GUT MICROBIOTA AND HTN REGULATION

KHOSRAVI MASOUD, M.D.
NEPHROLOGIST
GUILAN UNIVERSITY OF MEDICAL SCIENCES

HTN

IS THE LEADING RISK FACTOR FOR:

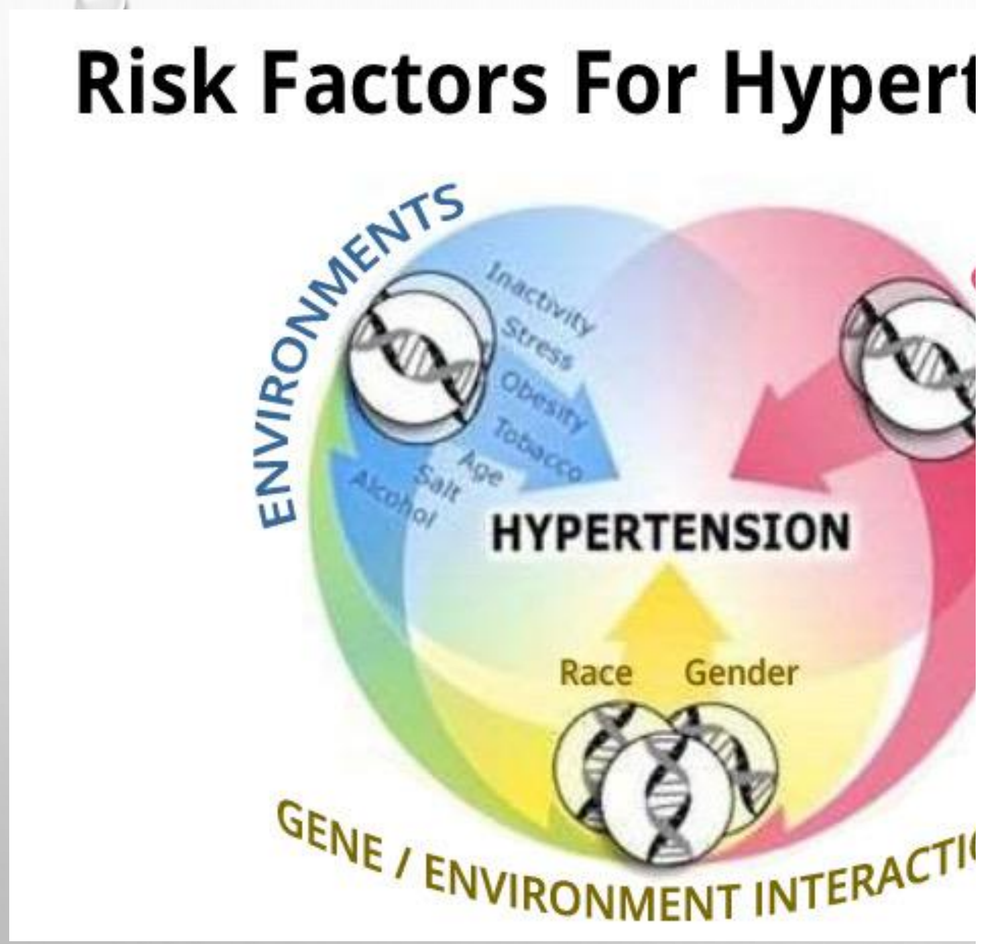
HEART DISEASE AND STROKE,

AND IS ESTIMATED TO CAUSE

9.4 MILLION DEATHS GLOBALLY EVERY YEAR.

Beyond Gut Feelings: how the gut microbiota regulates blood pressure
Nature Reviews Cardiology
Vol 15, January 2018

Gut Microbiome



https://pin.it/3I1UjiH

Beyond Gut Feelings: how the gut microbiota regulates blood pressure
Nature Reviews Cardiology
Vol 15, January 2018

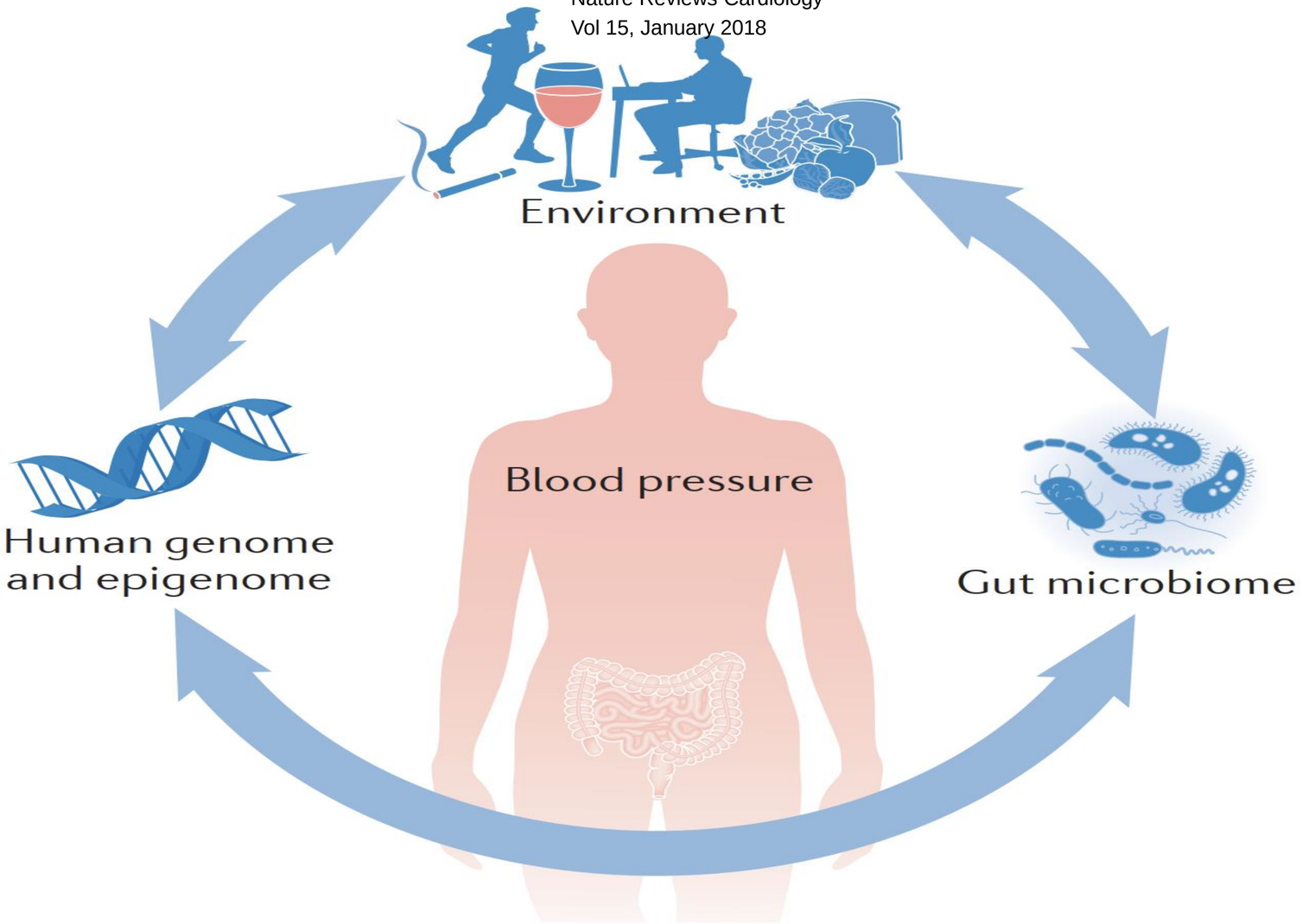


Figure 3 | **Hypertension as a multifactorial disease.** Future studies should address the interaction between the human genome and epigenome, the environment (nutrition), and the gut microbiome, and how they together determine blood-pressure levels.

Microbiota and hypertension

Numerous epidemiological studies have shown that a *high intake of fruit and vegetables* is associated with

a lower incidence of cardiovascular mortality and reduced BP.

Short-term intervention studies to assess diets such as the Dietary Approaches to Stop Hypertension (DASH) diet (which emphasizes the intake of vegetables, fruit, and low-fat dairy products) and the traditional Mediterranean diet have reported similar findings.

These findings have led to investigations on several micronutrients, including potassium, nitric oxide and, of most relevance to this Review, fiber.

As mentioned previously, some types of *fiber are considered prebiotics*, as they feed commensal bacteria in the colon and stimulate their growth.

Despite reports indicating that every 7 g of fiber consumed could lower the risk of CVD by 9%.

