Healthspan, Epigenetics, and the Microbiome

M. Elizabeth Swenor, DO
Medical Director Lifestyle, Integrative, Functional Medicine
Henry Ford Health

Healthy for a Lifetime Conference
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I have no financial disclosures

Objectives

1. Define Epigenetics, Lifespan, Healthspan, Transgenerational Inheritance, and the Human Microbiome

2. Discuss lifestyle modification for optimizing human healthspan, microbiota health, and reducing health risks of stress driven aberrant epigenetic changes
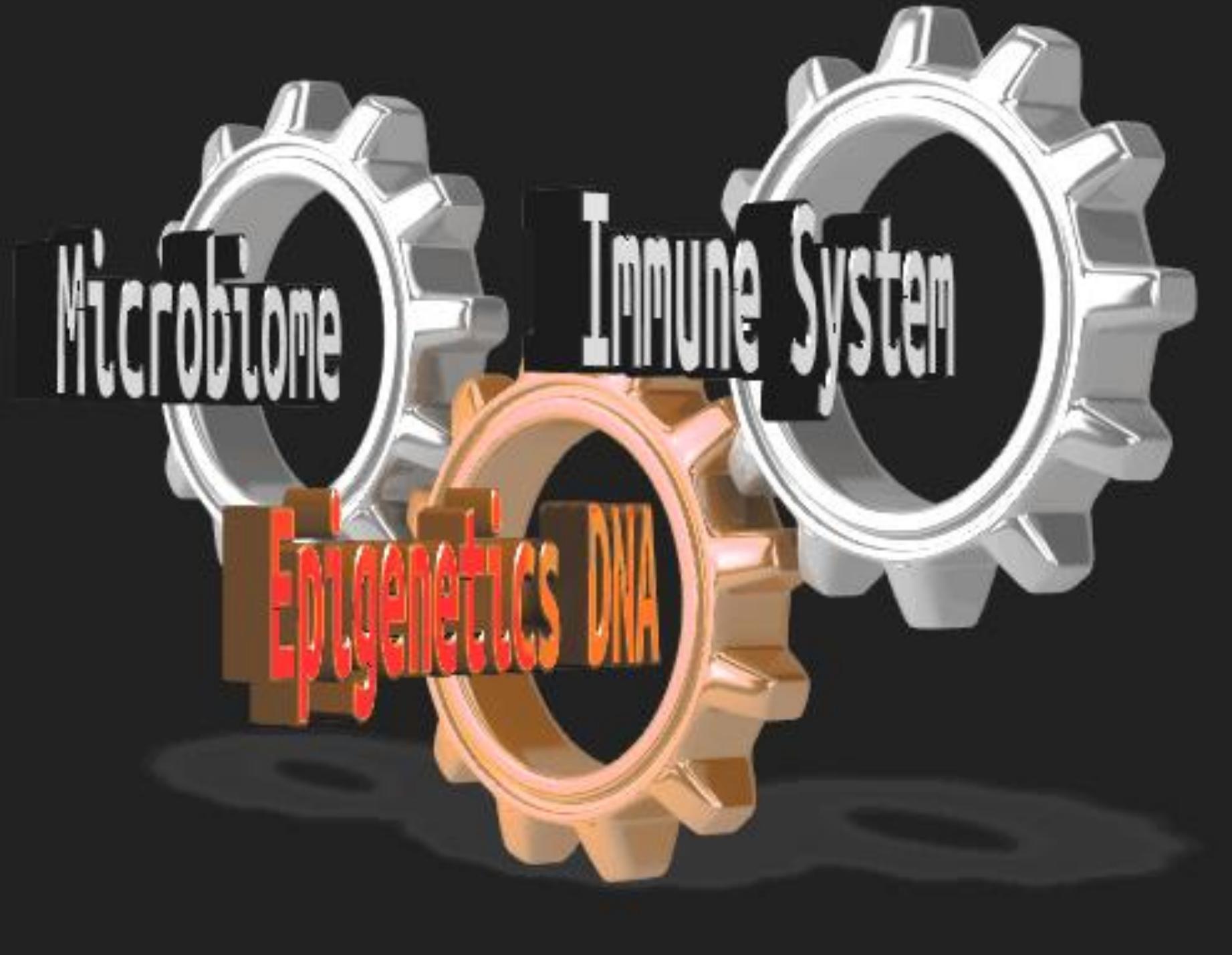
Sarah 62 yo Caucasian Female

CC: Fatigue, weight gain, uncontrolled T2DM, active Crohn's disease with diarrhea and bloating

PMHX

- Age 45 -NSTEMI- 99% stenosis mid-RCA and LAD stenosis
- 250 pounds. BMI 44.3 age 40
- Hypertension
- Hyperlipidemia
- Hashimoto's hypothyroidism
- T2DM HbA1C 8.5 no medications
- Crohn's disease
- Lupus
- Psoriasis
- Depression, anxiety, insomnia with daytime hypersomnolence
- Low Vitamin B12 and D3, Low magnesium

Your DNA is NOT Your Destiny (Epigenetics)

Why Your DNA Isn't Your Destiny | **Jan. 18, 2010**

Agouti Gene

Obese

Prone to cancer and diabetes

methyl groups

Thin Healthy
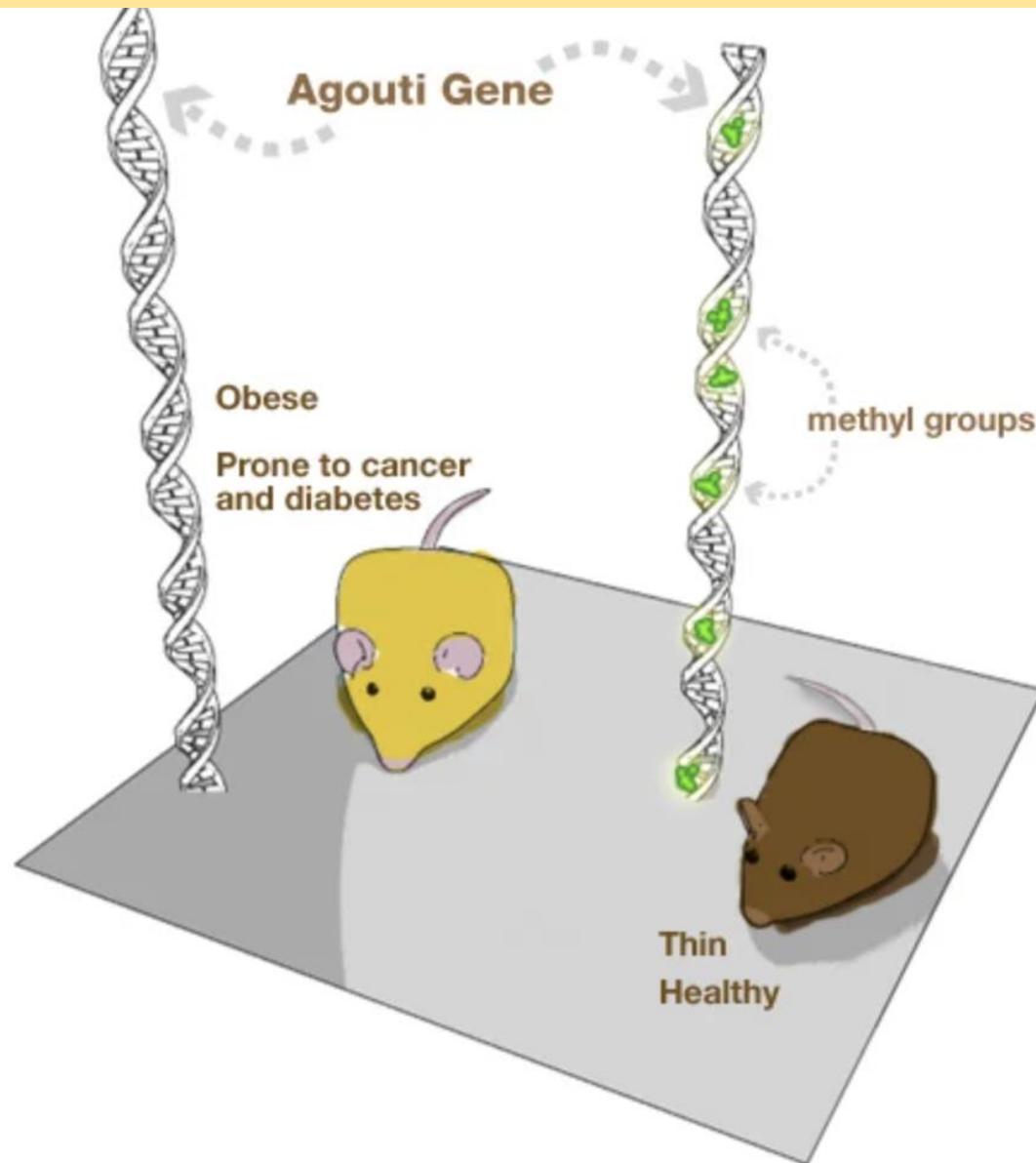
These Two Mice are Genetically Identical and the Same Age
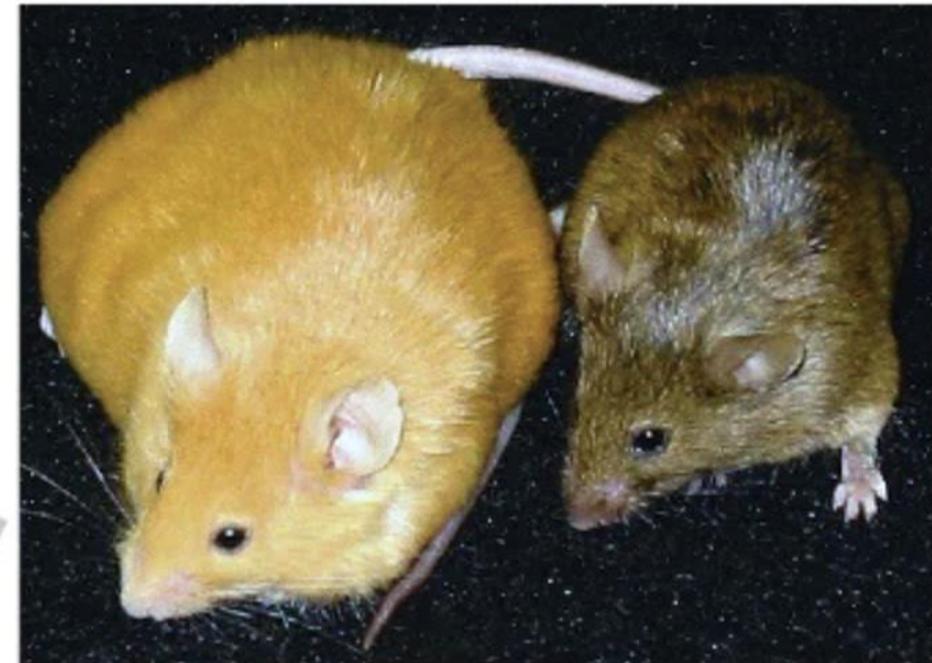
While pregnant, both of their mothers were fed Bisphenol A (BPA) but DIFFERENT DIETS:

The mother of this mouse received a **normal mouse diet**

The mother of this mouse received a diet **supplemented** with choline, folic acid, betaine and vitamin B12

Photo courtesy Randy L. Jirtle, PhD

**2000, Randy Jirtle, Professor Duke University**

Epigenetics

- epigenetics = on top of genetics

- chemical modifications of chromosomal DNA and/or structures that change the pattern of gene expression without altering the DNA sequence

