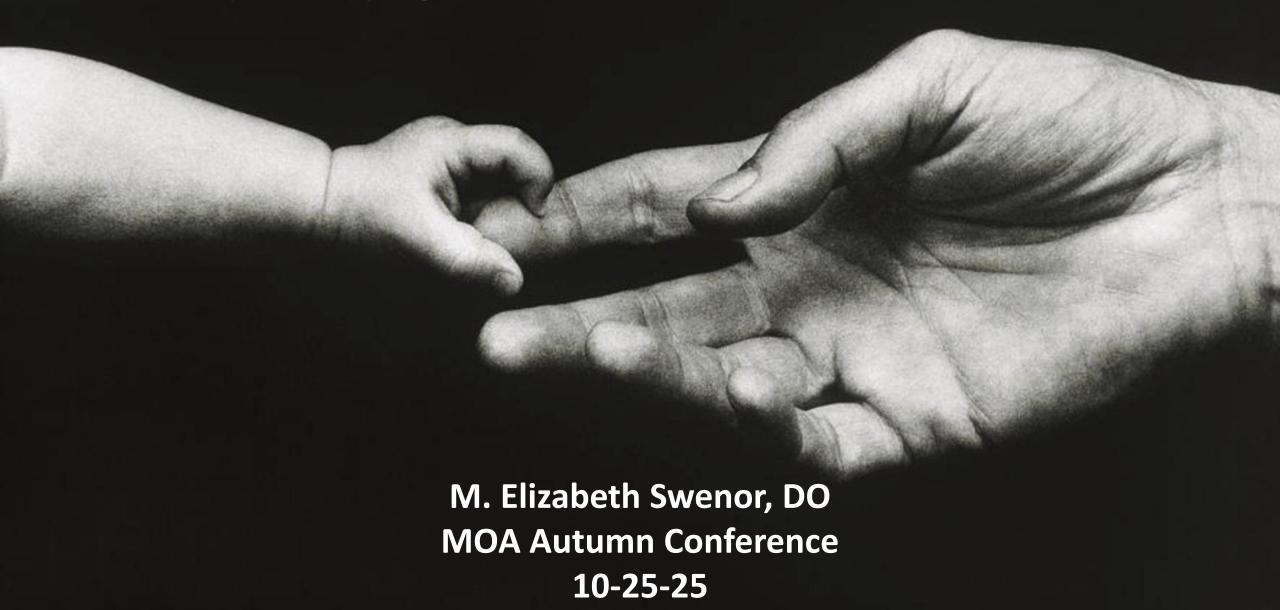
Lifestyle, Epigenetics, and the Microbiome



I have no financial disclosures

Objectives

- 1. Define Whole Person Health
- 2. 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



Whole-person health is an approach that integrates physical, mental, and social well-being by focusing on lifestyle choices like nutrition, exercise, sleep, and stress management, and encompasses the influences of social and environmental factors.



Whole person health emphasizes that true health is more than just the absence of disease and involves creating a lifestyle that promotes resilience, restores health, and prevents illness throughout life

Sarah 62 yo Caucasian Female CC: morbid obesity, fatigue, weight gain, uncontrolled T2DM, Crohn's disease with diarrhea and bloating

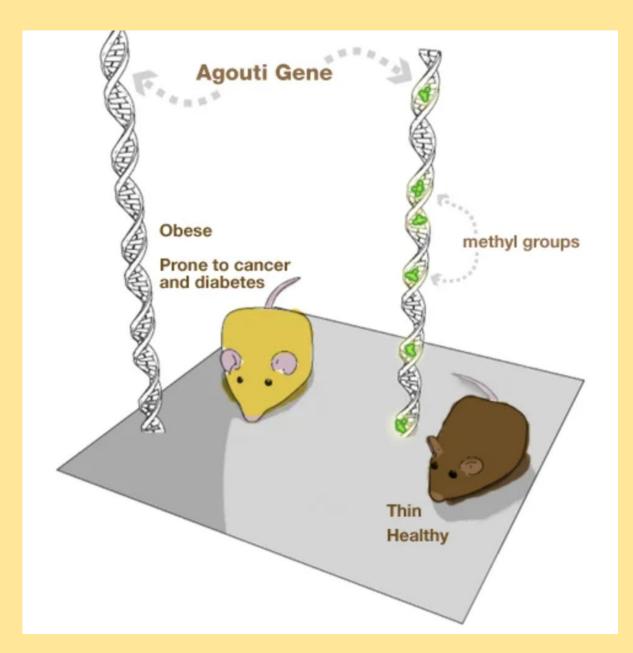


PMHX

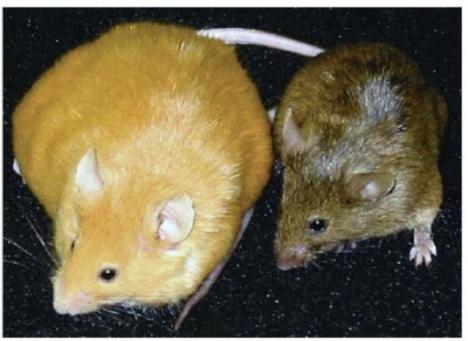
- Age 45 -NSTEMI- 99% stenosis mid-RCA and LAD stenosis
- 250 pounds. BMI 44.3
- Hypertension
- Hyperlipidemia
- Hashimoto's hypothyroidism
- T2DM HbA1C 8.5 non complaint with prescription medications
- Crohn's disease
- Lupus
- Psoriasis
- Depression, anxiety, insomnia with daytime hypersomnolence
- Low Vitamin B12 and D3, Low magnesium

Your DNA is NOT Your Destiny (Epigenetics)

Why the Recession Yemen: The Hasn't Been Co New Center The new science of epigenetics reveals how the choices you make can change your genes -and those of your kids



These Two Mice are Genetically Identical and the Same Age

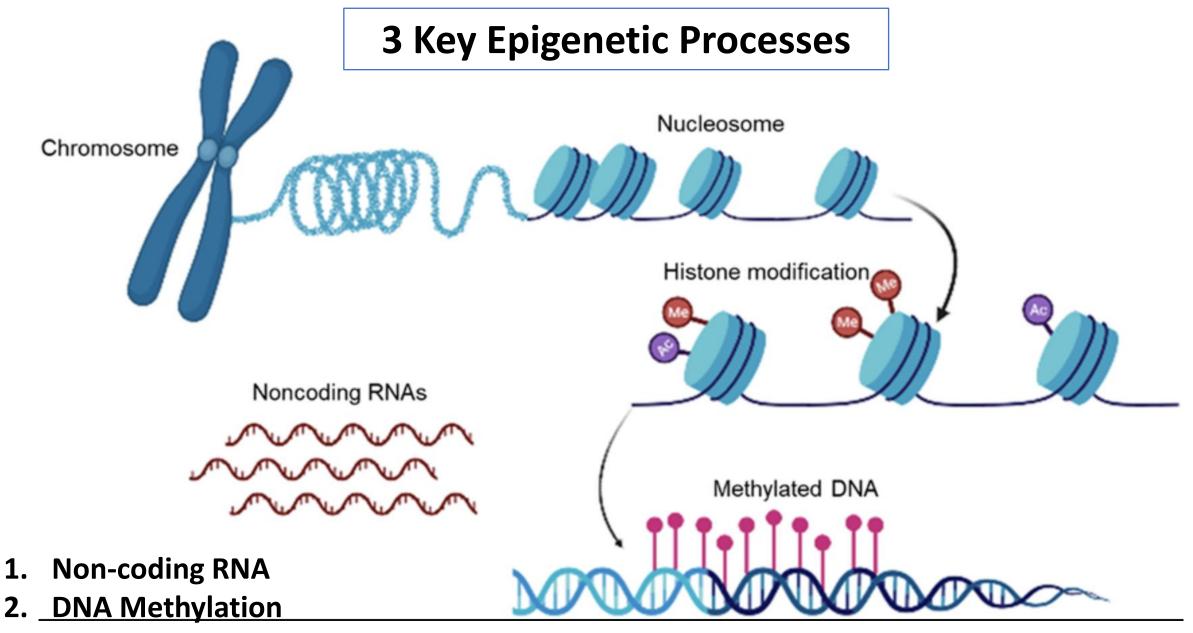


While pregnant, both of their mothers were fed Bisphenol A (BPA) but DIFFERENT DIETS:

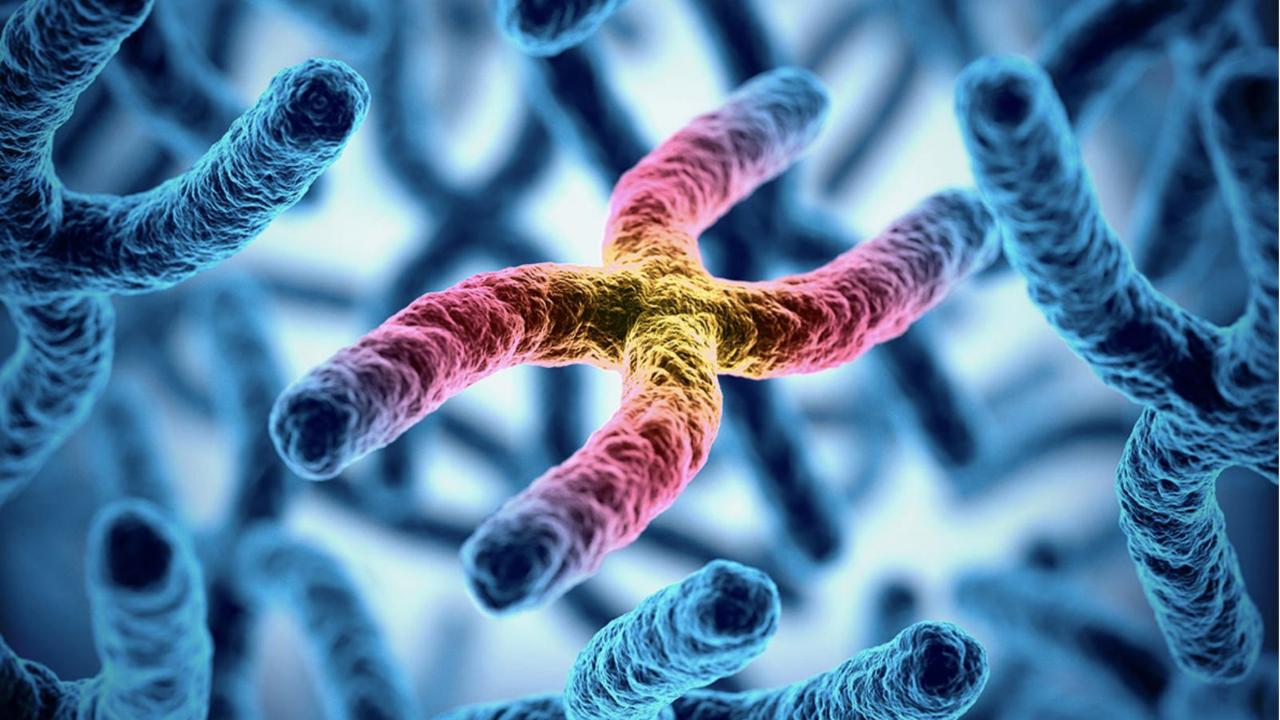
The mother of this mouse received a normal mouse diet

