



The Hidden Trifecta: Unraveling the Brain-Gut-Vagina Axis and Its Impact on Women's Health

Betsy Greenleaf, DO, FACOOG, FACOG,
MBA



The Hidden Trifecta The Gut Brain Vagina Connection

Dr. Betsy Greenleaf

DO, FACOOG(Distinguished), FACOG, FPMRS, MBA

V-A-G-I-N-A

- 65 % of Women Are Uncomfortable Saying the Word **VAGINA**
- Only 25% of Healthcare are bringing up pelvic and sexual health topics with their patients



Adobe Stock
Image 2023

<https://eveappeal.org.uk/wp-content/uploads/2016/07/The-Eve-Appeal-Vagina-Dialogues.pdf>

Simon JA, Kokot-Kierepa M, Goldstein J, Nappi RE. Vaginal health in the United States: results from the Vaginal Health: Insights, Views & Attitudes survey. Menopause. 2013 Oct;20(10):1043-8. doi: 10.1097/GME.0b013e318287342d. PMID: 23571518.

Alan W. Shindel, Sharon J. Parish,
CME Information: Sexuality Education in North American Medical Schools: Current Status and Future Directions (CME),
The Journal of Sexual Medicine, Volume 10, Issue 1, 2013, Pages 3-18, <https://doi.org/10.1111/j.1743-6109.2012.02987.x>.
(<https://www.sciencedirect.com/science/article/pii/S1743609515301259>)



83% Vaginitis

<https://www.uptodate.com/contents/approach-to-females-with-symptoms-of-vaginitis>

63% Sexual Dysfunction

<https://jamanetwork.com/journals/jama/fullarticle/188762#>

60% Urinary Tract Infections

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6502976/>

43.4% Pelvic Pain

<https://bmcpublikealth.biomedcentral.com/articles/10.1186/1471-2458-6-177>

19.1% Infertility

<https://www.cdc.gov/nchs/fastats/infertility.htm>



Affects more than just individuals



Families



Relationships



Work Performance





Debra



CHRONIC DISEASES IN AMERICA

6 IN 10

Adults in the US
have a chronic disease



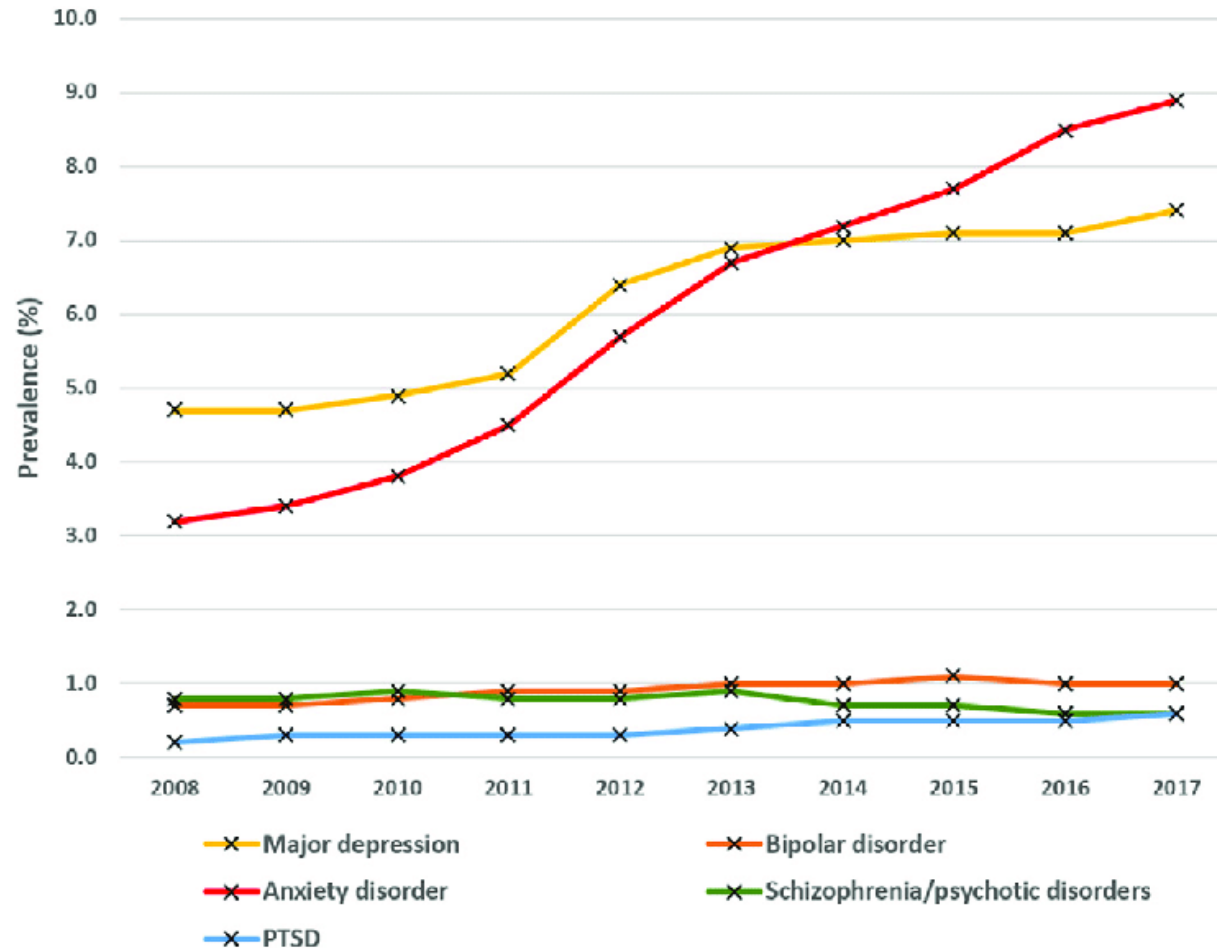
4 IN 10

Adults in the US
have two or more

THE LEADING CAUSES OF DEATH AND DISABILITY
and Leading Drivers of the Nation's \$4.1 Trillion in Annual Health Care Costs



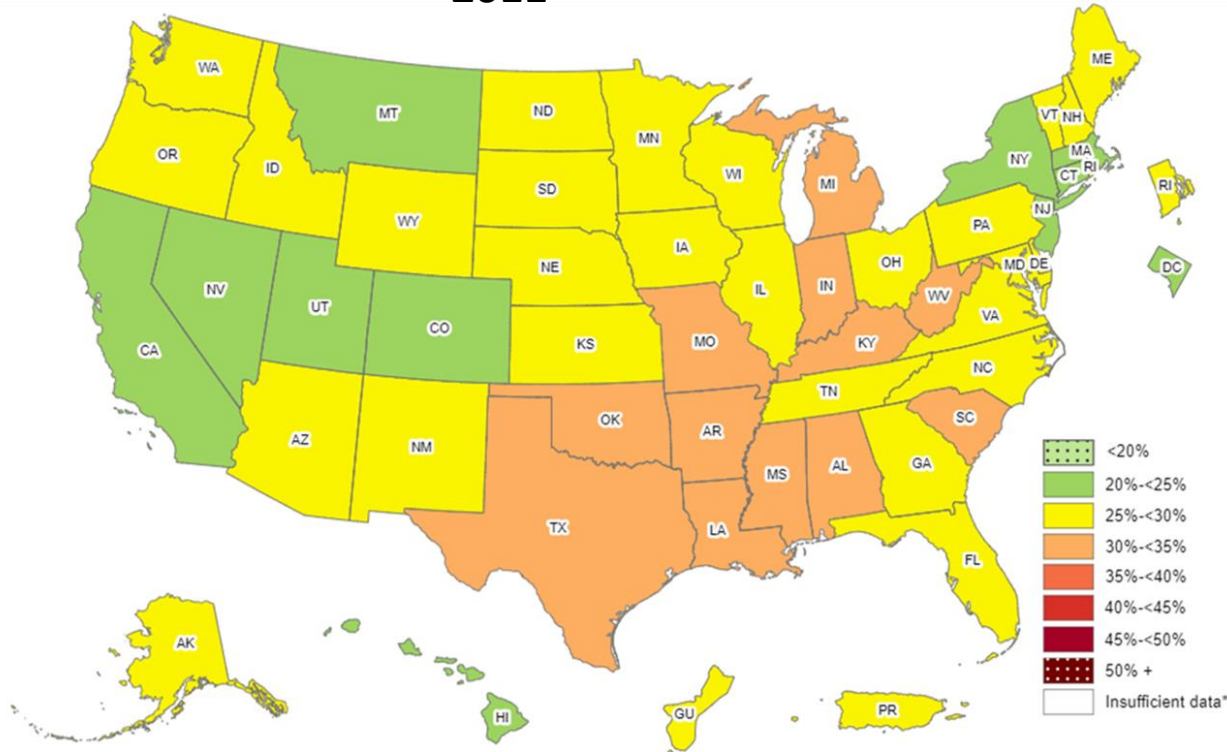
Depression and Anxiety Trending Up



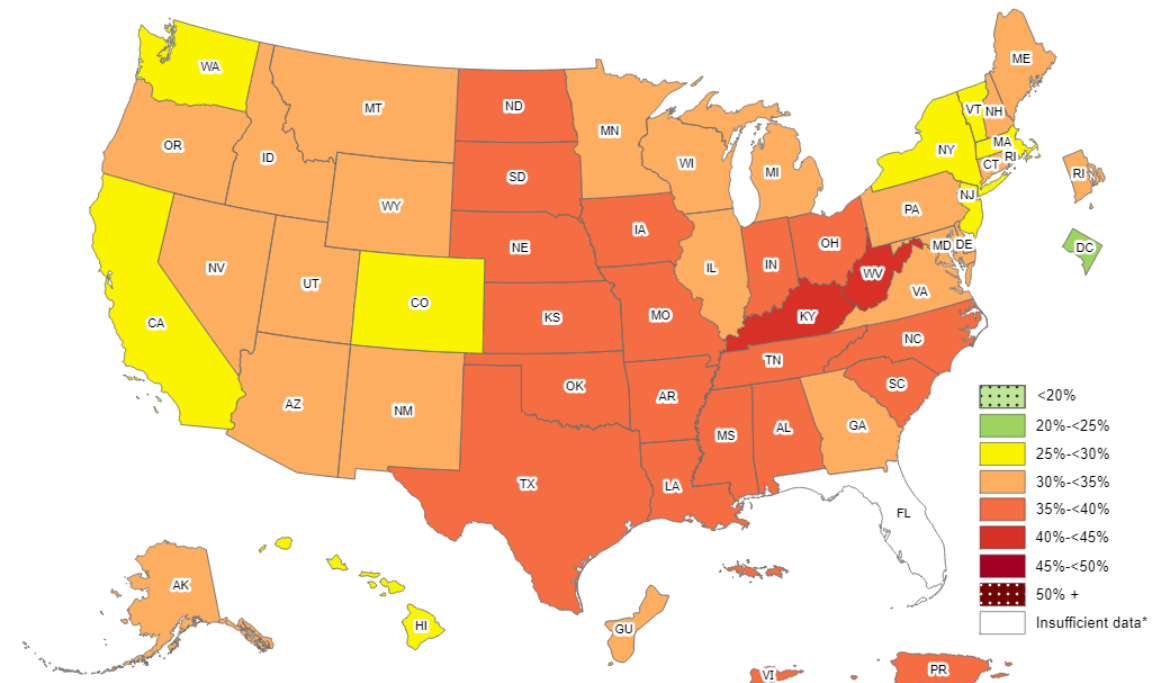
Adobe Stock Image

Rates of Obesity Have Increased

2011



2022



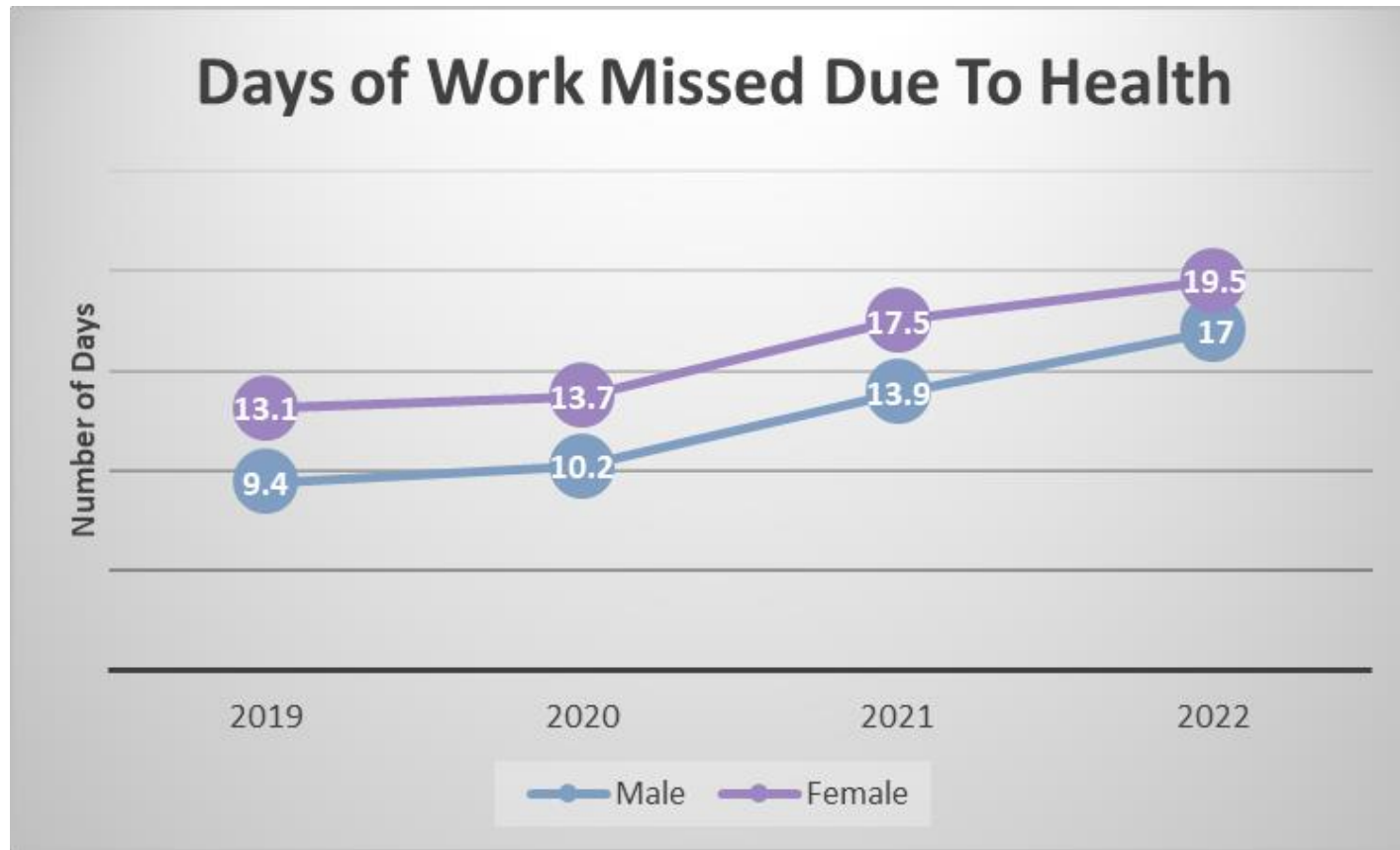


Women are going to the doctor but are they getting the answers they deserve?

📄 Percentage of having a doctor visit for any reason in the past 12 months for adults aged 18 and over, United States, 2019—2022

Year	Male	Female
2019	79.8	89.6
2020	78.9	87.5
2021	77.5	86.8
2022	78.8	87.7

Women are missing more work.....





Limitation in Women's Healthcare

- 1. Lack of Awareness:** Many healthcare professionals are not fully informed about conditions like endometriosis, pelvic inflammatory disease (PID), interstitial cystitis, and other pelvic health issues. This can lead to misdiagnoses or dismissal of symptoms.
- 2. Stigma** women's health complaints, especially around menstruation and pelvic pain. Women are sometimes told or believe their pain is "all in their head" or that it's "normal."
- 3. Overlapping Symptoms:** Many pelvic health problems can present with similar symptoms, making it difficult to differentiate one from another without specialized knowledge or diagnostic tests.
- 4. Limited Access:** Not all women have access to specialists, such as gynecologists or pelvic pain specialists, who might recognize their condition more readily.
- 5. Diagnostic Limitations:** Testing guidelines, accessibility, and insurance coverage do not match developing technology
- 6. Patient Advocacy:** Some women may not feel empowered to advocate for themselves or might not know the right questions to ask, which can delay obtaining the right diagnosis and treatment.