Non-Coding RNA

DNA Methylation

Chromatin Structure

DNA Sequence

Histone Modifications

Role of environmentally induced epigenetic transgenerational inheritance in evolutionary biology: Unified Evolution Theory
Environmental Epigenetics, 2021, 7(1), 1–12
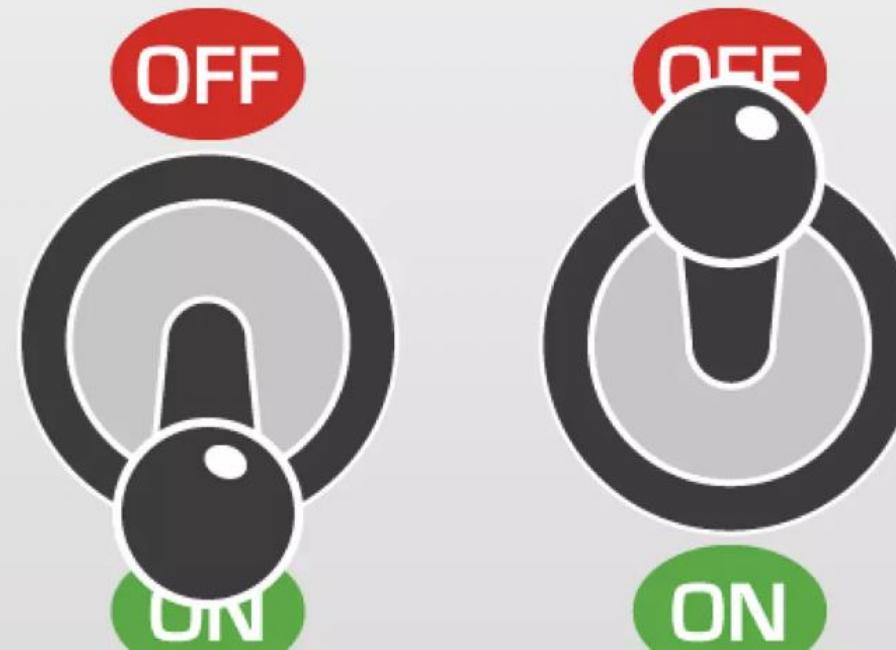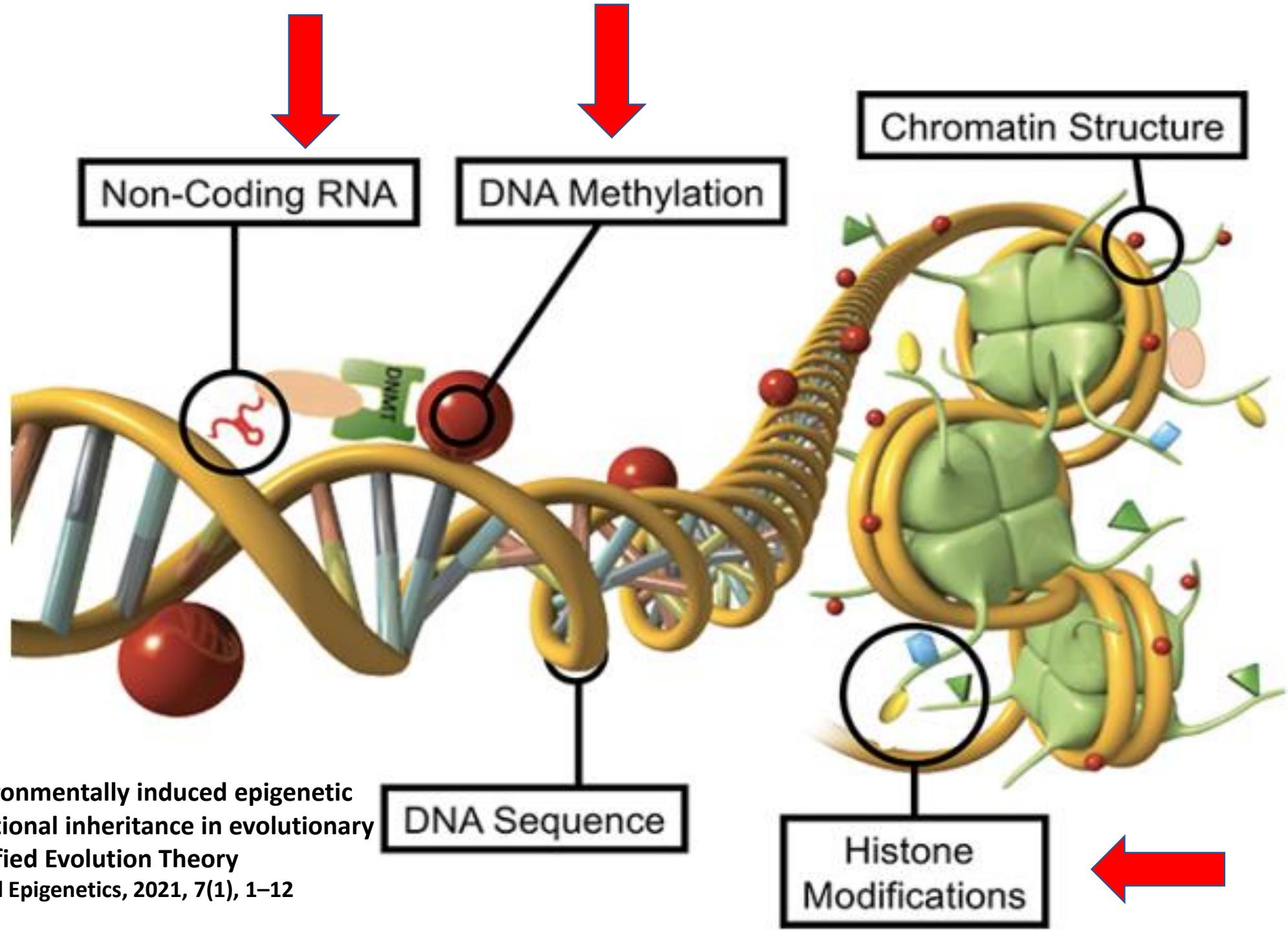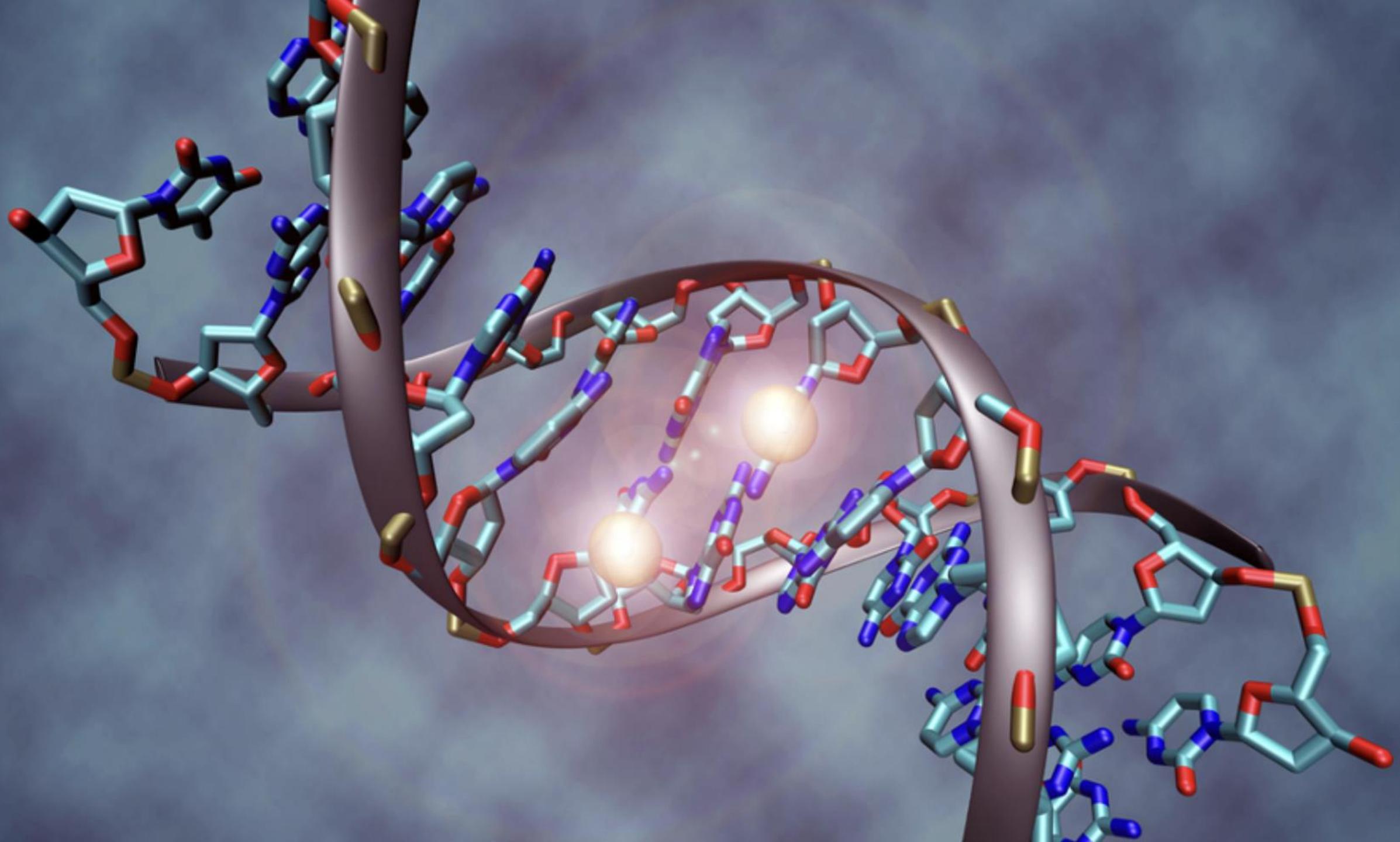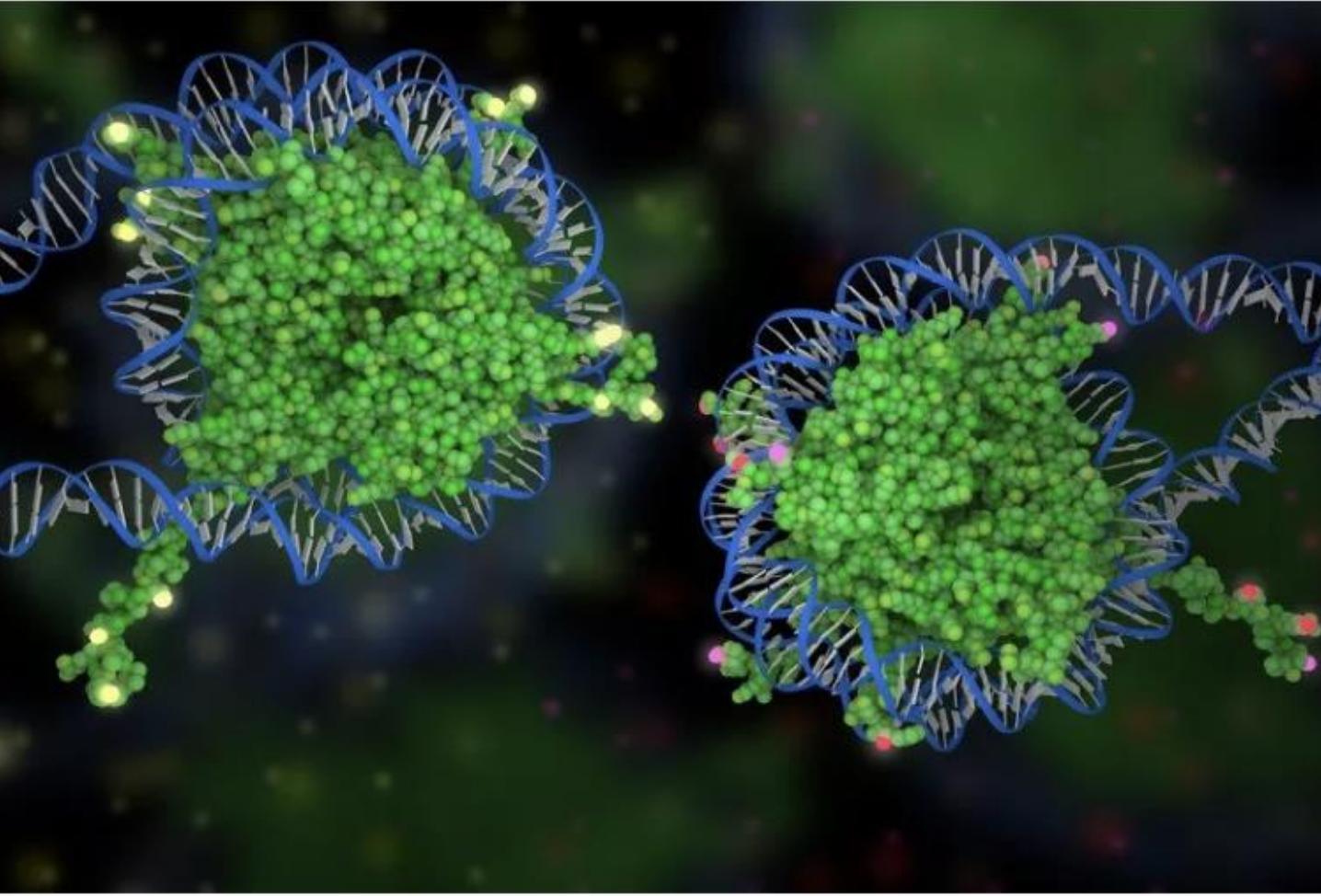
In cells, DNA (blue) is wrapped around proteins called histones (green) and decorated with chemical tags that affect which genes are turned on or off.

Changes in prostate gene expression in men undergoing an intensive nutrition and lifestyle intervention

Epidemiological and prospective studies indicate that comprehensive lifestyle changes may modify the progression of prostate cancer.

Fig. 4. Heat map of the gene ontology group "Intracellular Protein Traffic" illustrating the down-regulation of these 31 transcripts. Pre- and postcomprehensive diet and lifestyle intervention samples are indicated.
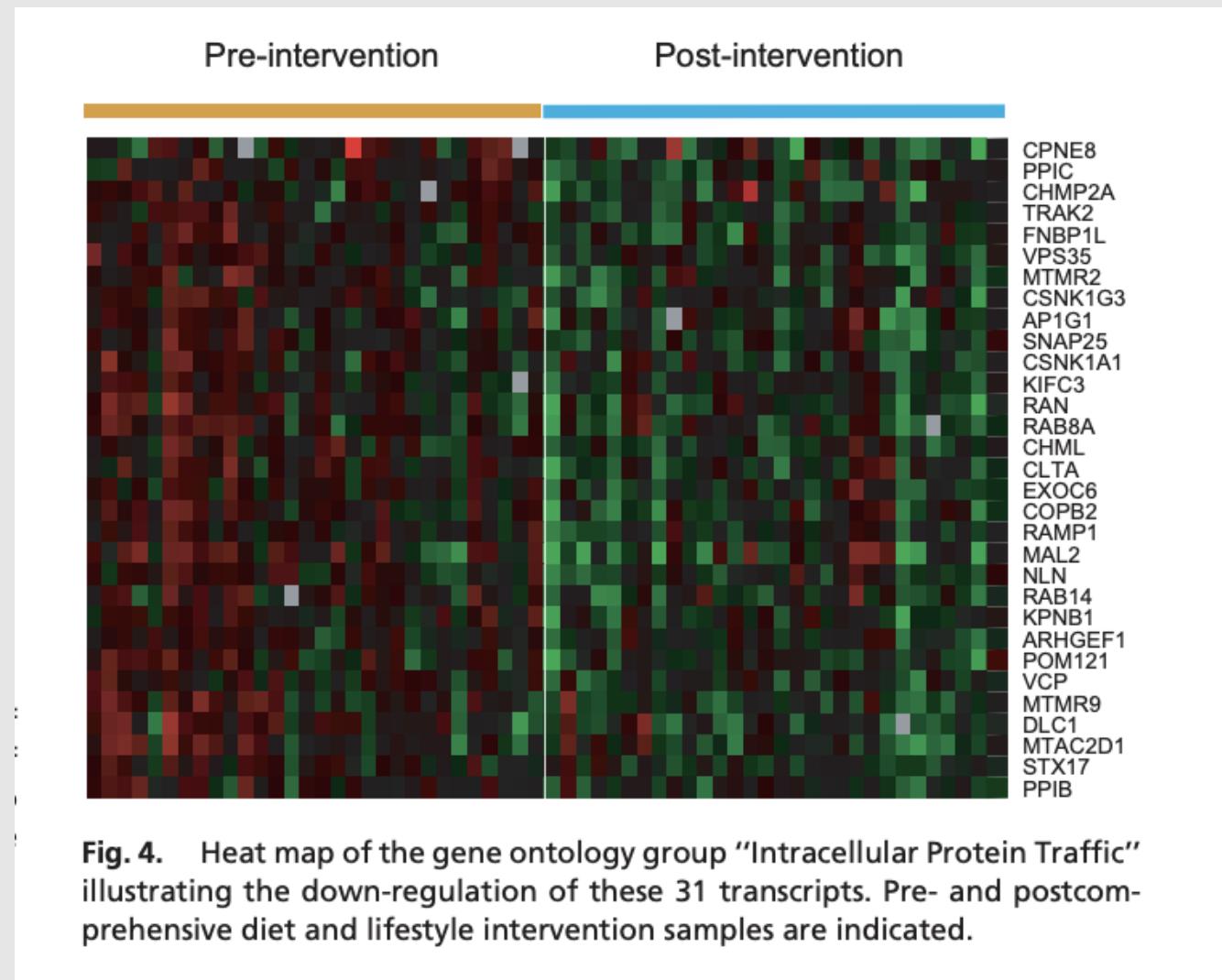
# LIFESTYLE AND NUTRITION FOR FOUR
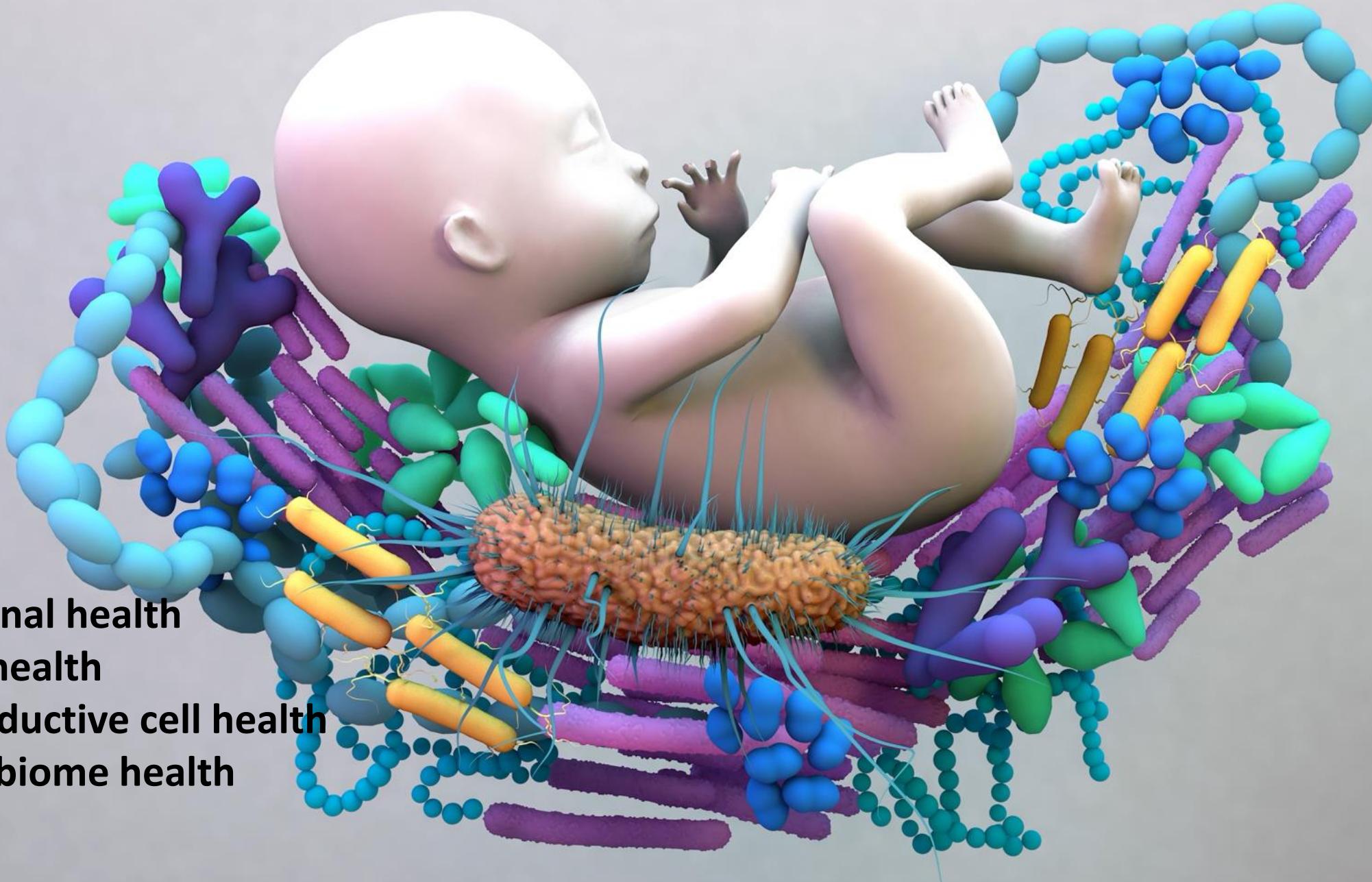
- **Maternal health**
- **Fetal health**
- **Reproductive cell health**
- **Microbiome health**

Transgenerational Inheritance Epigenetics in the Uterine Environment

Maternal diet:
Famine, Seasonal diet, LPD, HFD, Supplement use

Maternal and paternal genetic background

Others:
Maternal lifestyle, ART and exposure to environmental factors

Epigenetic modifications during development

Obesity

Metabolic syndrome

Cardiovascular diseases

Low birth weight

Development illness

Mental illnesses

Diabetes

Mother - 1st generation

Fetus - 2nd generation

Reproductive cells - 3rd generation

Three generations at once are exposed to the same environmental conditions (diet, toxins, hormones, etc.).

Maternal nutrition
- Over/undernutrition
- Vitamin D status
- Dietary methyl donors
- LCPUFA intakes
- Food pollutants

Neonatal and infant nutrition
- Human milk
- Formula milk
- Prebiotics/probiotics

Nutrition

- Maternal microbiota
- Mode of delivery
- Maternal and infant diet
- Antenatal and post-natal antibiotic exposure
- Urban/rural environment

Microbiome

Epigenome

- Human genome
- Environmental factors

First 1000 days of life

Epigenetics impact healthspan

Healthspan

The period of life spent in good health, free from the chronic diseases and disabilities of aging

65 years

Death

Lifespan

65 years

First comorbidity   Further comorbidities   Death

Healthspan

Care dependency: Low   Medium   High

Remaining lifespan after 65 years of age is characterised by a sharp decrease in healthspan approximately halfway between 65 years and death. The further you progress towards the end of your lifespan the more likely you acquire comorbidities which increase your care dependency.

April 13, 2023 – U.S. life expectancy has declined to 76.4 years, the shortest it's been in nearly two decades, according to December data from the CDC.

Life expectancy vs. health expenditure

From 1970 to 2018

Life Expectancy

Japan

Switzerland

Spain
Italy

Israel
South Korea   Australia   France   Norway

Sweden

Ireland

New Zealand   Canada

Portugal   Finland   Netherlands
Austria
UK   Belgium

Denmark   Germany

USA

2014
2010
2018

2005

2000

1995

1990

1985

1975

1970

84

83

82

81

80

79

78

77

76

75

74

73

72

71

70

$0 $1000 $2000 $3000 $4000 $5000 $6000 $7000 $8000 $9000 $10,000

Health Expenditure per capita

adjusted for inflation and price differences between countries (PPP)

Data source: OECD — Note: Health spending measures the consumption of health care goods and services, including personal health care (curative care, rehabilitative care, long-term care, ancillary services, and medical goods) and collective services (prevention and public health services as well as health administration), but excluding spending on investments.
Shown is total health expenditure (financed by public and private sources).   Licensed under CC-BY by the author Max Roser.

OurWorldinData.org – Research and data to make progress against the world's largest problems.

Chronic diseases are responsible for 7 in 10 deaths each year.

Did You Know

the world's human population is increasingly unwell?

Worldwide obesity has nearly **TRIPLED** since 1975

The **3** main culprits behind obesity and chronic illness are:

POOR DIET

SMOKING

SEDENTARY LIFESTYLE
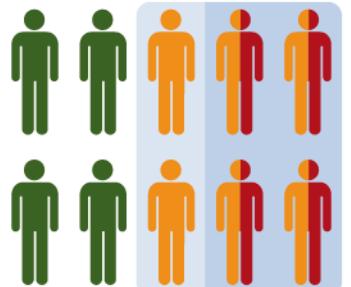
6 in **10** adults have at least **one** chronic disease.

