Flora Forever: How the Microbiome Shapes Women's Health & Longevity

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MOA 2023 Fall

Objectives

- Learners should gain understanding how the microbiome impact on health throughout the years
- While acknowledging the current scientific limitations, learners should be able to discuss the theories and research surrounding the microbiome's potential role in promoting longevity.
- understanding dietary, probiotic, and lifestyle interventions that have been proposed to support a health-promoting microbiome and extend healthy life expectancy.

Conflicts of interest

- None to disclose

Introduction: What do you want your health for?

- Mental well being
- Reduce risk of chronic disease
- Enhanced social interaction
- Empowerment and independence
- Cognitive health
- Improved quality of life
- Positive role modeling Women's Health and why the exposome?
- Women's health and why the microbiome

The Exposome

- The term "exposome" refers to the totality of environmental exposures that an individual encounters from conception onward.
- It encompasses everything a person is exposed to, including diet, lifestyle, chemicals, radiation, pollutants, and other external factors.
- The concept was introduced to offer a counterpart to the genome, emphasizing the importance of environmental factors in understanding disease and health.
- The exposome seeks to capture all the different exposures an individual might face over a lifetime and how those exposures interact with our genes to influence health outcomes.
- https://www.niehs.nih.gov/research/supported/exposure/bio/index.cfm

Key features

- Allostatic load: Totality of environmental exposures over a lifetime:
- our genetics provides the foundational code or blueprint for our biological processes
- epigenetics dictates how this blueprint is utilized, often influenced by our exposome.
- The interplay between these three concepts illustrates the complex relationship between our environment, genes, and health

Social Determinants of health

- The SDOH refer to the conditions in which people are born, grow, live, work, and age, including the health system.
- These conditions are shaped by the distribution of money, power, and resources at global, national, and local levels.
- SDOH primarily focus on the social environment and how it affects health outcomes.
- Examples include socioeconomic status, education, physical environment, employment, social support networks, and access to healthcare, food, literacy, housing

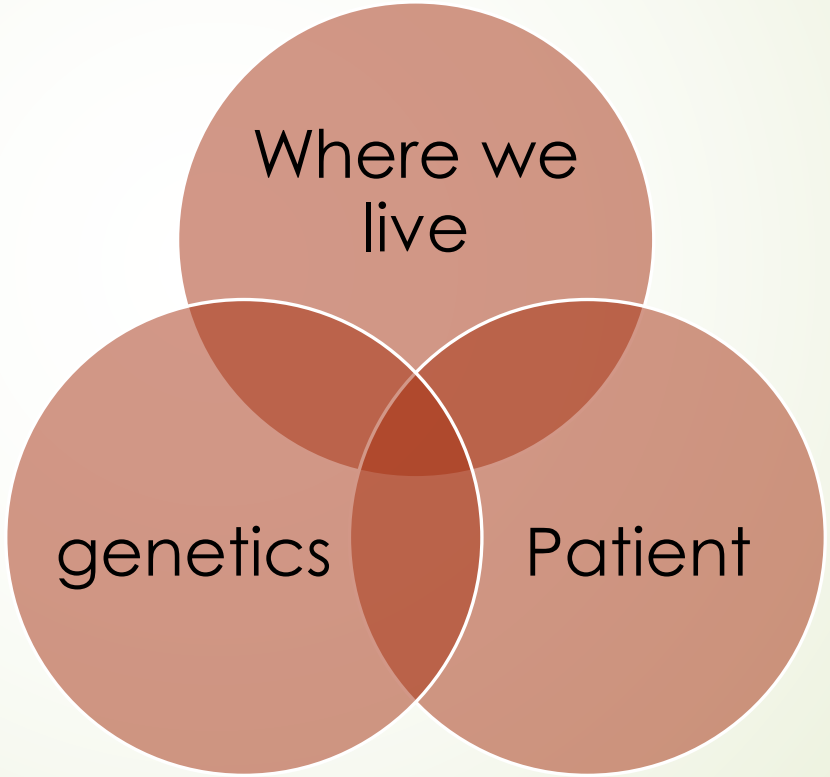
Case example

- 72 year old presented to the ED with progressive weakness, Neuro and Orthopedic assessed patient, no indication for surgical intervention
- He has not been able to walk and his wheelchair was left outside the hotel room this past winter and rested.
- Currently living with 20 other people in a hotel room
- He does not drink, smoke, never used illicit drugs
- The impact of the exposome