Adobe Stock
Image 2023

Womens' Health Testing is Stuck in the 1950's

- Pap Smear: Discovered 1916 not widely available until 1955
- Wet Mount: 1609 First Compound Microscope. Wet mount is still continued "gold standard" for women's health
- Ultrasound in Women's Health 1958 and still the staple of women's health.

Tan SY, Tatsumoto Y. George Papanicolaou (1883-1962): Discoverer of the Pap smear. Singapore Med J. 2015 Oct;58(10):586-7. doi: 10.1155/2015/586. PMID: 26512155. PMCID: PMC4613836.

Swales AL, Holster JL, Robinson JP. Pathway to the Papanicolaou smear: The development of cervical cytology in twentieth-century America and implications in the present day. Survey of Obstet. 2019 Oct;150(1):6-7. doi: 10.1016/j.ygyno.2019.04.004. Epub 2019 Apr 15. PMID: 30995961.

<https://www.cornell.edu/resources/1692-history-microscopy-timeline>

<https://www.cornell.edu/innovation/a-brief-history-of-the-sonogram-180978732/>



Since the dawn of Penicillin, we keep reaching for another pill for answers



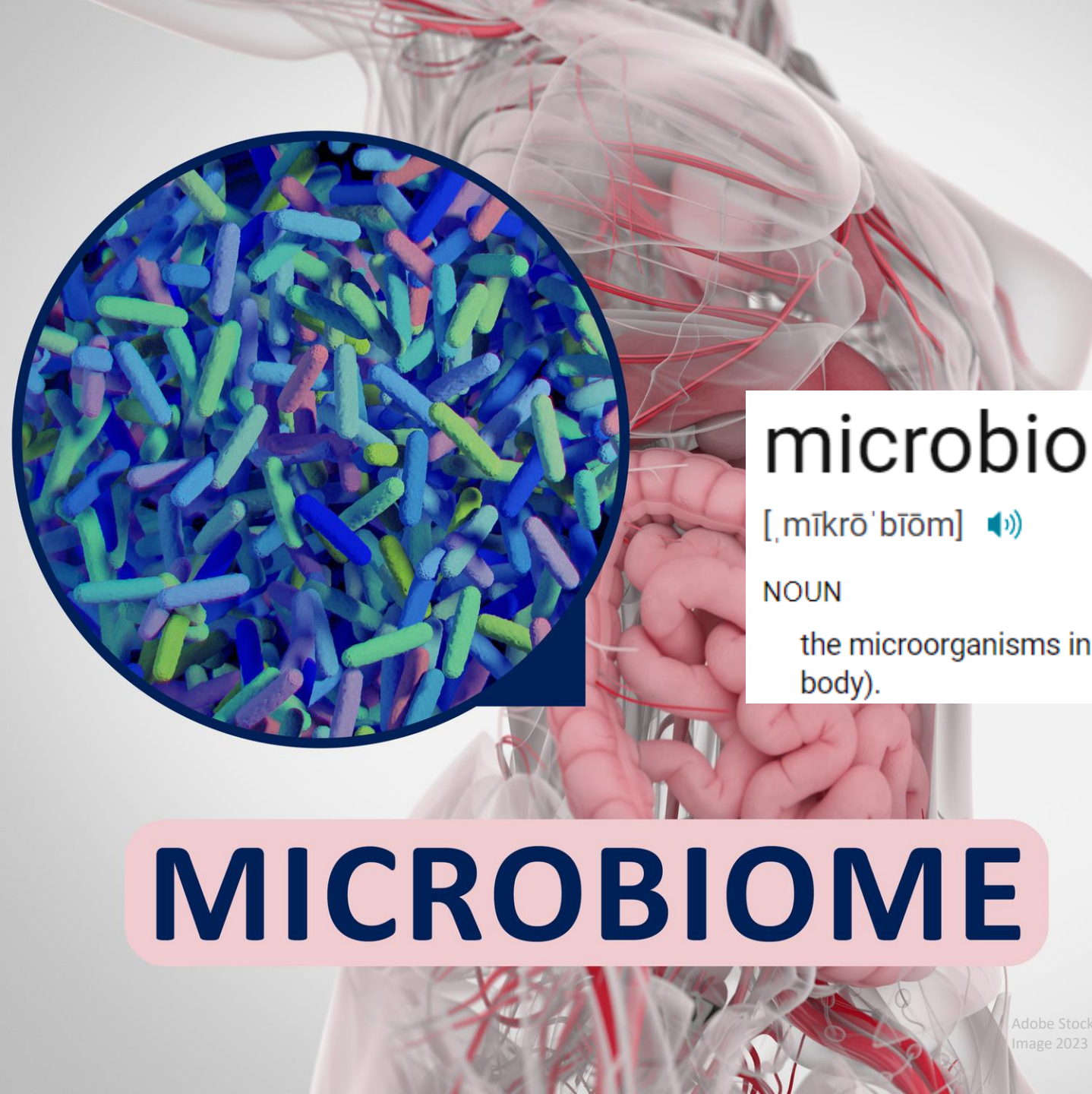
We are looking at the leaves, directing all our treatments at the top of the tree.....when we should be looking underground.





**There is something all of these
cases have in common**





microbiome

[ˌmɪkrōˈbɪəm] 🔊

NOUN

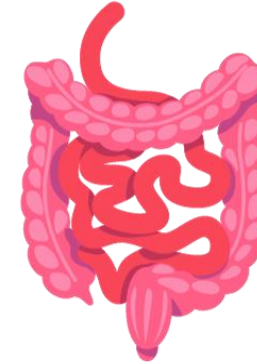
the microorganisms in a particular environment (including the body or a part of the body).

MICROBIOME

Function Composition Immunity



Gut Brain Axis



Mood Neurotransmitters Behaviour

Function Composition Immunity



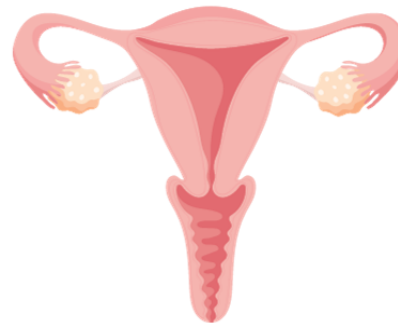
Gut Brain Axis

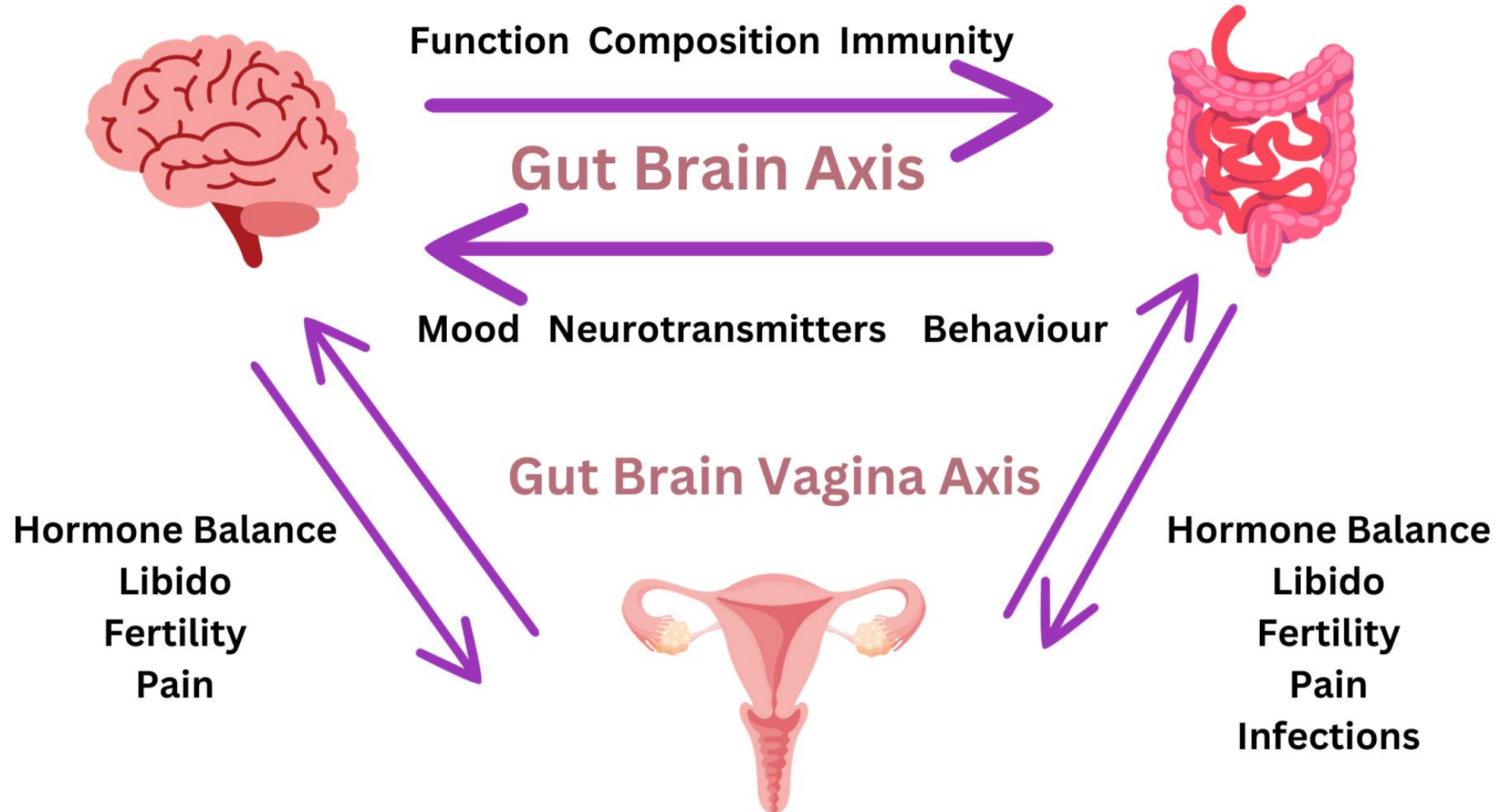


Mood Neurotransmitters Behaviour

Gut Brain Vagina Axis

Hormone Balance
Libido
Fertility
Pain



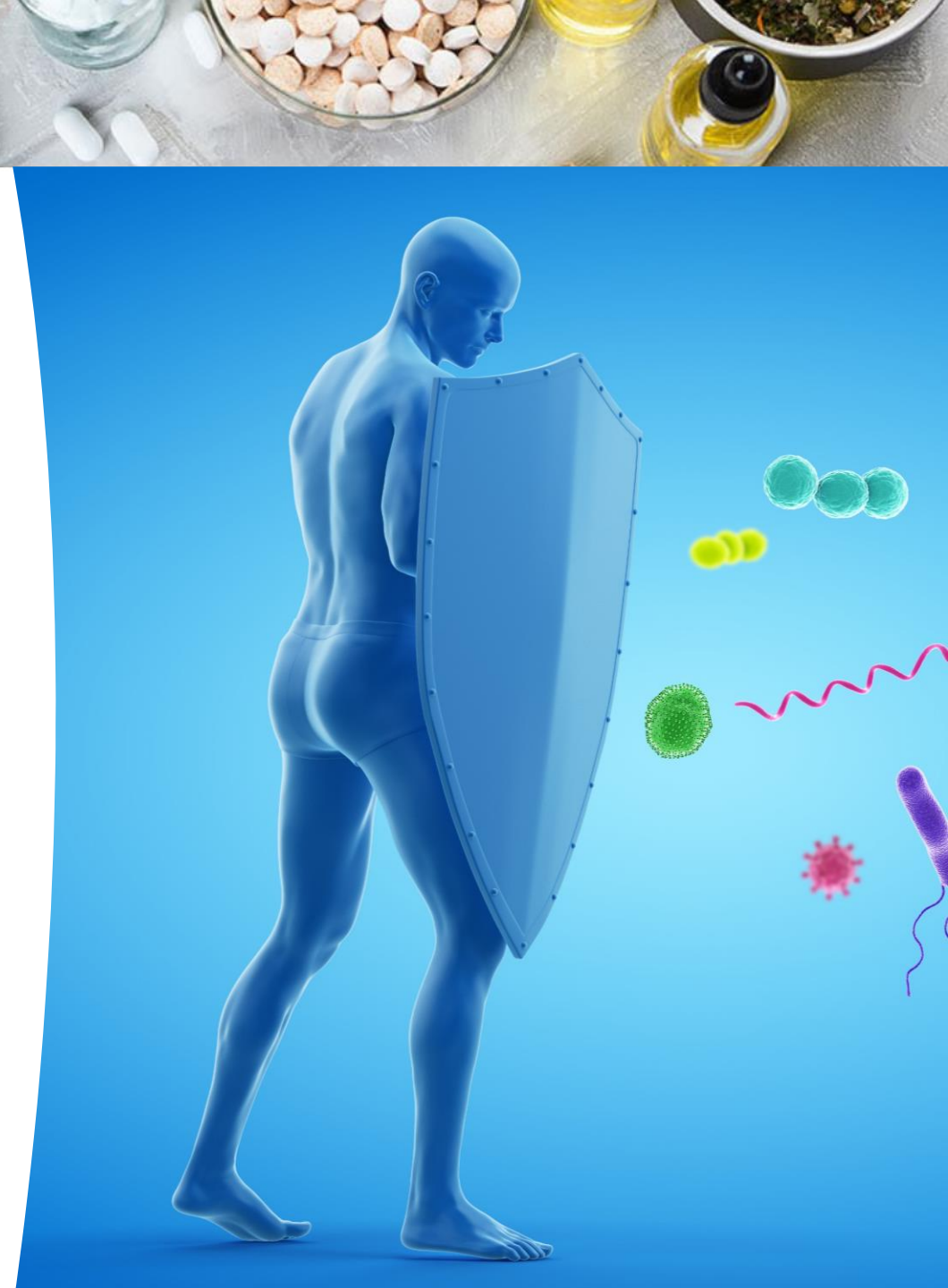


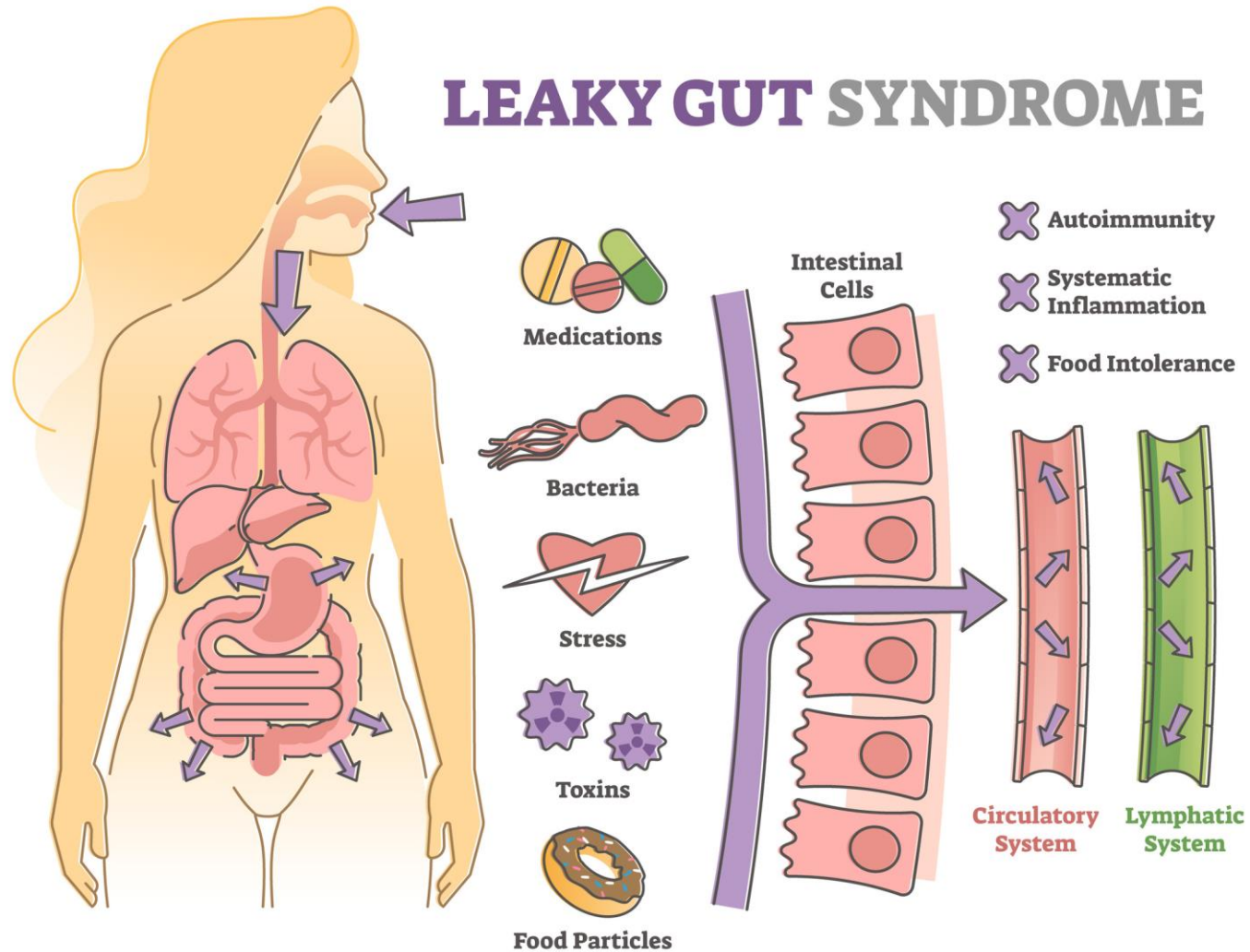
Neurotransmitters Made In The Gut

- Serotonin: Regulates mood, appetite, and sleep. It is estimated that 90% of the body's serotonin is produced in the gut.
- GABA (gamma-aminobutyric acid): regulates anxiety and helps to promote relaxation.
- Acetylcholine: regulation movement, depression, anxiety, memory and learning
- Substance P: pain sensation and inflammation.
- Dopamine: regulates movement, motivation, and reward.