4 in **10** adults have at least **2** chronic diseases.

The CDC estimates **eliminating** smoking, poor diet, and inactivity would **prevent**

80% of type 2 diabetes

40% of cancer

80% of heart disease

Most chronic diseases can be prevented by eating well, being physically active, avoiding tobacco and excessive drinking, and getting regular health screenings.

RESILIENCE DETERMINES HEALTHSPAN

Klasa et al. BMC Geriatrics (2021) 21:51
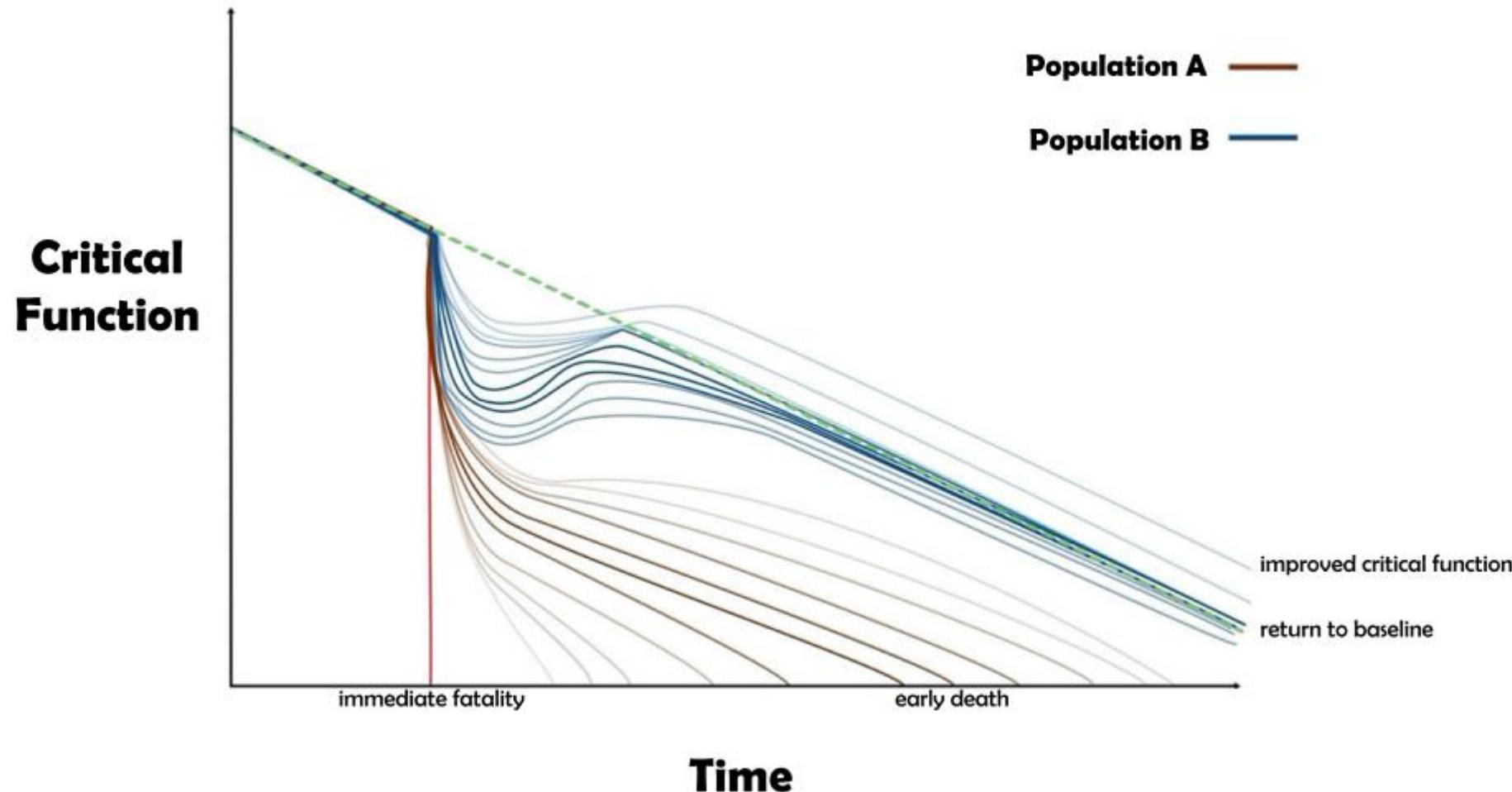
- Resilience significantly contributes to longevity at all ages, and it becomes even more profound at advanced ages.

- Nurturing your body, brain, and social connections can help you bounce back from stress.

- Healthy eating (mostly plants), physical activity, and regular sleep can improve your overall health, resiliency, and is your first line of defense against diseases.

- The gut microbiota is an "organ" with frontline exposure to environmental changes and insults.

- During the lifetime of an individual, the microbiome is exposed to challenges such as unhealthy diet, medications and infections.

- Impaired ability to bounce back to the pre-challenge baseline may lead to dysbiosis, decreased resiliency, and chronic disease.

Data from over 9,000 people reveal a distinct gut microbiome signature that is associated with healthy aging and survival in the latest decades of life.

Biological age: 40

Chronological age 35

Shorter Healthspan

Biological age: 30

Chronological age 35

Longer Healthspan

A systematic review of biological, social and environmental factors associated with epigenetic clock acceleration

Over 156+ publications on biological clocks report that SMOKING is the largest predictor of accelerated aging.
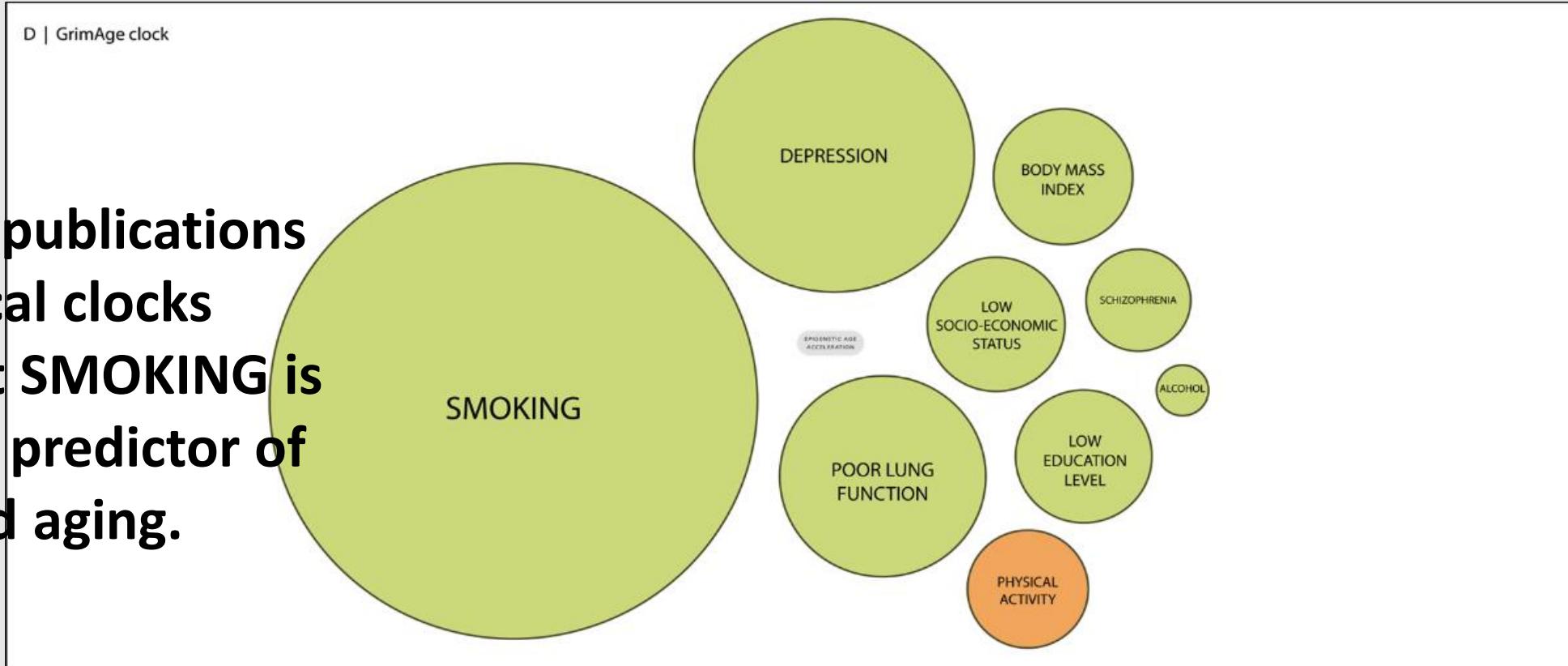
Major Lifestyle Recommendations
For Increasing Healthspan and Reducing Biological Age

Smoking-Related DNA Methylation is Associated with DNA Methylation Phenotypic Age Acceleration: The Veterans Affairs Normative Aging Study

Yang Yang,[1] Xu Gao,[2] Allan C. Just,[3] Elena Colicino,[3] Cuicui Wang,[4] Brent A. Coull,[5] Lifang Hou,[6] Yinan Zheng,[6] Pantel Vokonas,[7] Joel Schwartz,[4] and Andrea A. Baccarelli[2,*]

Smokers demonstrated a higher aging ratio, and both male and female smokers were predicted to be twice as old as their chronological age as compared to nonsmokers.

The results were carried out based on the blood profiles of 149,000 adults.

Cross-talk between gut microbiota and tobacco smoking: a two-sample Mendelian randomization study

Smoking affects the gut microbiota by:

- **Raising the pH of the intestinal environment**
- **Inducing chronic low-grade inflammation and inflammatory related diseases**
- **Promoting damaging oxidative stress which increases systemic inflammation**

Psychological and biological resilience modulates the effects of stress on epigenetic aging
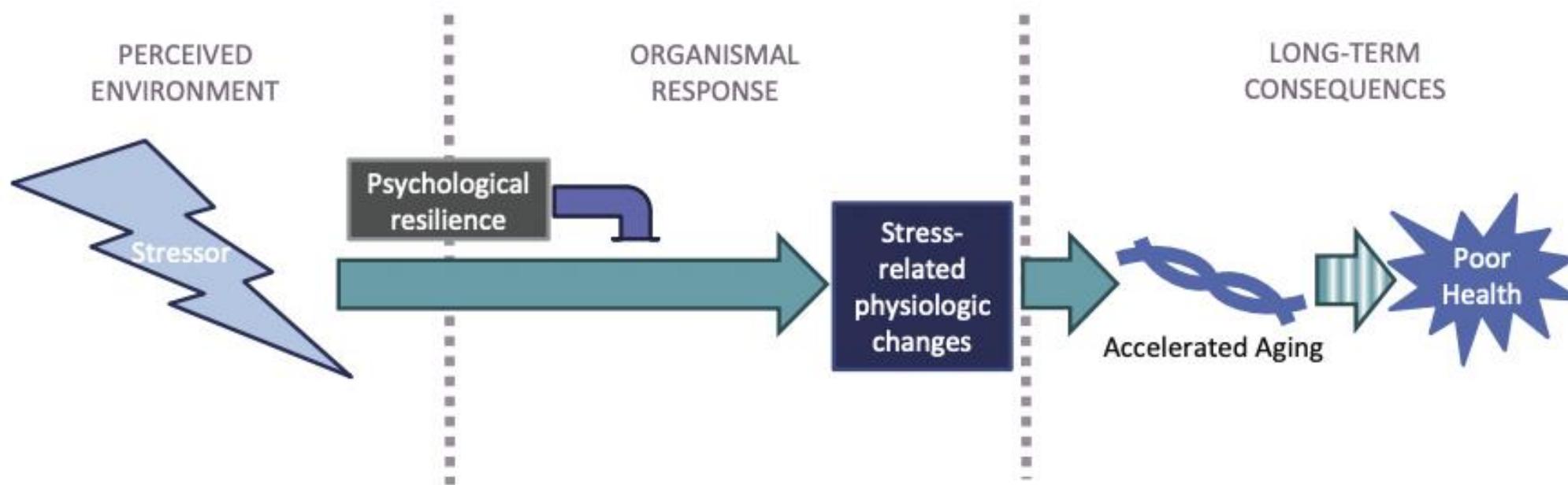
Cumulative life-time stress is associated with accelerated epigenetic aging

Personal life stress had greater impact in older compared to younger participants
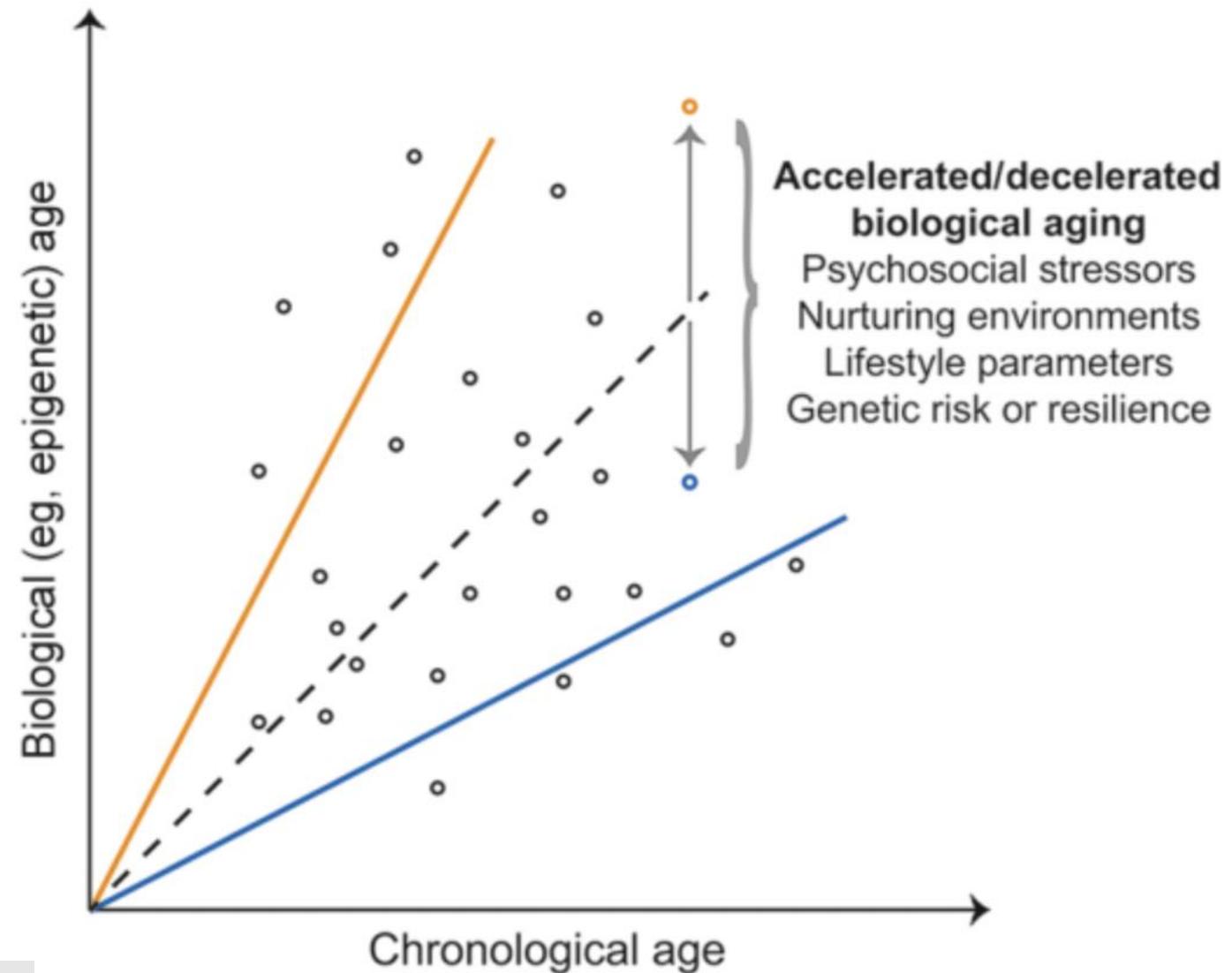
Accelerated/decelerated biological aging
Psychosocial stressors
Nurturing environments
Lifestyle parameters
Genetic risk or resilience