Beyond Gut Feelings: how the gut microbiota regulates blood pressure
Nature Reviews Cardiology
Vol 15, January 2018

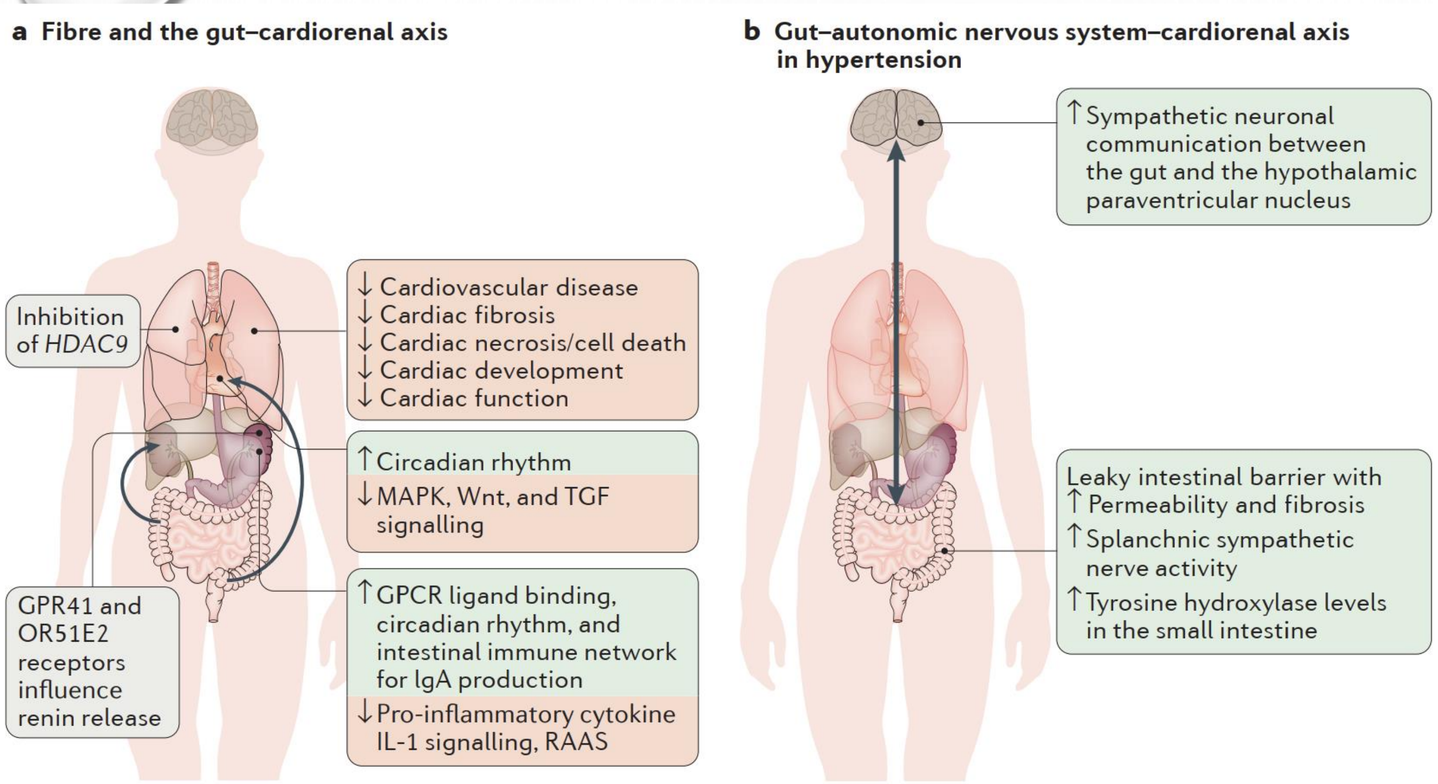
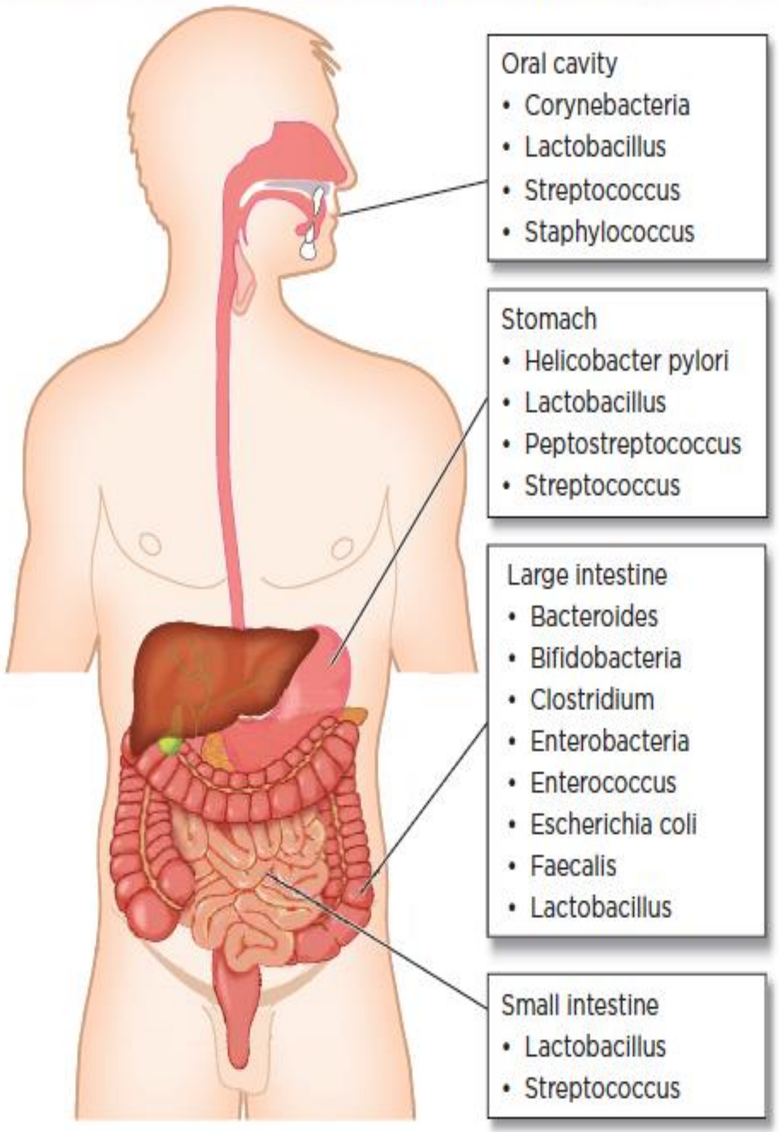


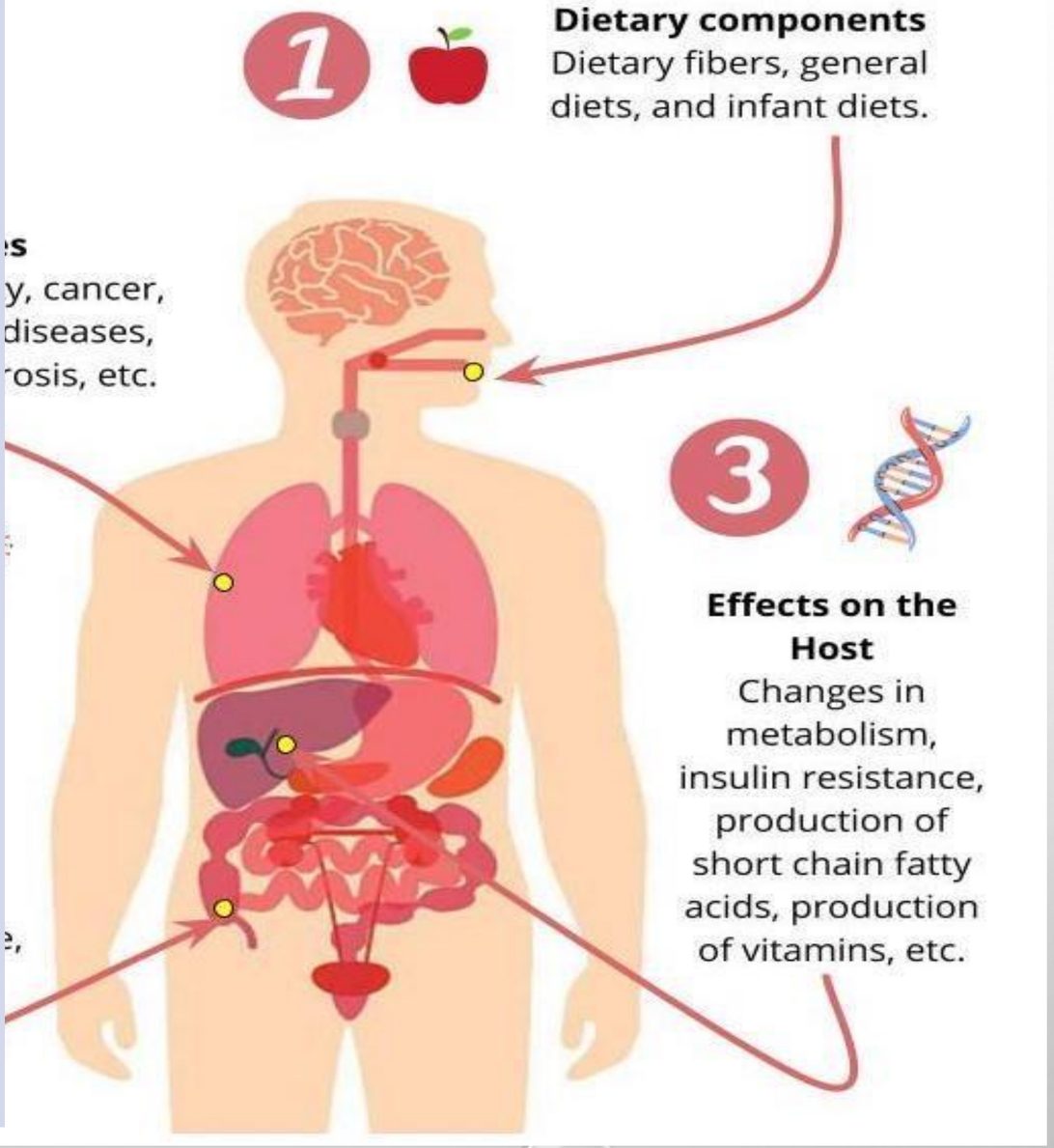
Figure 2 | **Mechanisms of the gut–autonomic nervous system–cardiorenal axis that regulate blood pressure.** **a** | A diet rich in resistant starches, which results in increased release of short-chain fatty acids (SCFAs), has several systemic effects that lead to a decrease in blood-pressure levels and cardiovascular disease in general. In the lung, SCFAs downregulate signalling pathways related to cardiac fibrosis, cardiac necrosis and cell death, and cardiovascular system development and function. Fibre and the SCFA acetate function independently of the G-coupled protein receptor (GPCR) GPR43, but act through histone deacetylase (HDAC9) in the lung. In the heart, fibre and acetate upregulate circadian rhythm pathways and downregulate mitogen-activated protein kinase (MAPK), Wnt, and transforming growth factor (TGF)-β signalling. In the kidney, fibre and acetate upregulate pathways related to GPCR ligand binding, circadian rhythm, and intestinal immune network for immunoglobulin (Ig) A production, and downregulate pro-inflammatory IL-1 signalling and the renin–angiotensin–aldosterone system (RAAS). In the kidney, the SCFA propionate seems to act through the olfactory receptor (Olfr78 in mice or OR51E2 in humans) and GPR41 (TABLE 1). **b** | Experimental models of hypertension, such as the spontaneously hypertensive rat (SHR) and the angiotensin II mouse model, have higher sympathetic neuronal communication between the gut and the hypothalamic paraventricular nucleus. Both animal models have a leaky intestinal barrier with increased permeability, fibrosis, and inflammatory markers, combined with altered tight junction proteins and decreased blood flow. The SHRs also have increased splanchnic sympathetic nerve activity and higher tyrosine hydroxylase levels in the small intestine. Together, these studies suggest the presence of a gut–sympathetic nervous system–cardiorenal axis in the regulation of blood pressure.