Key Features

- Focuses on social and economic conditions.
- Highlights the impact of distribution of resources and power on health outcomes.
- Includes factors like education, employment, social support, and access to healthcare.

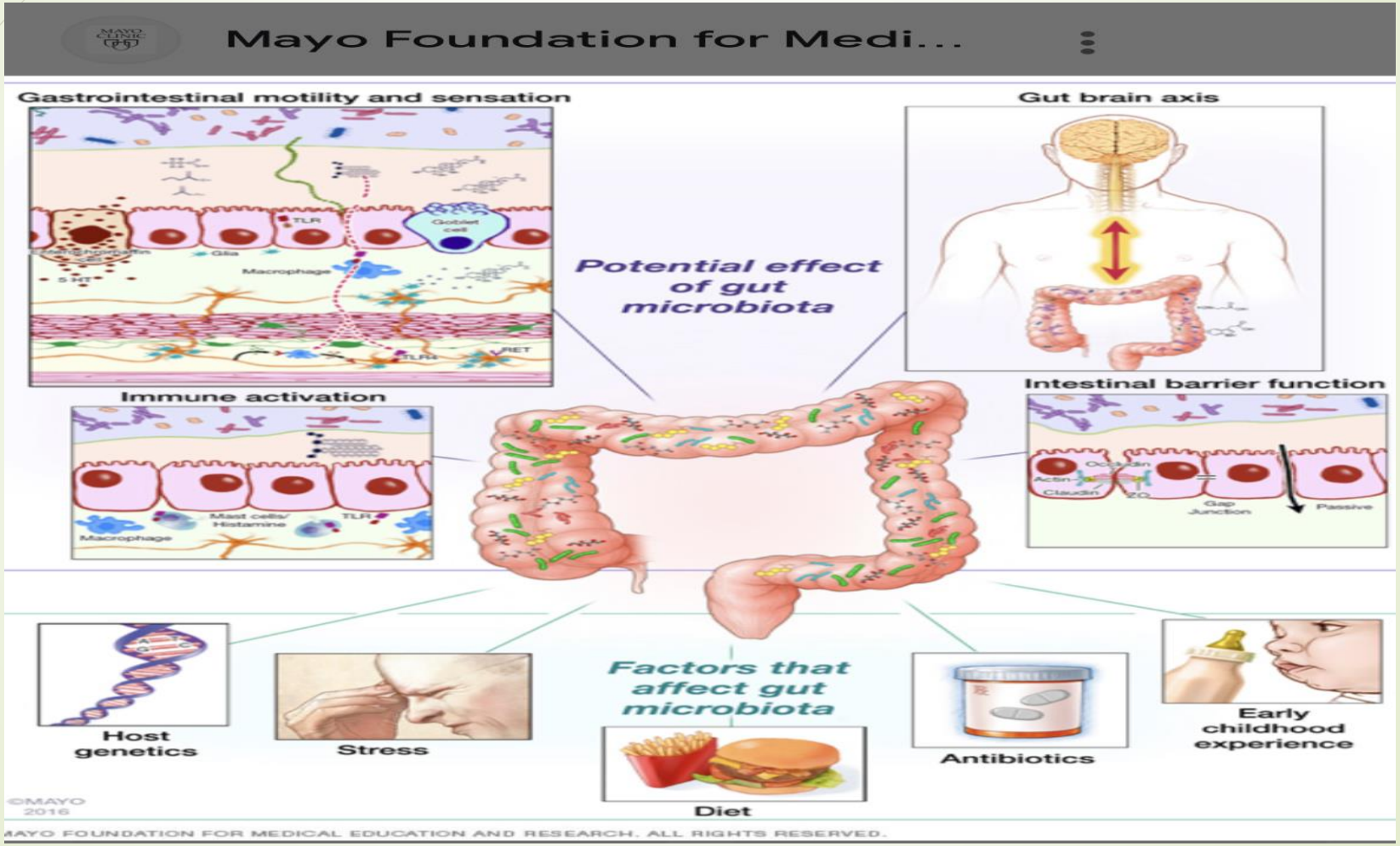
It all adds up = Allostatic load



The microbiome

- The importance of a healthy microbiome
- While bacteria are the most studied, the human microbiome also includes fungi, viruses, and other microorganisms.
- **Microbial "Cloud"**: People emit around a million biological particles an hour, meaning we're constantly surrounded by a personalized microbial "cloud".
- **Unique Like a Fingerprint**: Your microbiome is unique to you. While there might be similarities between your microbiome and those of close relatives, your microbiome will differ significantly from someone unrelated
- You are more bacteria than you are you

Gut Health


Mayo Foundation for Medi...
Gastrointestinal motility and sensation
Gut brain axis
Potential effect of gut microbiota
Immune activation
Intestinal barrier function
Factors that affect gut microbiota
Host genetics
Stress
Diet
Antibiotics
Early childhood experience
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Gut microbes at play, Metabolize, heal, inflame, Balance shifts each day

- The gut microbiota carry out many functions which can contribute to health homeostasis or disease, including metabolism of dietary components (eg, fiber, amino acids) and endogenous compounds (eg, bile acids, hormones), and biosynthesis of lipopolysaccharide (LPS), a cell wall component of gram-negative bacteria which triggers inflammation
- Fan Y, Pedersen O. Gut microbiota in human metabolic health and disease. *Nat Rev Microbiol*. 2021;19(1):55–71. doi: 10.1038/s41579-020-0433-9 [PubMed] [CrossRef] [Google Scholar]

Microbiome's sway,
Disease to health interplays,
Humans feel its weight.

- Studies in humans have observed correlations of gut microbiome composition with a wide range of conditions and diseases, including obesity, inflammatory bowel disease, colorectal cancer, depression, diabetes, and cardiovascular disease