Biological (eg, epigenetic) age

Chronological age
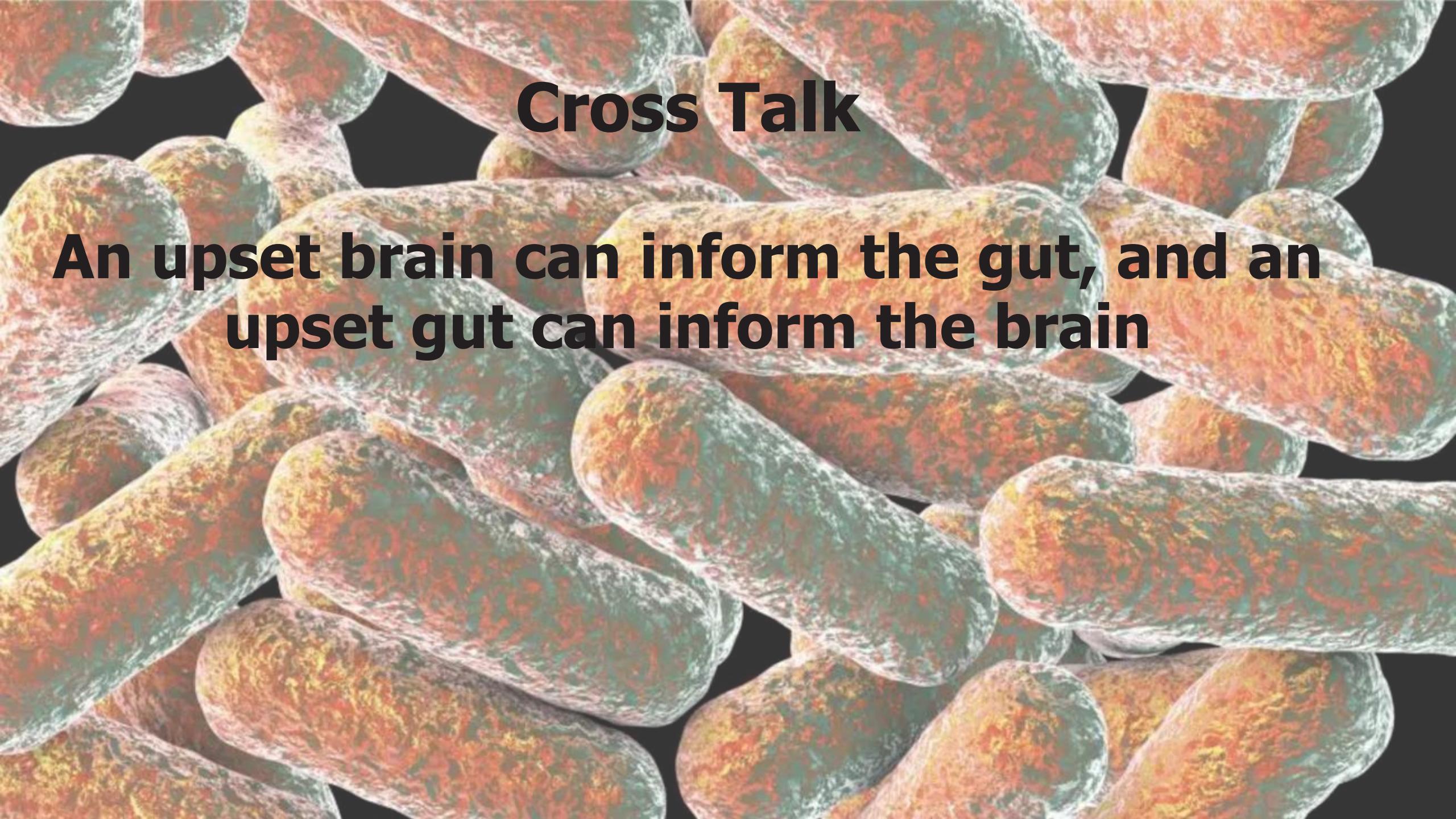
Cross Talk

An upset brain can inform the gut, and an upset gut can inform the brain

Vegetables

Fibre

Supplements i.e. Vitamin D, C, probiotics, prebiotics

Fermented foods

anti-inflammatory omega-3 rich, low fat, low carbohydrate

Positive mental health

Poor mental health

High fat, high sugar ultra- processed foods

A

Common findings:
↑ Bacteroidetes, Prevotella, SCFA, Bifidobacteria, Akkermansia, Roseburia, Lactilobacillus

↑ IL-10

↓ Firmicutes, Escherichia coli, Ruminococcus, Coprococcus

↓ VEGF, MCP-1, IL-17, IP-10, IL-12, CRP, IL-2, TNF, LPS

B

Common findings:
↑ Bacteroides, Bile acids, Bilophila wadsworth, Enterobacteriaceae, Firmicutes, Enterobacteriaceae, Escherichia, Klebsiella, and Shigella

↑ LPS, TMAO,

↓ Roseburia, SCFA, Bifidobacteria, Lactobacillus, Bacteroidetes, Lactic acid, Enterococcus

INFLAMMATION

Several studies reveal the benefits of deep-breathing exercises for at least five minutes, three to five times a day help to lower cortisol levels, ease anxiety and depression, improve memory, and improve vagal-parasympathetic tone.
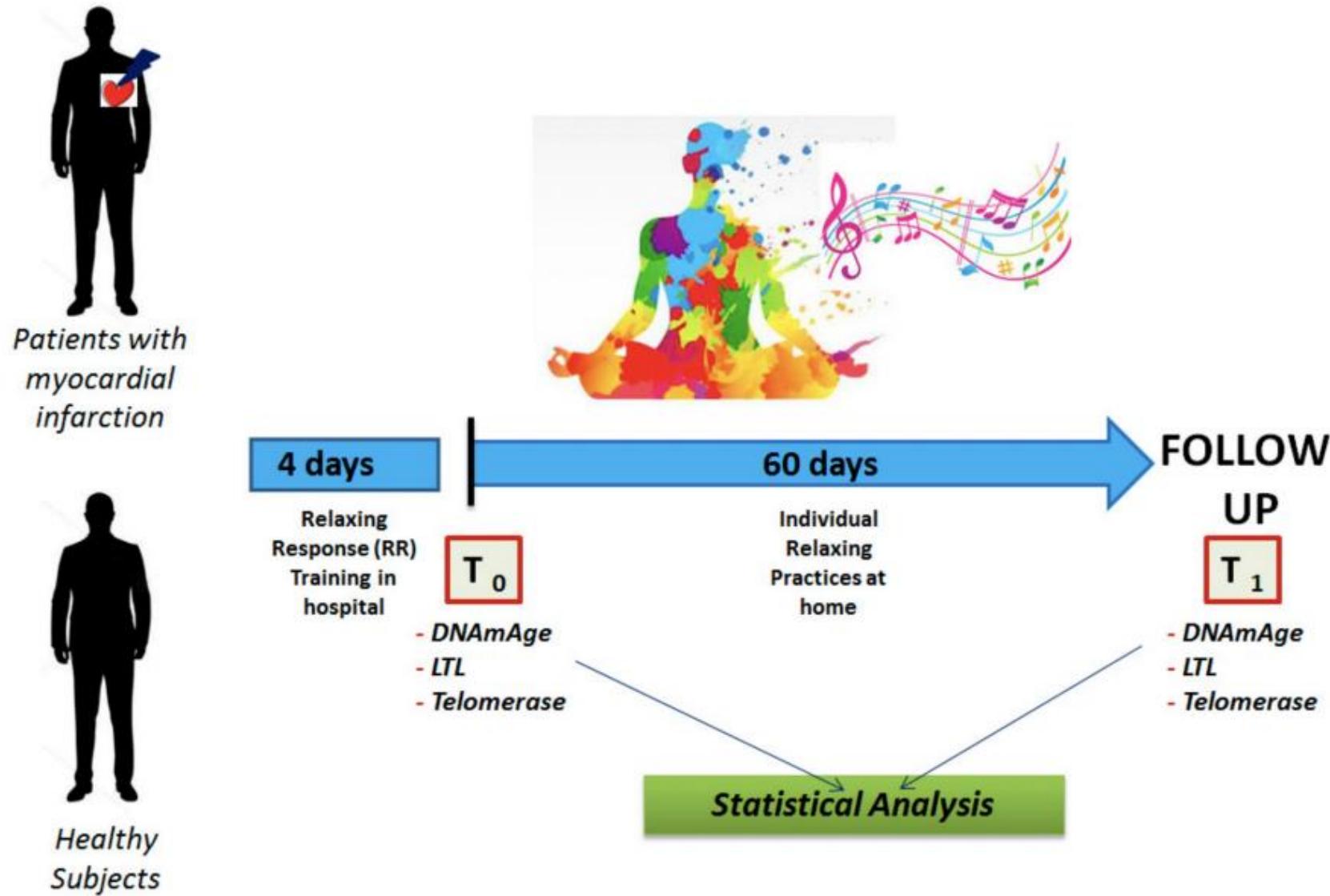
Exploring Epigenetic Age in Response to Intensive Relaxing Training: A Pilot Study to Slow Down Biological Age
Int. J. Environ. Res. Public Health 2019, 16, 3074; doi:10.3390/ijerph16173074

Social connection, whether with other people or through "compassionate attention" to yourself, is one of the most important ways to activate the vagal parasympathetic network.

- **23 meta-analyses published between 1994 and 2021, which include 1,187 longitudinal and cross-sectional studies with more than 1,458 million participants**

- **Loneliness is comparable to smoking up to 15 cigarettes a day**

- **Low social support is a significant predictor of inflammation.**

- **Chronic inflammation associated with low social integration impacts multiple diseases that represent the leading causes of disability and mortality worldwide, including cardiovascular disease, cancer, diabetes mellitus, chronic kidney disease, non-alcoholic liver disease, and autoimmune and neurodegenerative disorders.**

- Lower levels of loneliness and higher levels of wisdom, compassion, social support, and social engagement were associated with greater diversity of the gut microbiome

- Increased gut microbial diversity is associated with greater emotional well-being, particularly positive affect, larger social networks, and improved health and longevity

Epigenetic aging is accelerated in alcohol use disorder and regulated by genetic variation in APOL2

- **Epigenetic clock alcohol study on 331 individuals with Alcohol Use Disorder (AUD) and 201 healthy controls.**

- **Heavy, chronic alcohol consumption caused epigenetic age acceleration (EAA)**
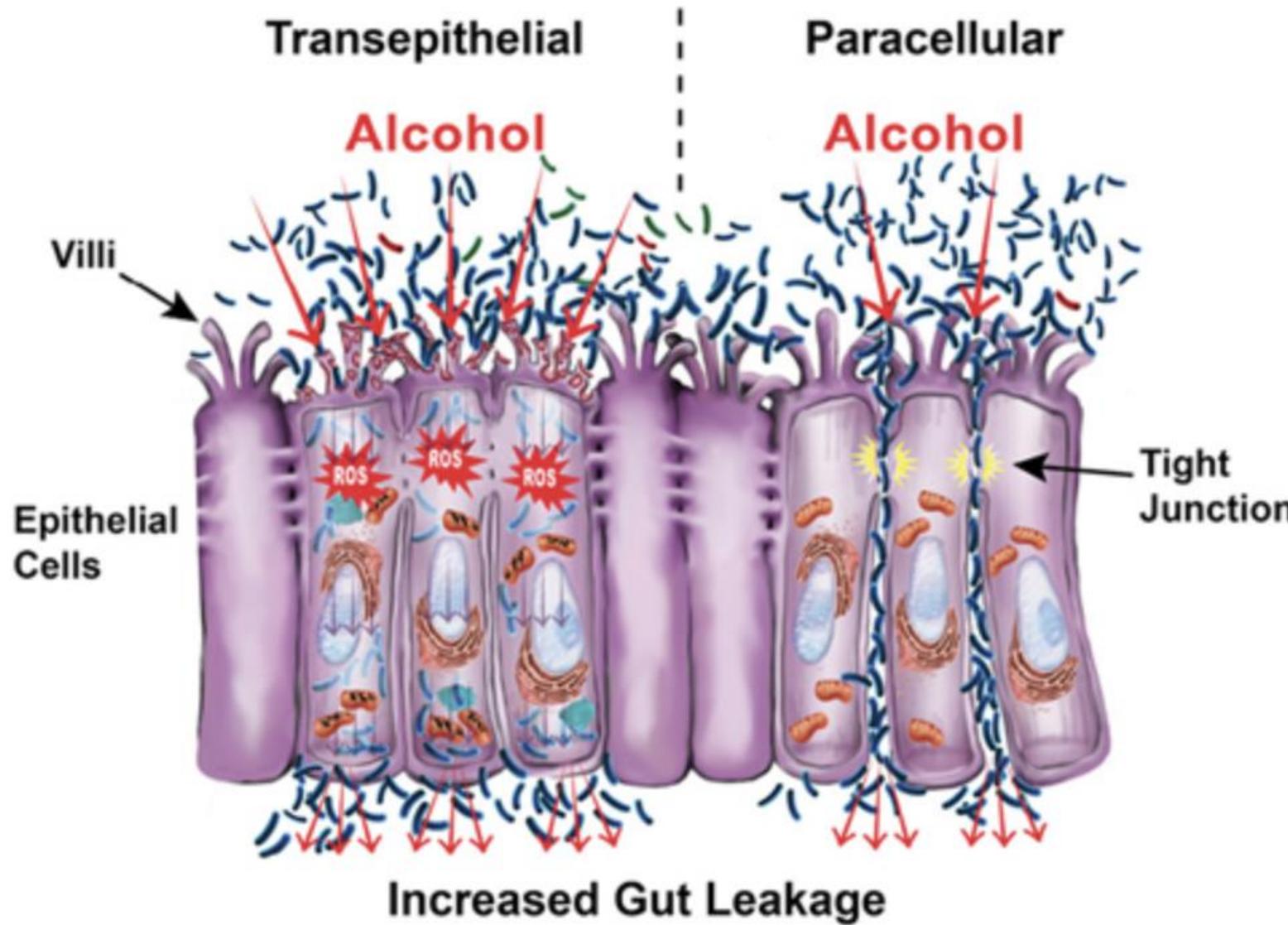
Alcohol and Intestinal Microbiota studies show that alcohol promotes both dysbiosis and bacterial overgrowth which in turn leads to an increase in the release of endotoxins, produced by gram-negative bacteria

RESEARCH NOTE

Open Access

Check for updates

A pilot prospective study of sleep patterns and DNA methylation-characterized epigenetic aging in young adults

Mary A. Carskadon[1,2*], Kenneth R. Chappell[5], David H. Barker[2,3], Anne C. Hart[4], Kayla Dwyer[5],
Caroline Gredvig-Ardito[1], Caitlyn Starr[5] and John E. McGeary[2,5]

- **Poorer sleep was associated with marked acceleration of epigenetic aging while better sleep was associated with decelerated epigenetic aging**

- **Participants with longer and more regular sleep showed reduced age difference by 2.48 years**

- **Those with shorter and more irregular sleep showed an increased age difference by 4.13 years**

Epigenetic aging and immune senescence in women with insomnia symptoms: Findings from the Women's Health Initiative Study
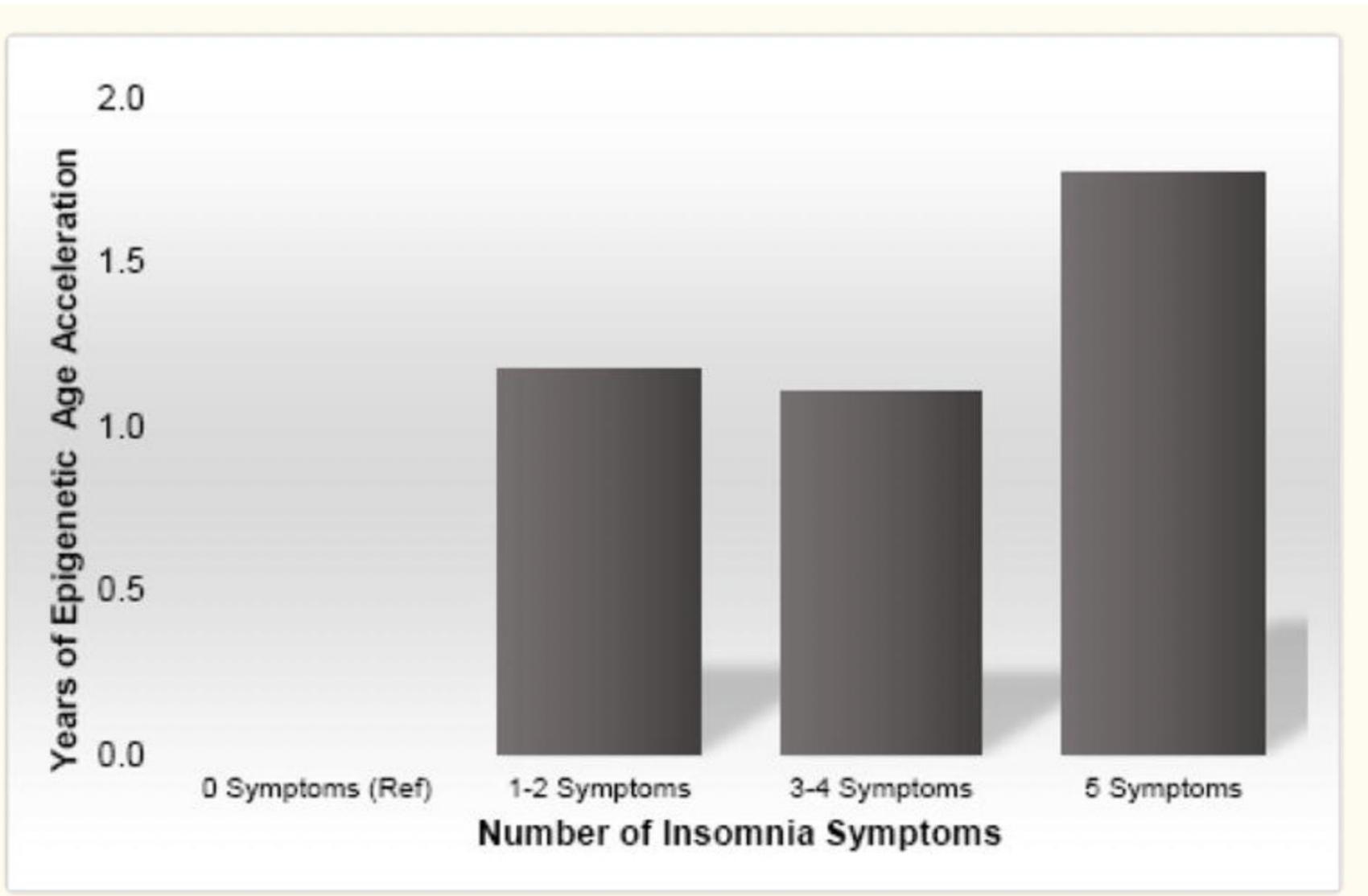
Exerkines in Health, Resilience and Disease
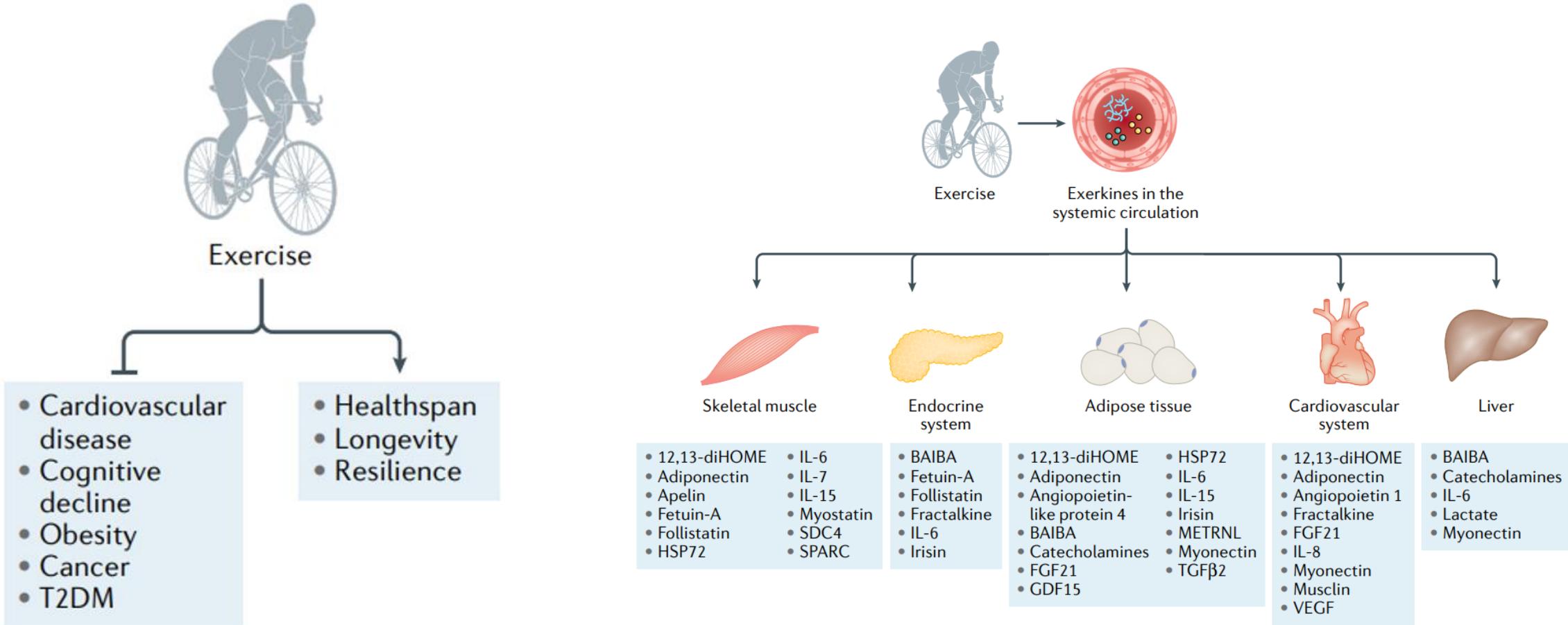
Progressive increase of physical activity level generates changes in the intestinal microbiota
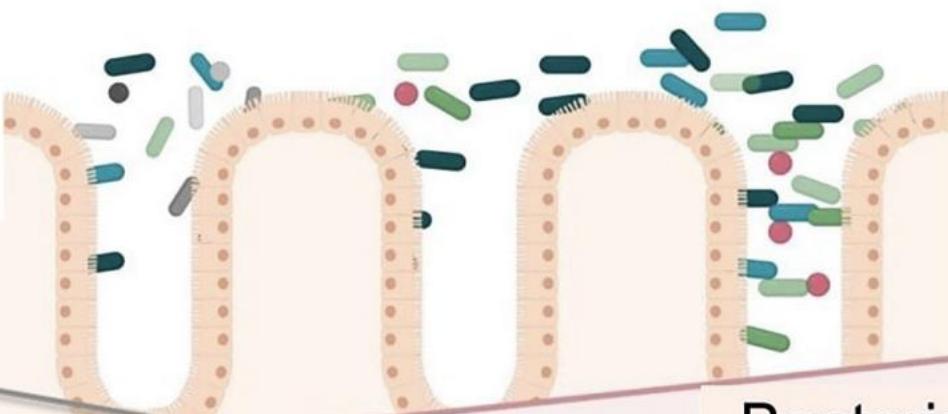
"LET FOOD BE THY MEDICINE AND MEDICINE BE THY FOOD"