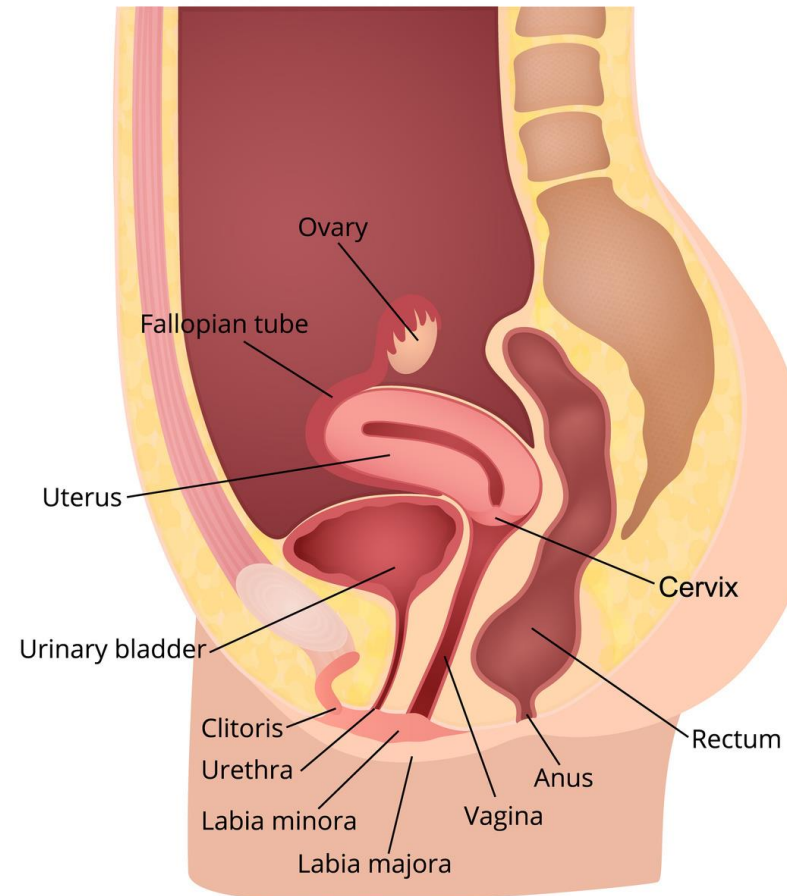
Immune System Made in the Gut

90% of Secretory IG A is made in the gut
T helper cells are activated in the gut
and bile and bacteria are considered
activating factors





FEMALE REPRODUCTIVE SYSTEM





Parasympathetic & Sympathetic

Parasympathetic



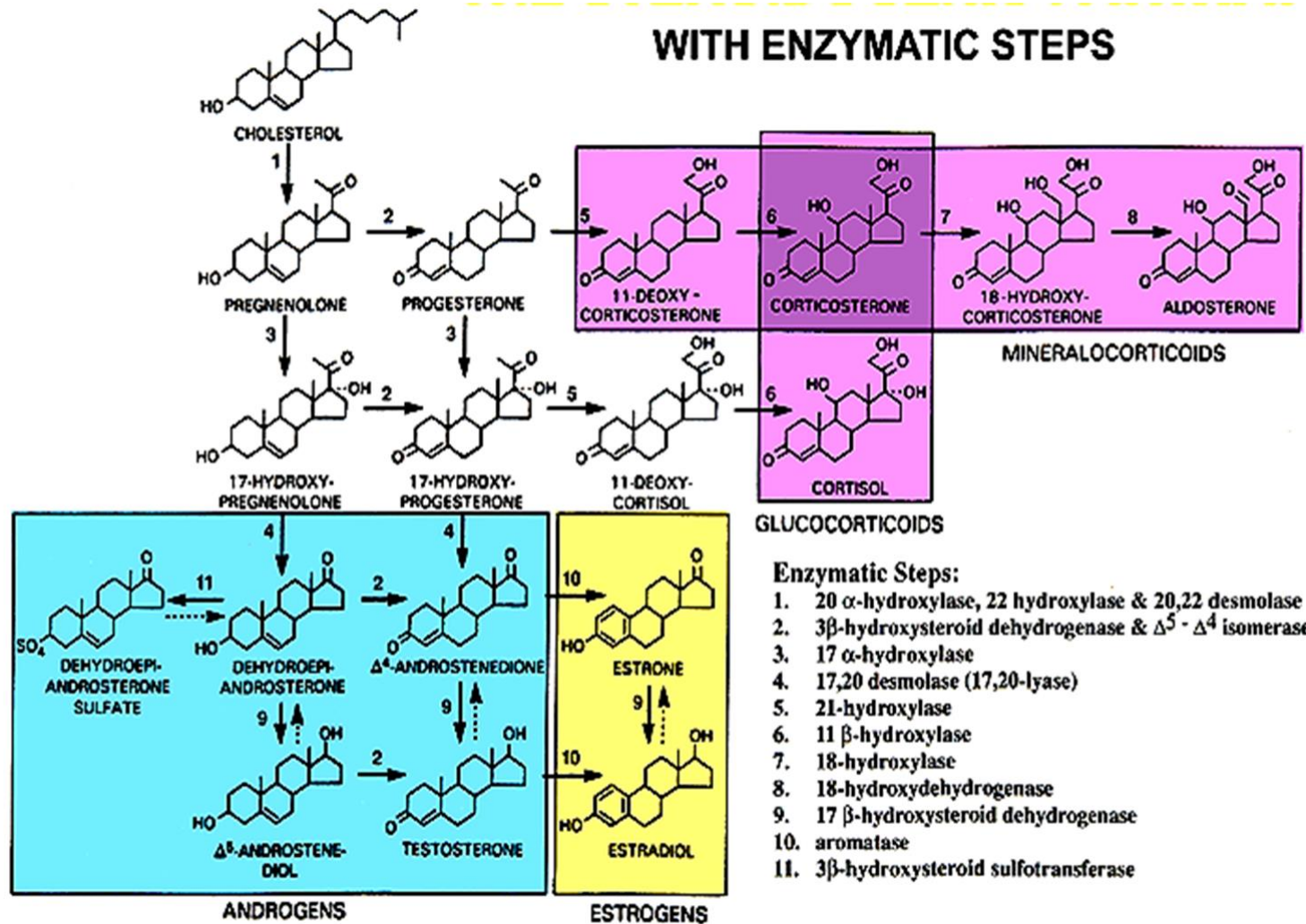
Sympathetic



Stress



WITH ENZYMATIC STEPS



Hormone Cascade



Toni & Terry

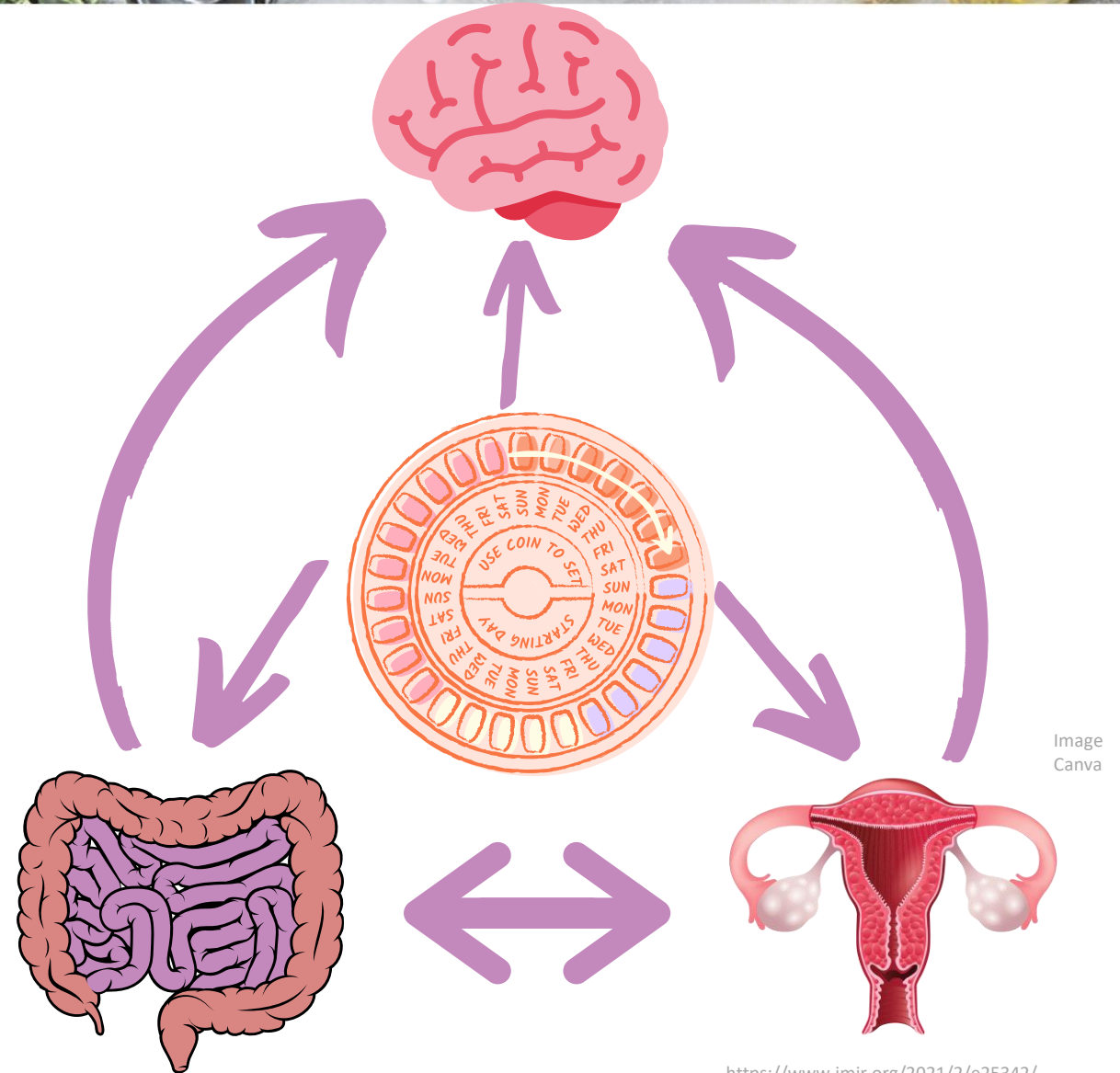


Toni & Terry

- Birth control for 10 years prior

Toni & Terry

- Birth control for 10 years prior





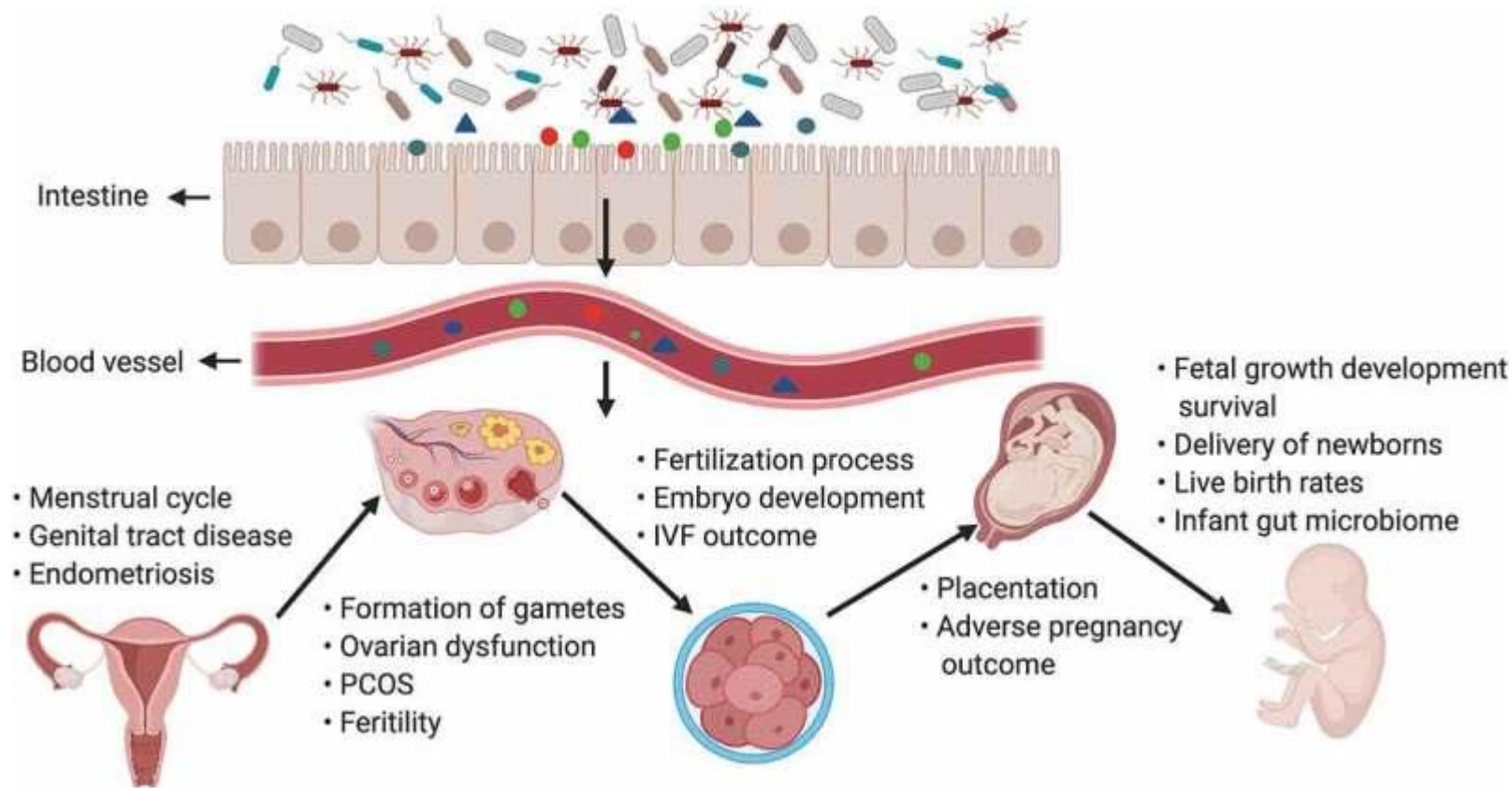
Vaginal Microbiome Affects Fertility

- Pregnancy Rates
- Success of IVF
- Pregnancy Outcomes
- Risk of Adverse Pregnancy Events