Beyond Gut Feelings: how the gut microbiota regulates blood pressure
Nature Reviews Cardiology
Vol 15, January 2018

Fig 2. **Distribution of major bacterial groups in the GI tract**



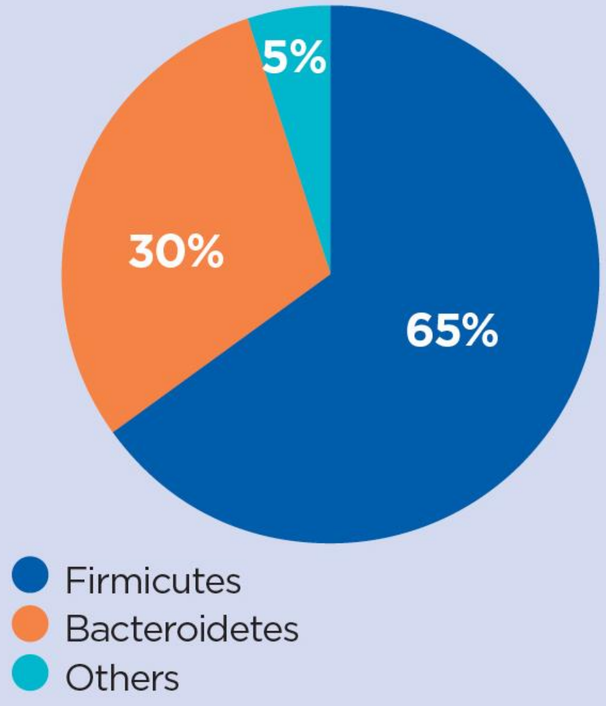
Nursing Times [online] November 2019 / Vol 115 Issue 11