Higher diet quality relates to decelerated epigenetic aging

Higher diet quality is associated with slower epigenetic age acceleration, and has beneficial effects on lifespan and health span.

Findings emphasize that adopting a healthy diet, mostly whole plants, is crucial for maintaining healthy aging.
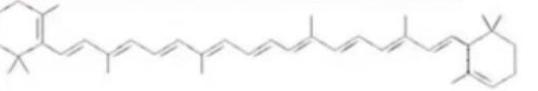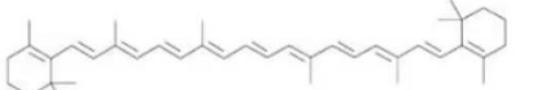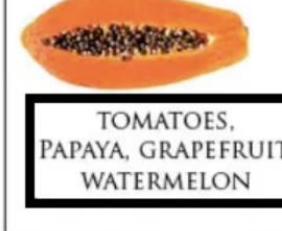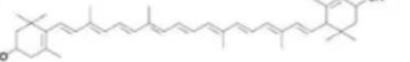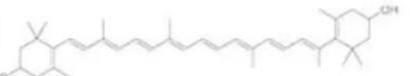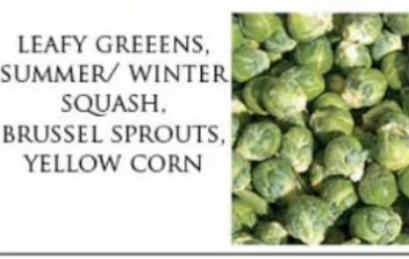
Advantages of the DASH diet

- Low in salt and sodium
- Rich in fresh fruits and vegetables
- Rich in low fat or nonfat dairy products
- Rich in whole grains, beans, seeds and nuts
- Fish and poultry (low in red meat)
- Rich in heart healthy fats
- Rich in potassium and calcium
- Low in added sugars and sweets
- Avoid foods with additives/preservatives

Advantages of the Mediterranean diet

- Primarily plant-based foods, such as fruits, vegetables, whole grains, legumes and nuts
- Replacing butter with healthy fats, such as olive oil and canola oil
- Using herbs and spices instead of salt to flavor foods
- Limiting red meat to no more than a few times a month
- Eating fish and poultry at least twice a week
- Enjoying meals with family and friends
- Drinking red wine in moderation (optional; one glass for women, one to two for men)
- Emphasizes fresh foods, no packaged or processed foods
- Advocates for getting plenty of exercise

**Carotenoids Are Associated With A Younger Epigenetic Age And A Reduced All-Cause Mortality Risk**

TYPE	CAROTENOID FOOD SOURCES
ALPHA-CAROTENE — Carrots: 416 g/d	CARROTS, PUMPKIN, WINTER SQUASH, PLANTAINS, COLLARD GREENS
BETA-CAROTENE — Carrots: 416 g/d	CARROTS, LEAFY GREENS, SWEET POTATO, CANTALOUPE, PUMPKIN
LYCOPENE — Watermelon: 134 g/d	TOMATOES, PAPAYA, GRAPEFRUIT, WATERMELON
LUTEIN/ ZEAXANTHIN	LEAFY GREEENS, SUMMER/ WINTER SQUASH, BRUSSEL SPROUTS, YELLOW CORN
BETA-CRYPTOXANTHIN	PUMPKIN, PAPAYA, SWEET PEPPER, ORANGE, CARROT

Image via shorturl.at/euILS

PLANT PROTEIN
per serving

ADVANTAGES

- Fiber
- Phytonutrients
- Vitamins & minerals
- Low or healthy fat profile
- No cholesterol

18g	17g	15g	6g	5g	5g	5g
Red Lentils boiled, 1 cup	**Edamame** boiled, 1 cup	**Black Beans** cooked, 1 cup	**Almonds** 1 oz	**Peas** cooked, 1 cup	**Baked Potato** 1 medium	**Spinach** boiled, 1 cup

ANIMAL PROTEIN
per serving

DISADVANTAGES

- Cholesterol
- Saturated fat
- No fiber
- Higher in calories
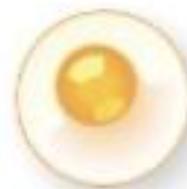
6g	20g	25g	25g
Egg cooked, 1	**Salmon** cooked, 3 oz	**Steak** cooked, 3 oz	**Chicken** cooked, 3 oz

Eating minimally processed whole plant foods such as vegetables, fruits, whole-grains, legumes, and nuts lower the risk of diabetes, heart disease, cancer, and promote overall health.

Source: USDA Nutrient Analysis Database

Dietary polyphenols influence gut microbiota composition in the host, maintain intestinal barrier integrity, improving the host's metabolism.

Intestinal microbiota metabolize polyphenols into bioactive metabolites that modulate the host's regulatory metabolism network, thus reducing inflammation and chronic disease risk.

Is the Use of Glyphosate in Modern Agriculture Resulting in Increased Neuropsychiatric Conditions Through Modulation of the Gut-brain-microbiome Axis?

Animal & Human Studies Suggest That Exposure to Glyphosate & Herbicide Adjuvants Can Induce Adverse Health Outcomes Mediated by the Microbiome

Environmental exposure to glyphosate and glyphosate-based herbicides has the potential to negatively influence neurodevelopment and behavior across generations indirectly through the gut-brain-microbiome axis. Potential mechanisms by which glyphosate may elicit these effects are through the disruption of the normally symbiotic relationship of the host and the gut microbiome. Given glyphosate can kill commensal members of the microbiome like *Lactobacillus* spp., Ruminococaeae and *Butyricoccus* spp., resulting in reductions in key microbial metabolites that act through the gut-brain-microbiome axis including indoles, L-glutamate and SCFAs. Glyphosate- resistant microbes in the gut have the potential to increase the production of pro-inflammatory cytokines and reactive oxygen species which may result in increased HPA activation, resulting in increased production of glucocorticoids which have implications on neurodevelopment. **In addition, maternal transfer of the gut microbiome can affect immune and neurodevelopment, across generations.**

The Health Effects of Genetically Modified Foods: a Brief Review

Genetically-modified foods have the potential to solve many of the world's hunger and malnutrition problems

The drawbacks can be expressed as environmental hazards, health hazards, economic concerns as well as legal issues.

The major health risks potentially associated with GM foods are toxicity, allergenicity, genetic hazards, and microbiome alterations.

A plant-forward diet <u>reduces the risk</u> of bowel cancer

Adherence to the WCRF/AICR Dietary Recommendations for Cancer Prevention and Risk of Cancer in Elderly from Europe and the United States: A Meta-Analysis within the CHANCES Project

Nicole Jankovic[1,2,*], Anouk Geelen[1], Renate M. Winkels[1], Blaise Mwungura[1], Veronika Fedirko[3], Mazda Jenab[4], Anne K. Illner[5,6], Hermann Brenner[7,8,9], José M. Ordóñez-Mena[7], Jessica C. Kiefte de Jong[10,11], Oscar H. Franco[10], Philippos Orfanos[12,13], Antonia Trichopoulou[12,13], Paolo Boffetta[13,14], Antonio Agudo[15], Petra H. Peeters[16], Anne Tjønneland[17], Göran Hallmans[18], H. Bas Bueno-de-Mesquita[19,20,21,22], Yikyung Park[23,24], Edith J. Feskens[1], Lisette C. de Groot[1], and Ellen Kampman[1] on behalf of the Consortium on Health and Ageing: Network of cohorts in Europe and the United States (CHANCES)

[1]Department Agrotechnology and Food Sciences, Division of Human Nutrition, Wageningen University, Wageningen, The Netherlands [2]Institute for Medical Informatics, Biometry and Epidemiology, Centre of Clinical Epidemiology, Faculty of Medicine, University Duisburg-Essen, Essen, Germany [3]Department of Epidemiology, Rollins School of Public Health, Winship Cancer Institute, Emory University, Atlanta, United States of America [4]Department Nutritional Epidemiology, International Agency for Research on Cancer, Lyon, France [5]Department of Nutrition & Health Sciences, Institut Polytechnique LaSalle Beauvais, Beauvais, France [6]Department of Dietary Exposure Assessment, Section of Nutrition and Metabolism, International Agency for Research on Cancer, Lyon, France [7]Division of Clinical Epidemiology and Aging Research, German Cancer Research Center (DKFZ), Heidelberg, Germany [8]Division of Preventive Oncology, German Cancer Research Center (DKFZ), Heidelberg, Germany [9]German Cancer Research Center (DKFZ), Heidelberg, Germany [10]Department of Epidemiology, Erasmus Medical Centre Rotterdam, University Medical Centre Rotterdam, Rotterdam, The Netherlands [11]Global Public Health, Leiden University College, The Hague, The Netherlands [12]Department of Hygiene, Epidemiology and Medical Statistics, School of Medicine, University of Athens, Athens, Greece [13]Hellenic Health Foundation, Athens, Greece [14]The Tisch Cancer Institute and Institute for Translational Epidemiology, Mount Sinai School of Medicine, New York, United States of America [15]Unit of Nutrition and Cancer, Cancer Epidemiology Research Program, Catalan Institute of Oncology (ICO-IDIBELL), Barcelona, Spain [16]Department of Epidemiology, Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht, The Netherlands [17]Danish Cancer Society Research Centre, Copenhagen, Denmark [18]Department of Public Health and Clinical Medicine, Umeå University, Umeå, Sweden [19]Department for

Meta-analysis of seven prospective cohort studies
362,114 participants (43% women) free from cancer
Age at enrolment > 60 years.
US and Europe (CHANCES & EPIC)
Median follow-up of 11 to 14 years

High dietary adherence <u>alone</u> associated with:
44 - 80% reduced risk colorectal cancer

12 - 32% reduced total risk of cancer
12 – 32% reduced risk of prostate cancer
6.4 additional years of life without any cancer

Dietary high adherence:
<70g red meat per day
<7g processed meat per day
>400g fruits and veggies per day
>25g fibre per day

Cancer Epidemiol Biomarkers Prev. 2017 PMID: 27793797

A plant-forward diet & lifestyle improves bowel cancer <u>prognosis.</u>

Adherence to the World Cancer Research Fund/American Institute for Cancer Research cancer prevention recommendations and colorectal cancer survival

Rui Song[1], Joshua Petimar[2,4], Molin Wang[2,3], Fred K. Tabung[1,5], Mingyang Song[1,2], Li Liu[6], Dong Hoon Lee[1], Edward L. Giovannucci, MD[#1,2,6], Xuehong Zhang, MD[#1,6], Stephanie A. Smith-Warner[#1,2]

[1]Department of Nutrition, Harvard T.H. Chan School of Public Health, Boston, MA

[2]Department of Epidemiology, Harvard T.H. Chan School of Public Health, Boston, MA

[3]Department of Biostatistics, Harvard T.H. Chan School of Public Health, Boston, MA

[4]Department of Population Medicine, Harvard Pilgrim Health Care Institute & Harvard Medical School, Boston, MA

[5]Division of Medical Oncology, Department of Internal Medicine, The Ohio State University College of Medicine and Comprehensive Cancer Center

[6]Channing Division of Network Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA

[#] These authors contributed equally to this work.

Abstract

Background: Cancer patients are recommended to follow cancer prevention guidelines due to inadequate evidence for specific recommendations for cancer survivors.

Methods: We examined whether diet and lifestyle scores measuring adherence to the 2018 World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR) cancer prevention guidelines were associated with colorectal cancer-specific and overall mortality among 1,491 colorectal cancer (CRC) patients in two prospective cohorts. Cox proportional hazards regression models were used to calculate the multivariable-adjusted hazard ratios (HRs) and 95% confidence intervals (CIs).

Results: During a median follow-up of 7.92 years, there were 641 deaths (179 CRC-specific deaths). Patients in the highest quartile of the post-diagnostic WCRF/AICR lifestyle score including diet, body mass index (BMI), and physical activity had a 24% lower risk (HR=0.76, 95% CI: 0.49-1.18) of CRC-specific mortality and a 37% lower risk (HR=0.63, 95% CI: 0.50-0.78) of overall mortality compared with the lowest quartile. When BMI was not included in the lifestyle score due to potential disease-related weight loss, stronger inverse associations were observed for both CRC-specific and overall mortality for the same comparison (CRC-specific: HR=0.50, 95% CI: 0.32-0.79; overall: HR=0.59, 95% CI: 0.47-0.75). The post-diagnostic WCRF/

Colorectal cancer-specific and overall mortality among 1,491 CRC patients in two prospective US cohorts

Follow-up for 7.9 years

High adherence to WCRF <u>diet and lifestyle:</u> pre-diagnosis:

50% reduced risk of cancer-related mortality

41% reduced risk of all-cause mortality

Reductions when corrected for BMI:
24% reduced risk of CRC-related mortality
37% reduced risk of all-cause mortality

WHAT FOOD INCREASES THE RISK OF COLORECTAL CANCER?