Adobe Stock Image

Gut Microbiome's Effect on Reproductive Health





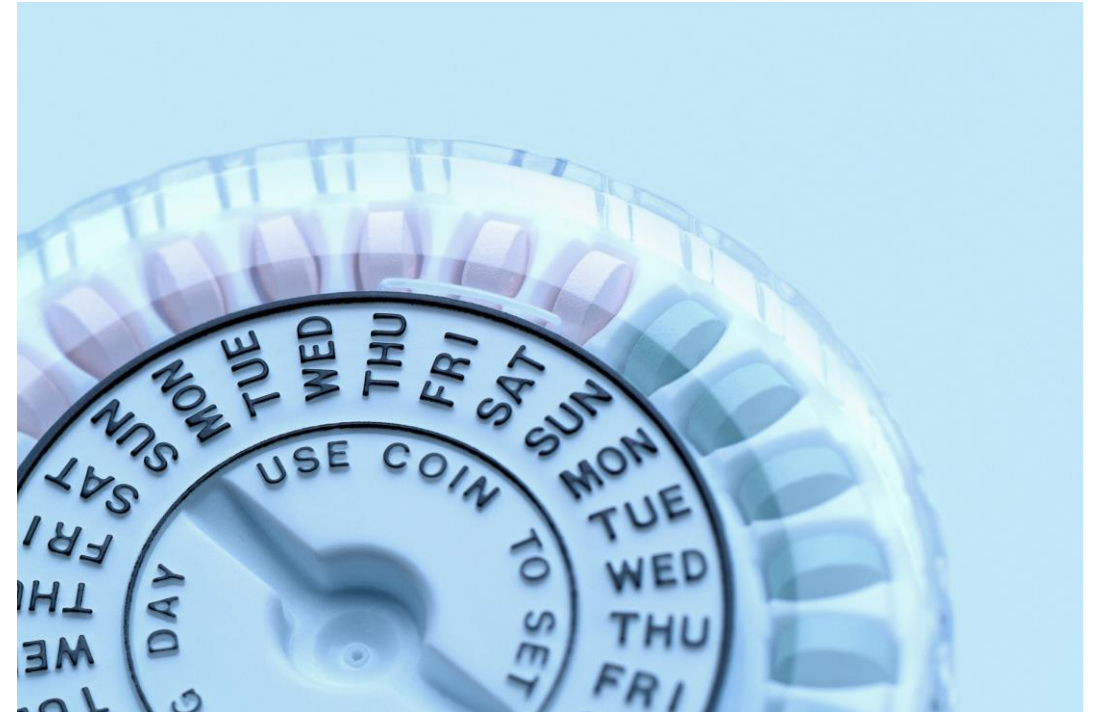
Oral Contraceptives Affect the Microbial Balance of the Vagina

Strain	Cultural characters	Identified Microorganisms	Total percentage (%)in various age groups	
			20–30 years	31–40 years
1	Oval budding cells	<i>Candida</i> sp.	10 (1 +)	24 (3+)
2	G + cocci	<i>Staphylococcus saprophyticus</i> .	18 (2 +)	13 (1+)
3	G + cocci in chains	<i>Streptococcus agalactiae</i>	23 (3 +)	11 (1 +)
4	G- coccobacilli	<i>E. coli</i>	28 (4+)	24 (3 +)
5	G + long filamentous rods	<i>Lactobacillus fermentum</i>	32 (2 +)	28 (4 +)

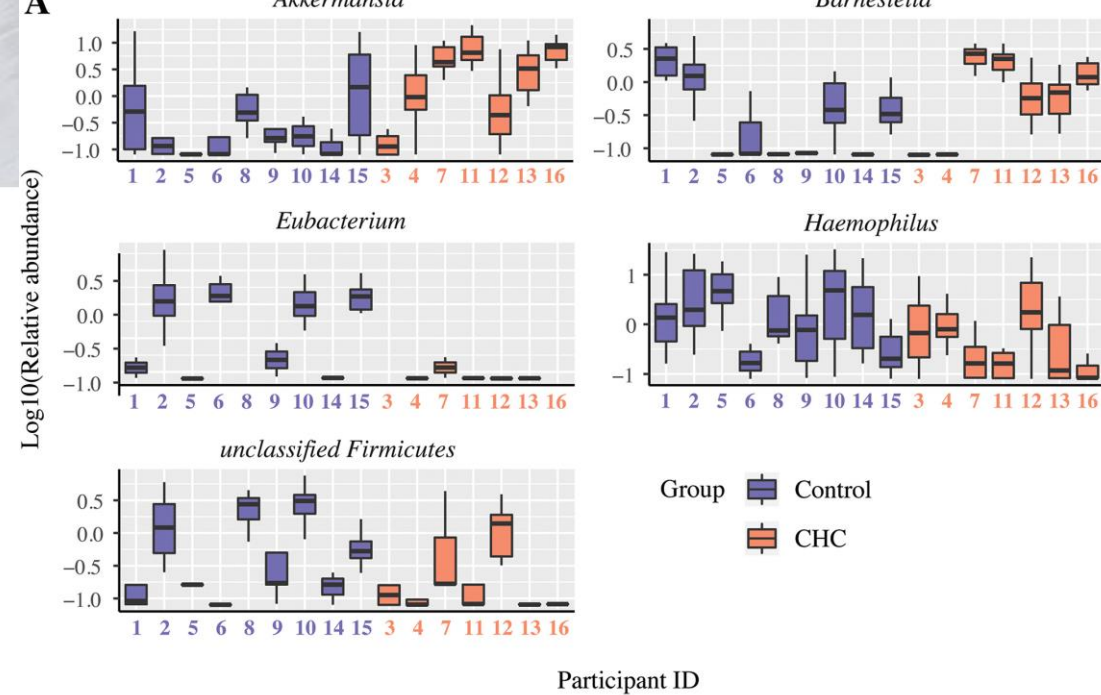


Micronutrient Malabsorption in Women on Oral Birth Control

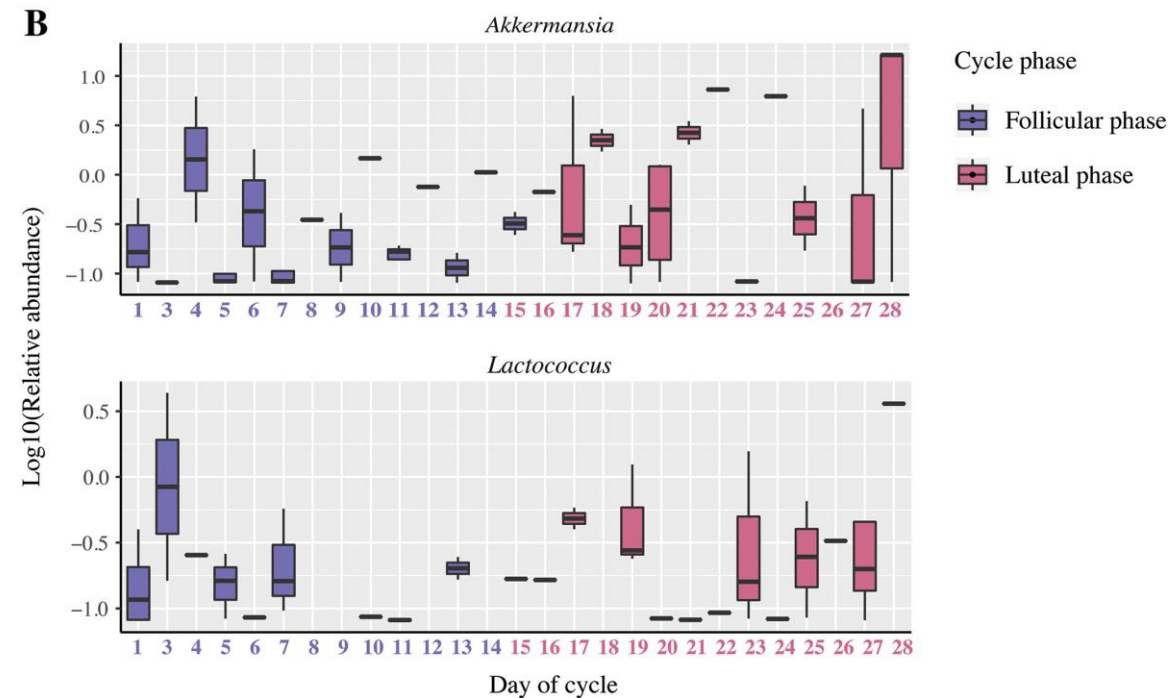
- Folic acid
- Vitamins B2
- B6
- B12
- Vitamin C
- Vitamin E
- Magnesium
- Selenium
- Zinc.



Adobe Stock



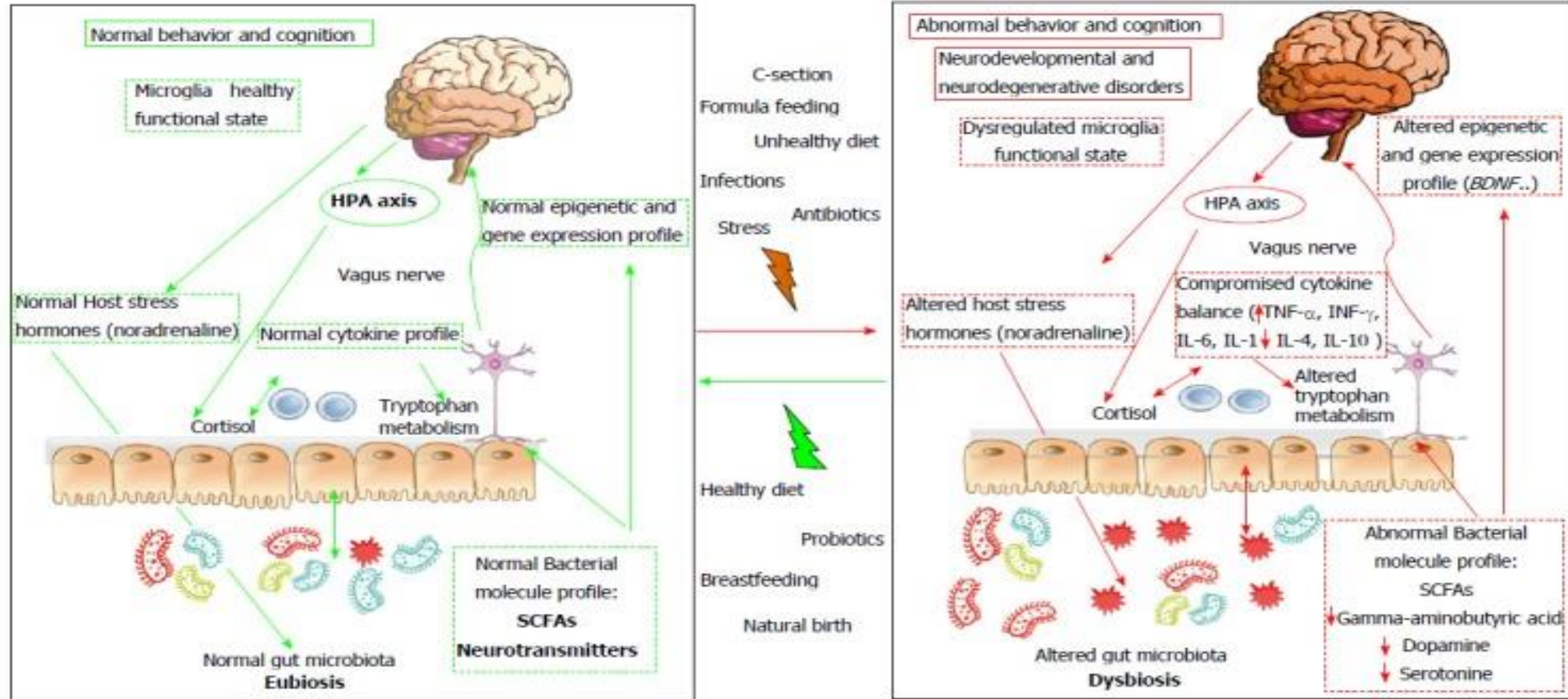
Oral Contraceptives Alter the Gut Microbiome



Sarah Kheloui, Andra Smith, Nafissa Ismail, Combined oral contraceptives and mental health: Are adolescence and the gut-brain axis the missing links?, *Frontiers in Neuroendocrinology*, Volume 68, 2023, 101041, ISSN 0091-3022, <https://doi.org/10.1016/j.yfrne.2022.101041>. (<https://www.sciencedirect.com/science/article/pii/S0091302222000644>)

• Mihajlovic, M. Leutner, B. Hausmann, G. Kohl, J. Schwarz, H. Rover, N. Stimakovits, P. Wolf, K. Maruszczak, M. Bastian, A. Kautzky-Willer, D. Berry
Combined hormonal contraceptives are associated with minor changes in composition and diversity in gut microbiota of healthy women
Environ Microbiol, 23 (6) (2021), pp. 3037-3047, [10.1111/1462-2920.15517](https://doi.org/10.1111/1462-2920.15517)

Gut Health Affects Mood





Debra

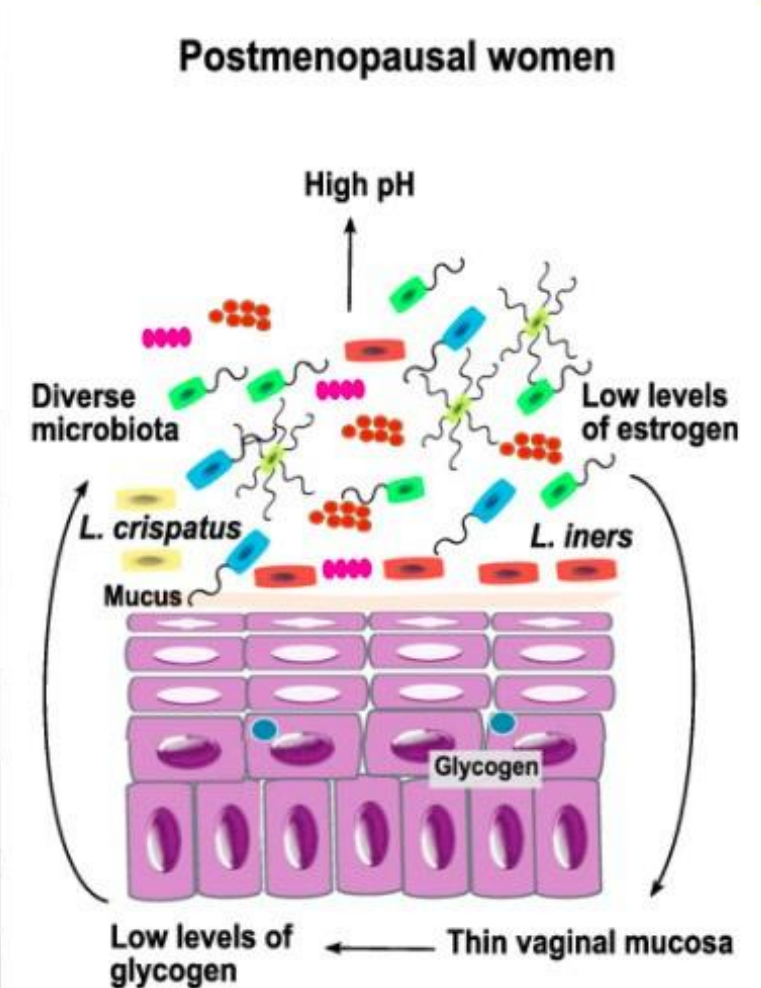
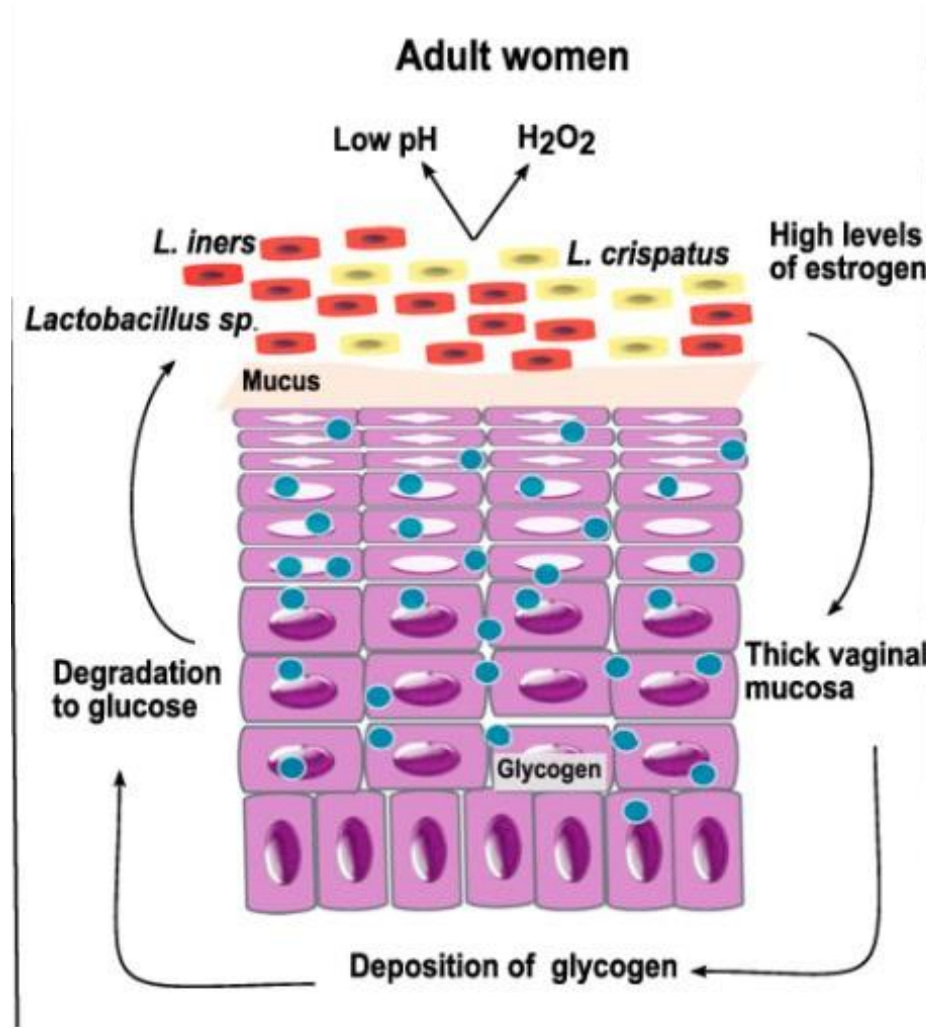