- Knight R, Callewaert C, Marotz C, et al. The microbiome and human biology. *Annu Rev Genomics Hum Genet*. 2017;18:65–86. doi: 10.1146/annurev-genom-083115-022438

Prenatal Microbiome

- Have a healthy baby
- importance of maternal microbiome
- How the exposome affects the prenatal microbiome
- **Maternal Microbiome and Infections in Pregnancy**
- https://pubmed.ncbi.nlm.nih.gov/33333813
- General changes in the gut, oral, and vaginal microbiomes in parallel with the hormonal changes throughout pregnancy.
- The changes that occur in the gut throughout pregnancy are complex and mediated by maternal factors, such as diet and antibiotic usage.
- The vaginal microbiome during pregnancy becomes more stably dominated by species of *Lactobacillus*, thereby decreasing in overall diversity.

Birth and the microbiome

- Vaginal deliveries and microbiome transfer
- Importance of establishment of the microbiome
- Over the first year of life, the infant gut microbiome undergoes rapid changes and begins to resemble the adult microbiome, especially as solid foods are introduced.
- It's crucial to understand that while there are general patterns in microbial colonization, there's also considerable variability between individual infants due to the multitude of factors influencing microbial establishment and growth

Mother's birth microbes, Antibiotics hold the key, Delivery's riddle.

- **Maternal vaginal microbiome composition does not affect development of the infant gut microbiome in early life**
- https://pubmed.ncbi.nlm.nih.gov/37065202
- we have shown in a large cohort of mother-infant pairs that exposure to the maternal vaginal microbiome during birth, as well as its composition, does not specifically influence the development of the infant stool microbiome in early infancy.
- Moreover, we have demonstrated that associations of delivery mode and infant stool microbiome composition appear to be impacted by exposure to intrapartum antibiotics and not primarily related to mode of delivery, which points to modifiable factors for future considerations.