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

Photo courtesy Randy L. Jirtle, PhD

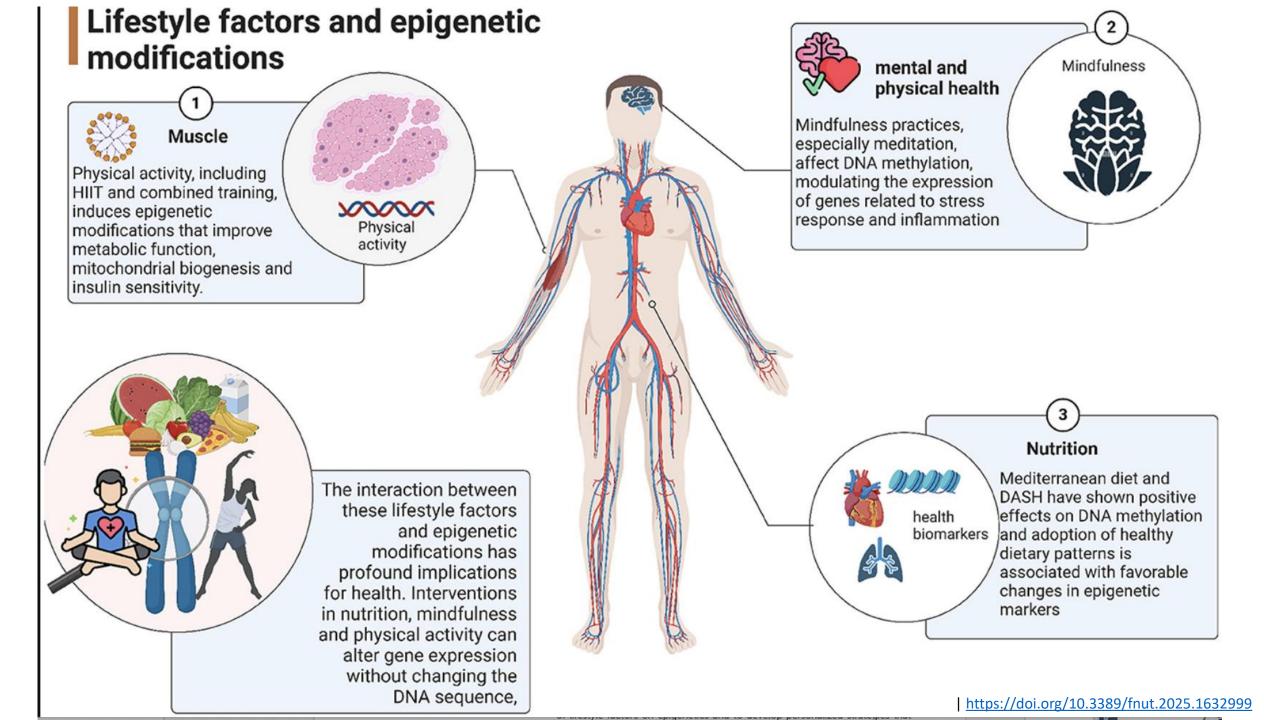


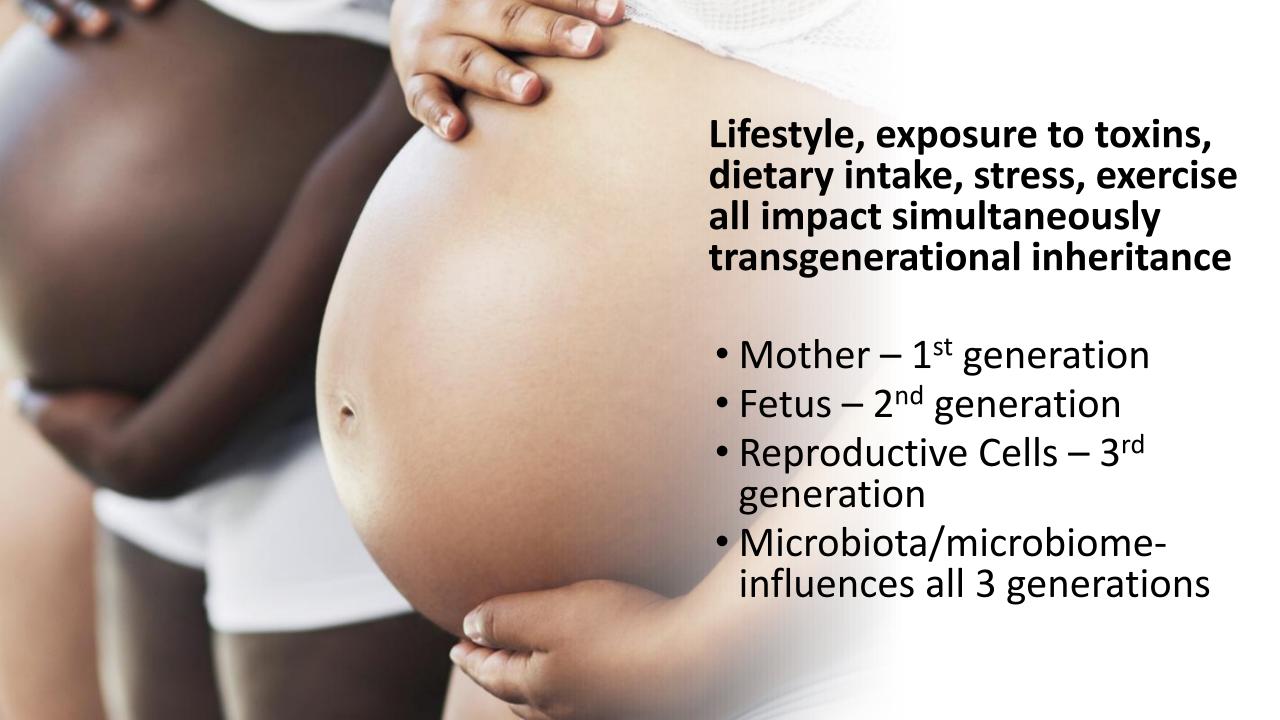
3. Histone modification

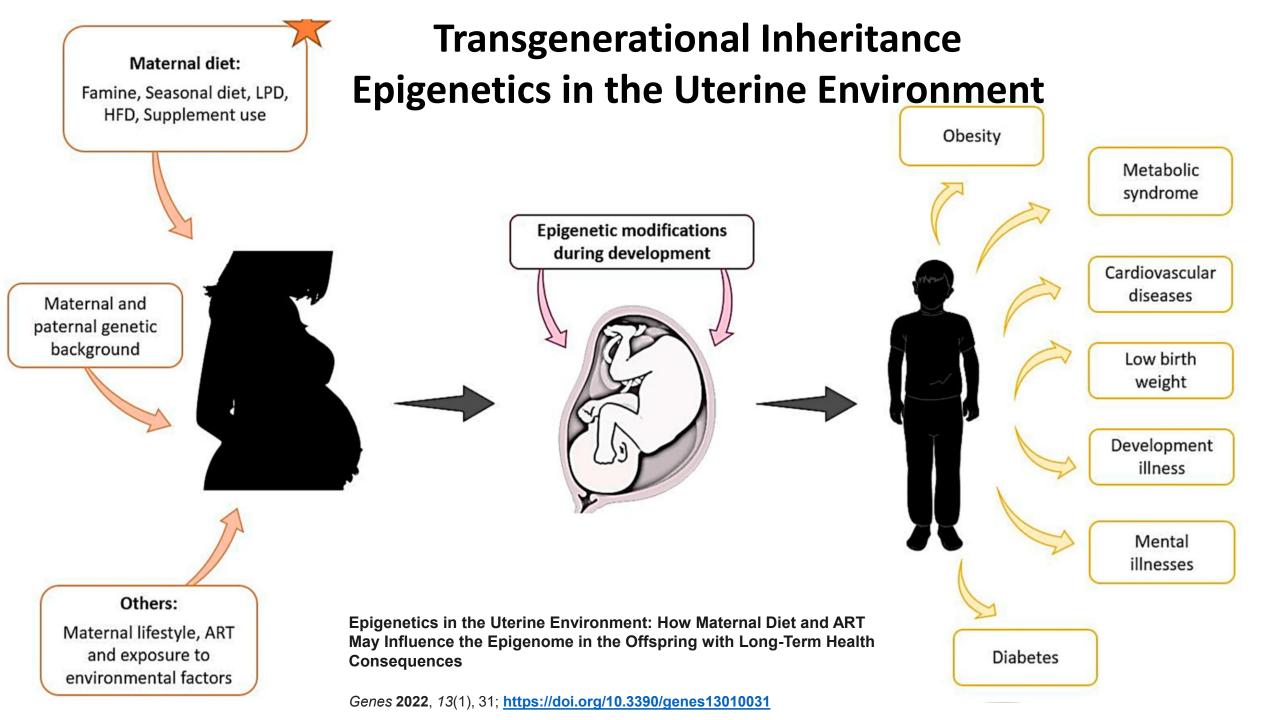












DNA Methylation in Cancer: Epigenetic View of Dietary and Lifestyle Factors

Lifestyle choices significantly impact cancer survival through epigenetic mechanisms, specifically by influencing DNA methylation, histone modifications, and microRNA expression

Dietary and lifestyle interventions aimed at modulating DNA methylation have potential for both cancer prevention and treatment through epigenetic mechanisms.