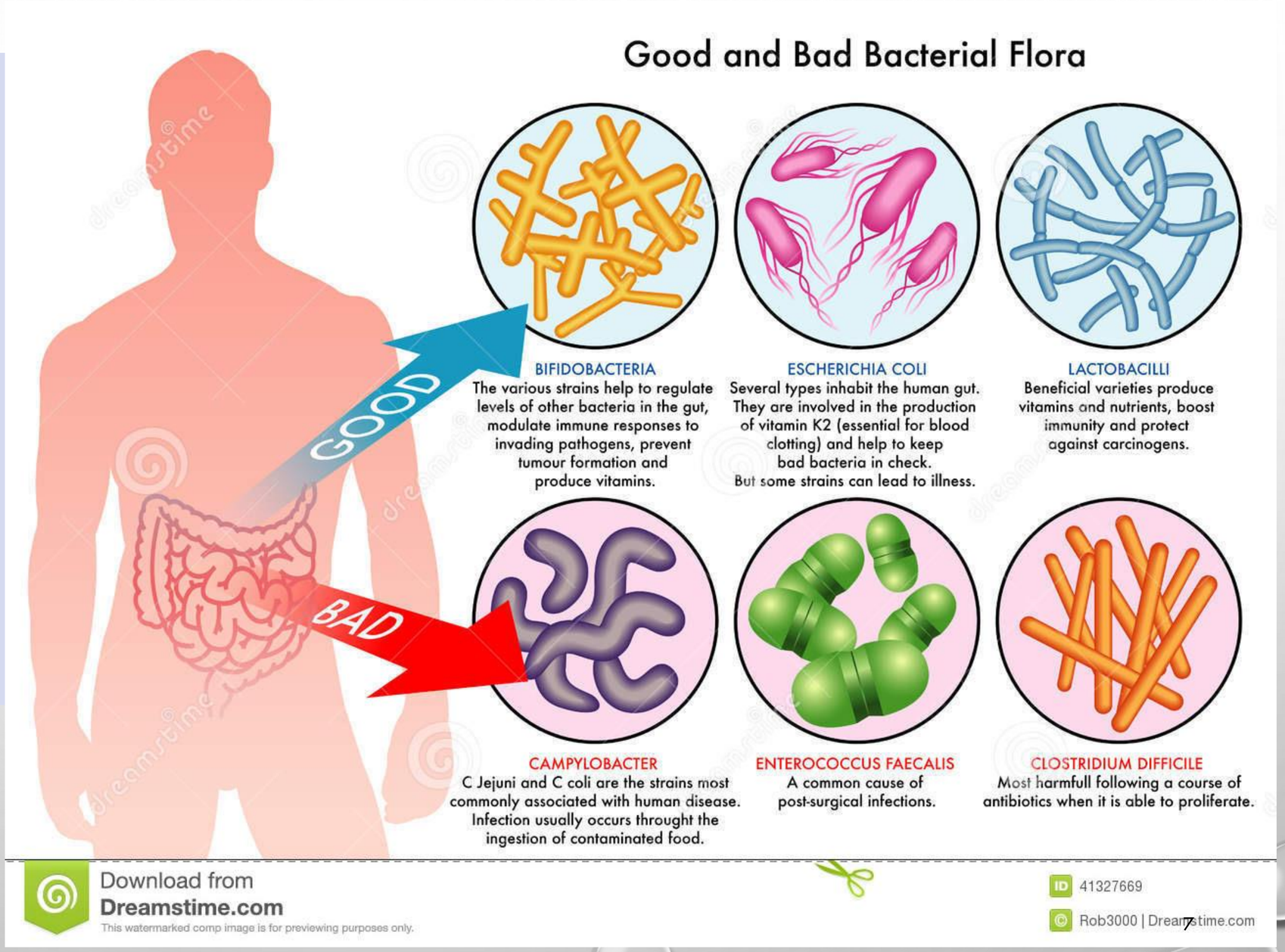


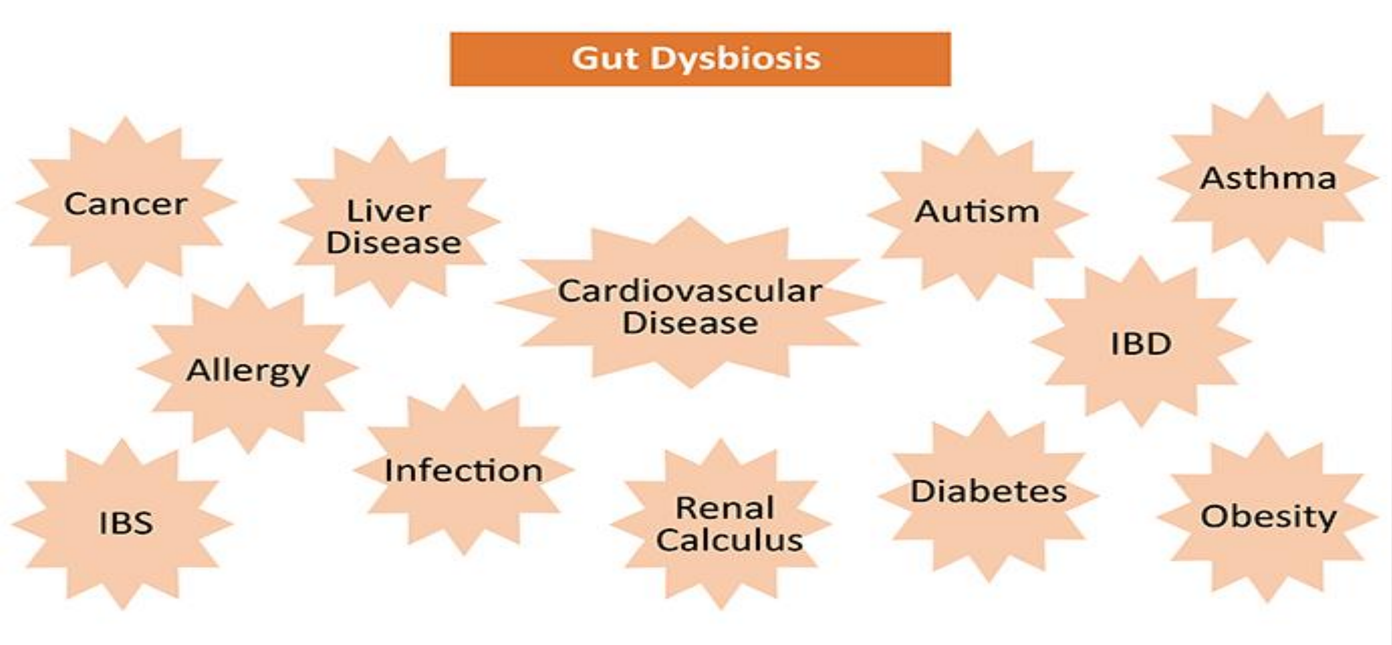
https://ysjournal.com/dietary-effects-on-the-human-gut-microbiome/

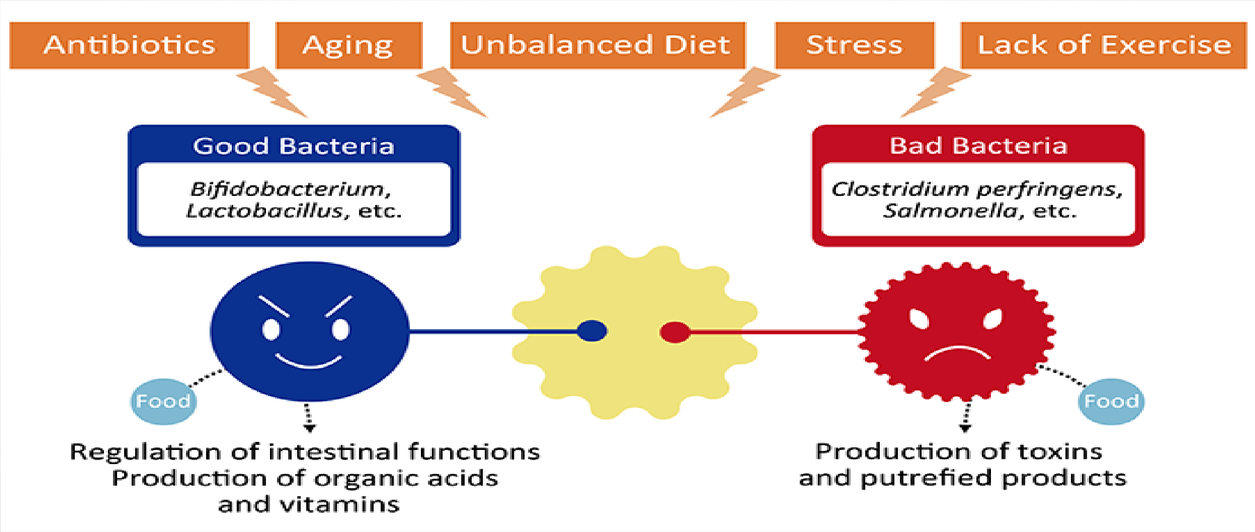
https://www.nursingtimes.net/clinical-archive/gastroenterology/gastrointestinal-tract-6-the-effects-of-gut-microbiota-on-human-health-21-10-2019/