Infant gut astray,
Asthma, obesity loom,
Childhood health at stake

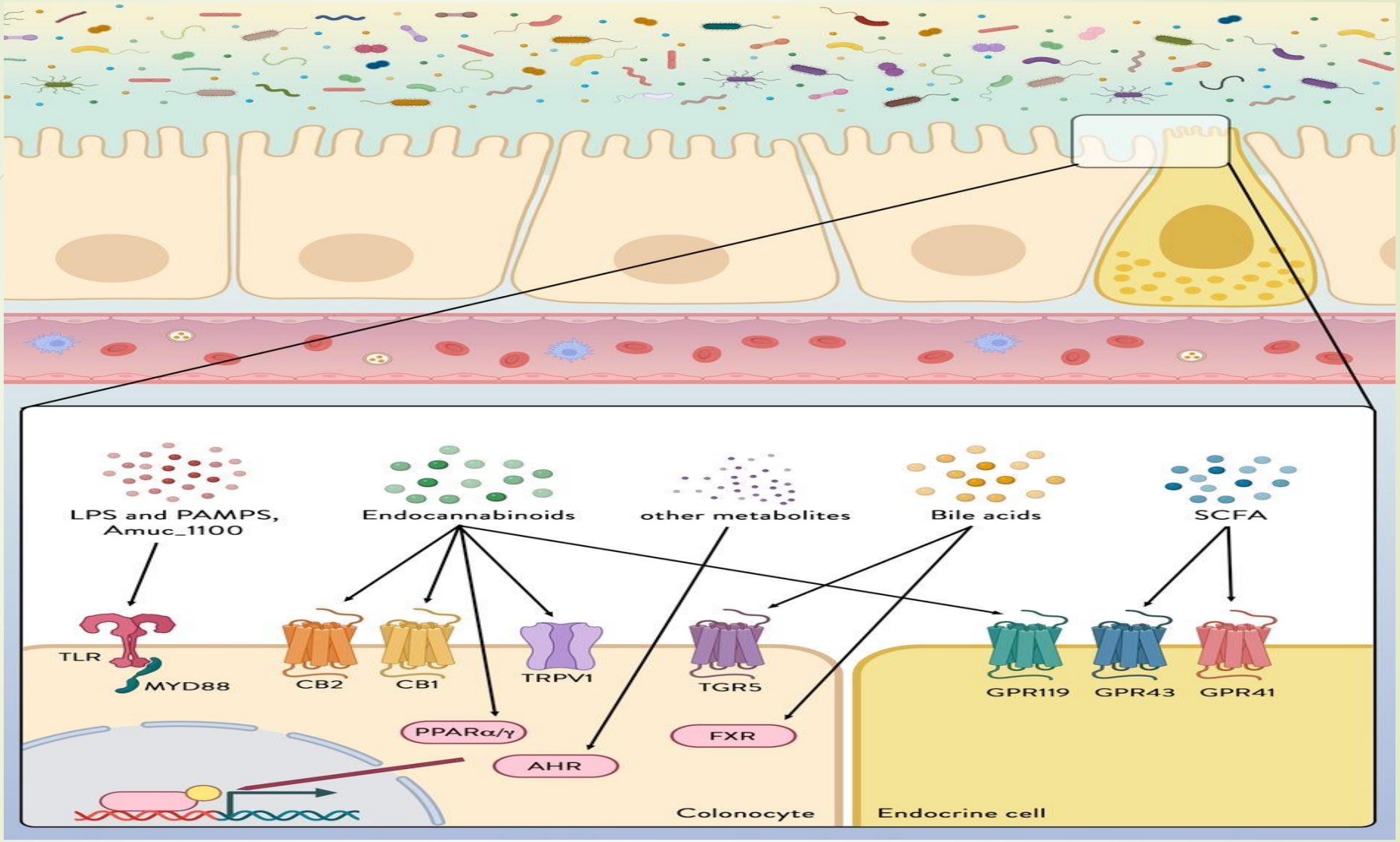
- Dysbiosis of the infant gut microbiome appears to be associated with adverse health outcomes in childhood including asthma, atopy, obesity, and various autoimmune diseases (Stiemsma and Michels, 2018).
- Dos Santos, S. J., Pakzad, Z., K. Albert, A. Y., Elwood, C. N., Grabowska, K., Links, M. G., Hutcheon, J. A., Maan, E. J., Manges, A. R., Dumonceaux, T. J., Hodgson, Z. G., Lyons, J., Mitchell-Foster, S. M., Gantt, S., Joseph, K. S., Van Schalkwyk, J. E., Hill, J. E., & Money, D. M. (2022). Maternal vaginal microbiome composition does not affect development of the infant gut microbiome in early life. *Frontiers in Cellular and Infection Microbiology*, *13*. https://doi.org/10.3389/fcimb.2023.1144254