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.

453 down-regulated transcripts after 30-day intensive lifestyle intervention

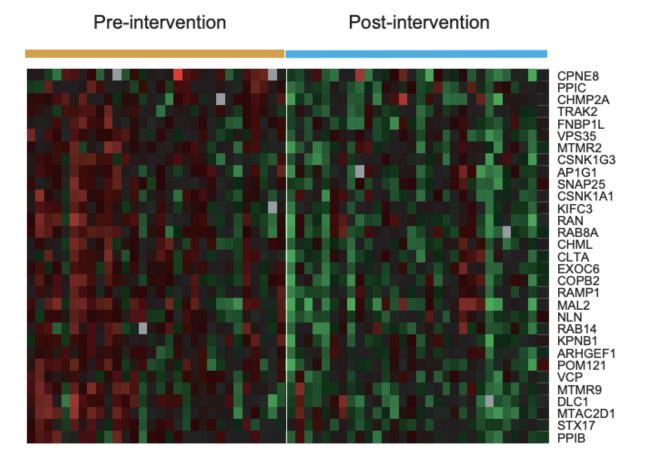


Fig. 4. Heat map of the gene ontology group "Intracellular Protein Traffic" illustrating the down-regulation of these 31 transcripts. Pre- and postcomprehensive diet and lifestyle intervention samples are indicated.



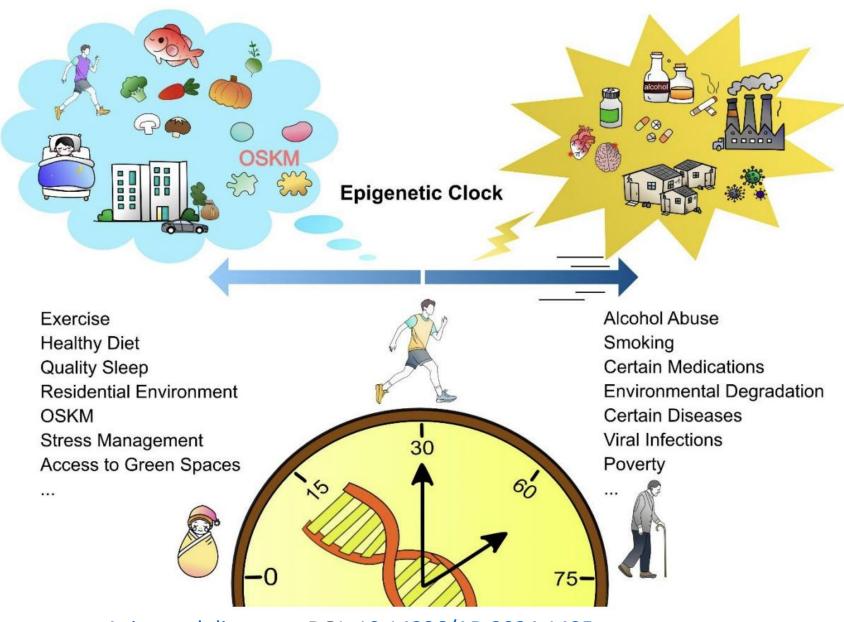




Epigenetic clocks, derived from DNA methylation patterns, are powerful aging biomarkers, capable of estimating biological age and assessing aging rates across diverse tissues with remarkable precision.

These clocks provide predictive insights into mortality and age-related disease risks, effectively distinguishing biological age from chronological age

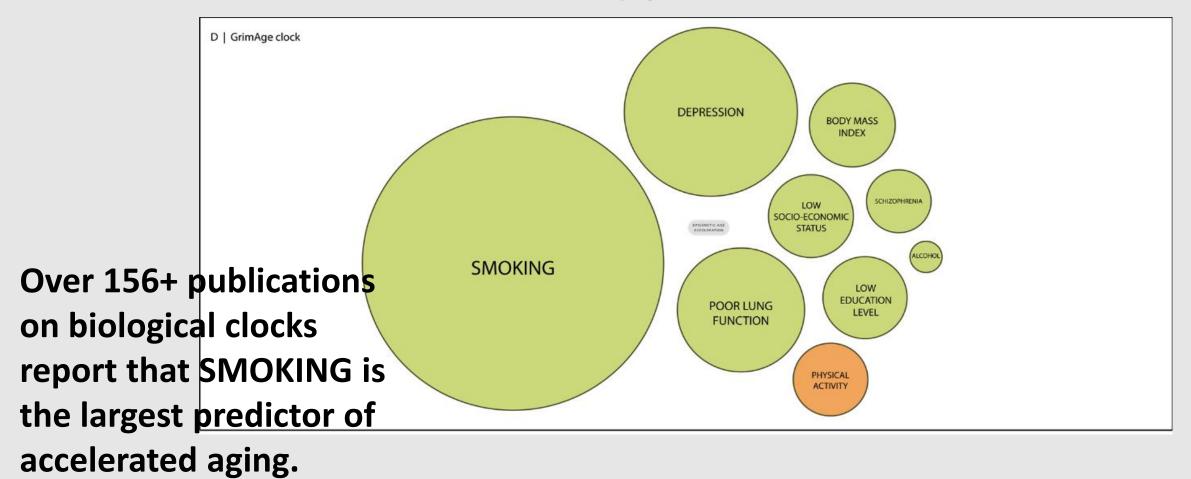
Epigenetic Clocks: Beyond Biological Age, Using the Past to Predict the Present and Future



Aging and disease >> DOI: 10.14336/AD.2024.1495



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



Major Lifestyle Recommendations For Increasing Healthspan and Reducing Biological Age

Int J Environ Res Public Health. 2019 Jul; 16(13): 2356.

Published online 2019 Jul 3. doi: 10.3390/ijerph16132356

PMCID: PMC6651499

PMID: 31277270

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.





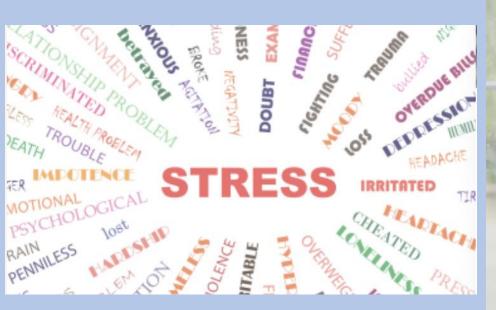
Cross-talk between gut microbiota and tobacco smoking: a two-sample Mendelian randomization study

BMC Medicine volume 21, Article number: 163 (2023)



Smoking affects the gut microbiota by:

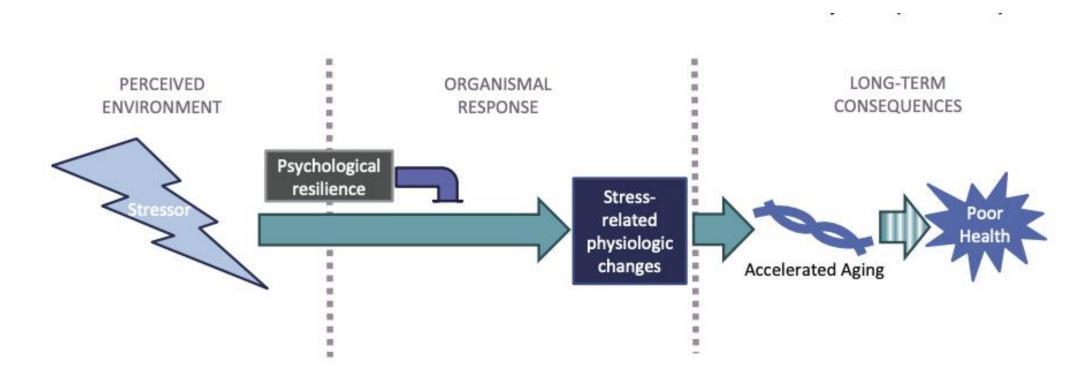
- Raising the pH of the intestinal environment
- Inducing chronic low-grade inflammation and inflammatory related diseases
- Promoting damaging oxidative stress which increases systemic inflammation





Psychological and biological resilience modulates the effects of stress on epigenetic aging

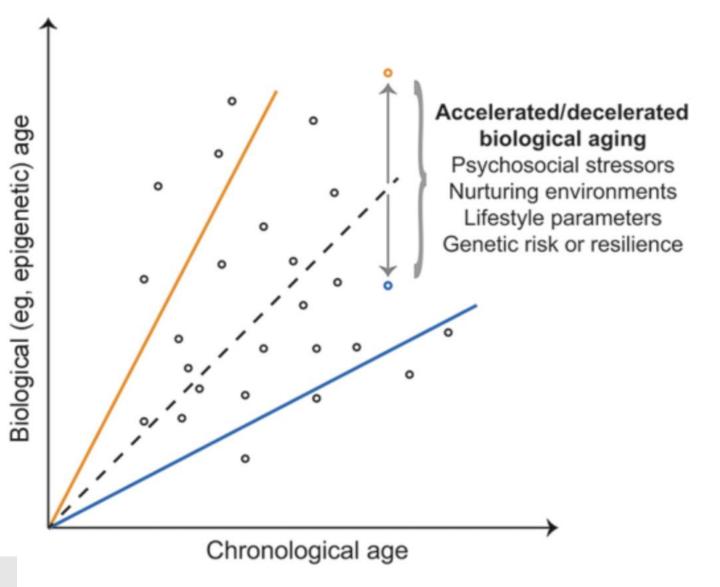
Translational Psychiatry (2021) 11:601



Model of relationships between cumulative stress, resilience, physiology, and aging.

Cumulative life-time stress is associated with accelerated epigenetic aging

Personal life stress had greater impact in older compared to younger participants



Dialogues Clin Neurosci. 2019 Dec; 21(4): 389-396.