Fig 1. **Human gut microbiota**

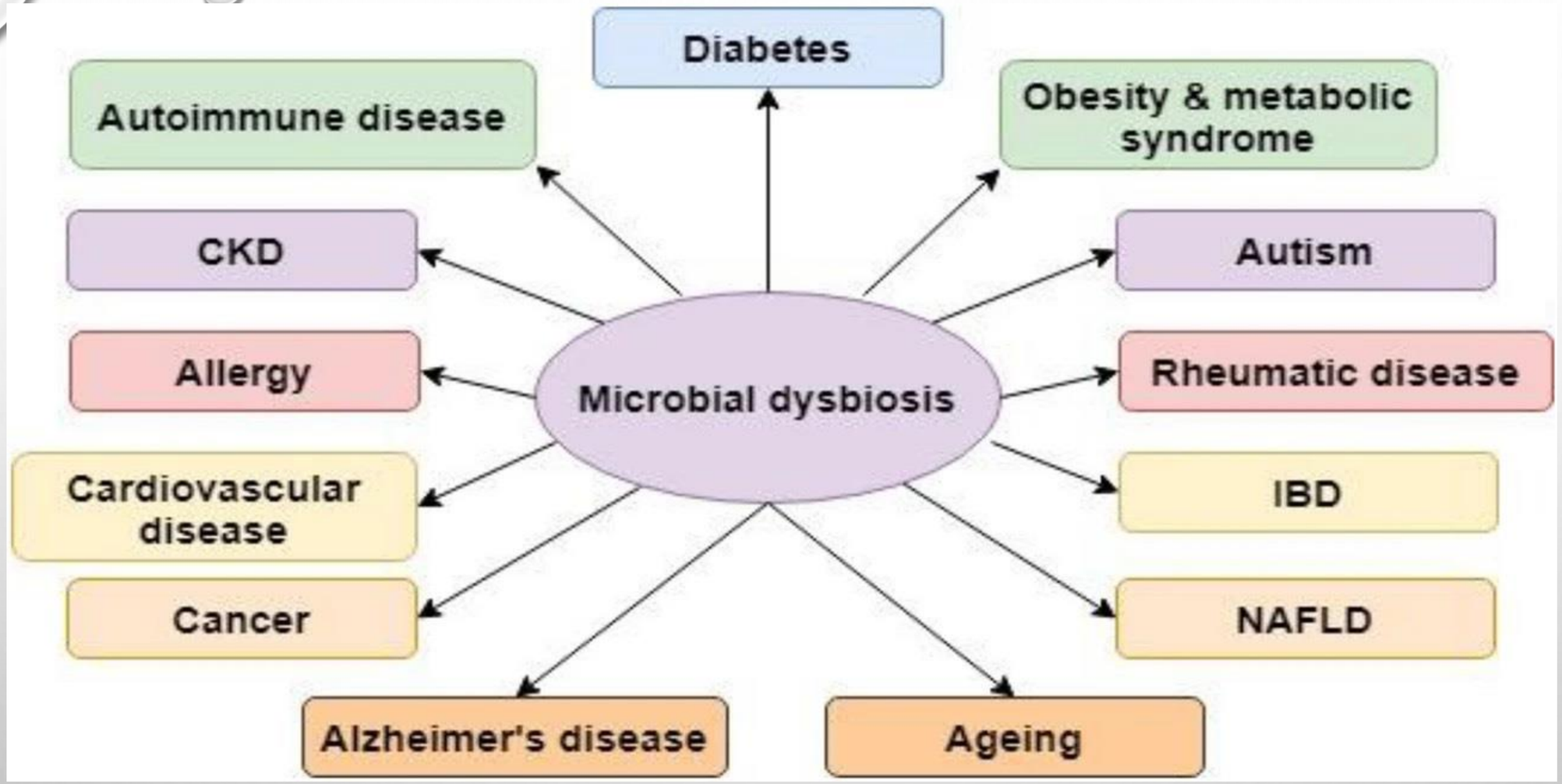








https://morinagamilk-ingredients.com/about/story/microbiota/

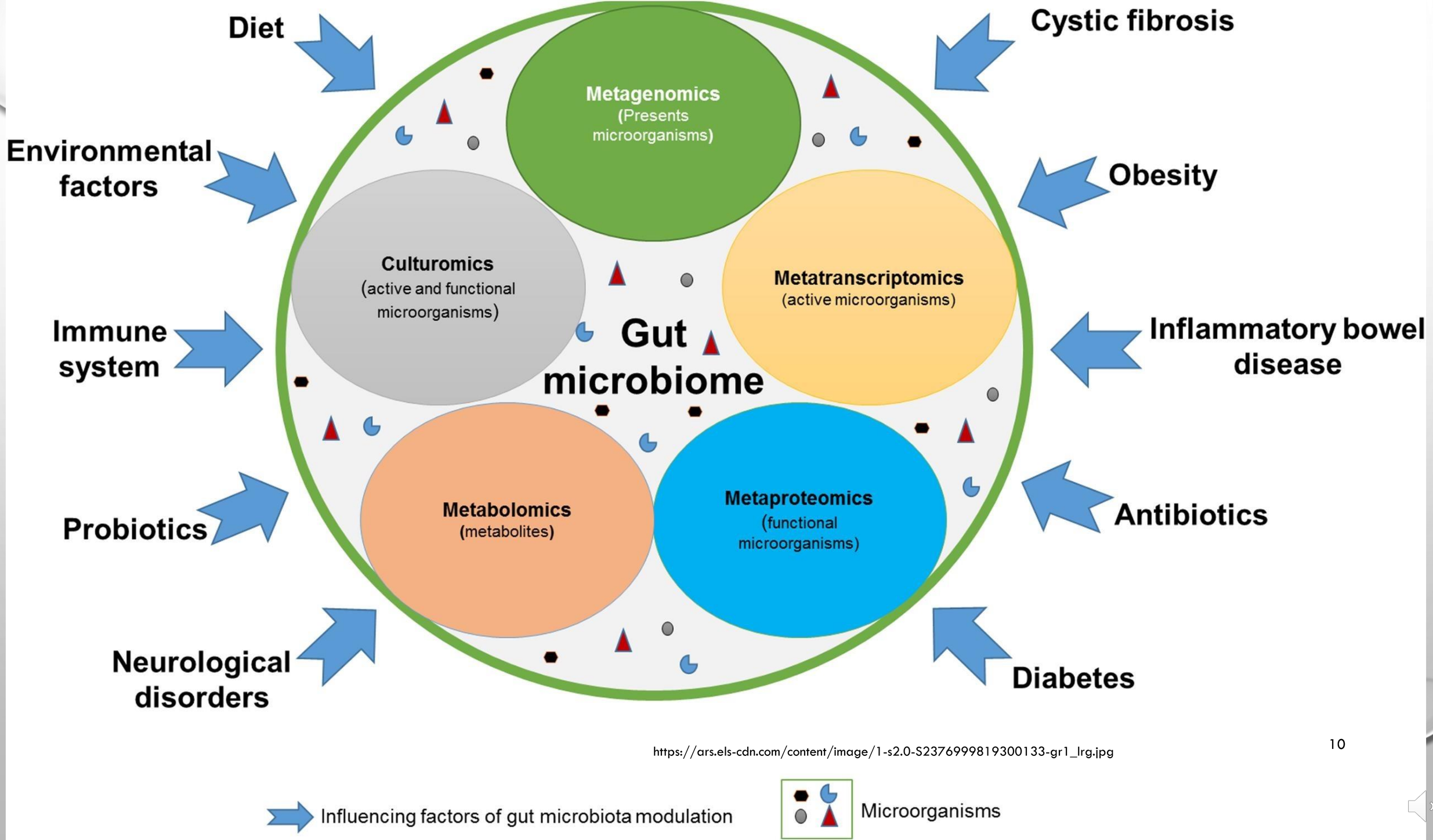


Review article | Published: 11 February 2021

Epigenetic Regulation of Gut Microbial Dysbiosis

Shivani Srivastava, Archana Singh, Kumar Sandeep ✉ & Durgavati Yadav ✉

Indian Journal of Microbiology **61**, 125–129 (2021) | Cite this article



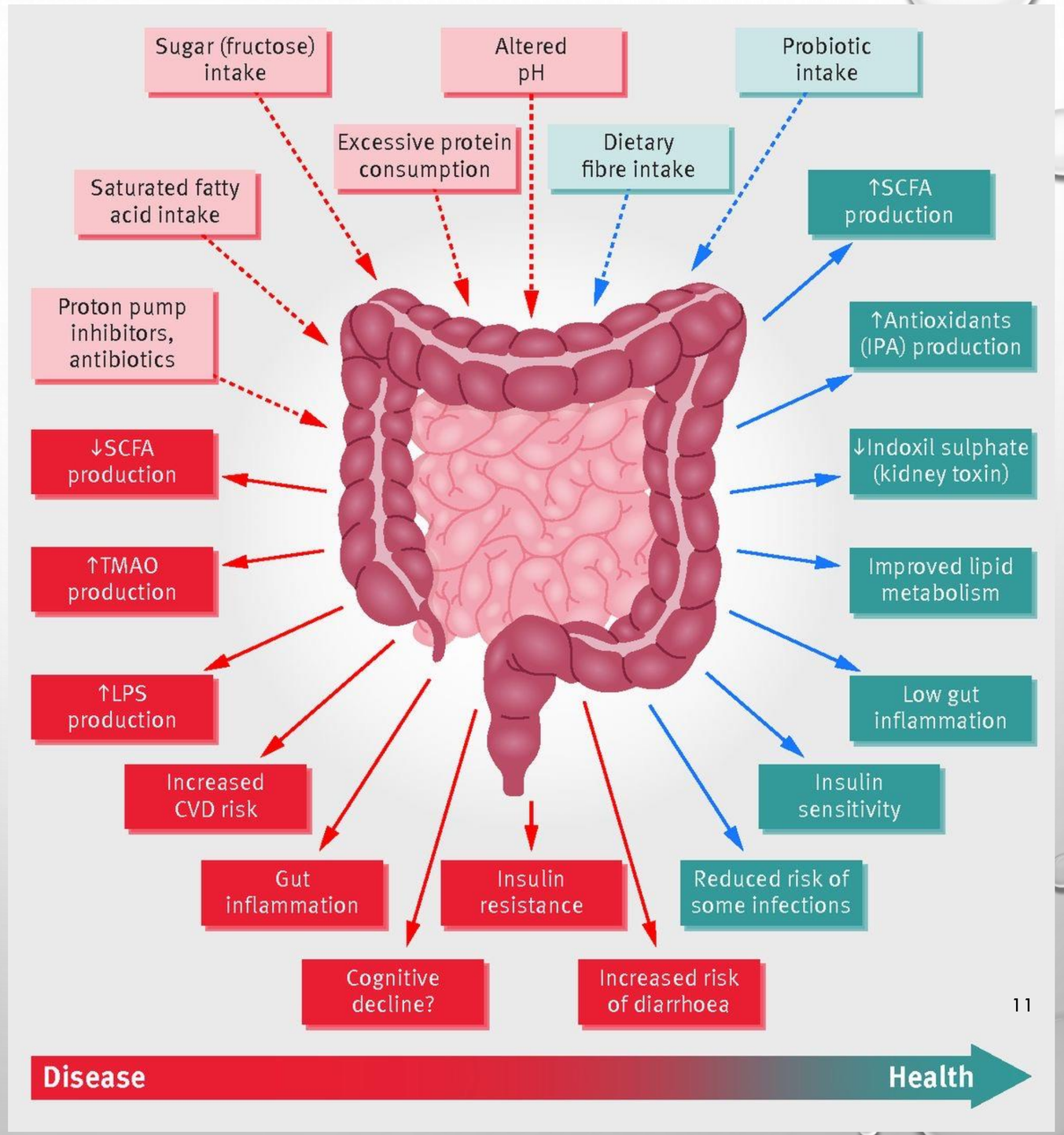
https://ars.els-cdn.com/content/image/1-s2.0-S2376999819300133-gr1_lrg.jpg

The body of a healthy individual is thought to contain
approximately 3.8×10^{13} bacterial cells

Beyond Gut Feelings: how the gut microbiota regulates blood pressure
Nature Reviews Cardiology
Vol 15, January 2018

Gut microbiota is the collection of bacteria that inhabit in the gastrointestinal tract producing a diverse ecosystem about 10^{14} microorganisms.