MEAT

10–30% increased risk for each increment of 100g/day of total or red meat, with no clear limit threshold identifiable. Chapelle N, et al. Gut. 2020

IARC, 2015
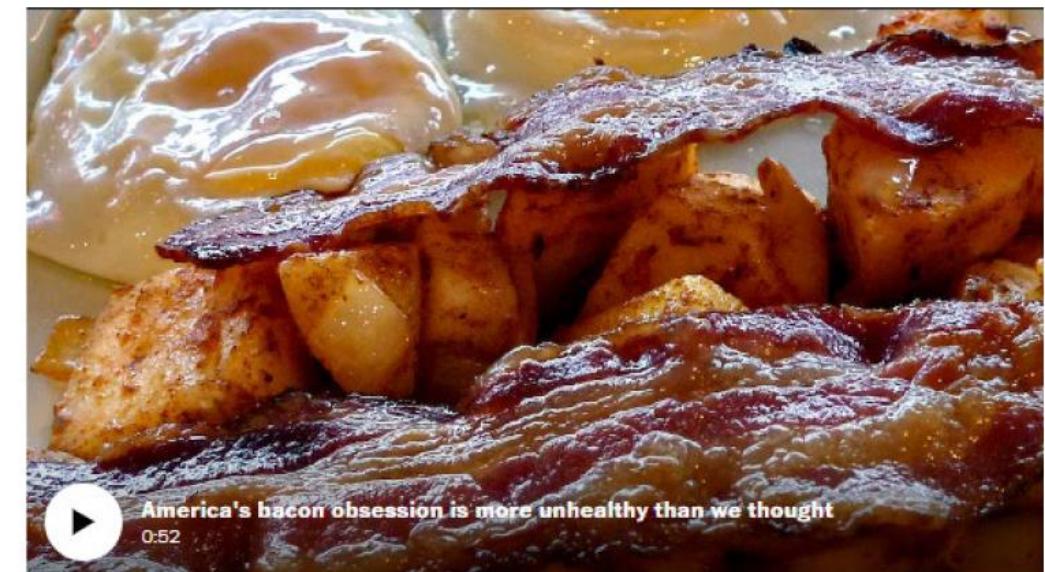
All DISEASE BEGINS IN THE GUT

HIPPOCRATES

PROPORTION OF UNIQUE GENES IN THE HUMAN BODY

MICROBIAL GENES
~2,000,000

~99%

HUMAN GENES
~23,000
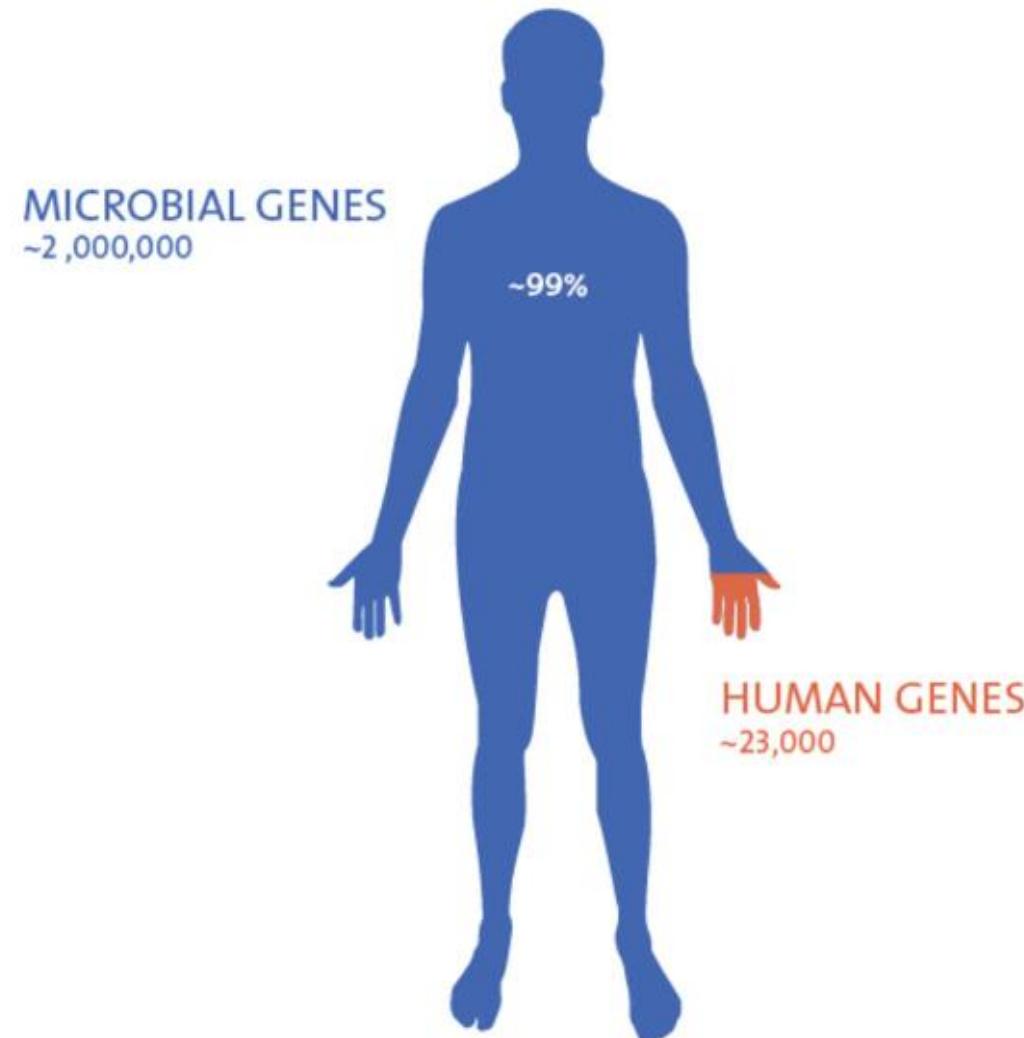
Ninety-nine percent of the unique genes in your body are bacterial. Only about one percent is human.

Image credit: amnh.org

Front Immunol. 2020; 11: 594150.
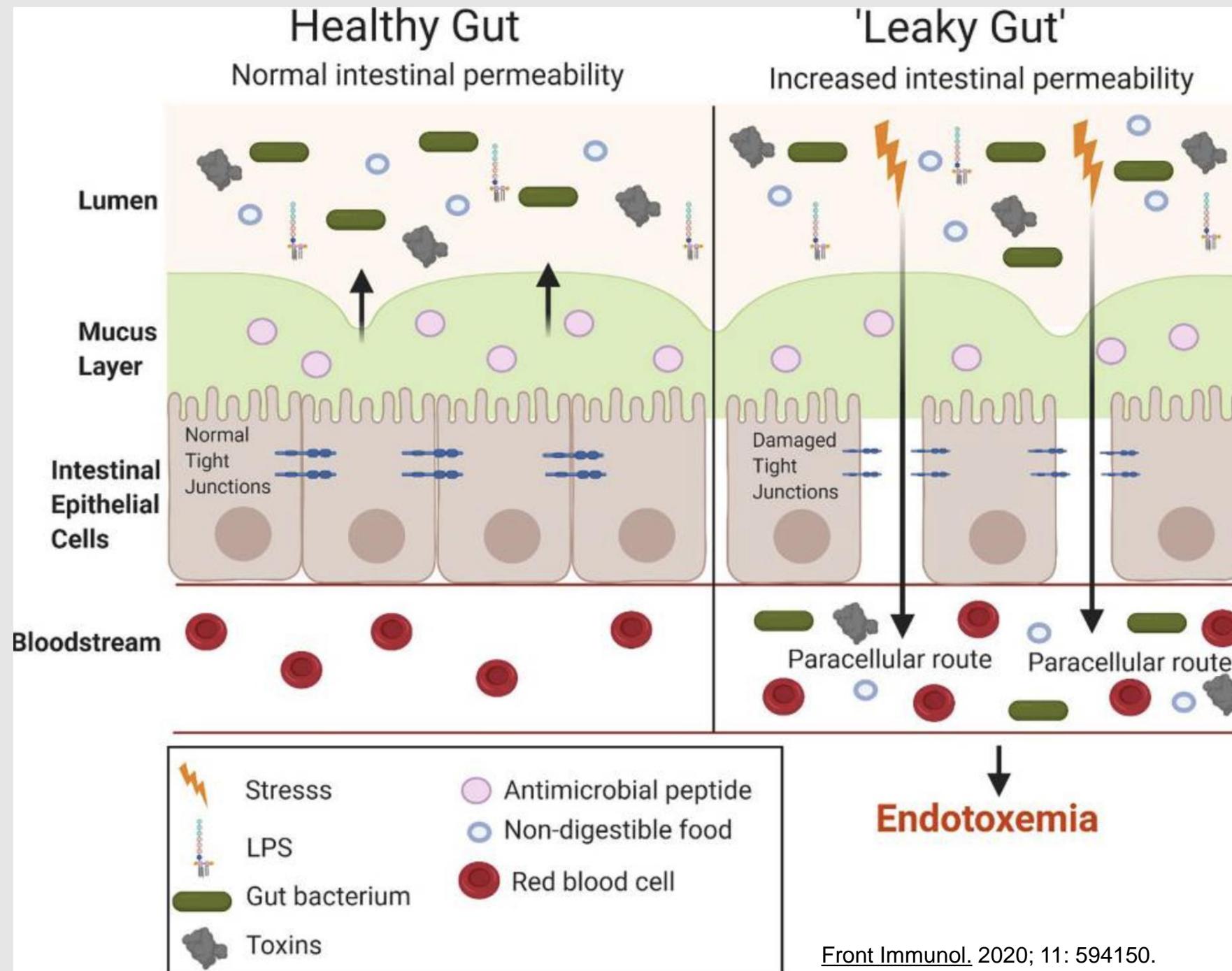
Normal duodenal mucosa
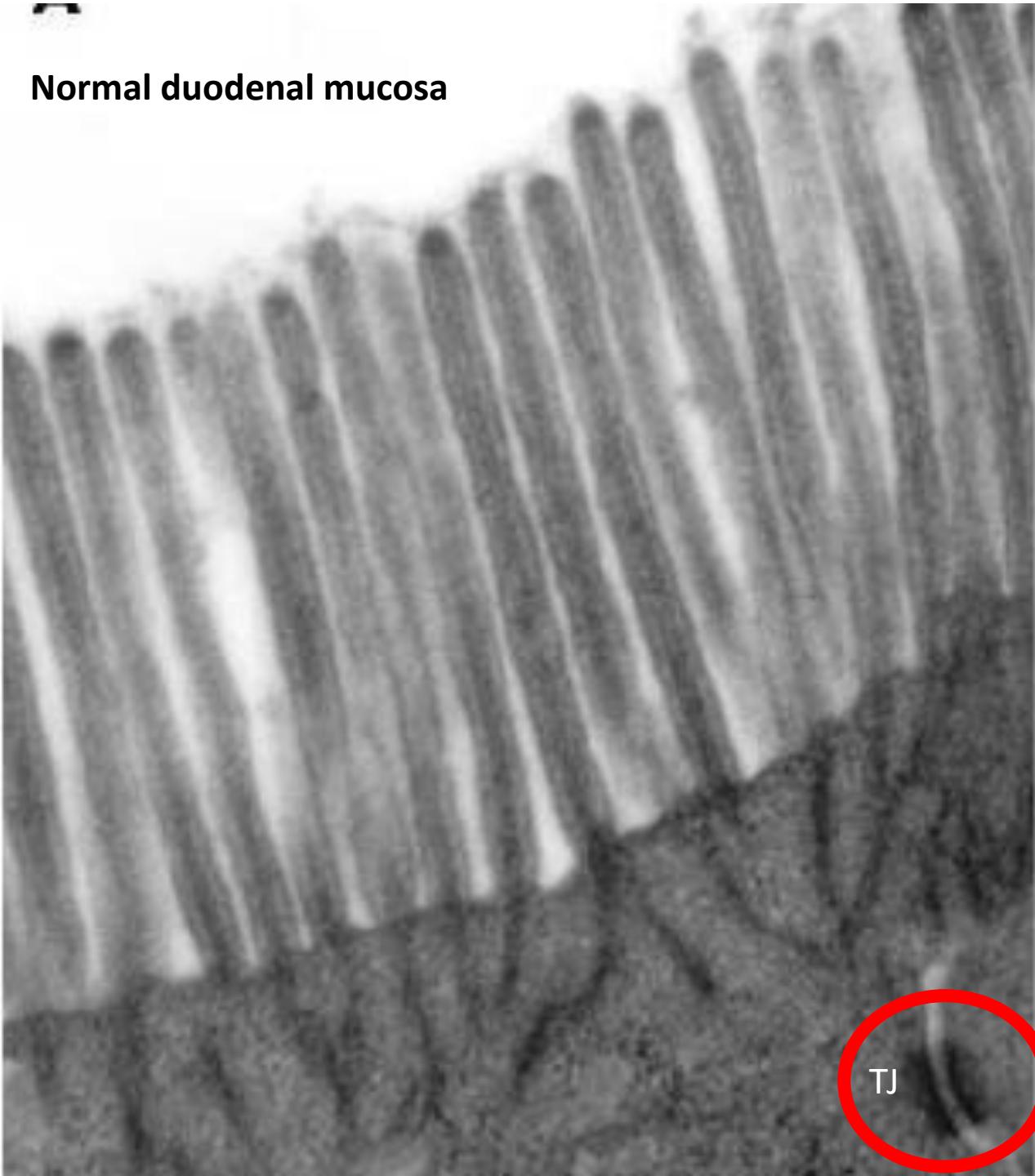
Autoimmune Thyroiditis
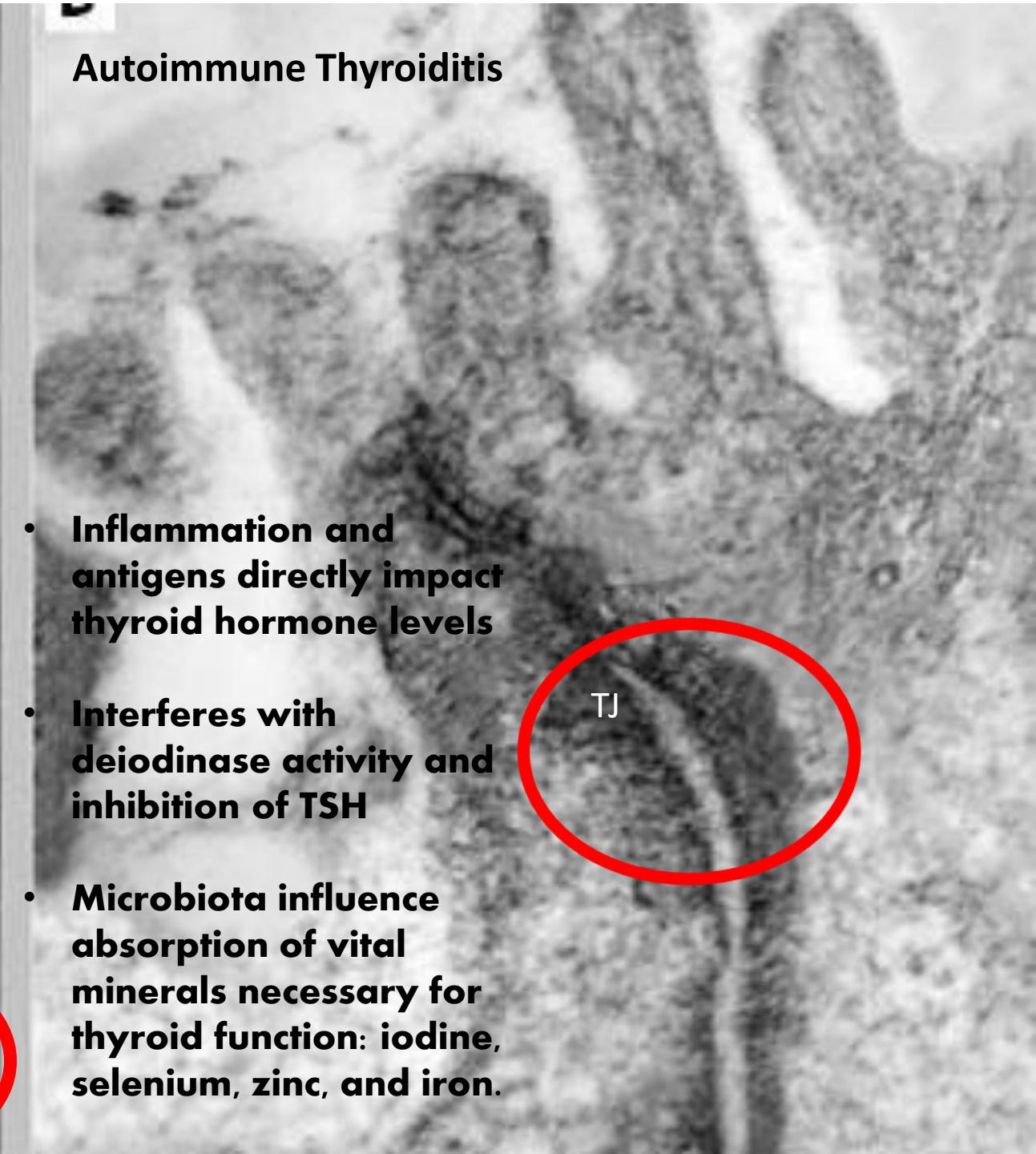
- **Inflammation and antigens directly impact thyroid hormone levels**

- **Interferes with deiodinase activity and inhibition of TSH**

- **Microbiota influence absorption of vital minerals necessary for thyroid function: iodine, selenium, zinc, and iron.**

TJ

Functional Interactions Between Enterocytes, Immune Cells, and Microbiota

- **RED- Gut Epithelial Cells**

- **GREEN- Dendritic Cells**

- **BLUE- Beta Cells**

- **WHITE- T-Cells**

400 µm
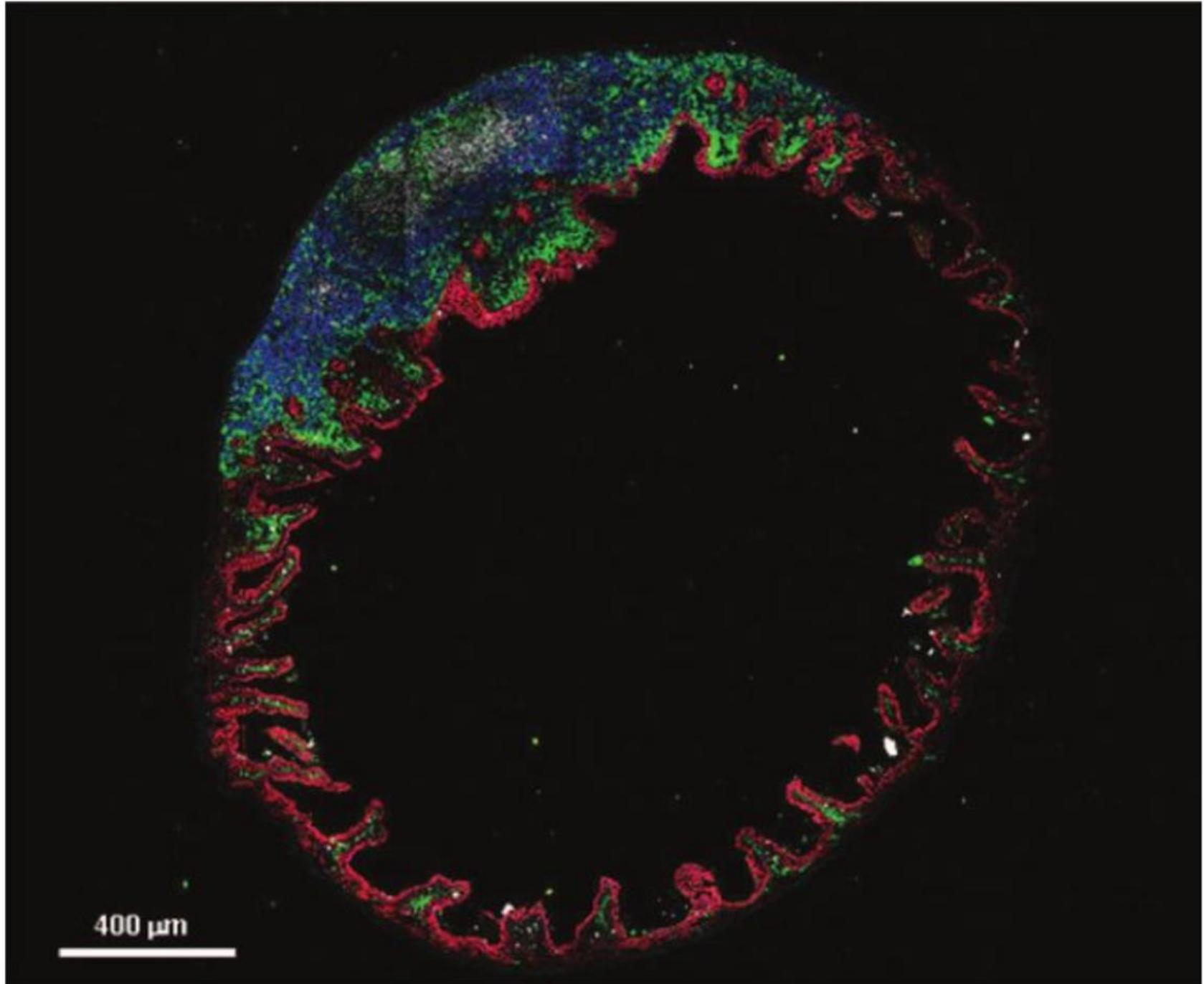
Immune Dendritic Cell inserted in the gut epithelial layer and into intestinal lumen.