Epigenetics as a key link between psychosocial stress and aging: concepts, evidence, mechanisms 2

Anthony S. Zannas, MD

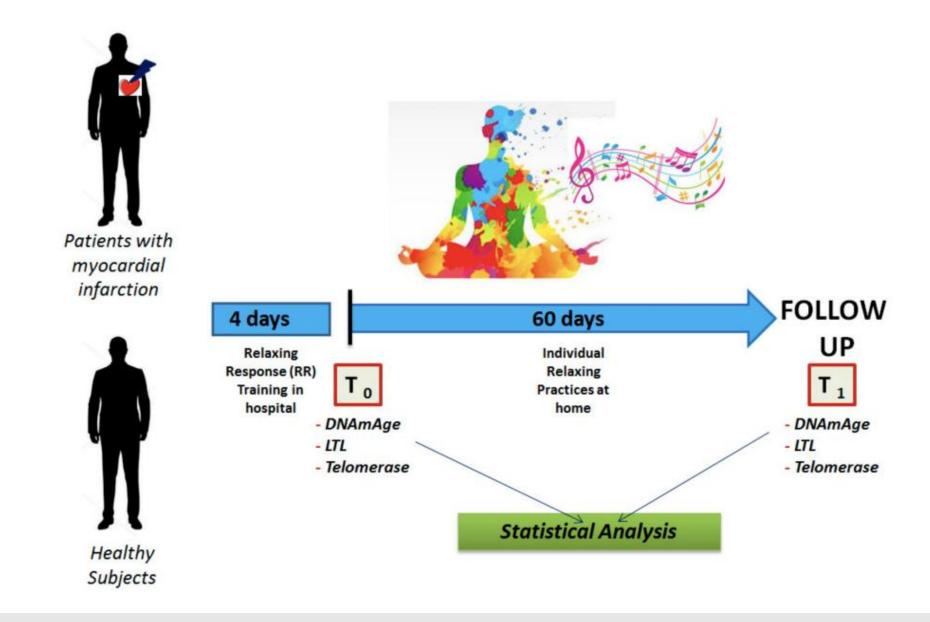
Several studies reveal the benefits of deep-breathing on stimulating the vagus nerve (parasympathetic tone)

Recommend deep breathing 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.



- Studies published between 2013 and 2023.
- · RCT Pranayama interventions with non-yoga control groups.
- Primary outcomes, including psychological well-being, quality of life, physiological parameters, and treatment-related side effects.
- Pranayama has been shown to be an effective complementary therapy for cancer patients, enhancing their well-being and quality of life

Cureus. 2024 Feb 22;16(2):e54688. doi: 10.7759/cureus.54688



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

Epigenetic clock analysis in long-term meditators

A 2017 study found that long-term meditators (ages 52 and older) were protected from the accelerated epigenetic aging that was observed in non-meditating controls in the same age group.

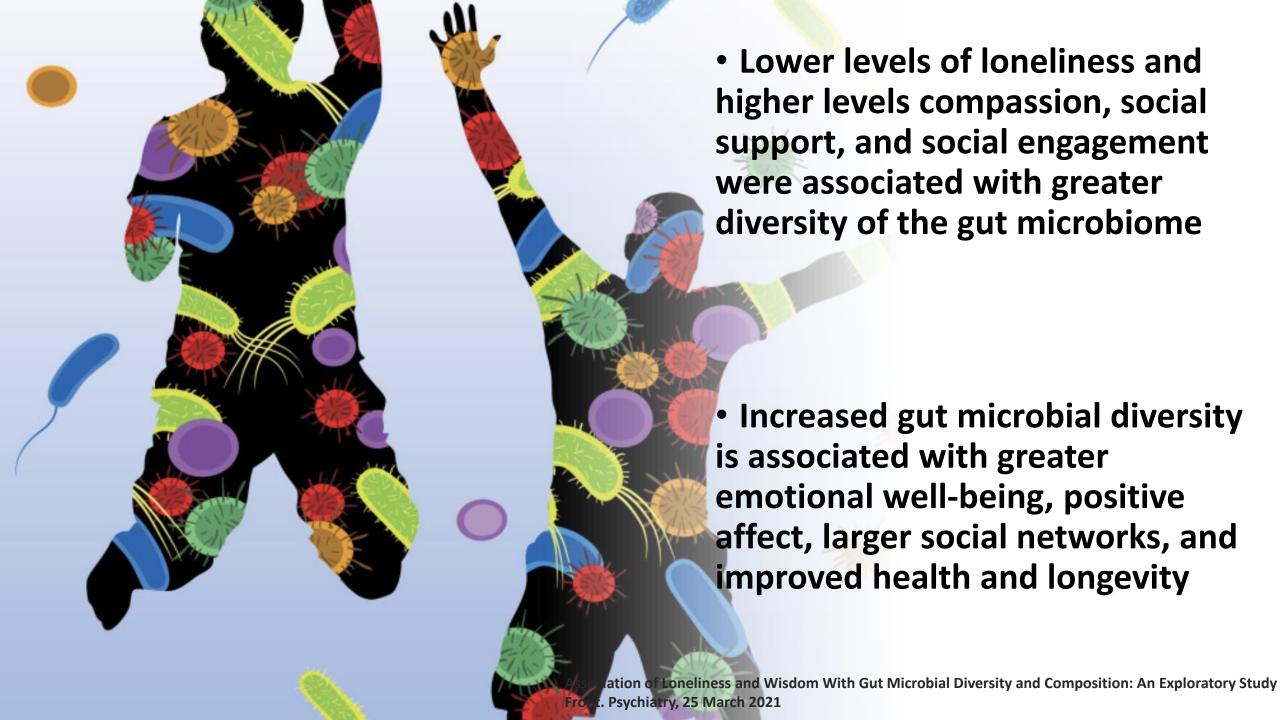
The mechanisms by which pranayama is thought to influence the epigenetic clock are largely linked to its effects on stress reduction and cellular health.

- Reduced oxidative stress
- Reduced systemic inflammation
- Modulation of the autonomic nervous system's stress response
- Support for increasing telomere length



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.



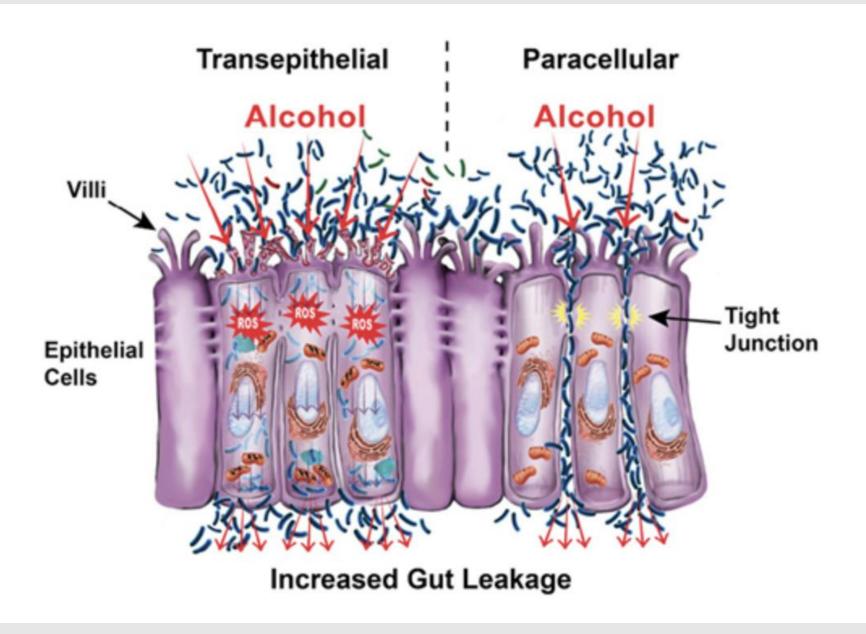




Epigenetic aging is accelerated in alcohol use disorder and regulated by genetic variation in APOL2

Neuropsychopharmacology (2020) 45:327 - 336

- 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

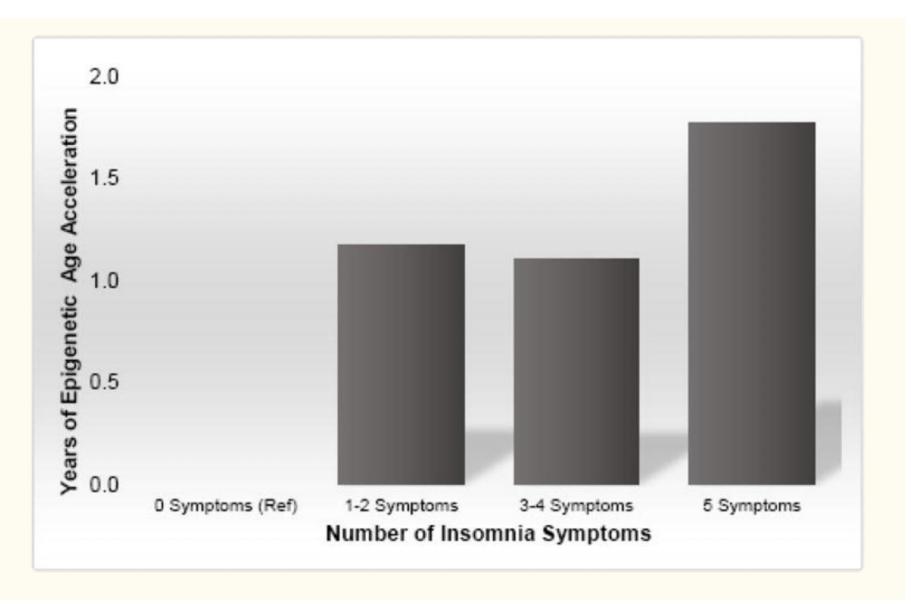
A pilot prospective study of sleep patterns and DNA methylation-characterized epigenetic aging in young adults

Mary A. Carskadon^{1,2*}, Kenneth R. Chappell⁵, David H. Barker^{2,3}, Anne C. Hart⁴, Kayla Dwyer⁵, Caroline Gredvig-Ardito¹, Caitlyn Starr⁵ 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

Biol Psychiatry. 2017 Jan 15; 81(2): 136-144.





Physical Activity Is Associated With Decreased Epigenetic Aging: Findings From the Health and Retirement Study

ABSTRACT

Background: Epigenetic aging measures or clocks are DNA methylation-based indicators of biological aging, linked to health outcomes and disease risk. Physical activity and exercise may influence epigenetic aging, suggesting a pathway through which it promotes healthier aging and reduces chronic disease burden. In this study, we assessed the association between self-reported moderate-to-vigorous physical activity and epigenetic age acceleration (EAA) in participants of the Health and Retirement Study, followed biennially for 12 years from 2004 to 2016.