Kamada, N., Seo, S. U., Chen, G. Y., and Nunez, G. (2013).
Role of the gut microbiota in immunity and inflammatory disease.
Nat. Rev. Immunol. 13,321–335. doi: 10.1038/nri3430



https://www.bmj.com/content/361/bmj.k2179

Factors affecting gut Microbiota composition:

Genetic 12% and Diet 57%

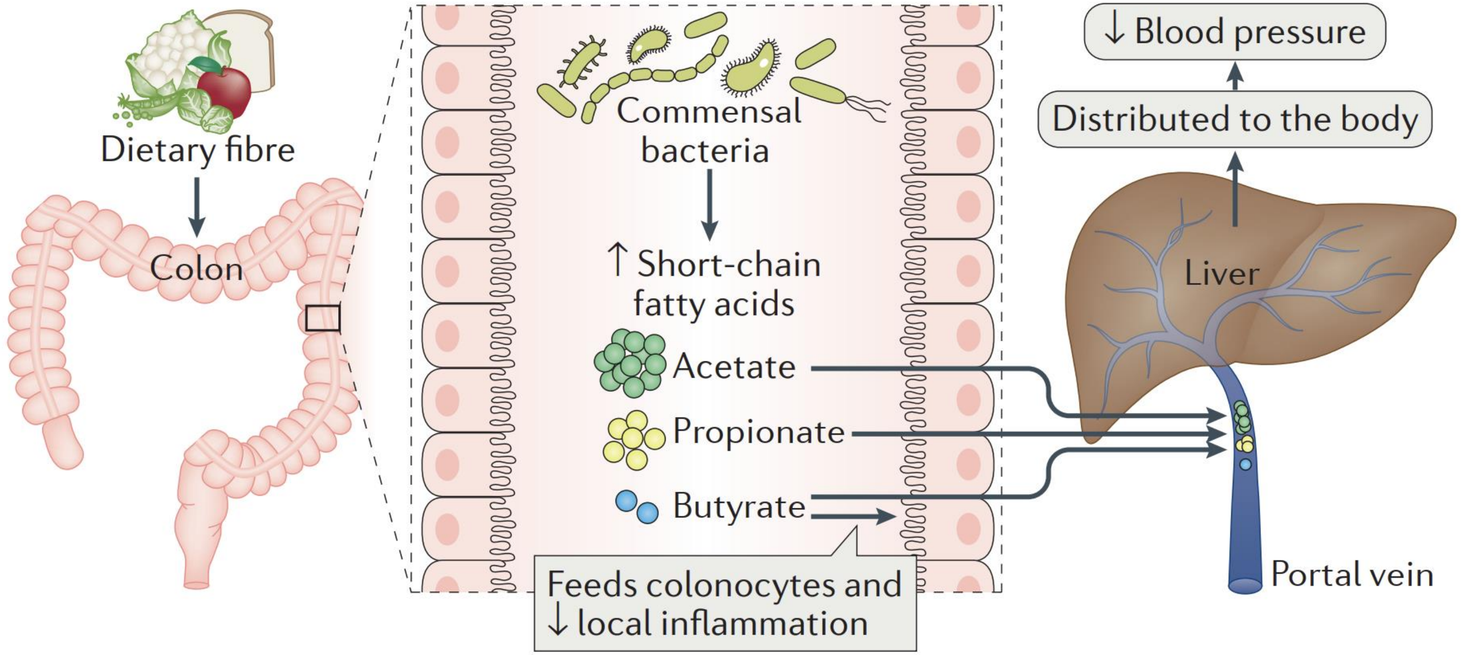


Figure 1 | **Influence of diet on gut microbiota and blood pressure.** Dietary fibre is mostly undigested until it reaches the colon, where it feeds commensal bacteria, decreasing the proliferation of pathogenic bacteria. The fermentation of fibre generates short-chain fatty acids (SCFAs). Acetate, propionate, and butyrate account for 80% of the SCFAs produced by the microbiota, found in roughly 60:25:15 ratios, respectively, within the colon. Butyrate is used by colonocytes to maintain the intestinal barrier and decrease local inflammation, but small amounts are transported with acetate and propionate to the liver through the portal vein. Propionate is metabolised by the hepatocytes, whereas acetate and smaller proportions of propionate and butyrate are released into the systemic circulation, where they can reach organs involved in the regulation of blood pressure.

Beyond Gut Feelings: how the gut microbiota regulates blood pressure
Nature Reviews Cardiology
Vol 15, January 2018

GUT MICROBIOTA IN HUMAN HYPERTENSION

THE HUMAN GUT MICROBIOME IN PATIENTS WITH HYPERTENSION HARBOURED LOWER MICROBIAL DIVERSITY THAN THE GUT MICROBIOME FROM A HEALTHY INDIVIDUAL.

HOWEVER, BOTH BP-LOWERING MEDICATION AND A HISTORY OF HYPERTENSION AMONG THE HEALTHY INDIVIDUALS COULD BE CONFOUNDING FACTORS IN THIS SETTING.

Beyond Gut Feelings: how the gut microbiota regulates blood pressure
Nature Reviews Cardiology
Vol 15, January 2018

TWO MAIN ENTEROTYPES WERE IDENTIFIED;

THE GUT MICROBIOTA IN PATIENTS WITH *PREHYPERTENSION* AND
IN PATIENTS WITH *HYPERTENSION* HAD A HIGHER PERCENTAGE OF
AN ENTEROTYPE RICH IN BACTERIA FROM THE GENUS ***PREVOTELLA***,

WHEREAS

THE GUT MICROBIOTA OF *HEALTHY CONTROLS* WERE MOSTLY MADE UP OF AN ENTEROTYPE RICH IN BACTERIA FROM
THE GENUS ***BACTEROIDETES***.

Beyond Gut Feelings: how the gut microbiota regulates blood pressure
Nature Reviews Cardiology
Vol 15, January 2018

Olfr78 is localized in the smooth muscle cells of arteries, in autonomic nerves in the heart and gut, and in the renal juxtaglomerular complex.

Olfr78 might be involved in renin regulation.

Propionate increased the release of renin.

REVIEWS

Table 1 | **Receptors for short-chain fatty acids and their effect on blood pressure**

Short-chain fatty acid	Effect on blood pressure	Receptors
Acetate	↓ Blood pressure[8]	GPR41, GPR43, Olfr78, HDAC9
Propionate	↓ Blood pressure (through GPR41)[93,97] or ↑ blood pressure (Olfr78)[93]	GPR41*, GPR43, Olfr78*
Butyrate	Unknown	GPR41, GPR43, GPR109A

*Receptors shown to have an effect in blood-pressure levels *in vivo*. Besides GPR41 and Olfr78, other receptors have not been characterized in hypertension. GPR41, G-protein-coupled receptor 41 (also known as free fatty acid receptor 3); GPR43, G-protein-coupled receptor 43 (also known as free fatty acid receptor 2); GPR109A, G-protein-coupled receptor 109A (also known as hydroxycarboxylic acid receptor 2); HDAC9, histone deacetylase 9; Olfr78, olfactory receptor 51E2.

Beyond Gut Feelings: how the gut microbiota regulates blood pressure
Nature Reviews Cardiology
Vol 15, January 2018

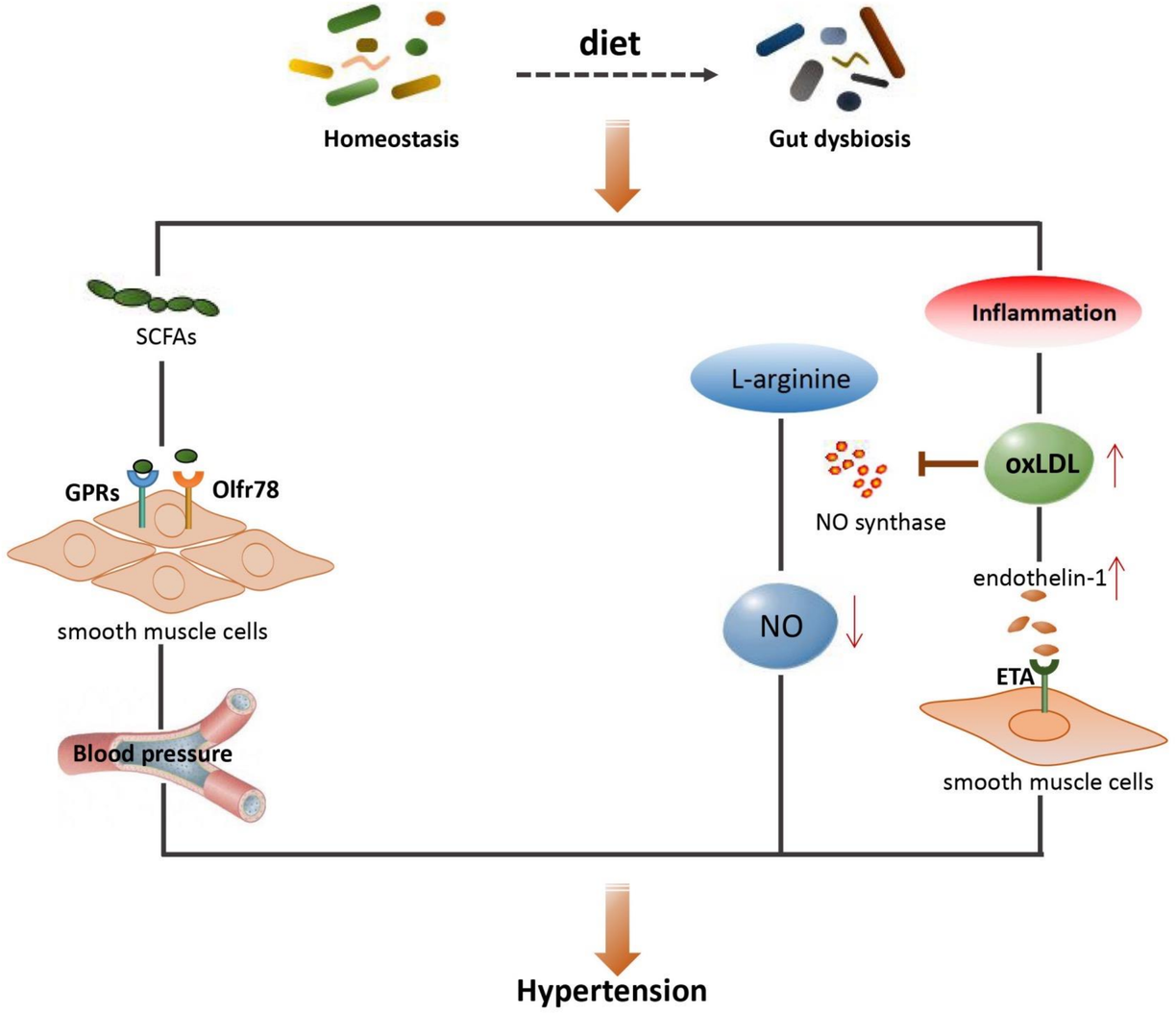


FIGURE 3 | The main mechanisms between gut microbiota and hypertension. SCFAs, short-chain fatty acids; GPRs, G-protein-coupled receptors; Olfr78, olfactory receptor 78; NO, nitric oxide; OxLDL, oxidized low density lipoprotein; ETA, endothelin receptor A.

