the individual patient and their needs to make informed changes to ensure optimal outcomes

Tangible insight into functional potential of the microbiome and the association with health as a key motivator to assist behaviour change

A key clinical tool in dietetic practice to improve patient outcomes across a range of conditions

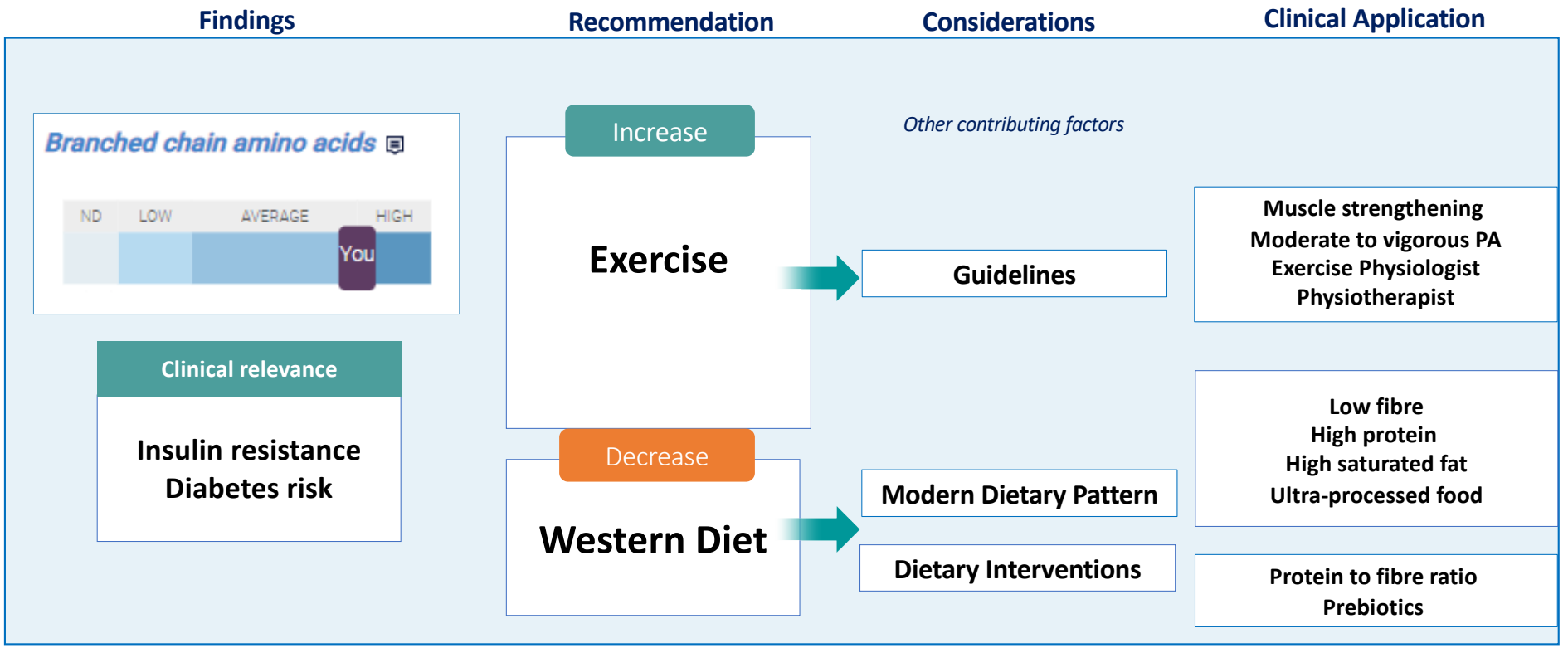


Dietary interventions to address high TMA potential



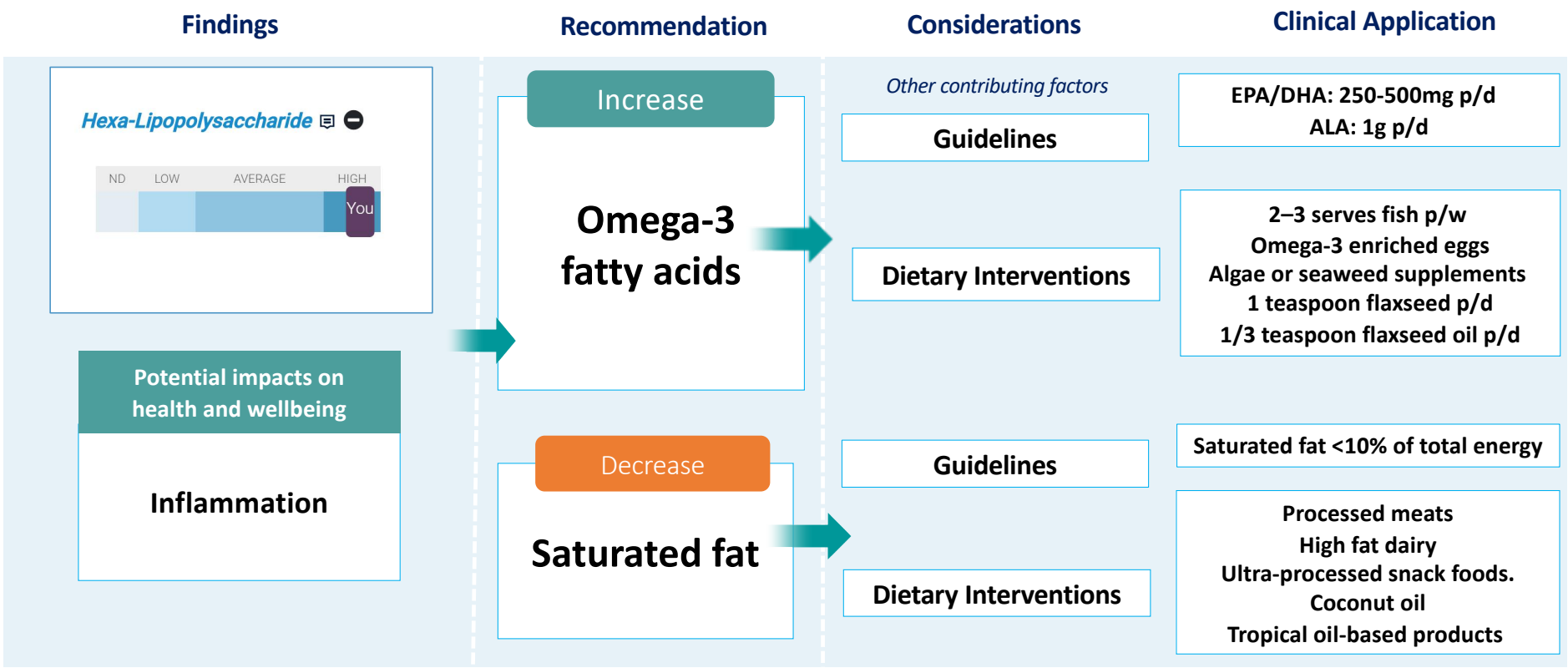
The Heart Foundation,2019. https://www.heartfoundation.org.au/getmedia/d5b9c4a2-8ccb-4fe9-87a2-d4a34541c272/Nutrition_Position_Statement_-_MEAT.pdf

Dietary interventions to address high BCAA potential



Australia's physical activity and sedentary behaviour guidelines and the Australian 24-Hour movement guidelines. (2019, April 12). https://www1.health.gov.au/internet/main/publishing.nsf/Content/health-pubhlth-strateg-phys-act-guidelines

Dietary interventions to address Hexa-Lipopolysaccharide



The Heart Foundation, 2019. https://www.heartfoundation.org.au/getmedia/6e89409a-3660-4ce8-81fa-92b113510043/Nutrition_Position_Statement_-_DIETARY_FAT_FINAL-4.pdf

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- Descriptions of key species and microbial
- Metabolites linked to health and disease
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