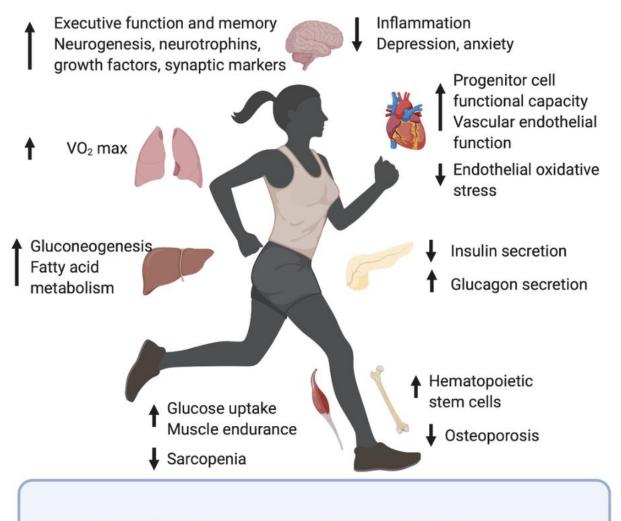
Methods: Leukocyte DNA methylation was measured from venous blood samples collected in 2016 and second-generation epi-

Findings highlight that both sustained and recent physical activity were significant independent predictors of slower epigenetic aging

each wave, r more catcionally, we with EAA, ctivity over

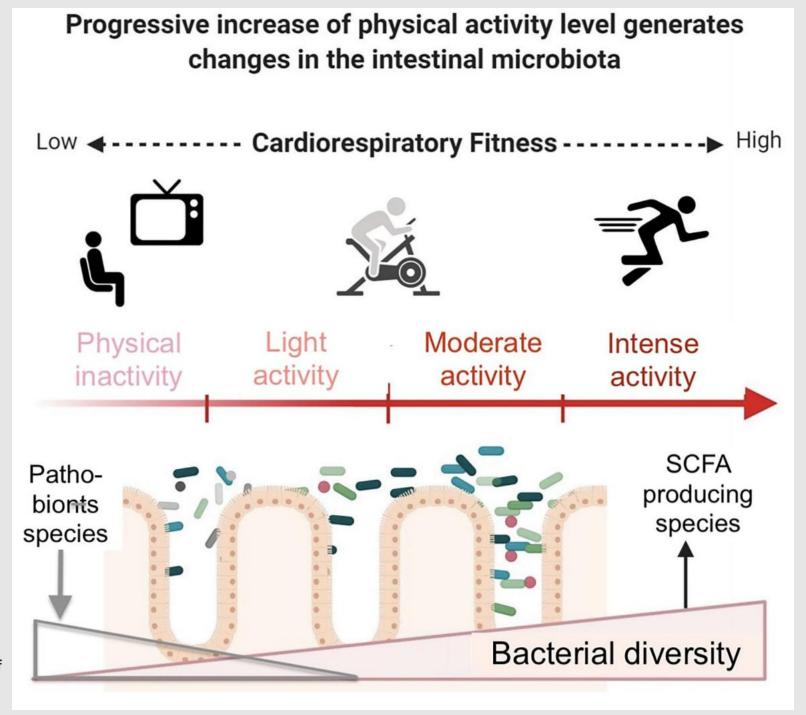
Results: In 2016, 58% of the participants were classified as physically active. In cross-sectional analysis, physically active participants had lower EAA than inactive participants: -1.26 (95% confidence interval (CI): -1.59, -0.93) years for GrimAge acceleration, -1.70 (95% CI: -2.26, -1.15) for PhenoAge acceleration and -0.05 (95% CI: -0.06, -0.04) years per chronological year for DunedinPACE, adjusted for age, gender, race/ethnicity, education, total wealth and current smoking status. The associations attenuated slightly but remained significant after further adjusting for body mass index, mobility limitations and chronic disease diagnosis. We found evidence of effect modification in the association between physical activity and EAA by social factors, with stronger associations in males compared to females for DunedinPACE ($P_{\text{interaction}} = 0.04$) and a positive association between physical activity and increased EAA among Hispanics compared to non-Hispanic Whites for GrimAge ($P_{\text{interaction}} = 0.009$). Our longitudinal analysis using SLCMA identified both accumulation and most recent physical activity in 2016 as the strongest predictors of EAA.

Conclusions: Our findings highlight physical activity as a robust factor associated with slower epigenetic aging, with both accumulation and concurrent physical activity as the strongest predictors. These results underscore the role of physical activity in promoting healthier biological aging, suggesting its potential as a target for interventions aimed at mitigating age-related health decline.



Longevity effects: exercise >150 but <2000 minutes/week.

Combination of aerobic and resistance exercise



Interplay Between Exercise and Gut Microbiome in the Context of Human Health and Performance Front. Nutr., 10 June 2021



Higher diet quality relates to decelerated epigenetic aging

Am J Clin Nutr 2022;115:163-170.

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.

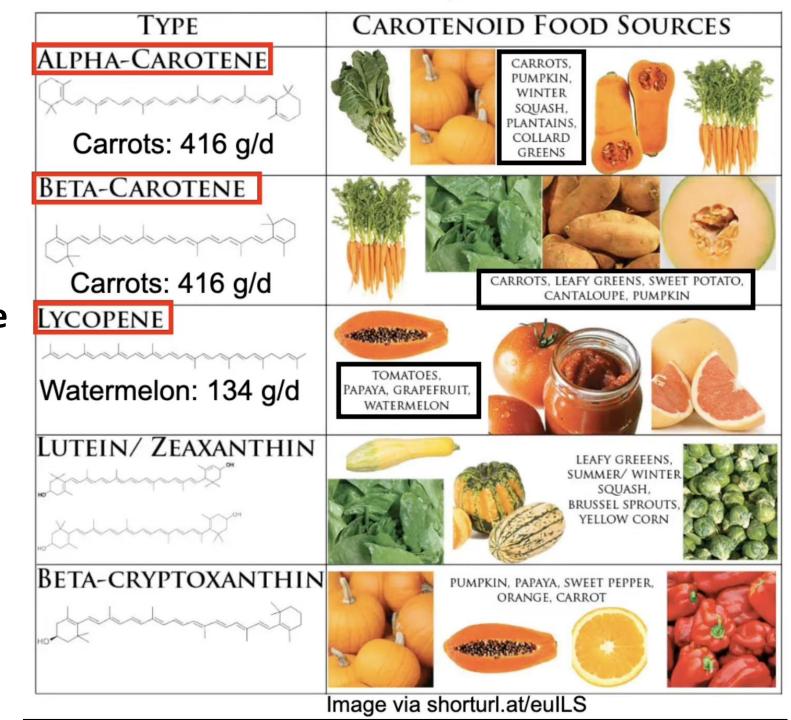
Advantages of the DASH diet

- 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





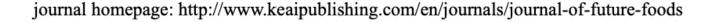
Available online at www.sciencedirect.com





Journal of Future Foods

Journal of Future Foods 3-4 (2023) 289–305

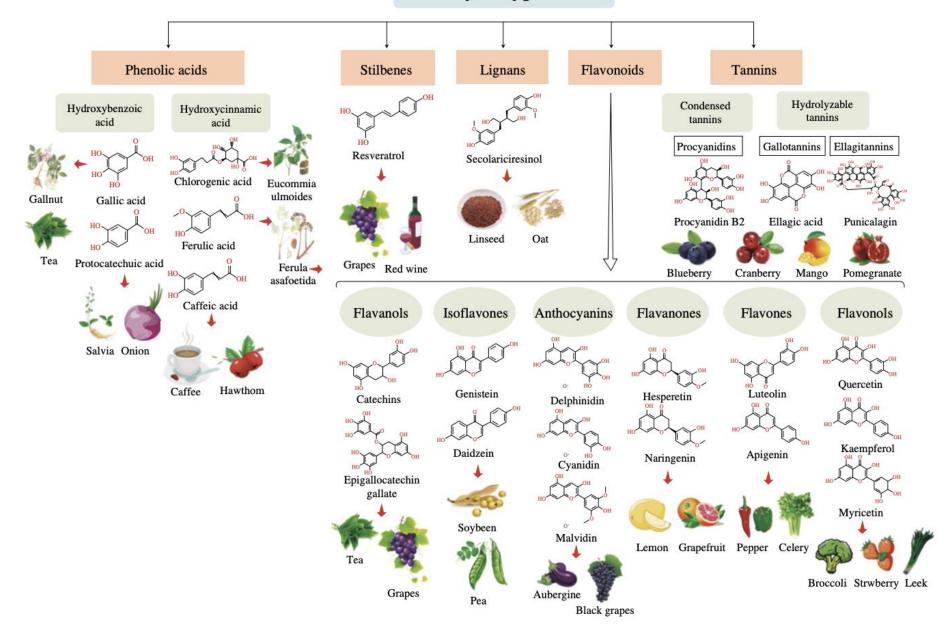




Research progress on classification, sources and functions of dietary polyphenols for prevention and treatment of chronic diseases

Dietary polyphenols are the most abundant antioxidants in daily diet and widely distributed in plants and plant-based foods, including vegetables, fruits, cereals, nuts, and beverages (e.g., tea, coffee, red wine). Over the past decades, there has been rising scientific interest in their diverse benefits to human health, since dietary polyphenols display various bioactivities, such as antioxidant activity, anti-inflammatory activity, anti-cancer, anti-microbial activity, neuro-protective activity, among others. Various studies have demonstrated that diet with polyphenols is strongly related to decrease the risk of chronic diseases

Dietary Polyphenols











FRUITS & VEGETABLES

Apples, Berries, broccoli, carrots, grapes, lettuce, tomatoes

HERBS & SPICES

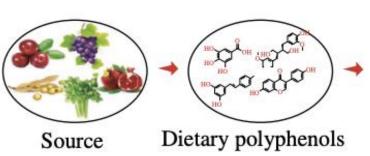
Caraway, celery seed (dried), cinnamon, cloves, common sage, curry (powder), ginger (dried), Mexican oregano, parsley (dried), peppermint (dried), red chicory, rosemary(dried), spearmint (dried), star anise, sweet basil (dried), and thyme