G-protein-coupled receptors (GPCRs)
SCFAs can stimulate host GPCRs regulated pathways to affect renin secretion and therefore blood pressure.

Furusawa, Y., Obata, Y., Fukuda, S., Endo, T. A., Nakato, G., Takahashi, D., et al. (2013). Commensal microbe-derived butyrate induces the differentiation of colonic regulatory T cells. Nature 504, 446–450. doi: 10.1038/nature12721

The activity of endothelin-1 on blood vessels is concentration dependent, that is,
endothelin-1 produces: vasodilatory effects at
low concentrations by activating the endothelial receptor B (ETB)
and promoting NO production, but

produces vasoconstriction at
high concentrations by increasing ox-LDL production in plaques and activating the endothelial receptor A (ETA).

Boulanger, C., and Luscher, T. F. (1990). Release of endothelin from the porcine aorta, inhibition by endothelium-derived nitric oxide. J. Clin. Invest. 85, 587–590. doi: 10.1172/jci114477

The Role of Gut Microbiota in Atherosclerosis and Hypertension
Junli Ma and Houkai Li*
Frontiers in Pharmacology, September 2018 | Volume 9 | Article 1082

HIGH-FIBRE INTAKE WAS ASSOCIATED WITH DOWNREGULATION OF PRO-INFLAMMATORY IL-1 SIGNALLING,

AND

UPREGULATED GPCR LIGAND BINDING AND INTESTINAL IMMUNE SIGNALLING FOR IMMUNOGLOBULIN A PRODUCTION.

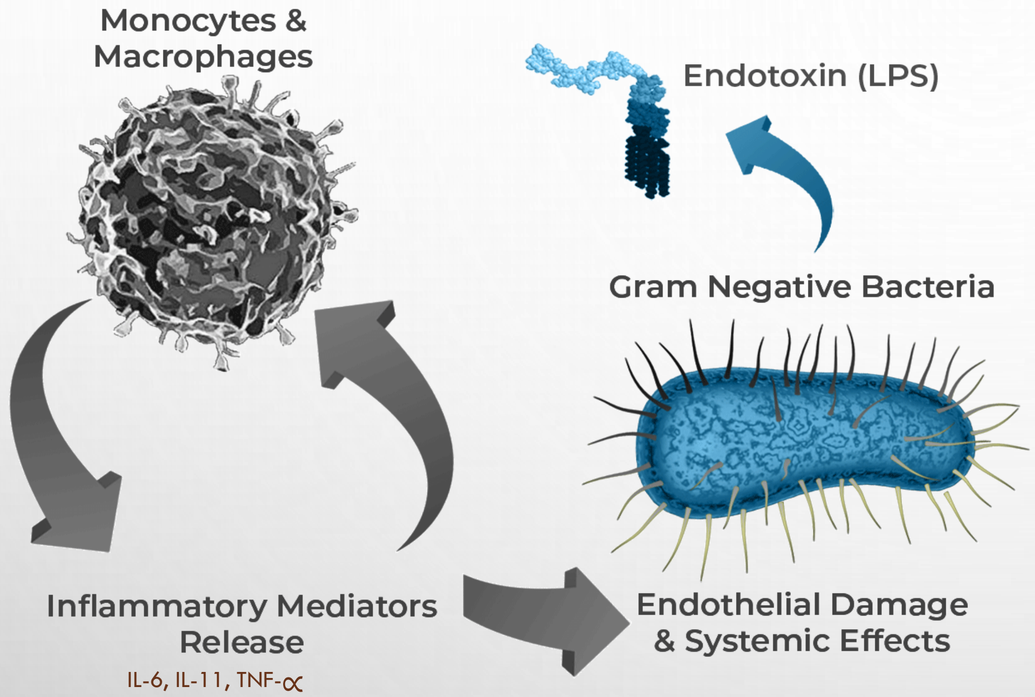
DIETS LOW IN FIBER ARE OFTEN RICH IN OTHER NUTRIENTS SUCH AS:
FAT, PROTEIN, AND REFINED SUGARS.
WHICH MIGHT ALSO INFLUENCE THE GUT MICROBIOTA AND BP.

Beyond Gut Feelings: how the gut microbiota regulates blood pressure
Nature Reviews Cardiology
Vol 15, January 2018

CHOLINE, ***PHOSPHATIDYLCHOLINE***, **AND** ***L- CARNITINE***
ARE ESSENTIAL DIETARY NUTRIENTS FOUND IN FOODS
RICH IN CHOLESTEROL, SUCH AS **RED MEAT.**

TANG AND COLLEAGUES HAVE SHOWN THAT A GUT
METABOLITE
OF DIETARY CHOLINE AND PHOSPHATIDYLCHOLINE,
KNOWN AS
TRIMETHYLAMINE N-OXIDE ***(TMAO),*** IS ASSOCIATED
WITH
DEVELOPMENT OF ***ATHEROSCLEROSIS***.
L-CARNITINE WAS SUBSEQUENTLY DESCRIBED AS
ANOTHER SOURCE OF TMAO.

Beyond Gut Feelings: how the gut microbiota regulates blood pressure
Nature Reviews Cardiology
Vol 15, January 2018



https://spectraldx.com/science/

HTN??!

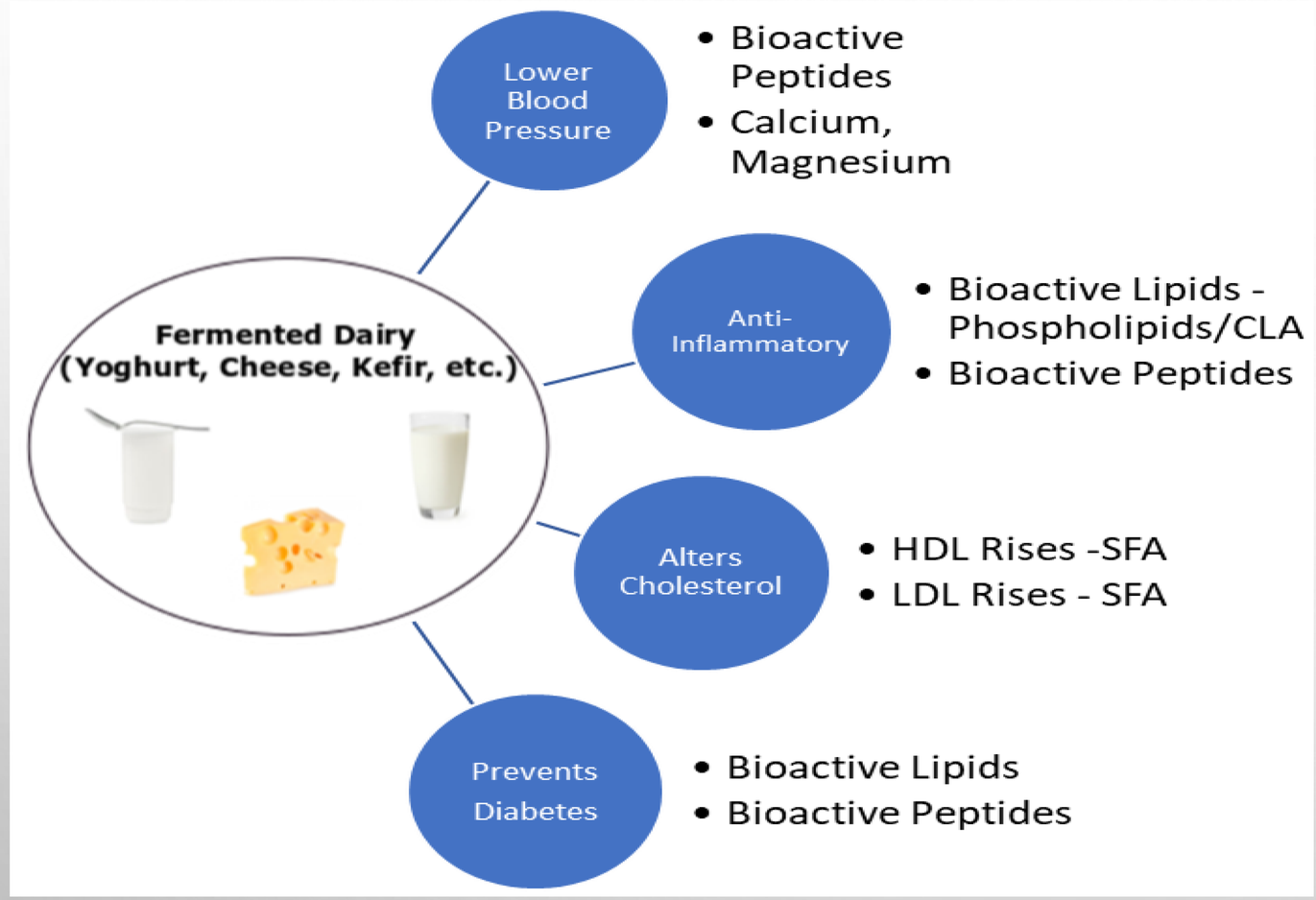
Septic shock
hypotension
MODS
Atherosclerotic plaque