Gestational Age:

- **Preterm Infants**: Preterm births can lead to a different microbiome trajectory, especially if the infant spends time in the neonatal intensive care unit (NICU).
- Preterm infants often have reduced microbial diversity and an increased presence of potentially pathogenic microbes

The Microbiota-Gut Axis in Premature Infants: Physio-Pathological Implications https://pubmed.ncbi.nlm.nih.gov/35159189

- In this narrative review, the current evidence on the influence of the microbiota-gut-brain axis focusing on preterm infants and their health status later in life.
- The preterm infant intestinal microbiome is influenced by several factors, beginning from prenatal life.
- Postnatal changes in the microbiota composition may affect the preterm neonatal course, as well as long-term outcomes.



https://www.google.com/url?sa=i&url=https%3A%2F%2Fgut.bmj.com%2Fcontent%2F71%2F5%2F1020&psig=AOvVaw1453REANvsKOXWfBvMwlHS&ust=1697598176818000&source=images&cd=vfe&opi=89978449&ved=0CBAQjRxqFwoTCMiknZSM_IEDFQAAAAAdAAAAABAt

Short Chain Fatty Acids(SCFA)

- What are they?
- How do they relate to the microbiome
- Feed the colonocytes
- Some bacteria, like *Bifidobacterium* species in breastfed infants, help break down human milk oligosaccharides (HMOs) into short-chain fatty acids, which provide energy for gut cells and have anti-inflammatory properties.

How to make positive changes

- **SCFA**s, for instance, have been shown to improve gut health by **modulating the epithelial barrier integrity,** water absorption and mucous production and gut motility
  - doi: 10.1038/ijo.2017.52, doi: 10.1113/JP276431
- **SCFA**s can also directly or indirectly impact on the gut-brain axis by regulating different immune, endocrine, epigenetic and humoral mechanisms , as well as by **directly stimulating vagal and sympathetic nerve signaling**
  - doi: 10.1007/s12035-014-8914-3, 10.1371/journal.pone.0212856.
- In addition to their systemic actions, **SCFA**s can, to a minimum extent, cross the blood-brain barrier, playing a role as neuroactive substances. In fact, **SCFA-free fatty acid receptors 3 and 2 expression in the brain** has already been demonstrated, giving strength to the potential **gut-brain crosstalk**,
  - doi: 10.1074/jbc.M211609200

Breast feeding and the microbiome

- How breastfeeding influences infant microbiota
- Benefits for immunity
- **Shaping the Gut Microbiota by Breastfeeding: The Gateway to Allergy Prevention?**
- PMID: 30873394