Dendritic cells are ==**central to the initiation of primary immune responses**== and are pivotal in the generation of adaptive immunity
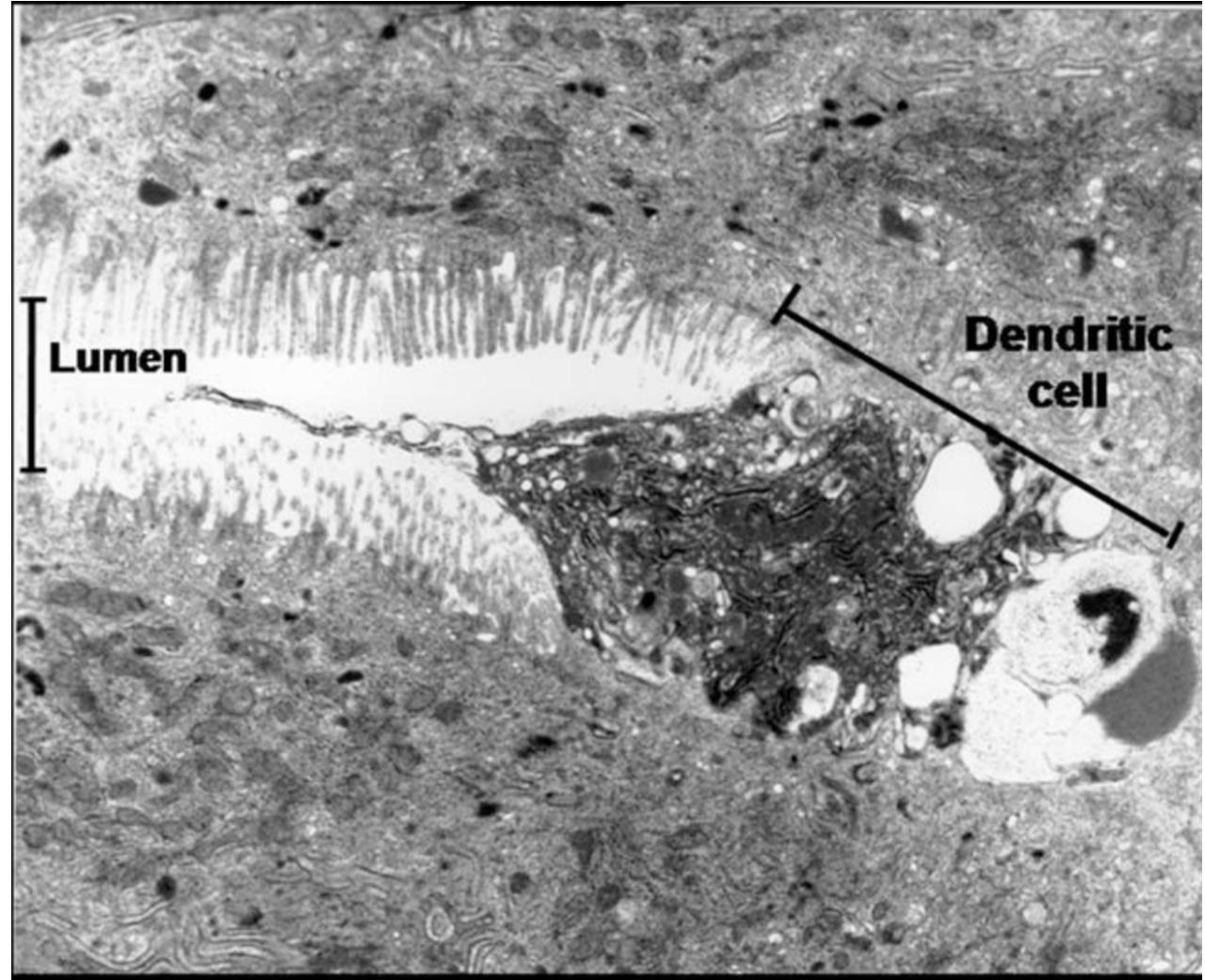
Inflammatory bowel diseases 2010
<u>Intestinal dendritic cells: Their role in bacterial recognition, lymphocyte homing, and intestinal inflammation</u>

Our ancestral human diet

Should it be a paradigm for contemporary nutrition?

- Modern man emerged over 200,000 years ago

- Human genome has remained unchanged

- Genetically we are adapted to the foods present 200,000 years ago.

- Fruits and vegetables, provided greater than 50% of energy intake, Americans today consume less than 16%.

- High plant-based dietary intake made ancestral diets base-yielding, unlike today's acid-producing pattern.

- Fiber consumption was estimated to be 100-150 g/day and the average American today consumes less than 10 g/day

The plant-based diet microbiome

- **More short chain fatty acids than meat eaters**
  - **Protect the intestinal barrier, regulating our immune system and control our appetite and blood sugar**

- **Better at suppressing the growth of colon cancer cells**
  - **Butyrate triggers apoptosis of pre-cancerous cells**

- **Far lower levels of secondary bile acids**
  - **Secondary bile acids are pro-inflammatory & pro-carcinogenic to our gut lining**

- **The plant-based microbiomes lacked the ability to metabolize carnitine (from meat) and choline (from eggs)**
  - **Individuals with elevated serum TMAO are 3.4 times more likely to develop CRC**

Angelis M, et al. Diet influences the functions of the human intestinal microbiome. 2020
Bae S, et al. Plasma choline metabolites and colorectal cancer risk in the Women's Health Initiative Observational Study. *Cancer Res.*

Low Fiber High Fat Diet Has Been Associated with Immune Dysregulation

Inflammatory Autoimmune Diseases

- Parkinson's Disease
- Rheumatoid Arthritis
- Multiple Sclerosis
- Irritable Bowel Disease
- Type 1 DM
- Eczema & Psoriasis
- Food Allergies
- Asthma

NCD- Chronic Diseases

- Obesity
- Metabolic Disorders
- NAFLD
- Irritable Bowel Syndrome and digestive disorders
- Heart Disease

Immune and Genetic Dysregulation

- Alzheimer's Dementia
- Cancer

EAT PLANTS

Commensal Bacteria

FIBER PLANTS

Short Chain Fatty Acids

Short Chain Fatty Acids

- Beneficial microbiota find fiber from whole plant foods, ferment it, and produce by-products called **short-chain fatty acids**.
- SCFAs have numerous beneficial functions and travel and communicate with different systems in our bodies.
- 90% of SCFAs are metabolized by the microbiota for energy or absorbed by intestinal cells
- A smaller % is circulated through peripheral circulation to other tissues
- SCFA's serve as 10% of daily caloric requirements for humans
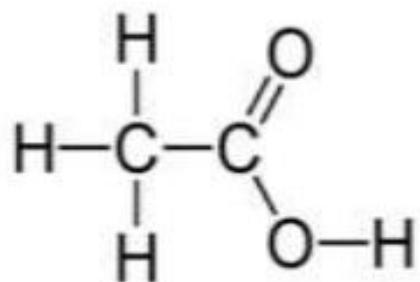
Acetic acid (acetate)   Propionic acid (propionate)   Butyric acid (butyrate)
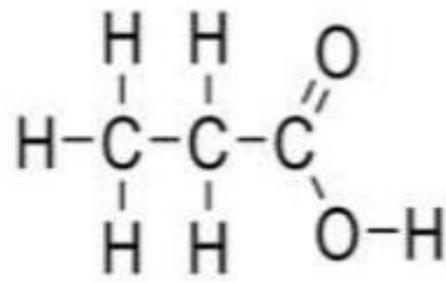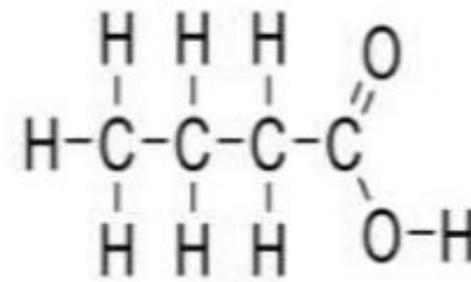
- Short-chain fatty acids (SCFAs) are important for overall health maintenance.

- SCFAs have an important role in lipid and glucose metabolism homeostasis.

- SCFA cross the BBB and regulate neurotransmitters.

- SCFAs can modulate immunological activity.

Systemic Effects of SCFA
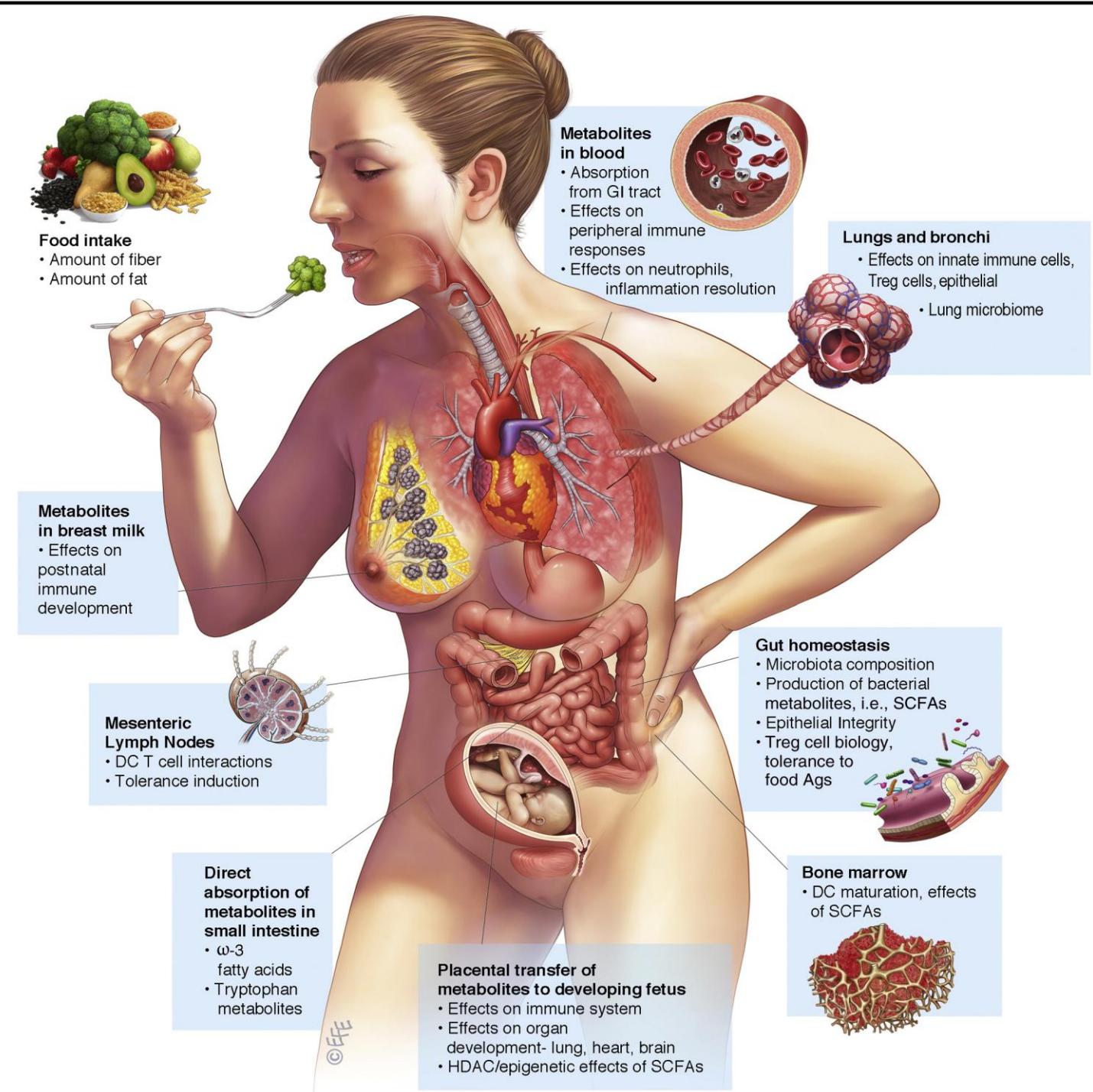
The Impact of Dietary Fiber on Gut Microbiota in Host Health and Disease

Type, quality, and origin of our food shape our gut microbes and affect their composition and function, impacting host-microbe interactions.

- Enhance mucous and anti-microbial function
- Increase tight junction proteins
- SCFA reduce oxygen levels
- SCFA maintain functional immune system