Debra

- Post Menopause
- Vaginal Dryness
- Low Libido
- History of recurrent urinary tract infections
- Weight Gain

Debra

- Post Menopause
- Vaginal Dryness
- Low Libido
- History of recurrent urinary tract infections

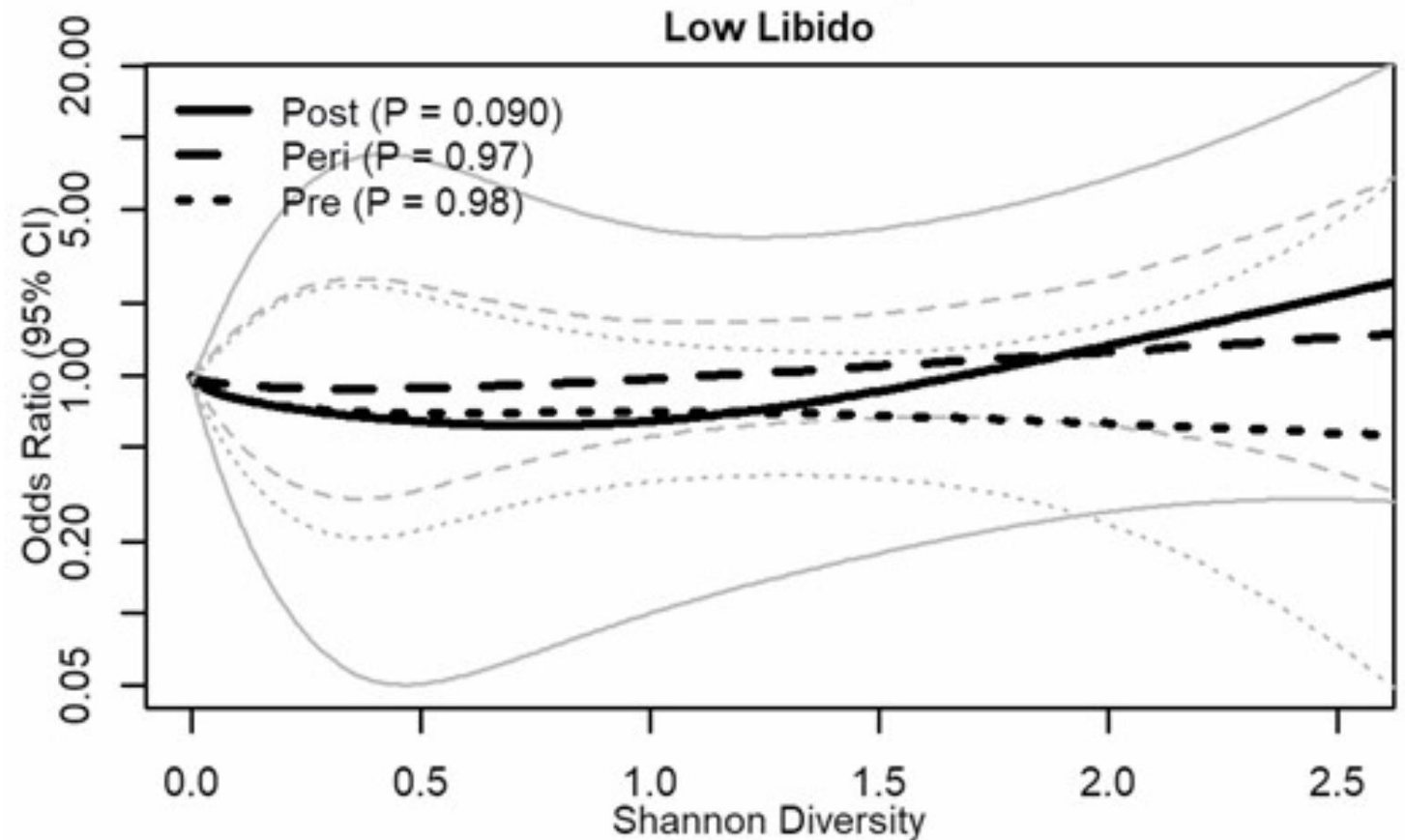


emanticscholar.org/paper/Vaginal-microbiota-and-its-role-in-HIV-transmission-Petrova-Broek/6506724483daef93919b47f618ba9bc36bf9eaed



Vaginal Microbiome and Libido

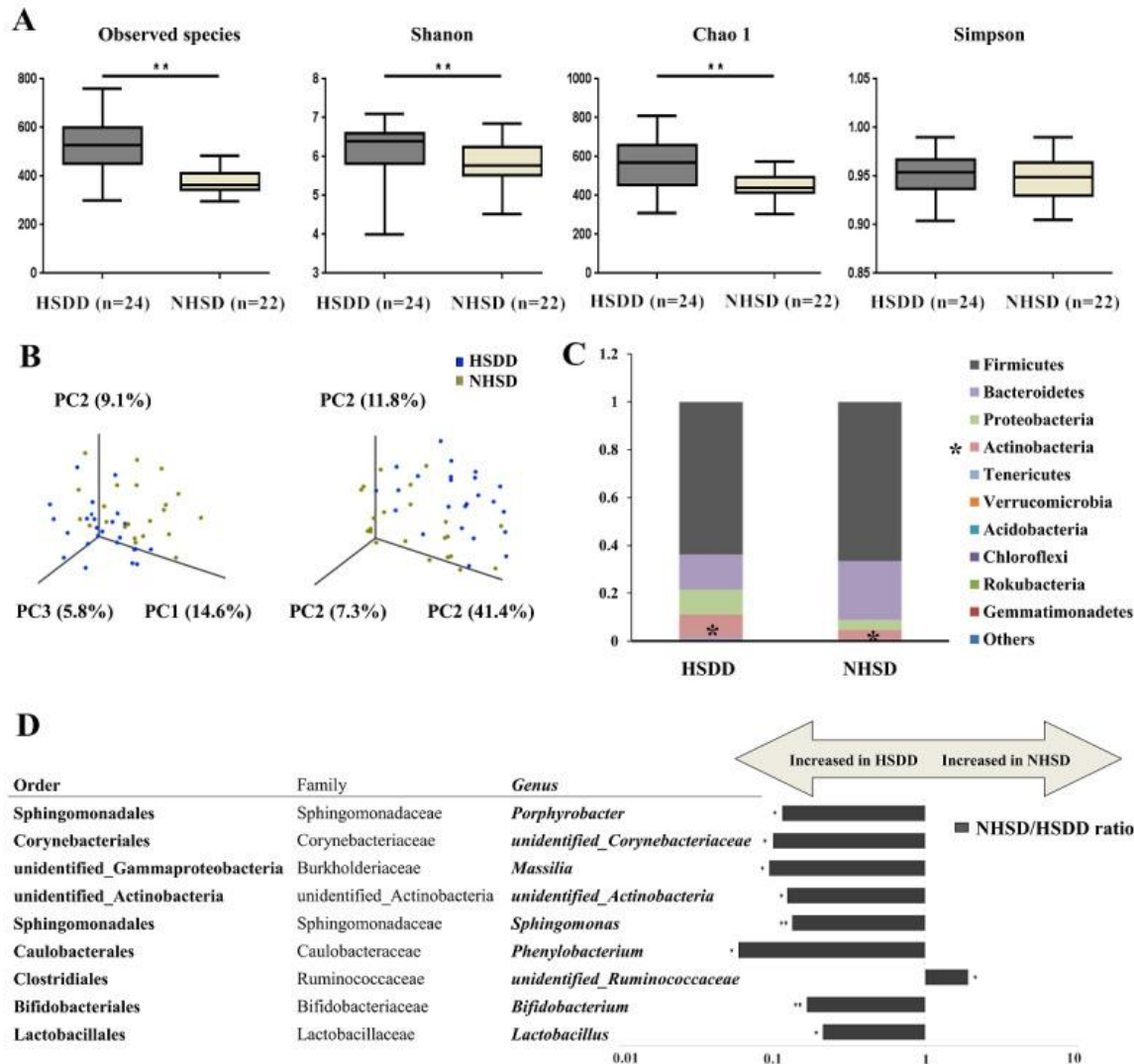
Among postmenopausal women, higher Shannon diversity was associated with lower odds of vaginal atrophy, vaginal dryness, and low libido, up to a threshold; then higher odds beyond the threshold





There are microbiome differences in the guts of women with Hypoactive Sexual Desire Disorder

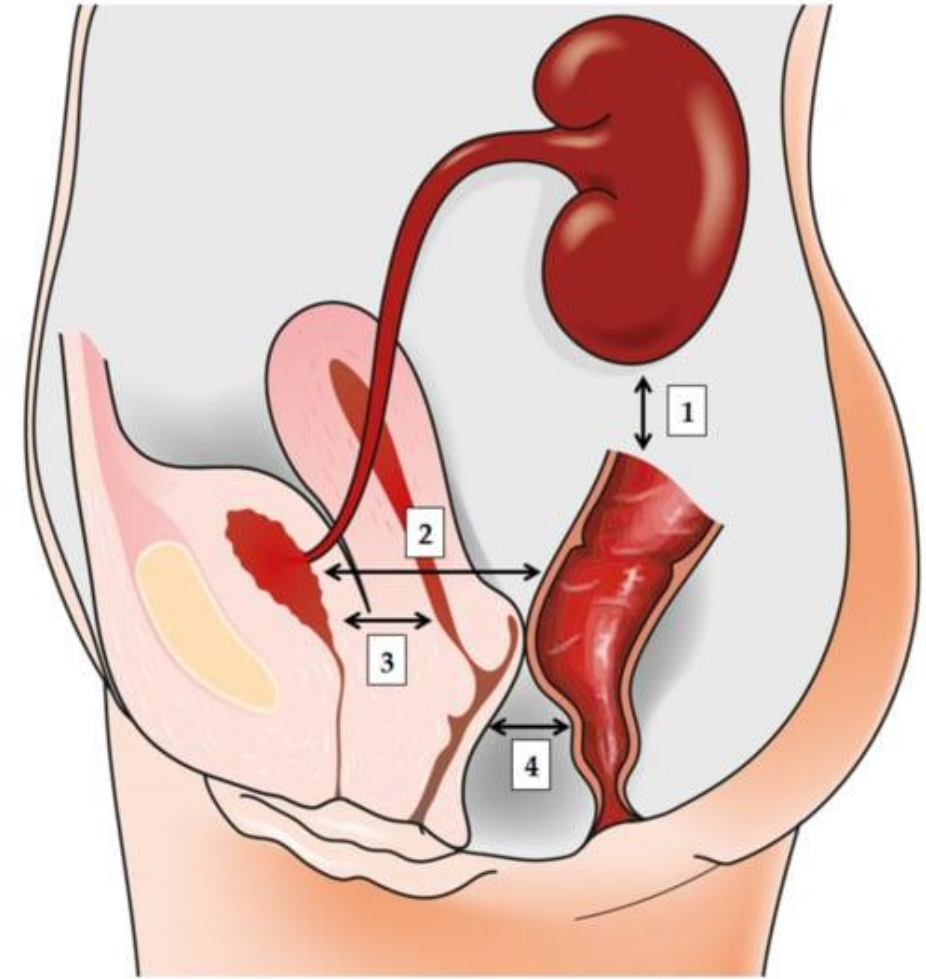
Additionally, there are gut sex differences between males and females
With menopausal women's microbiome matching more closely with men.



Due to microbiome research, we have a new understanding

of the bidirectional communication of organisms between the

- Bladder-Vagina
- Vagina-Gut
- Bladder-Gut
- Kidney-Gut



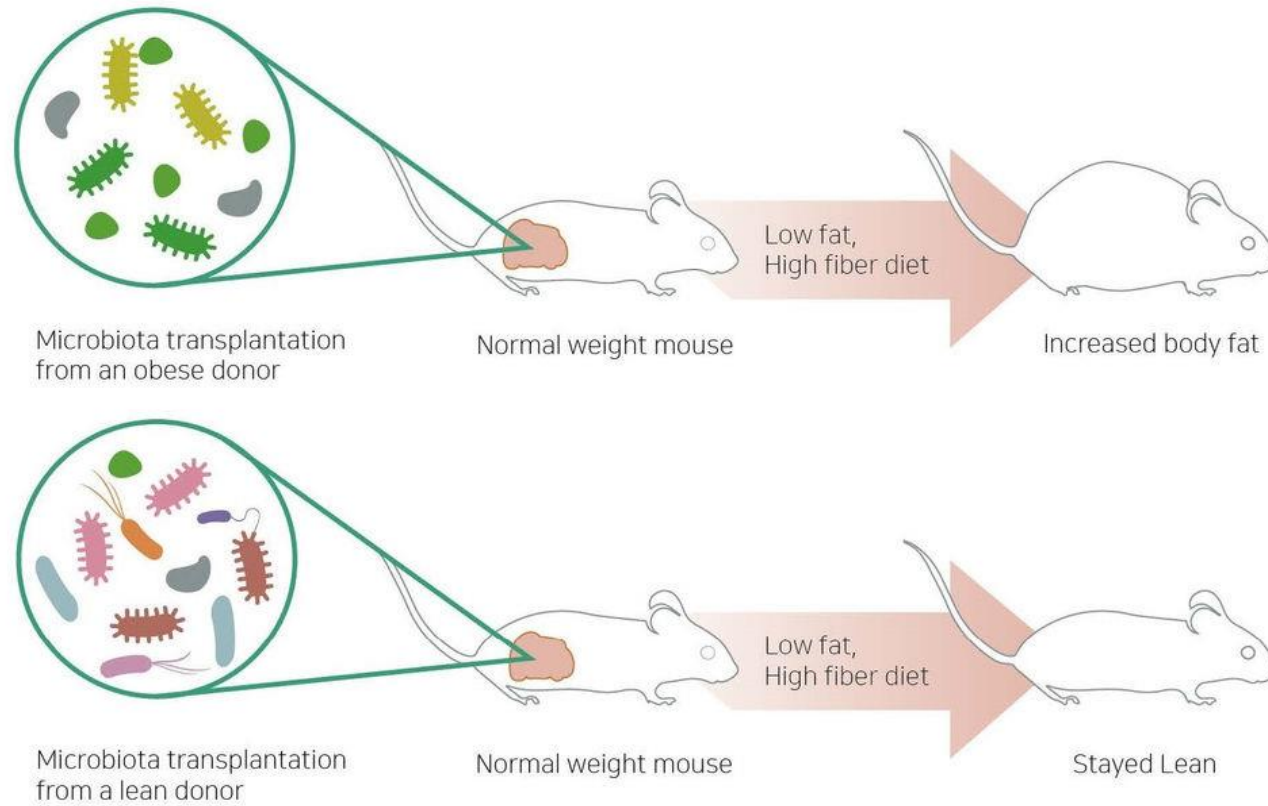


- To often we are using an atomic bomb when we need a sniper

- One course of antibiotic such as ciprofloxacin can throw off the microbiome for a full year
- Other antibiotics can kill the intended target but then promote the overgrowth of other organisms increasing the risk of sepsis



Microbiome's Impact on Obesity



Ridaura VK, Faith JJ, Rey FE, Cheng J, Duncan AE, Kau AL, Griffin NW, Lombard V, Henrissat B, Bain JR, Muehlbauer MJ, Ilkayeva O, Semenkovich CF, Funai K, Hayashi DK, Lyle BJ, Martini MC, Ursell LK, Clemente JC, Van Treuren W, Walters WA, Knight R, Newgard CB, Heath AC, Gordon JI. Gut microbiota from twins discordant for obesity modulate metabolism in mice. *Science*. 2013 Sep 6;341(6150):1241214. doi: 10.1126/science.1241214. PMID: 24009397; PMCID: PMC3829625.