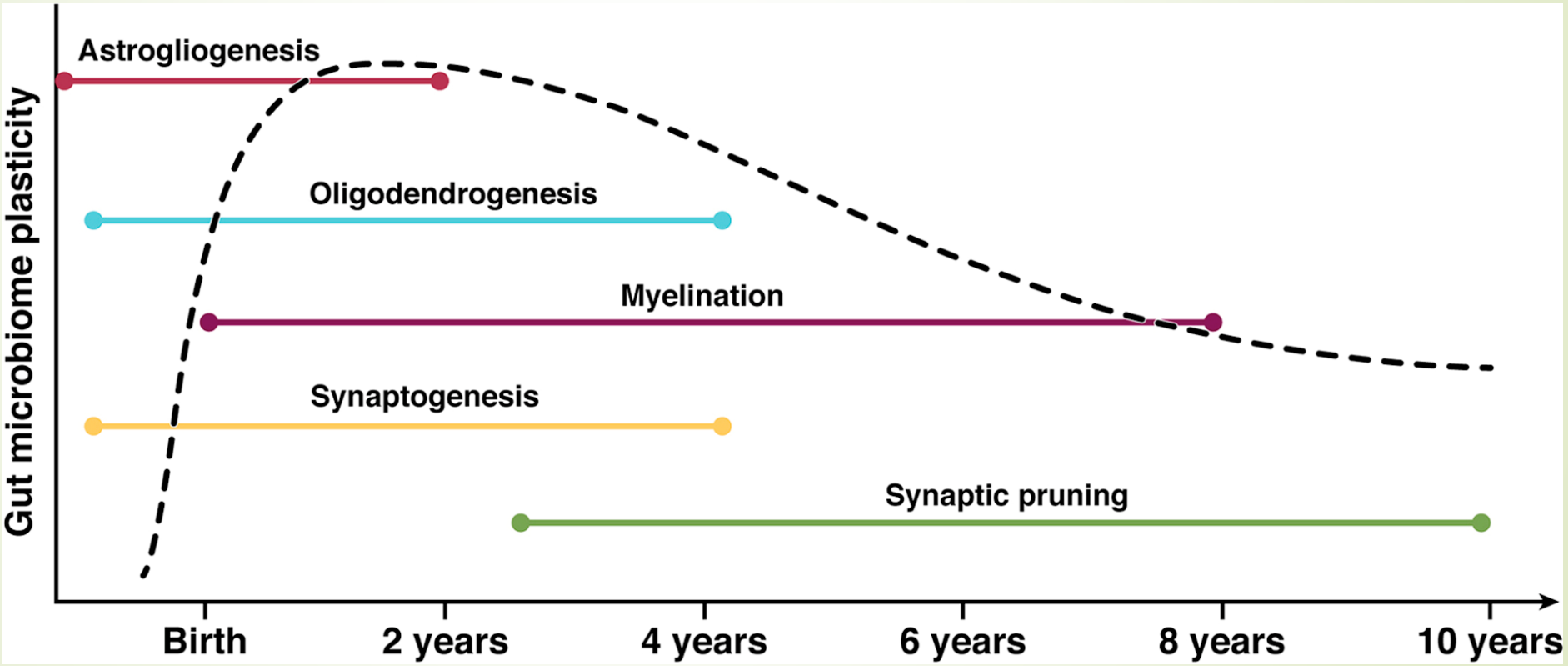
Infant feeding

- **Breastfed Infants**: Breast milk contains its own microbiota and beneficial compounds like oligosaccharides that promote the growth of specific bacteria. Breastfed infants often have guts dominated by *Bifidobacterium* species which thrive on human milk oligosaccharides.
- **Formula-fed Infants**: The microbiome of formula-fed infants can be more diverse earlier on and might include more *Bacteroides* and *Lactobacillus* among others. The exact composition can also depend on the specific components of the formula.