OTHER FOODS

Cacao, cocoa powder, dark chocolate, flaxseed meal, olive oil, olives

DRINKS

Beer, coffee, teas (black, green, oolong), and wine



Glucose uptake ↑ Glucose consumption ↑ Oxidative stress ↓ Insulin resistance ↓

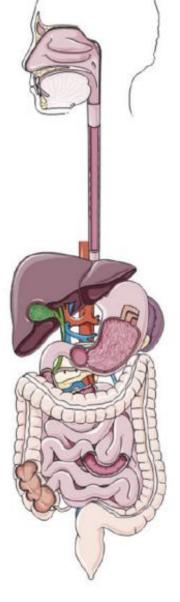


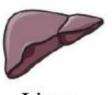
Muscle

Insulin secretion \uparrow Oxidative stress \downarrow Inflammation \downarrow Apoptosis of β -cell \downarrow Pancreas β -cell function \uparrow

Glucose uptake ↑ Oxidative stress ↓ Adipocyte dyafunction ↓ Lipogenesis ↓

Adipose tissue





Liver

Glucose uptake ↑
Glucose production ↓
Gluconeogenesis ↓
Insulin resistance ↓
Oxidative stress ↓
Inflammation ↓
Neoglycogenesis ↓
Lipid metabolism balance ↑



Blood vessel

Oxidative stress ↓
Blood glucose ↓
Vascular endothelial dysfunction ↓
Protein glycation ↓



Digestive enzymes activities ↓
Glucose transport proteins ↓
Insulin secretion ↑
DPP-IV activity ↓
GLP-1 ↑
SCFAs levels ↑
Oxidative stress ↓
Inflammation ↓
Modulation of intestinal flora ↑

The effect of polyphenols on DNA methylation-assessed biological age attenuation: the DIRECT PLUS randomized controlled trial Eat Your Greens

Increased Dietary Polyphenols Slow the Epigenetic Aging Process

As reported in Clinical Epigenetics (Yaskolka Meir and Keller et al.), the team employed a variety of DNA methylation-based

richer in polyphenols prompted the more significant slowing of DNA methylation-based epigenetic aging when measured by the Li (Li et al.) and Hannum (Hannum et al.)

epigenetic clocks. Greater intake of polyphenols from sources such as green plant products induced more significant DNA methylation-based epigenetic age attenuation according to the Li epigenetic clock, which corresponded to increased levels of polyphenols such as hydroxytyrosol, tyrosol, urolithin C, and urolithin A in the urine. Additionally, the dietary changes evaluated in this clinical trial prompted beneficial effects on multiple health conditions (e.g., fatty liver, age-related brain atrophy, and cardiovascular risk), which may contribute to healthy aging, and supported weight loss in each intervention group

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

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

Antioxidants 2022 Jun; 11(6): 1212.



WHAT FOOD INCREASES THE RISK OF EPIGENETIC CHANGES AND COLORECTAL CANCER?

RED 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

A Plant-Forward Diet reduces the risk of CRC

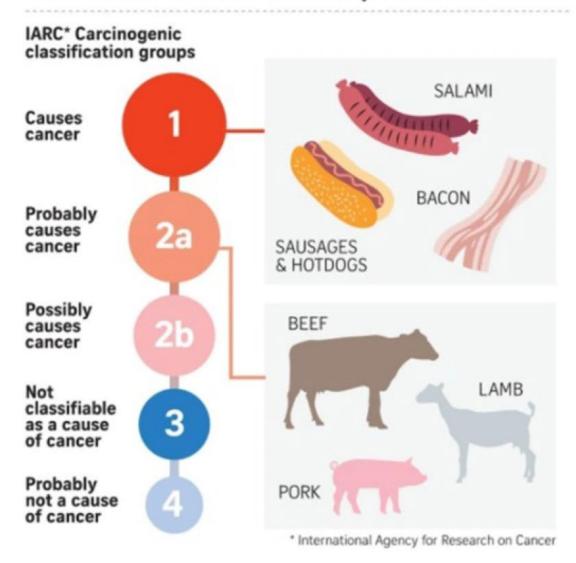
- 123 773 participants of the Nurses' Health Study and the Health Professionals Follow-up Study
- (3 143 158 person-years)
- 3077 of them had developed CRC.
- Healthy and unhealthy plant-based diet indices were calculated using repeated food frequency questionnaire data.
- An unhealthy UP plant-based diet is associated with higher CRC incidence.
- A healthy plant-based diet rich in whole grains, fruits and vegetables is associated with lower incidence of CRC
- Replacing refined grains with healthy plant foods such as whole grains, fruits and vegetables is associated with lower CRC incidence.

Clin Transl Med. 2022 Aug 23;12(8):e893.

doi: 10.1002/ctm2.893

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

WHO classification of red and processed meats



The Washington Post

Democracy Dies in Darkness

ECONOMIC POLICY

Hot dogs, bacon and other processed meats cause cancer, World Health Organization declares





A new World Health Organization study found that processed meet like bacon and hot dogs cause cancer. It is the most prominent group to declare it a cause. (Video: Jenny Starrs/The Washington Post)

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:

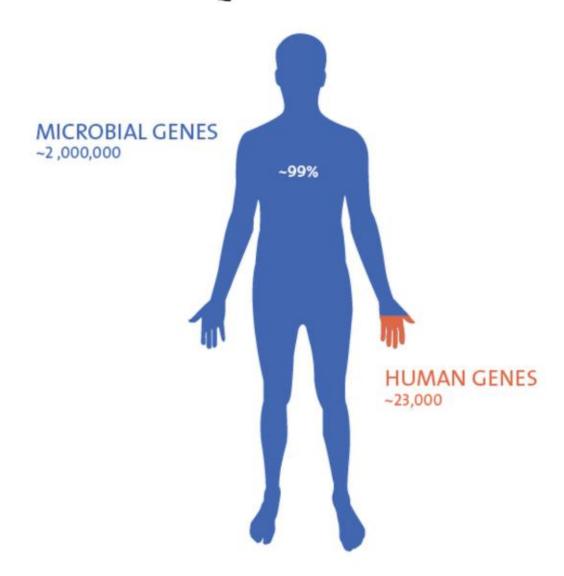
"Remarkable reciprocal changes in mucosal biomarkers of cancer risk in aspects of the microbiota and metabolome known to affect cancer risk"

- More beneficial SCFAs
- Less carcinogenic secondary bile acids
- Reduced mucosal proliferation rate