Karen



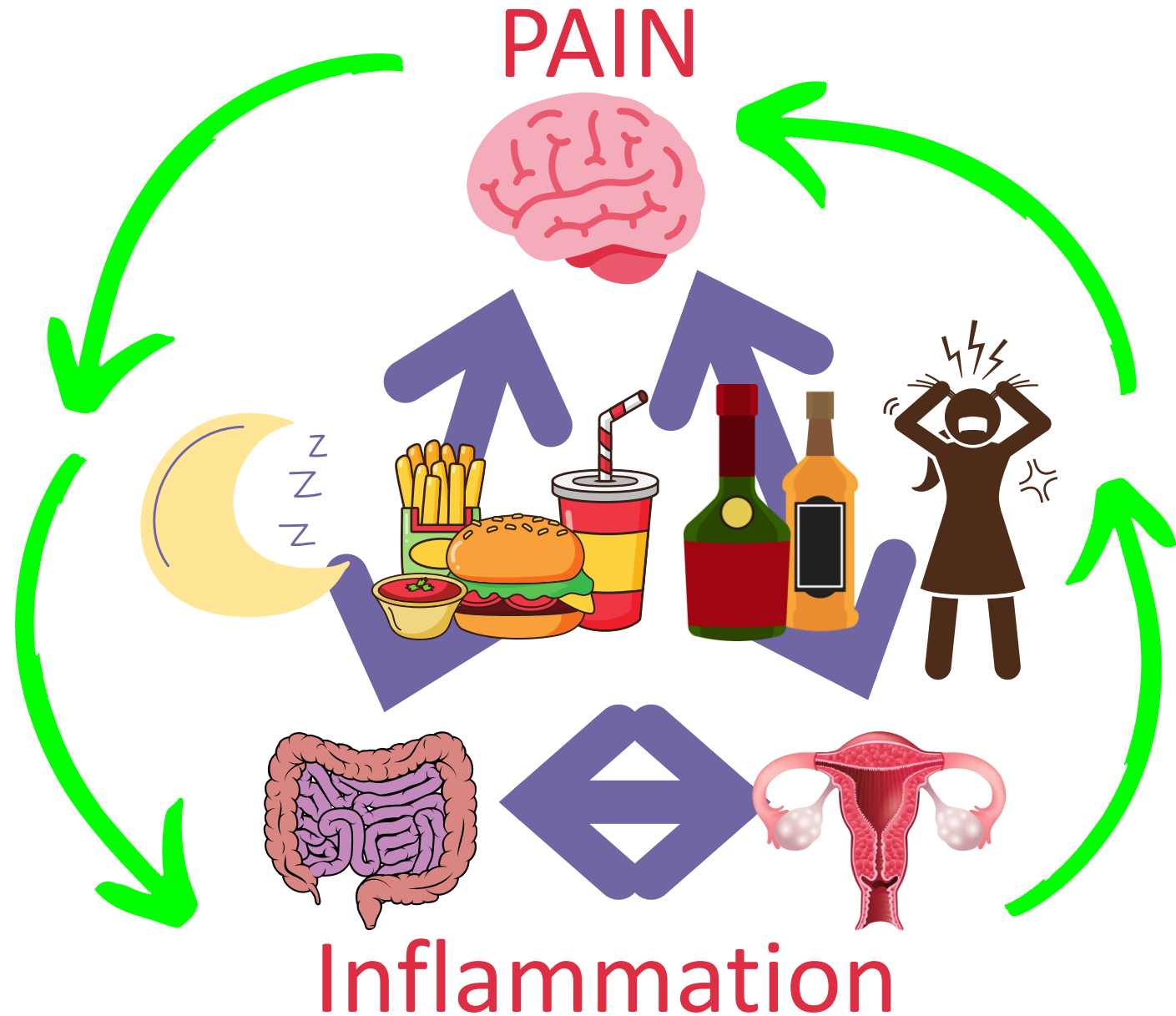


Karen

- History of Pelvic Pain
- Stress
- Lack of Sleep
- Take Out
- Alcohol
- Autoimmune
Conditions

Karen

- History of Pelvic Pain
- Stress
- Lack of Sleep
- Take Out
- Alcohol
- Autoimmune Conditions



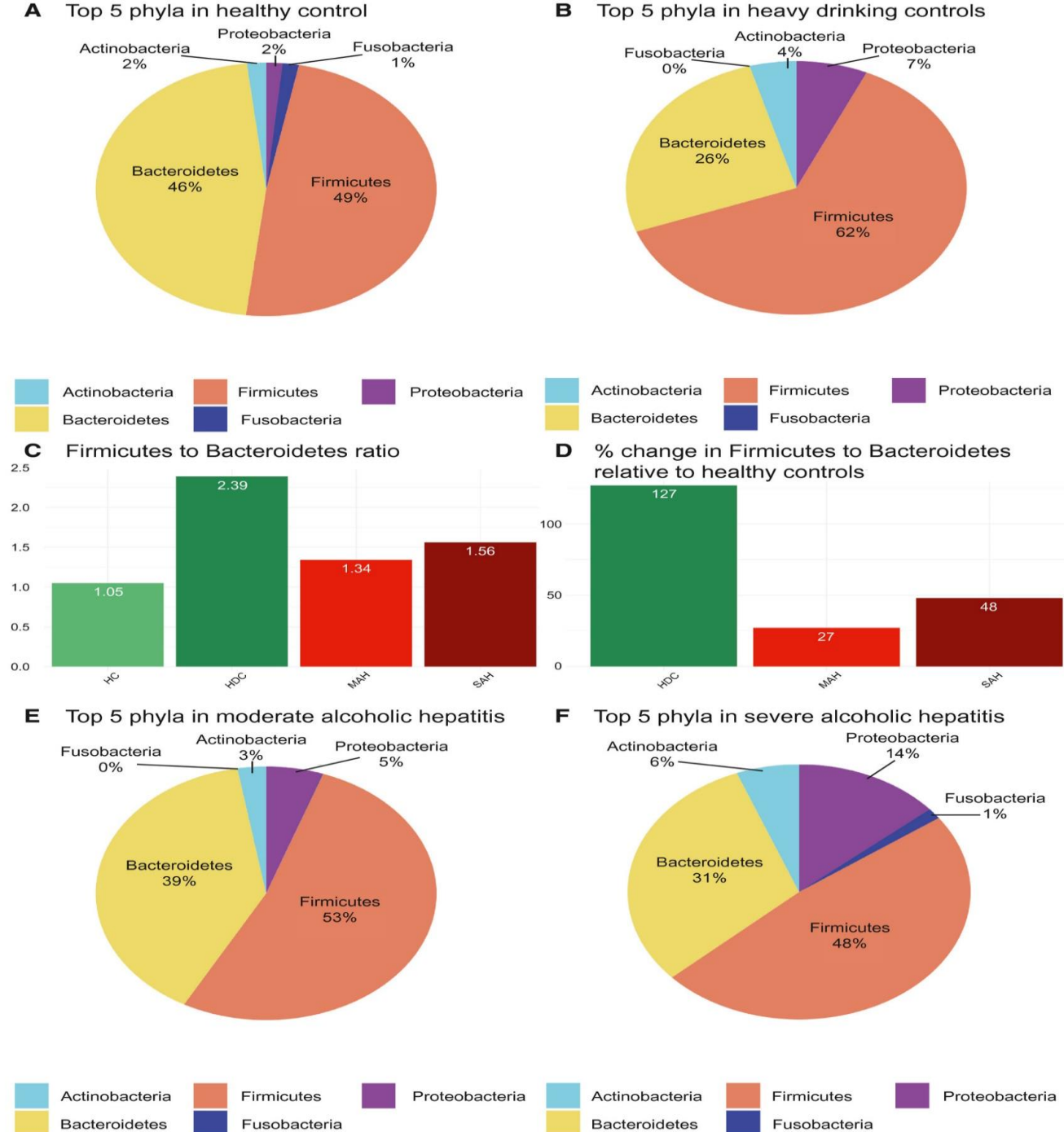
Alcohol and the Microbiome

2 billion people worldwide drink alcohol on a daily basis

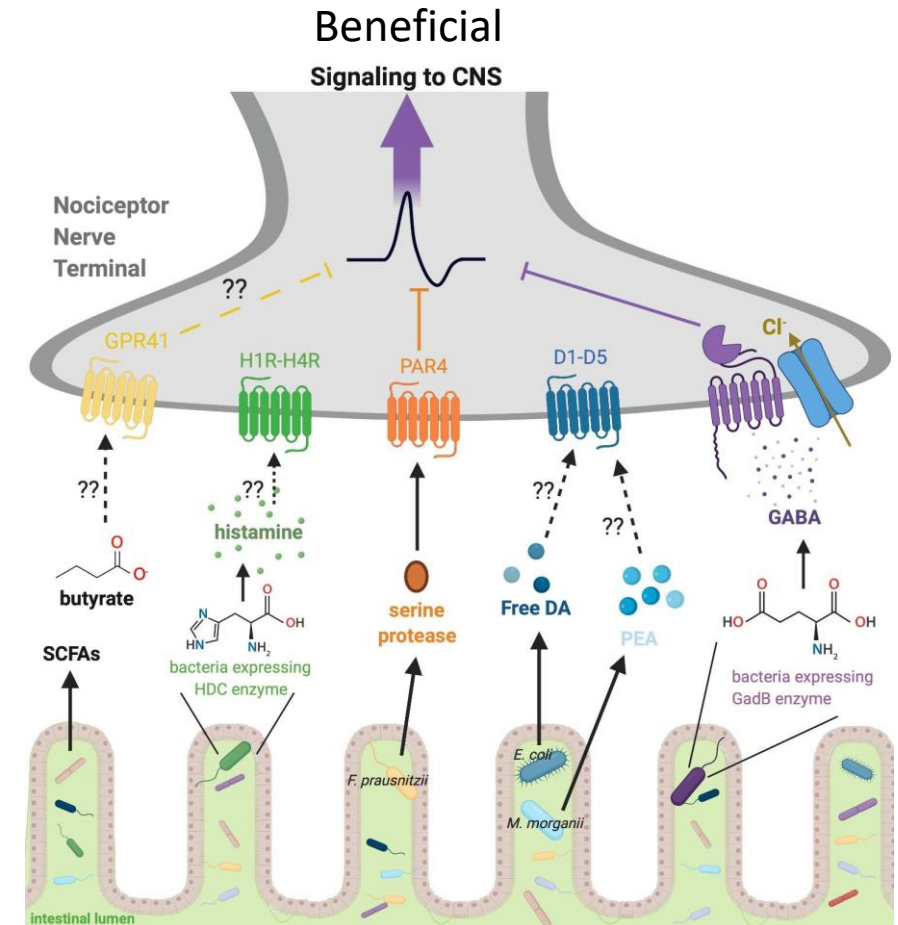
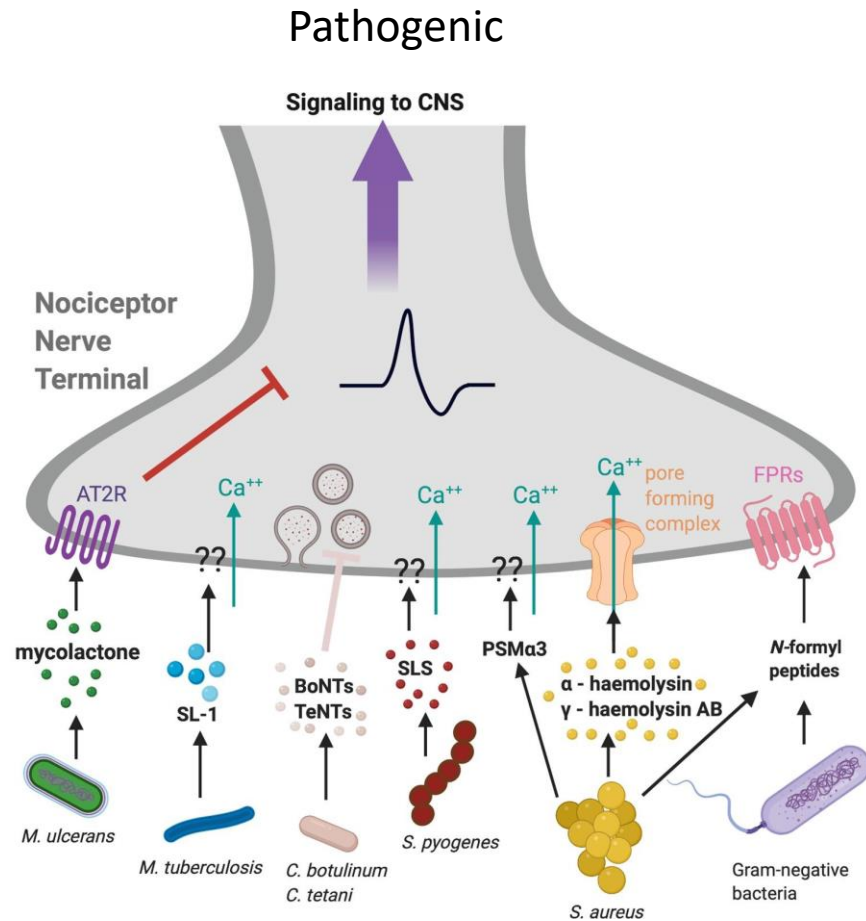
Studies show that alcohol consumption disrupts the intestinal barrier via increasing oxidative stress burden in the intestine, which in turn disrupts tight junctions and promotes intestinal hyperpermeability
Triggering proinflammatory reactions

Engen, Phillip A., et al. "The gastrointestinal microbiome: alcohol effects on the composition of intestinal microbiota." *Alcohol Research: Current Reviews*, vol. 37, no. 2, summer 2015, pp. 223+. *Gale Academic OneFile*, link.gale.com/apps/doc/A455285146/AONE?u=temple_main&sid=bookmark-AONE&xid=ca150c6d. Accessed 22 Sept. 2023.