Infancy and microbiome health

- Key stages of microbiota development
- How it affects growth and immunity
- The microbiome in infancy is **less diverse and less stable than that of an adult**. The microbiome of an infant is dependent on many factors- mode of delivery, milk consumption, medication exposure, environment. Weaning signals a significant change in diet, after which Proteobacteria become far less abundant.
- **Childhood Development and the Microbiome: The Intestinal Microbiota in Maintenance of Health and Development of Disease During Childhood Development**
- Victoria Ronan,[1] Rummanu Yeasin,[1,2] and Erika C. Claud
- https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8714606/

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8714606/bin/nihms-1764068-f0001.jpg



recommendations

- **Breastfeeding** is encouraged when possible, as breast milk provides beneficial microbes and prebiotics that nourish the infant gut microbiome.
- **Limiting unnecessary antibiotic use** in both mothers and infants can help preserve the natural development of the infant microbiome.
- **Skin-to-skin contact** shortly after birth can facilitate the transfer of beneficial microbes to the infant.
- **Exposure to diverse environments** and limited use of antimicrobial products can support a richer, more diverse microbiome.

Microbiome continuum

- **Immune System Development**:
- The gut microbiome is intricately linked with the immune system. The microbial communities in the gut help 'train' the developing immune system, teaching it to differentiate between harmful pathogens and harmless or beneficial microbes.
- Proper immune training by the microbiome can help reduce the risk of autoimmune conditions and allergic reactions.
- **Nutrient Metabolism**:
- The microbiome assists in the digestion of certain nutrients, especially complex carbohydrates.
- Some bacteria, like *Bifidobacterium* species in breastfed infants, help break down human milk oligosaccharides (HMOs) into short-chain fatty acids, which provide energy for gut cells and have anti-inflammatory properties.
- **Protection Against Pathogens**:
- Beneficial microbes can outcompete and limit the colonization of pathogenic bacteria by consuming available nutrients and producing compounds that inhibit harmful bacteria.