Lipopolysaccharide

levels in the blood have been inversely correlated with adherence to the Mediterranean diet, but no association has been found with hypertension.

Beyond Gut Feelings: how the gut microbiota regulates blood pressure
Nature Reviews Cardiology
Vol 15, January 2018

Probiotics, milk peptides, and BP



the fermentation of milk with Lactobacillus helveticus released peptides with the amino acid sequences isoleucine–proline–proline and valine–proline–proline, which have the capacity to inhibit ACE, resulting in lower BP levels in experimental models such as the SHR121–123.

Beyond Gut Feelings: how the gut microbiota regulates blood pressure
Nature Reviews Cardiology
Vol 15, January 2018

https://mdpi-res.com/d_attachment/foods/foods-07-00029/article_deploy/foods-07-00029.xml

Probiotics, milk peptides, and BP

A meta-analysis of 14 randomized, placebo-controlled clinical trials involving a total of 702 participants who ingested probiotic fermented milk reported a modest, albeit statistically significant decrease in systolic (−3 mmHg) and diastolic (−1 mmHg) BP.

The BP-lowering effect was more pronounced in patients who were hypertensive (−3.98 mmHg systolic BP) than in participants who were normotensive (−2.09mmHg),

and was more pronounced in the six Japanese studies (−6.12 mmHg) than in the eight European studies (−2.08 mmHg)124, suggesting that other genetic or environmental factors might be involved.

Dong,J.Y. et al. Effects of Probiotic Fermented Milk on Blood Pressure: A Meta-Analysis of Randomized Controlled Trials
Br. J. Nutrition. 110, 1188-1194 (2013).

The type of probiotics used differed between each study, with combinations that included Enterococcus faecium, Streptococcus thermophiles, Lactobacillus acidophilus, Lactobacillus helveticus, Lactobacillus reuteri, Lactobacillus casei, Lactobacillus plantarum, Bifidobacteria infantis, Saccharomyces cerevisiae, and Bifidobacterium animalis

Khalesi, S., Sun, J., Buys, N. & Jayasinghe, R. Effect of probiotics on blood pressure: a systematic review and meta-analysis of randomized, controlled trials. Hypertension 64, 897–903 (2014)

Gut microbiota and antihypertensive drugs

Drug metabolism can be influenced by interactions between specific bacterial strains and the host diet.

For example, digoxin,
can be inactivated by the strain DSM2243 of the Actinobacterium Eggerthella lenta (E. lenta).

Haiser, H. J. et al. Predicting and manipulating cardiac drug inactivation by the human gut bacterium Eggerthella lenta. Science 341, 295–298 (2013)

Gut microbiota and antihypertensive drugs

The metabolism of commonly used antihypertensive drugs such as *ACEi, β-blockers, and ARBs*
have been associated
with interindividual variation of the human gut microbiome in 1,135 Dutch individuals from population-based cohorts.

Zhernakova, A. et al. Population-based metagenomics analysis reveals markers for gut microbiome composition and diversity. Science 352, 565–569 (2016).

Approximately 13.7% of patients with hypertension are estimated to be treatment-resistant.
A case study published in 2015 described an improvement in BP control after intensive antibiotic (Minocycline) therapy in a patients with treatment-resistant hypertension.

Qi, Y., Aranda, J. M., Rodriguez, V., Raizada, M. K. & Pepine, C. J. Impact of antibiotics on arterial blood pressure in a patient with resistant hypertension — a case report. Int. J. Cardiol. 201, 157–158 (2015)

Pregnancy, gut microbiota, and BP

Infants who
are delivered vaginally have a microbiome that resembles their own mother's vaginal microbiota, whereas those delivered by caesarean section have predominantly bacterial communities found on the skin surface.

Dominguez-Bello, M. G. et al. Delivery mode shapes the acquisition and structure of the initial microbiota across multiple body habitats in newborns. Proc. Natl Acad. Sci. USA 107, 11971–11975 (2010)

A borderline association between intake of
fiber during pregnancy and the
infant's diastolic BP at 6 months of age
has been described.

Aaltonen, J. et al. Evidence of infant blood pressure programming by maternal nutrition during pregnancy: a prospective randomized controlled intervention study. J. Pediatr. 152, 79–84.e2 (2008).

Pregnancy, gut microbiota, and BP

a prospective study in 33,399 primiparous women showed that daily or weekly intake of probiotics from milk-based products was associated with lower risk of pre-eclampsia.

Brantsaeter, A. L. et al. Intake of probiotic food and risk of preeclampsia in primiparous women: the Norwegian Mother and Child Cohort Study. Am. J. Epidemiol. 174, 807–815 (2011).

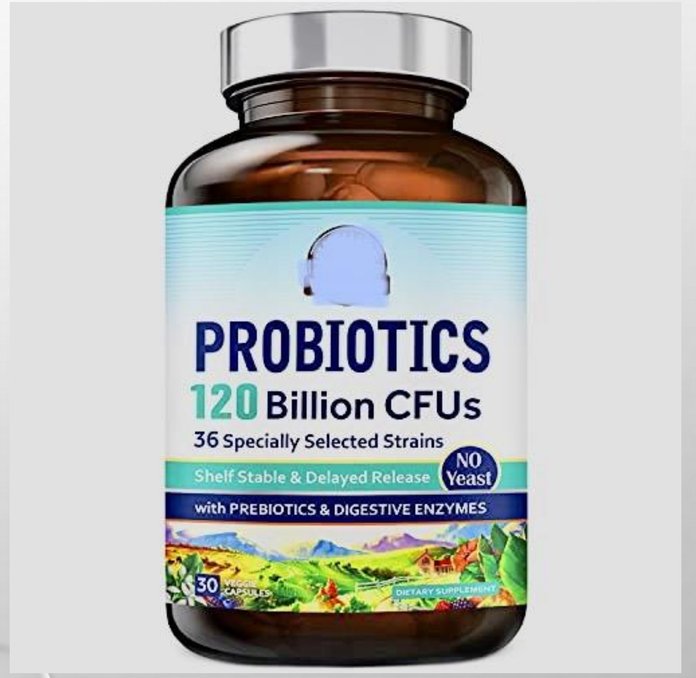
GUT MICROBIOTA-TARGETED THERAPY OF CVD

Given the contributions of gut microbiota to the development of *CVD*, they have emerged as a potentially important target for CVD therapy.

The most frequently used approaches to manipulate the Gut microbiota include probiotic, prebiotic, natural components, fecal transplantation, and so on.

Daliri, E. B., Lee, B. H., and Oh, D. H. (2017). Current perspectives on antihypertensive probiotics. Probiot. Antimicrob. Proteins 9, 91–101. doi: 10.1007/s12602-016-9241-y

He, M., and Shi, B. (2017). Gut microbiota as a potential target of metabolic syndrome: the role of probiotics and prebiotics. Cell Biosci. 7:54. doi: 10.1186/s13578-017-0183-1



Key points

- High dietary intake of fruit, vegetables, and fibre is associated with lower blood pressure levels
- Short-chain fatty acids, such as acetate and propionate, released by the fermentation of fibre by the gut microbiota are linked to lower blood-pressure levels in experimental models of hypertension
- A growing body of literature supports a role for the gut microbiota in the development and maintenance of high blood-pressure levels
- Limited evidence suggests that the manipulation of the gut microbiota (such as through faecal transplants, or the use of antibiotics or probiotics) might be a novel therapeutic approach for the treatment of hypertension
- The composition of human gut microbiota in the setting of high blood-pressure levels should be assessed to determine the complex nature of essential hypertension, given that gut microbiota can interact with the the host's environment and genome

Beyond Gut Feelings: how the gut microbiota regulates blood pressure
Nature Reviews Cardiology
Vol 15, January 2018


سپاس بسیار