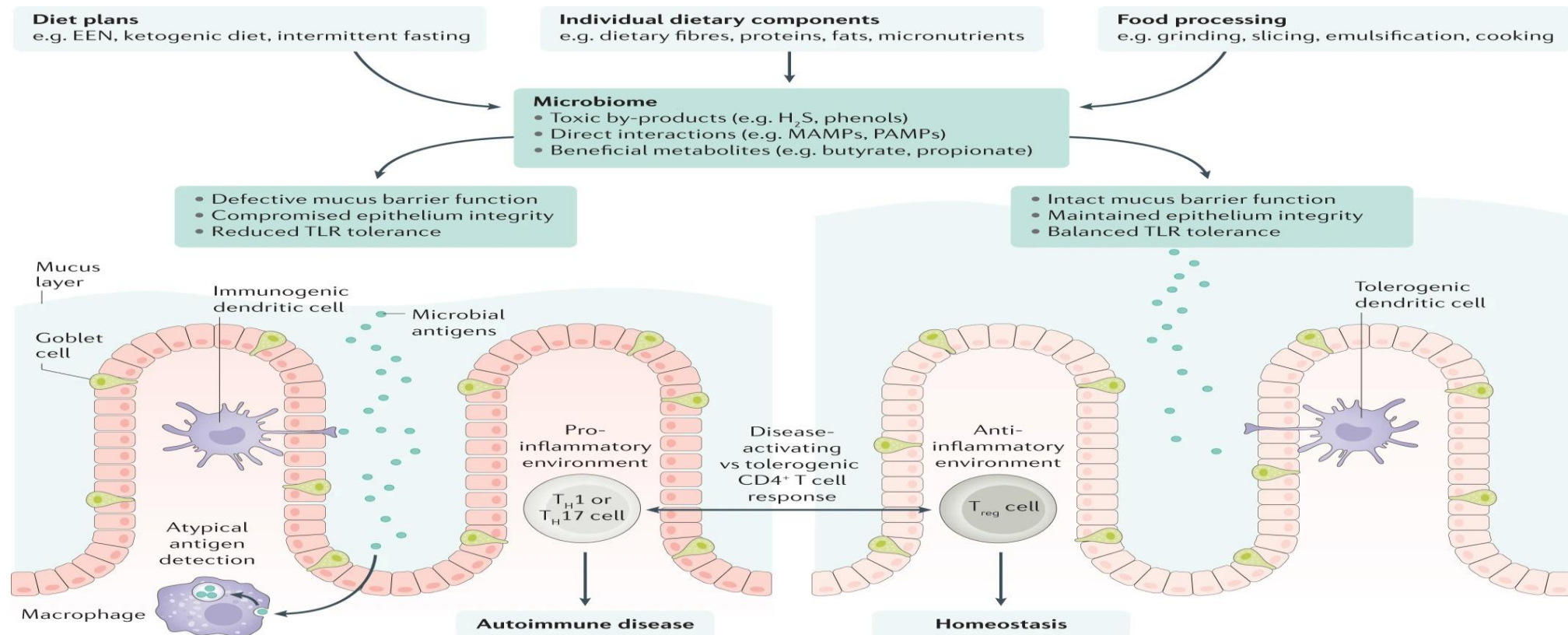
Smirnova, E., Puri, P., Muthiah, M.D., Daitya, K., Brown, R., Chalasani, N., Liangpunsakul, S Shah, V.H., Gelow, K., Siddiqui, M.S., Boyett, S., Mirshahi, F., Sikaroodi, M., Gillevet, P. and Sanyal, A.J. (2020), Fecal Microbiome Distinguishes Alcohol Consumption From Alcoholic Hepatitis But Does Not Discriminate Disease Severity. *Hepatology*, 72: 271-286. <https://org.libproxy.temple.edu/10.1002/hep.31178>



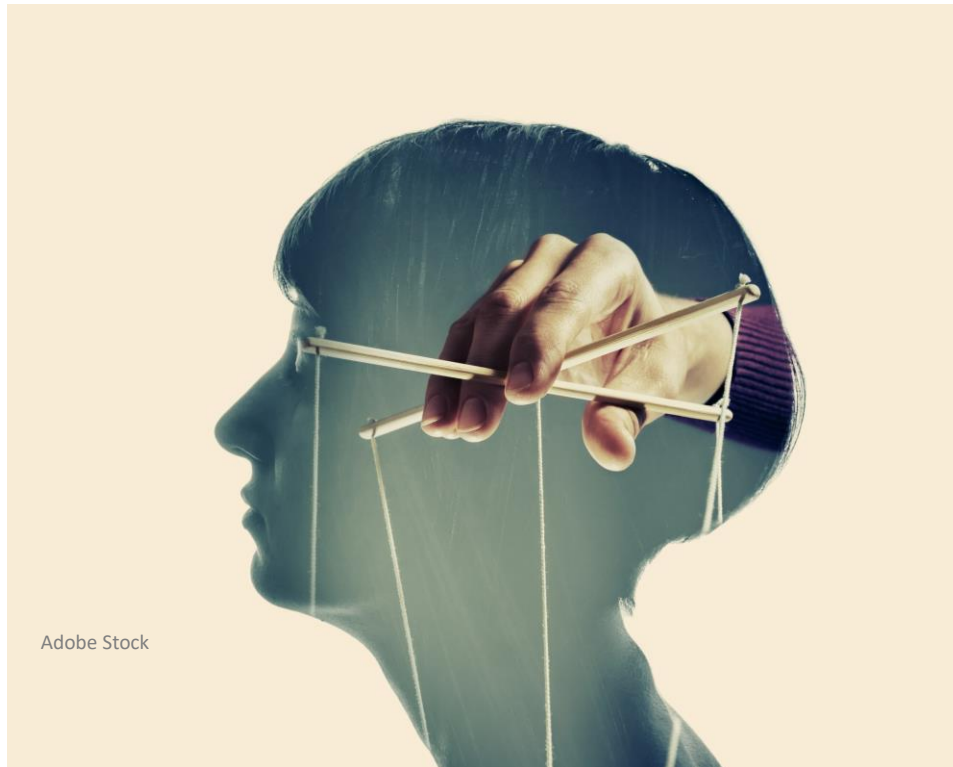
Microbes and Pain



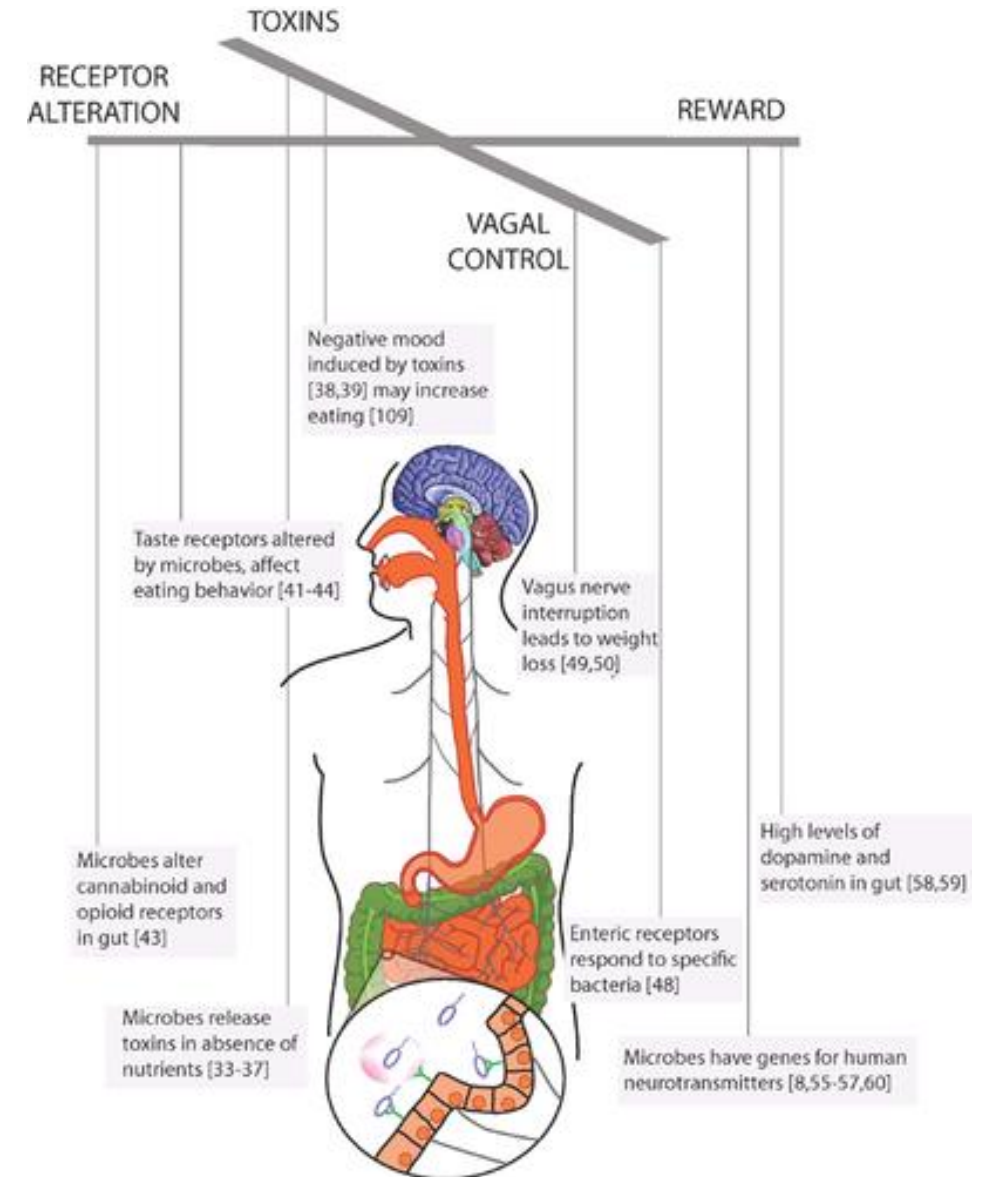
Diet & Role In Autoimmunity



Microbes are our puppetmasters



Alcock, Joe & Maley, Carlo & Aktipis, C.. (2014). Is eating behavior manipulated by the gastrointestinal microbiota? Evolutionary pressures and potential mechanisms. *BioEssays*. 36. 10.1002/bies.201400071.





Endometriosis & The Microbiome

- *Pseudomonas* was overrepresented in peritoneal fluid among women with endometriosis across multiple studies but was also observed to be increased in vaginal, endometrial, and intra-lesional samples.
- Among bacteria noted across different anatomical samples, *Gardnerella* was found to be increased in cervical but decreased in endometrial, fecal, and vaginal samples of patients with endometriosis
- *Atopium* was found to be decreased in vaginal and cervical samples from patients with endometriosis.
- *Sphingobium* was found to be increased in vagina, endometrium, and peritoneal fluid from patients with endometriosis.
- *Streptococcus* was found to be increased in peritoneal, endometrial, and cervical samples from women with endometriosis.





Hormones Affect Pain Perception

Table 1 Summary of functional-imaging studies specifically addressing the question of hormonal influences on pain perception

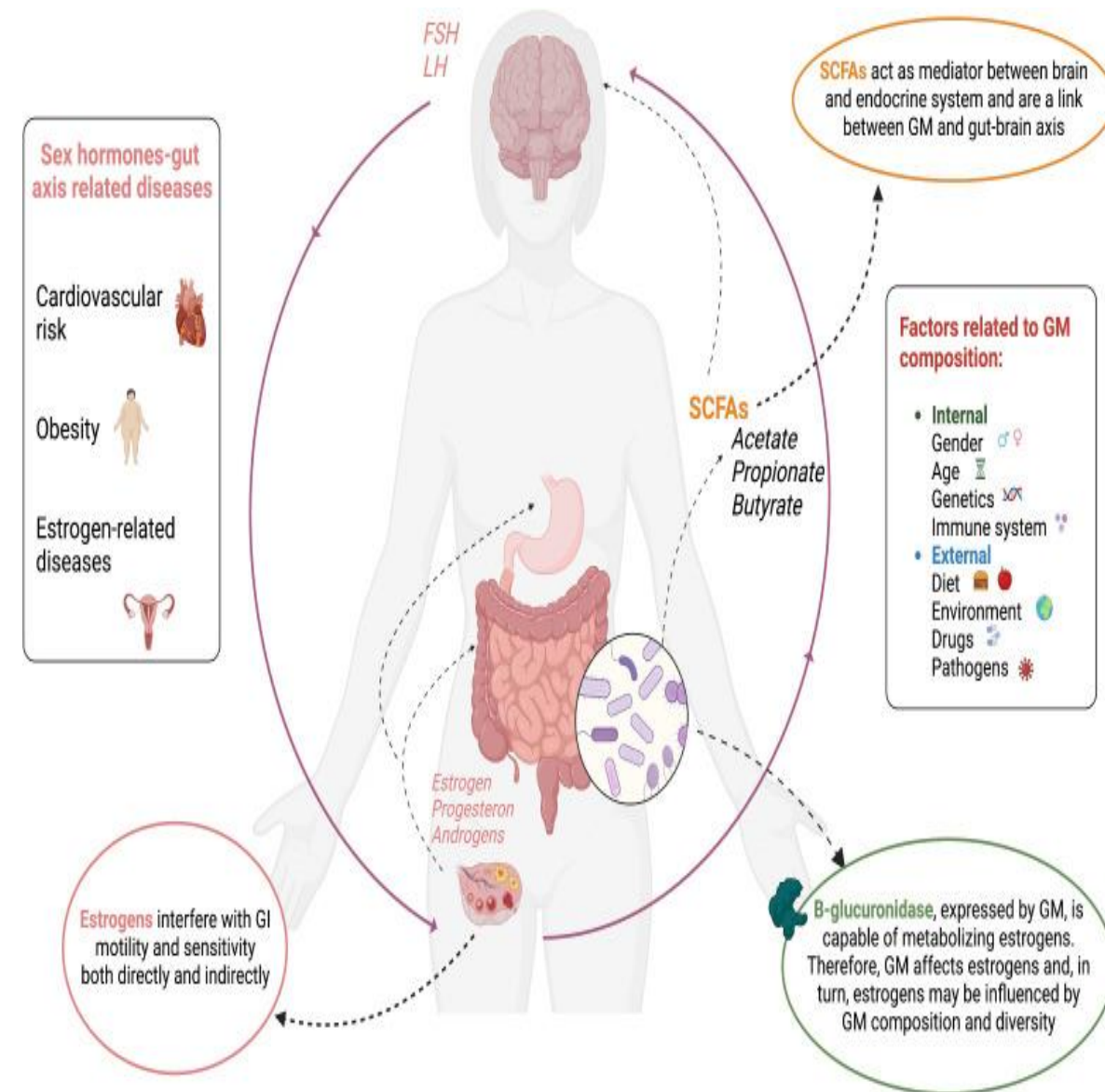
From: [Sex Hormones and Pain: The Evidence From Functional Imaging](#)

Study	Technique	Patients, <i>n</i>	Stimulus (site)	Timing	Differences observed			
					Estradiol	Progesterone	Behavioral response	Imaging response
Choi et al. [32]	FMRI	18	Hot water (finger)	F + L	Yes	Yes	Yes	Yes
de Leeuw et al. [33]	FMRI	9	Thermal (left masseter)	M + F	Yes	No	No	Yes
Smith et al. [34]	PET; ¹¹ [C] carfentanil	8	Hypertonic saline (masseter)	early F ± E2	Yes	No	Yes	Yes

E2 estradiol; *F* follicular; *FMRI* functional magnetic resonance imaging; *L* luteal; *M* menstrual; *PET* positron emission tomography

Hormones and Microbiota

- Hormone production influenced by microbiota
 - B glucuronidase produced by microbes aids in food estrogen usage
- Hormones can influence what types of microbes present
 - Postmenopausal women have a microbiome similar to men
 - Polycystic Ovarian patients have decreased diversity of microbome
 - reduced butyrate production, higher BMIs and higher testosterone serum concentrations
 - dysbiosis may lead to insulin resistance and alterations in glucose metabolism, higher insulin levels stimulate the ovary in producing androgens, thus perpetuating the pathogenetic mechanism of PCOS



[https://Calcaterra V, Rossi V, Massini G, Regalbuto C, Hruby C, Panelli S, Bandi C, Zuccotti G. Precocious puberty and microbiota: The role of the sex hormone-gut microbiome axis. Front Endocrinol \(Lausanne\). 2022 Oct 21;13:1000919. doi: 10.3389/fendo.2022.1000919. PMID: 36339428; PMCID: PMC9634744. www.ncbi.nlm.nih.gov/pmc/articles/PMC7952237/](https://Calcaterra V, Rossi V, Massini G, Regalbuto C, Hruby C, Panelli S, Bandi C, Zuccotti G. Precocious puberty and microbiota: The role of the sex hormone-gut microbiome axis. Front Endocrinol (Lausanne). 2022 Oct 21;13:1000919. doi: 10.3389/fendo.2022.1000919. PMID: 36339428; PMCID: PMC9634744. www.ncbi.nlm.nih.gov/pmc/articles/PMC7952237/)



The future is
ingesting specific
microbes

- Are microbes the new medicine?



- William Shakespeare
"To be or not to be?"



Dr. Betsy Greenleaf
"To test or not to test?"