Alterations in this ecosystem lead to Increased susceptibility to

- Infection
- IBD
- CRC

Cell Host & Microbe 23, June 13, 2018

Goblet Cell

Mucus Layer

Mucus Layer

B *Muc2*
DAPI

Mucus
Layer

Mucus Layer

Mucus Layer

Cell 167, 1339–1353, November 17, 2016
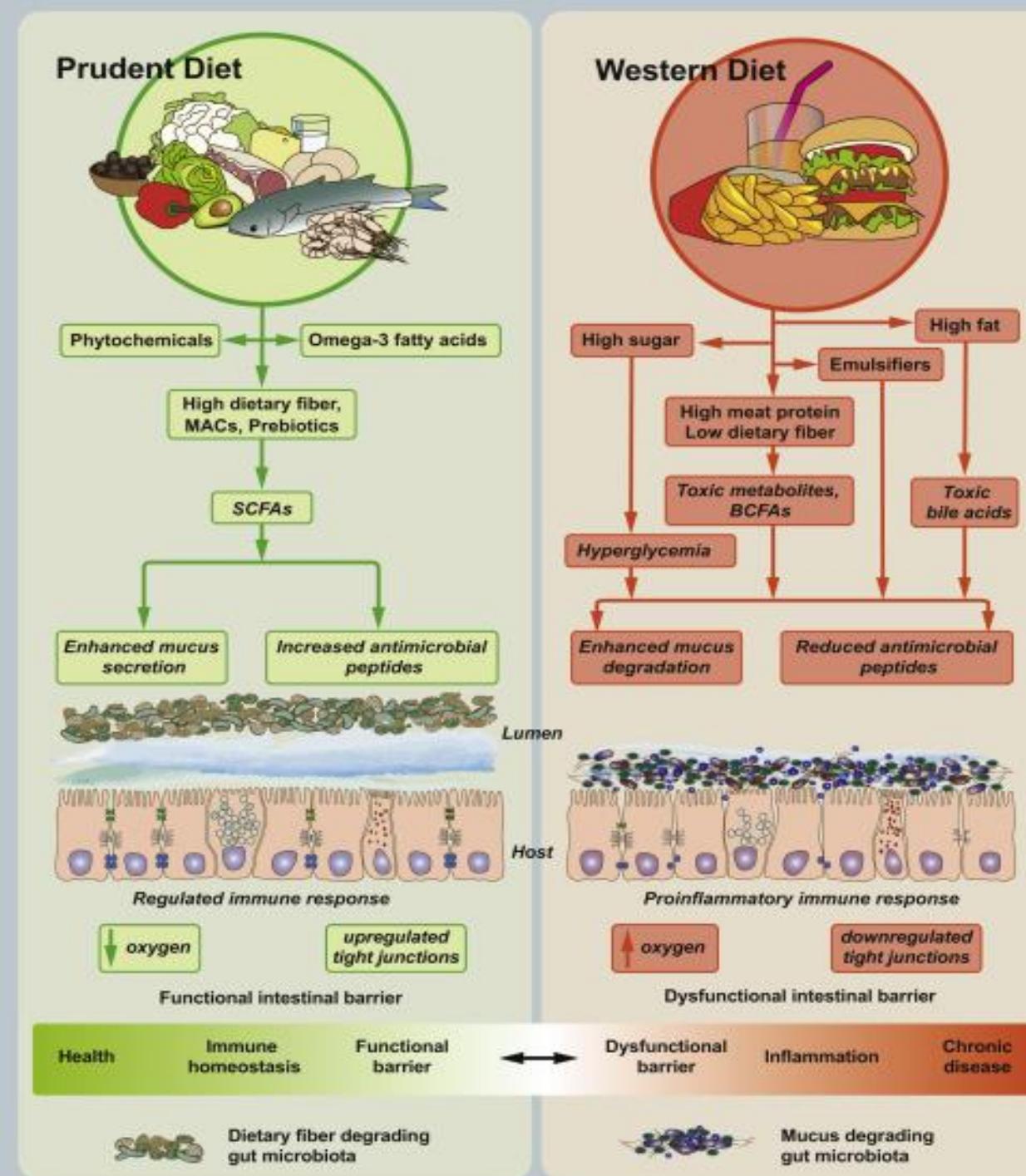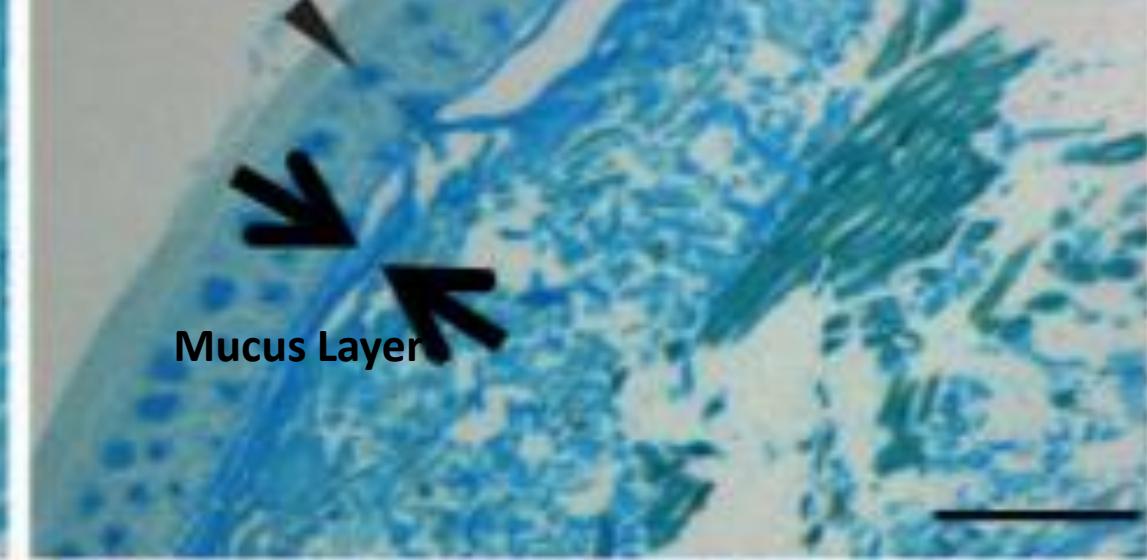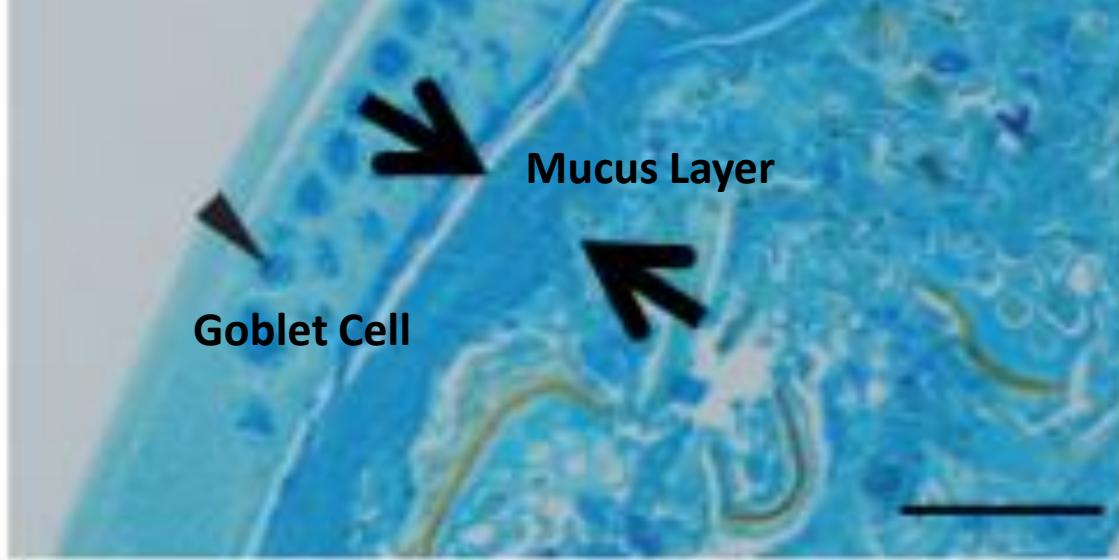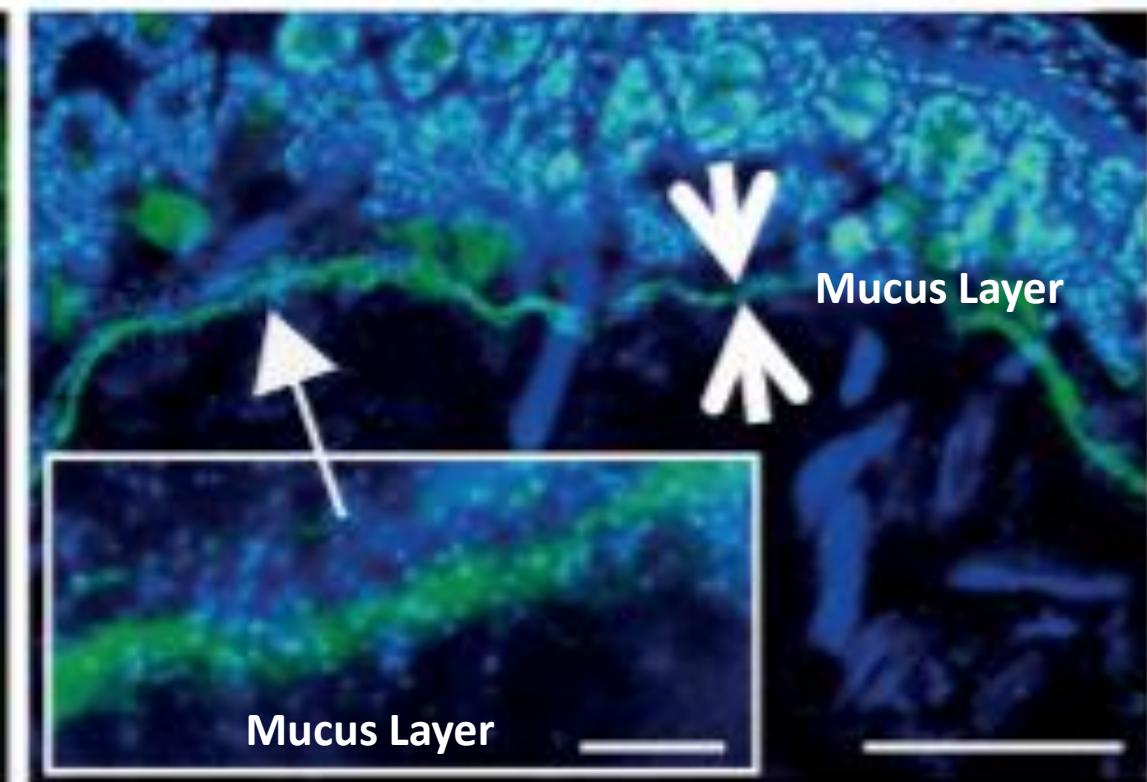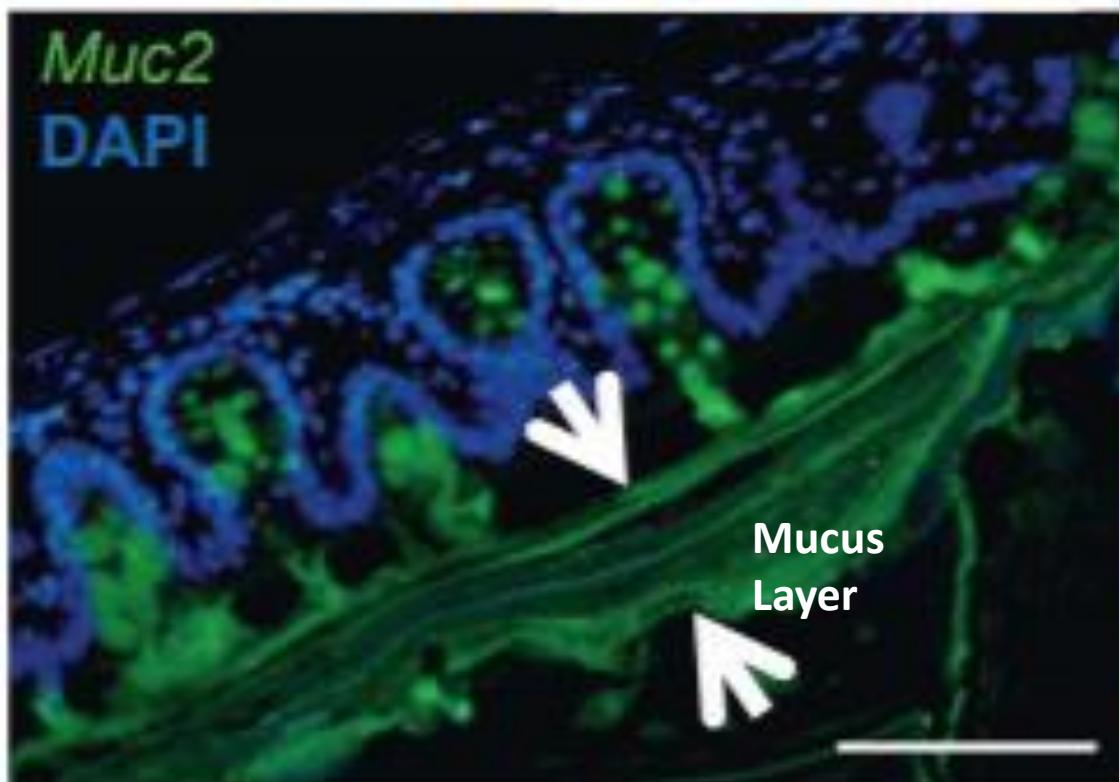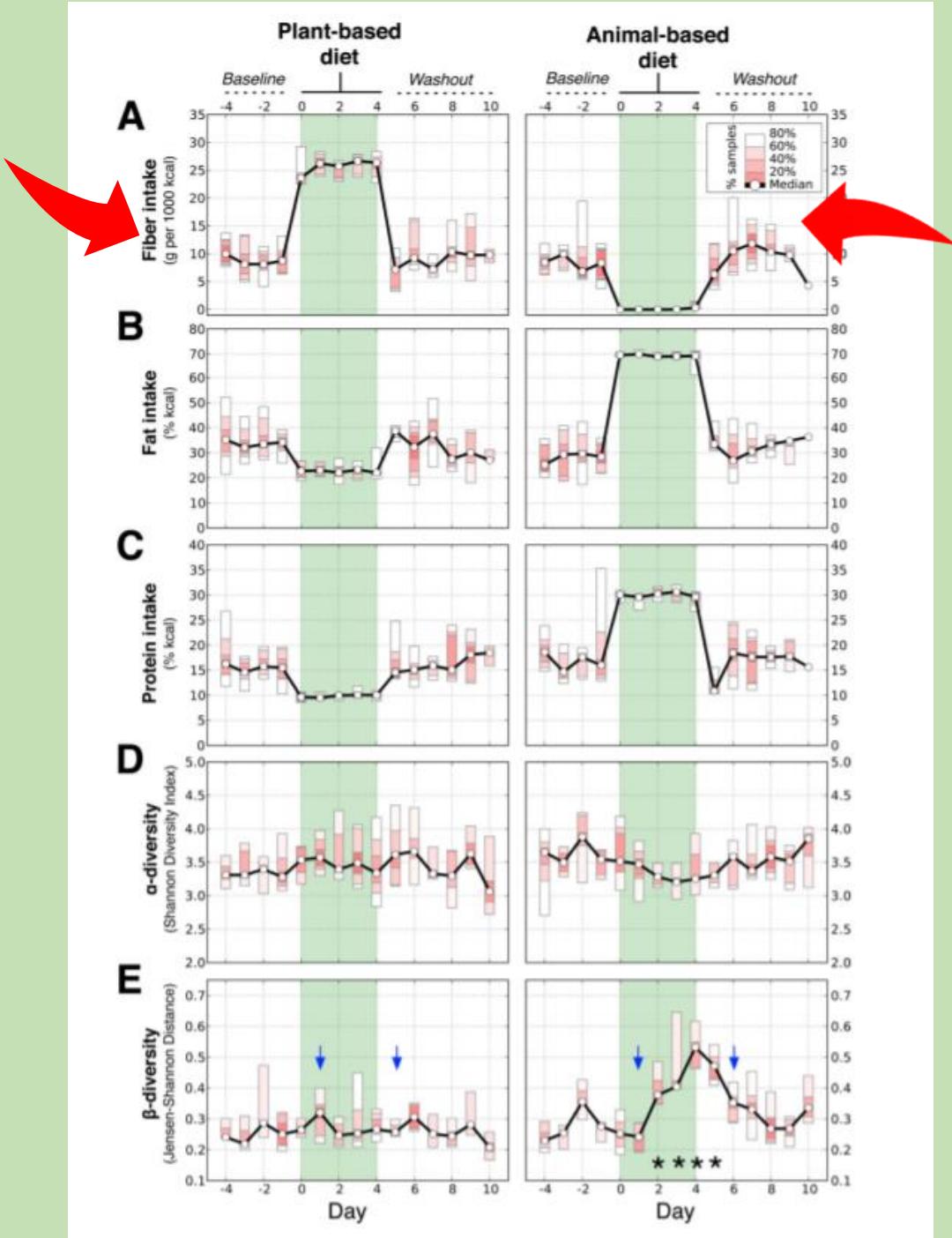
- Higher fiber intake in plant- based diet compared to animal- based diet

- Less gut microbiota diversity on an animal-based diet compared to a plant-based diet

- Community difference were apparent after 1 day of diet reaching the gut

Button et al, Nature 2014 (Harvard & University of California)

Fat, Fiber and Cancer Risk in African Americans and Rural Africans

Plant-based diet rapidly reverses harmful changes

Within 14 days of switching from Standard American Diet to high-fiber plant-based diet:

"Remarkable reciprocal changes in mucosal biomarkers of cancer risk in aspects of the microbiota and metabolome known to affect cancer risk"

- **More beneficial SCFAs**
- **Less carcinogenic secondary bile acids**
- **Reduced mucosal proliferation rate**
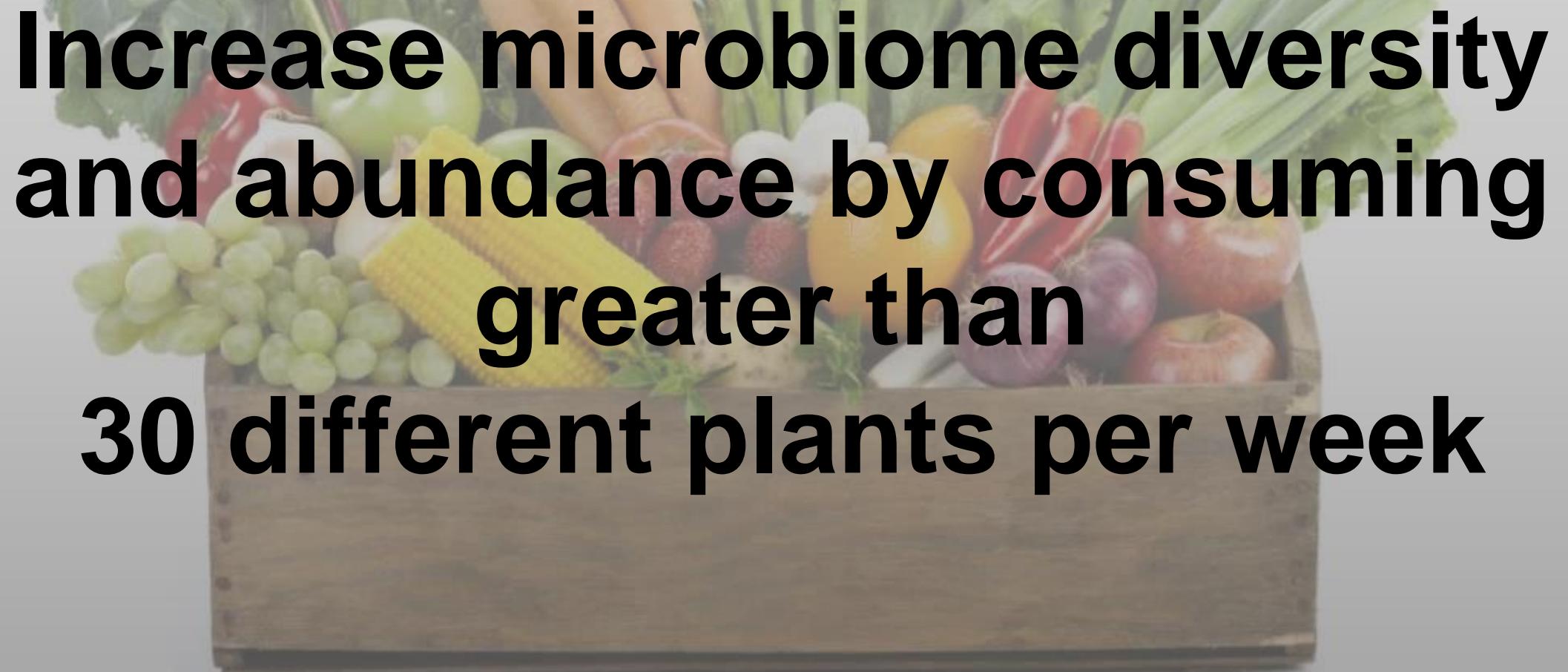
Increase microbiome diversity and abundance by consuming greater than
30 different plants per week
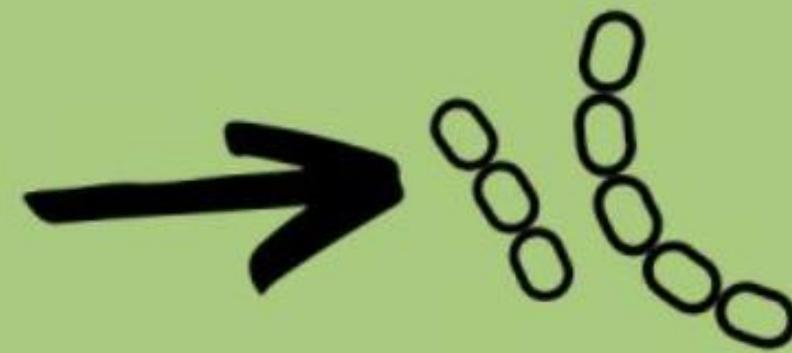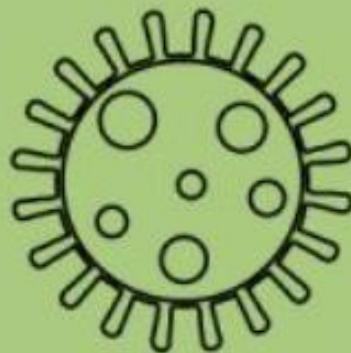
prebiotics

Fibers that feed
good bacteria

probiotics

Live beneficial bacteria
in your gut

postbiotics

Metabolites produced
by good bacteria

BYOB: Bring Your Own Biome

Thank you

M. Elizabeth Swenor, DO
Henry Ford Health
Medical director Lifestyle, integrative, Functional medicine
mswenor1@hfhs.org
313-585-6633