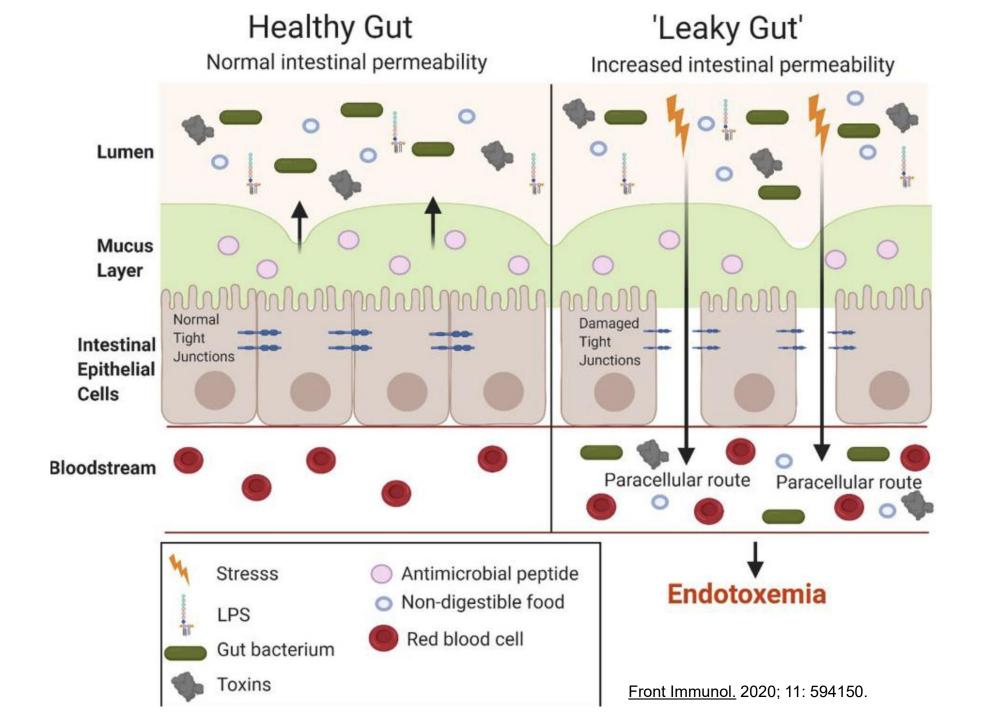


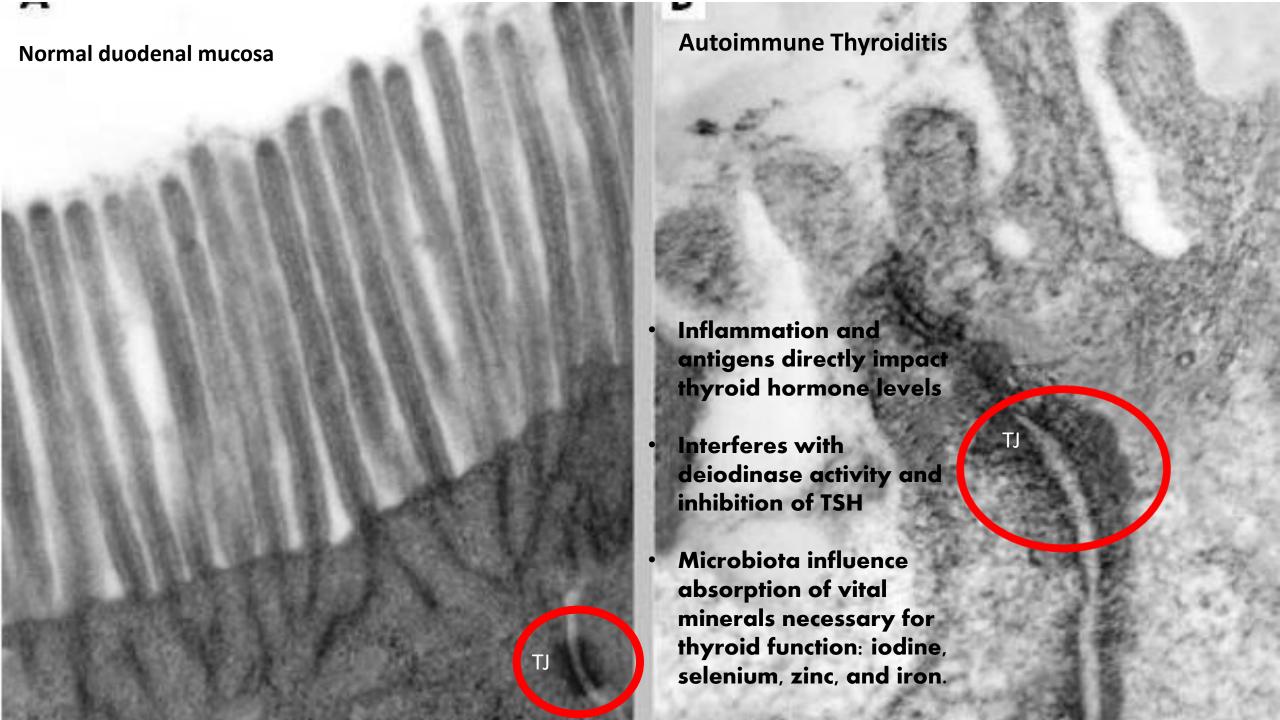
PROPORTION OF UNIQUE GENES IN THE HUMAN BODY



Ninety-nine percent of the unique genes in your body are bacterial. Only about one percent is human.

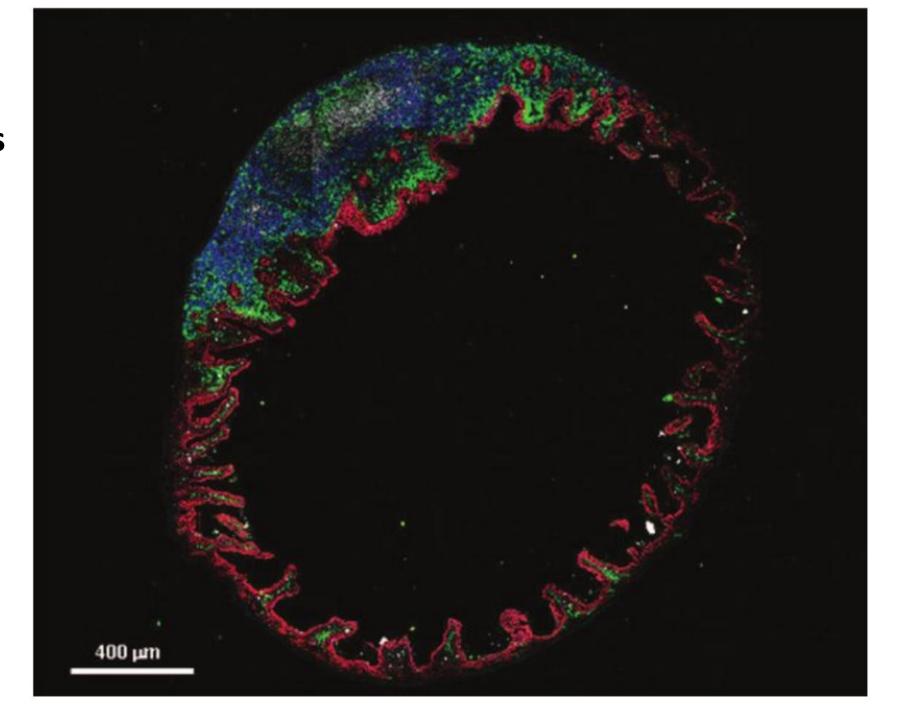
Image credit: amnh.org





Functional Interactions Between Enterocytes, Immune Cells, and Microbiota

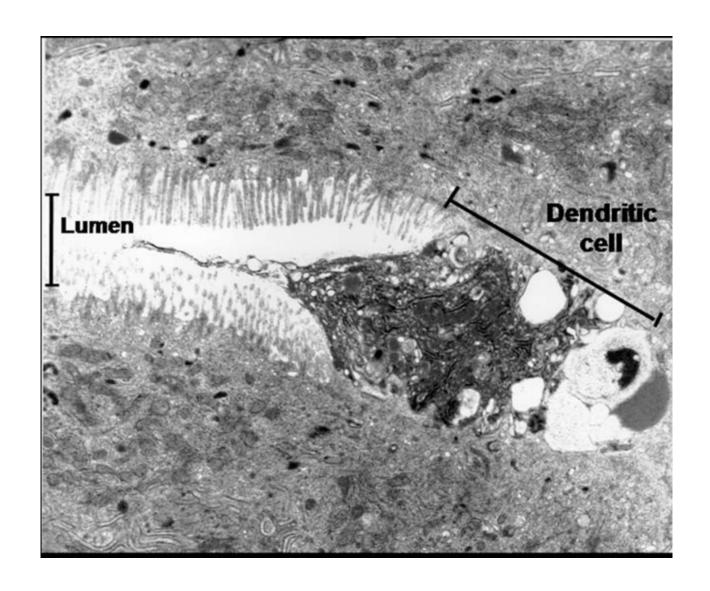
- RED- Gut Epithelial Cells
- GREEN- Dendritic Cells
- BLUE- Beta Cells
- WHITE- T-Cells



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
Intestinal dendritic cells: Their role in bacterial recognition, lymphocyte homing, and intestinal inflammation



Our ancestral human diet

Should it be a paradigm for contemporary nutrition?

S Boyd Eaton ¹

Proc Nutr Soc. 2006 Feb;65(1):1-6. doi: 10.1079/pns2005471

- 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 baseyielding, 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

EAT 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

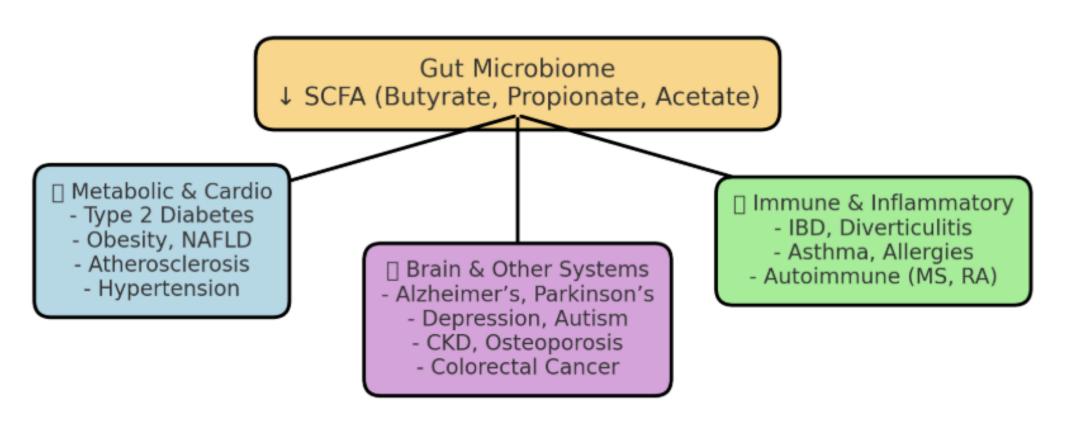
Acetic acid (acetate)

Propionic acid (propionate)

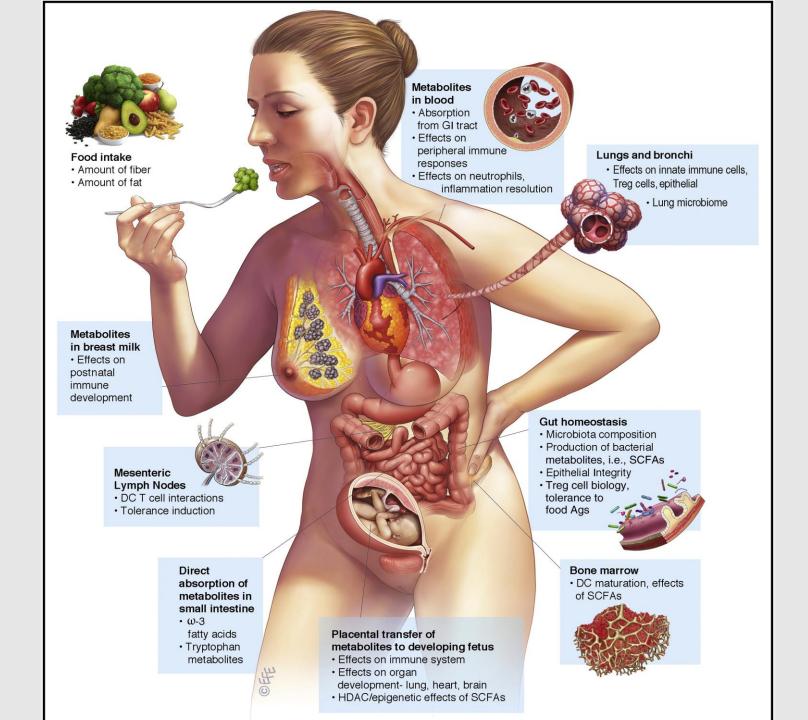
Butyric acid (butyrate)

Immune Dysregulation

Low Fiber → Low SCFAs → Chronic Diseases



Systemic Effects of SCFA



Immunity 2014 40833-842DOI: (10.1016/j.immuni.2014.05.014)