Next Generation Sequencing
PCR

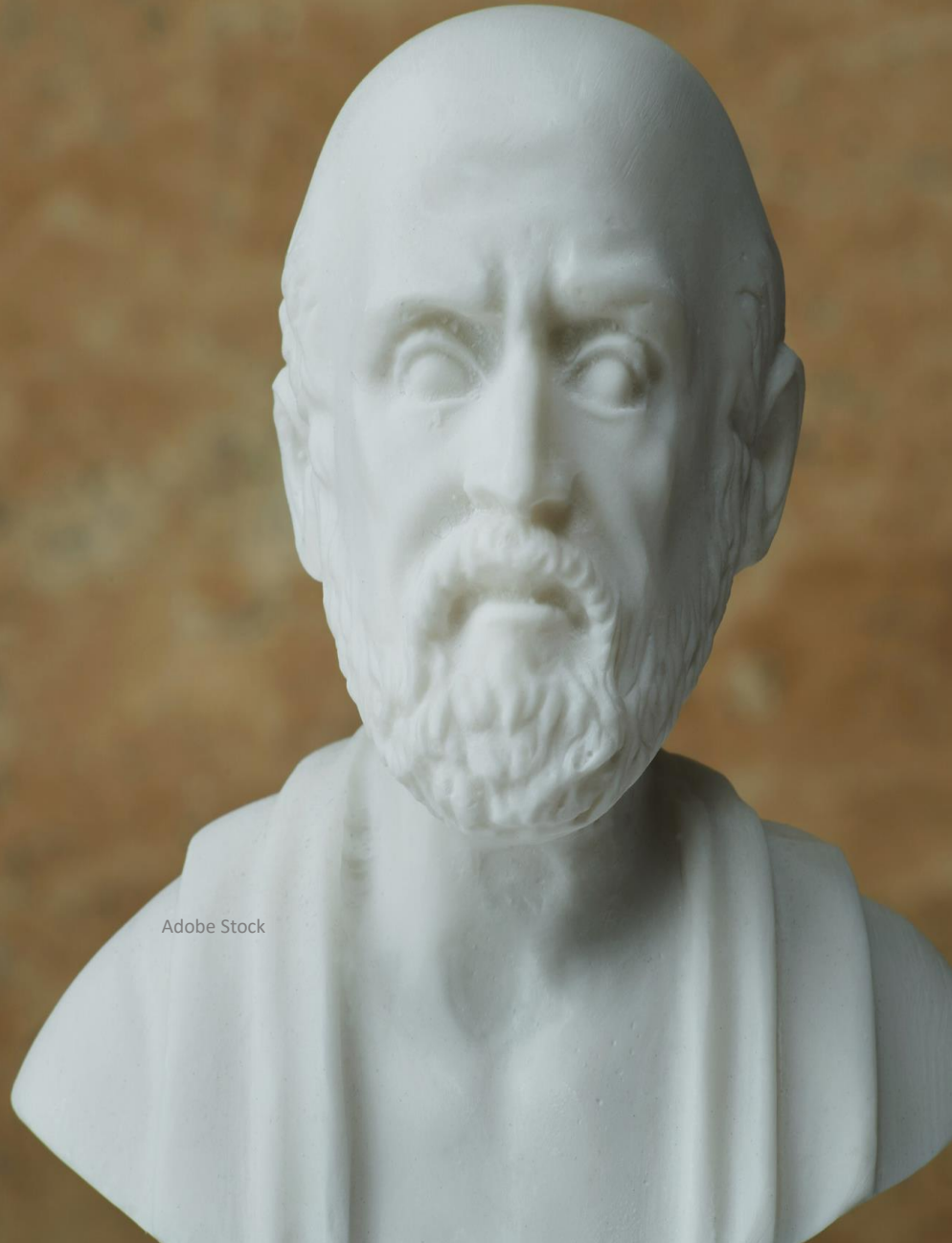


Oral
Stool
Vagina

But the constant is.....

Healthy Foods





Adobe Stock



" Let Food Be Thy Medicine,
and Medicine Be Thy Food."
-Hippocrates 440 BC

<https://www.bloomsburycollections.com/book/hippocrates-now-the-father-of-medicine-in-the-internet-age>



Nutrients are important

Antidepressant foods have:

- ▶ Folate
- ▶ Iron
- ▶ Long chain omega-3 fatty acids (EPA, DHA)
- ▶ Magnesium
- ▶ Potassium
- ▶ Selenium
- ▶ Thiamine
- ▶ Vitamin A
- ▶ Vitamin B6
- ▶ Vitamin B12
- ▶ Vitamin C
- ▶ Zinc



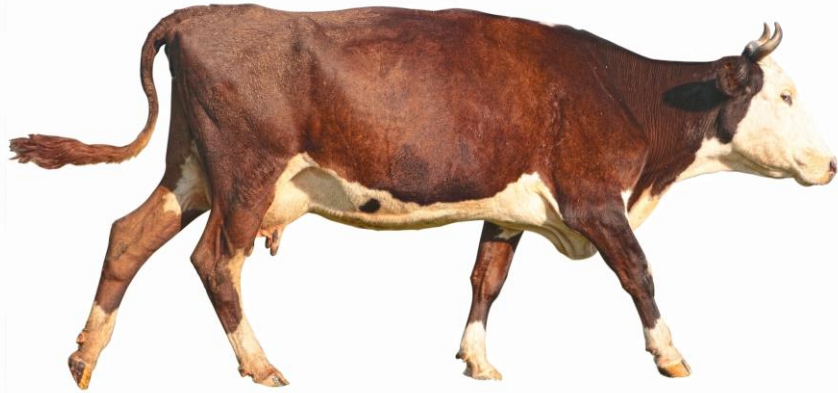
Food category	Mean AFS
Vegetables	48%
Organ meats	25%
Fruits	20%
Seafood	16%
Legumes	8%
Meats	8%
Grains	5%
Nuts & seeds	5%
Dairy	3%

Diversity leads to health

- Low microbiome biodiversity is associated with an increased risk of disease and dysfunction
- Changing diet to whole foods increases microbiome biodiversity

Semi, Z., Erikka, L., Inge, H., Vivian, V., Panayiotis, L., Emily, V., Wells, P. M., Steves, C. J., Herzig Karl-Heinz, Cristina, M., Jarvelin Marjo-Riitta, Rashmi, S., & Gunter, M. J. (2021). Markers of metabolic health and gut microbiome diversity: findings from two population-based cohort studies. *Diabetologia*, 64(8), 1749-1759.
<https://doi.org/10.1007/s00125-021-05464-w>







- Fruits and vegetables:
- Whole grains
- Legumes
- Fermented foods
- Nuts and seeds
- Healthy fats



#IHSNY24
IHSYMPOSIUM.COM





Adobe Stock

Aim for one serving of fermented foods daily

- Sauerkraut
- Kimchi
- Pickles
- Yogurt
- Kombucha
- Kefir



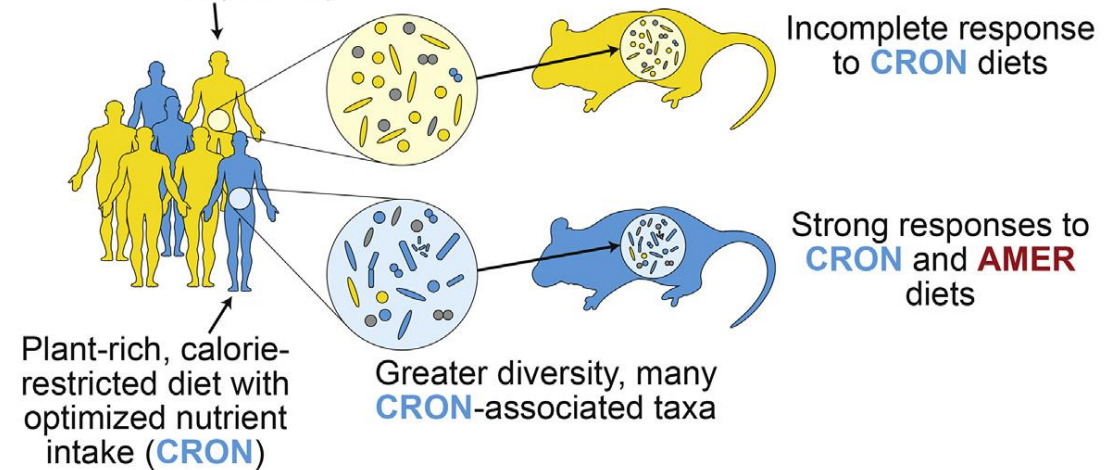
How do we make a change?



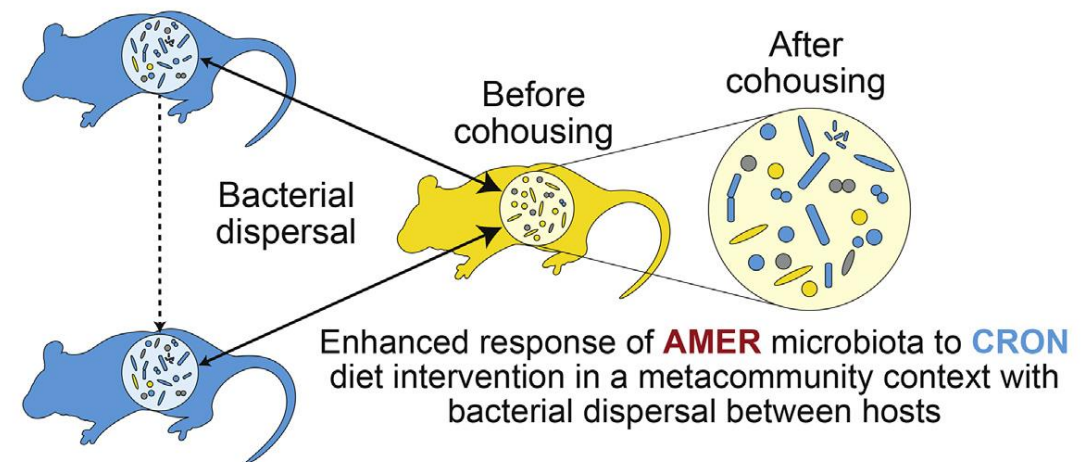
Change takes time

- You can't change microbiome diversity overnight by switching to a healthy diet.
- Westernized communities are associated with lower biodiversity

Typical unrestricted American diet (**AMER**)



Simulated metacommunity with sequential cohousing



The company you keep can influence your microbiome

- ▶ Humans emit 10 Million biological particles per hour





Other factors affecting the microbiome

Further research on the microbiome

- **Air pollution** – NIEHS-funded research found breathing ultrafine particles, a component of air pollution, altered the gut microbiome and changed lipid metabolism in mice with atherosclerosis.
<https://www.niehs.nih.gov/health/topics/science/microbiome/index.cfm>
- **Antimicrobial products** such as triclosan affected gut microbiome resulting in altered stress response, antibiotic resistance, and heavy metal resistance.
<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6546352/>
- **Artificial sweeteners** – Sucralose, and acesulfame potassium is associated with chronic inflammation and weight gain <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5647777/>
- **Flame retardants** – Early life exposure to types of flame retardants called polybrominated diphenyl ethers (PBDEs) and polychlorinated biphenyls (PCBs) can have a life-long impact on disease risk, which the gut microbiome may shape.
- **Heavy metals** – changed the gut microbiome and altered molecular pathways in bacteria that are important to biological functions like DNA repair.
- **Pesticides** – Exposure to the widely used agricultural insecticide diazinon changed the gut microbiome adding to toxic effects on the nervous system.





Meditation improves Microbiome

- ▶ Individuals who practice deep meditation
 - ▶ Improved microbiome diversity
 - ▶ found to have increased numbers of bacteria species associated with wellbeing
 - ▶ intestinal markers associated with improved barrier function





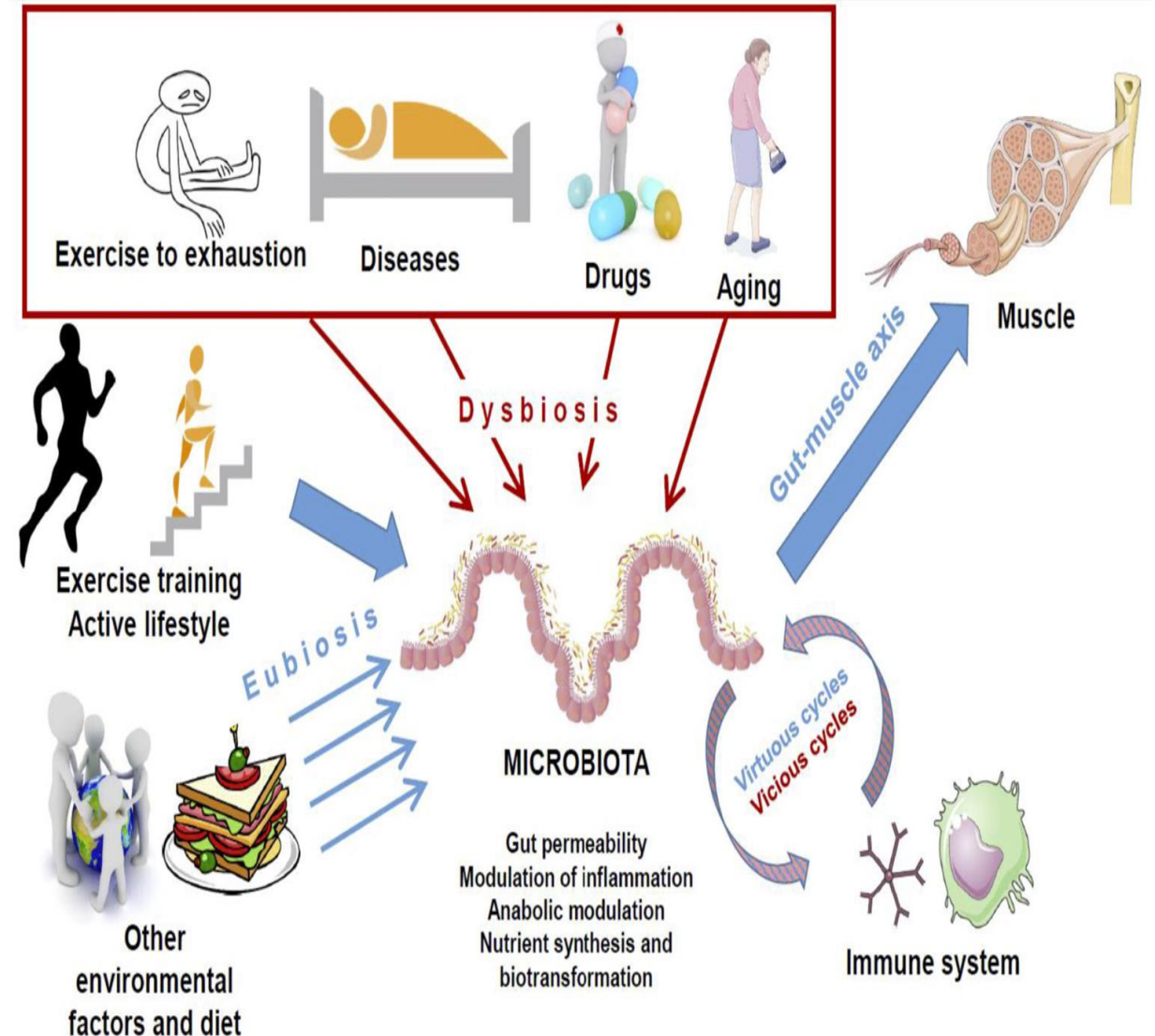
Adobe Stock

Sleep & Microbiome

- Microbe diversity with adequate sleep
- Microbes have demonstrated their own circadian rhythm separate from environmental cues

Exercise & Microbiome

- Positive modulator of biodiversity
 - However excess, strenuous exercise can result in inflammation and gut disturbances
- Gut Muscle Axis
 - Resulting in protein utilization
 - Muscle development





What should we do next.....

- Start the conversation about pelvic and sexual health
- Understanding the effects of stress on hormones and then hormones on the microbiome and stress on the microbiome
- Remember to look under the rocks
 - Gut Microbiome
 - Vaginal Microbiome
- Question: are our current therapies helping or harming the microbiome





Her Mighty Spirit: Flourishing, Empowered, Mentally Inspired, Medically Sound

- Sources of Imbalance
 - Hormones
 - Microbiome
 - Stress
- Causes of Stress
 - Food
 - Environment
 - Mental Health
 - Illness
 - Medicine



A trio of power, all must align, For a woman's health to truly shine





Friday 10:45am – 11:45am

**The Hidden Trifecta: Unraveling the
Brain-Gut-Vagina Axis and Its Impact on
Women's Health**

Please scan this QR code on you mobile
or tablet device to access the session feedback survey



The Hidden Trifecta: Unraveling the Bra
in-Gut-Vagina Axis and Its Impact on Wo
men's Health