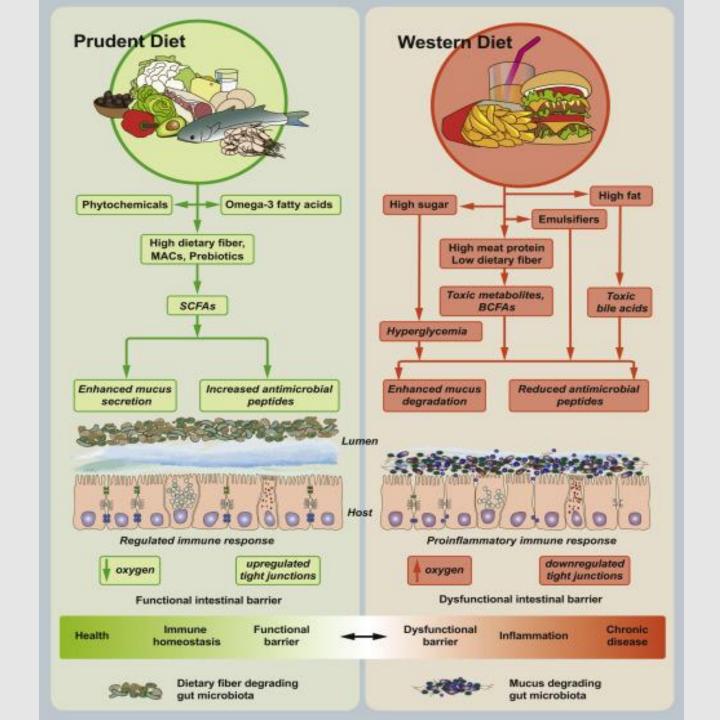
The Impact of Dietary Fiber on Gut Microbiota in Host Health and Disease

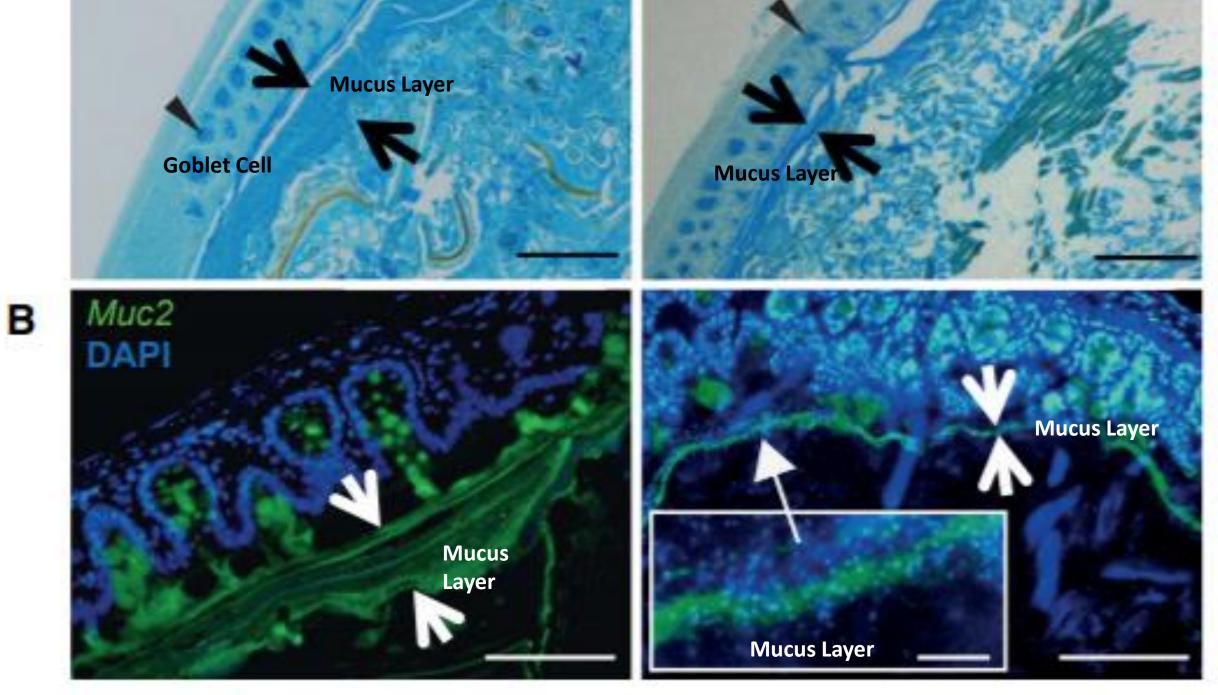
Type, quality, and origin of our food shape our gut microbes and affect their composition and function, impacting host-microbe interactions.

- 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 167, 1339–1353, November 17, 2016

Brain-Gut-Microbiome (BGM) bidirectional communication system:

- Neuroendocrine
- Neuronal
- Immune

Diet

- Modulates the microbiome
- Modulates structure and function of the brain through these communication channels

Preclinical and Clinical Studies focusing on dietary habits of psychiatric and neurologic disorders

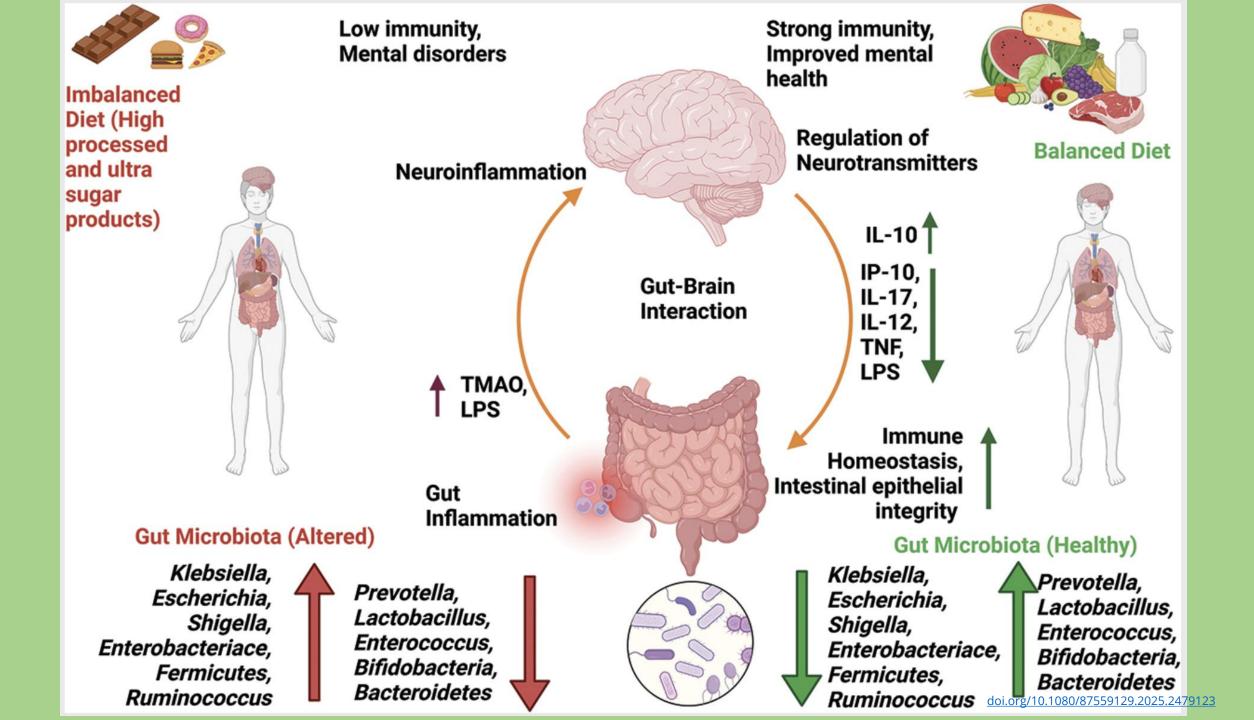
Depression -Anxiety

• Cognitive decline, dementia -Eating disorders

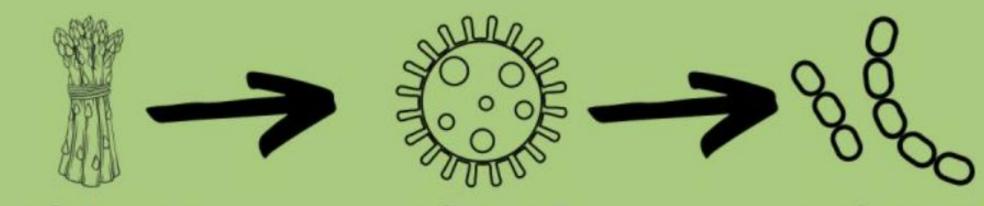
Parkinson's Disease -ADHD

- Autism Spectrum Disorder
- Epilepsy

Clinical studies have demonstrated that the diet induced anti-inflammatory effects mediated by microbial metabolites from dietary fiber and polyphenols have an impact on brain health, structure, and function.



Increase microbiome diversity and abundance by consuming greater than 30 different plants per week



prebiotics

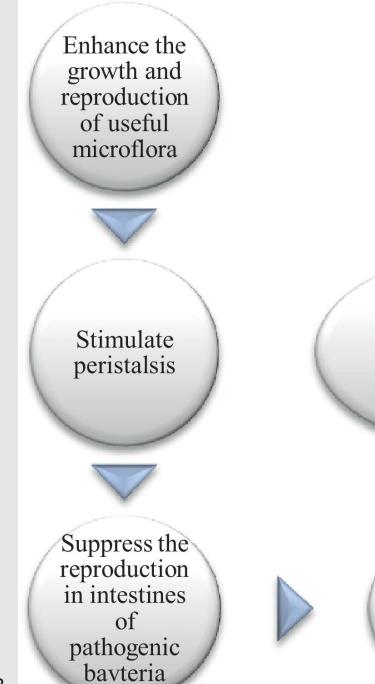
Fibers that feed good bacteria

probiotics

Live beneficial bacteria in your gut postbiotics

Metabolites produced by good bacteria

Functions of Prebiotics



Stimulate local immunity

PREBIOTIC

FUNCTIONS

Reduce the

formation of

toxic

chemicals and

gases



Maintain an optimal pH in the intestine



Remove exces of the mucus from the walls of small intestine



Improve the work of digestive system

Future Foods
Volume 4, December 2021, 100043

ProbioticsFact Sheet for Health Professionals

https://ods.od.nih.gov/factsheets/Probiotics-HealthProfessional/

There are currently no formal recommendations for or against the use of probiotics in healthy people. However, some expert bodies of health professionals provide guidance on the use of specific probiotic strains in people with certain health conditions. These groups also offer guidance for clinicians and consumers on choosing probiotic products.

<u>U.S. Department of Health & Human Services</u>
National Institutes of Health
Division of Program Coordination, Planning, and Strategic Initiatives