Teenager to young adult

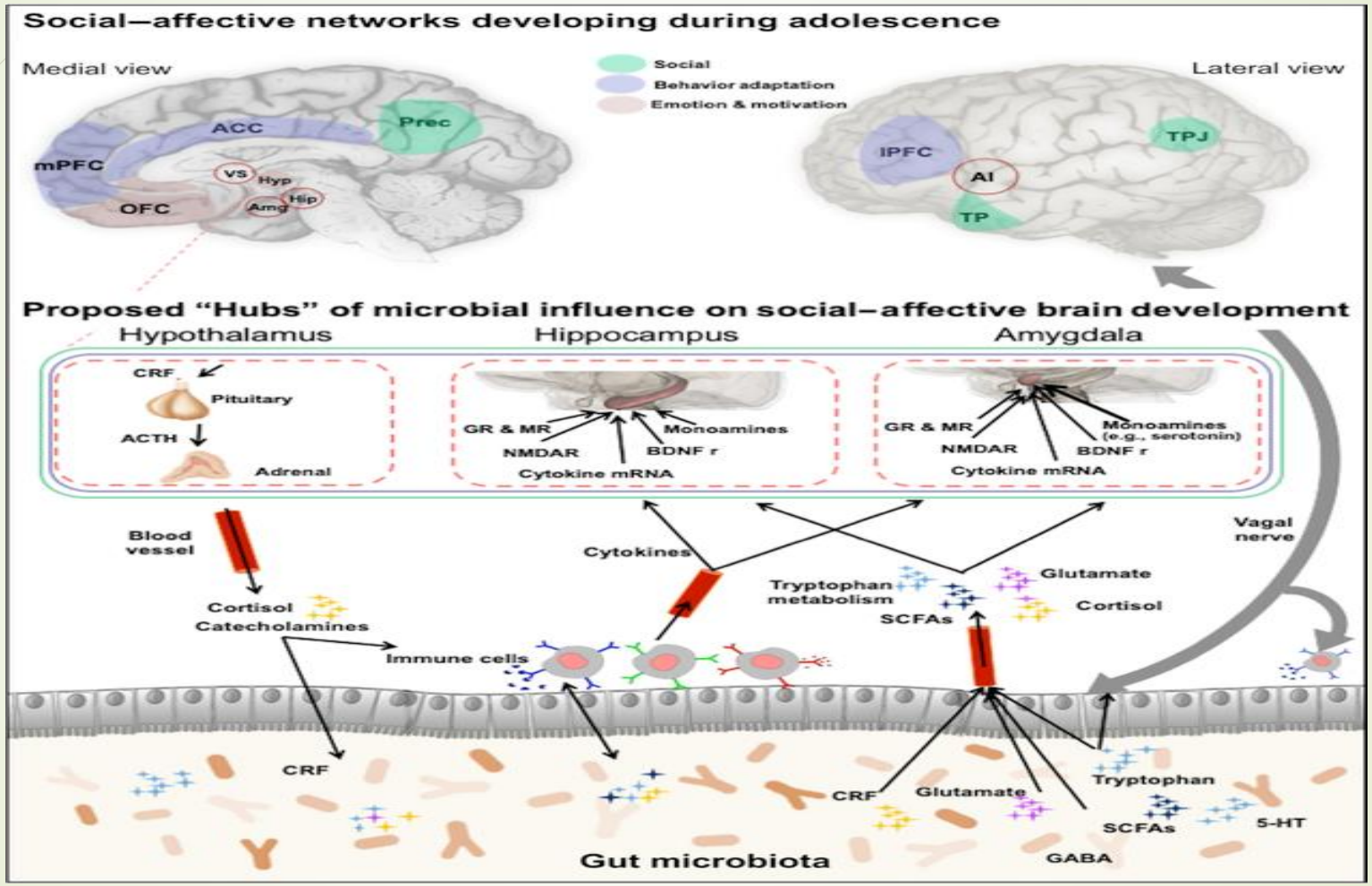
- Menarche and the microbiome
- Influence of lifestyle choices
- **Dysbiosis**: An imbalance in the skin's microbial community can exacerbate acne. A healthy skin microbiome can help keep P. acnes in check. However, factors like excessive washing, harsh skin treatments, or certain medications can disrupt the balance, potentially worsening acne.
- **Inflammatory Response**: While P. acnes can exist on the skin without causing harm, under certain conditions, it can trigger an immune response. When sebum (oil) production increases, as seen during puberty, P. acnes can proliferate in the hair follicles. The bacteria feed on the lipids in sebum and can produce waste products and fatty acids that irritate the lining of the follicle, leading to inflammation and the familiar red, swollen pimples.

ACNE

- **Beyond Bacteria**: While bacteria play a prominent role in acne, there's emerging research on the role of skin fungi, particularly the genus *Malassezia*, in acne and other skin conditions.
- **Gut-Skin Axis**: There's growing interest in the connection between the gut microbiome and skin health. Some studies suggest that gut dysbiosis might influence acne, and certain probiotics or dietary interventions can potentially benefit acne sufferers.

- **Brain Development**:
- The gut-brain axis is a bidirectional communication pathway between the gut and the brain. Emerging research suggests that the gut microbiome might influence brain development and behavior, although this area is still under investigation.
- **Risk of Chronic Diseases**:
- Early-life disruptions in the microbiome have been linked to a higher risk of chronic conditions later in life, such as asthma, obesity, type 1 diabetes, and celiac disease.
- **Necrotizing Enterocolitis (NEC) in Preterm Infants**:
- NEC is a severe intestinal condition in premature infants. A disturbed microbiome with reduced diversity and an overabundance of certain potentially harmful bacteria has been linked to an increased risk of NEC.
- **Asthma and Allergic Diseases**:
- Imbalances in the early-life microbiome have been associated with a higher risk of allergic diseases and asthma. For instance, reduced exposure to certain microbes early in life (known as the hygiene hypothesis) might increase the risk of allergies.
- **Obesity**:
- Early-life antibiotic use and disruptions in the microbiome have been associated with an increased risk of overweight and obesity in later childhood.
- **Mood and Behavior**:
- While still an emerging area of research, there are indications that the gut microbiome might influence mood and behavior through the gut-brain axis.

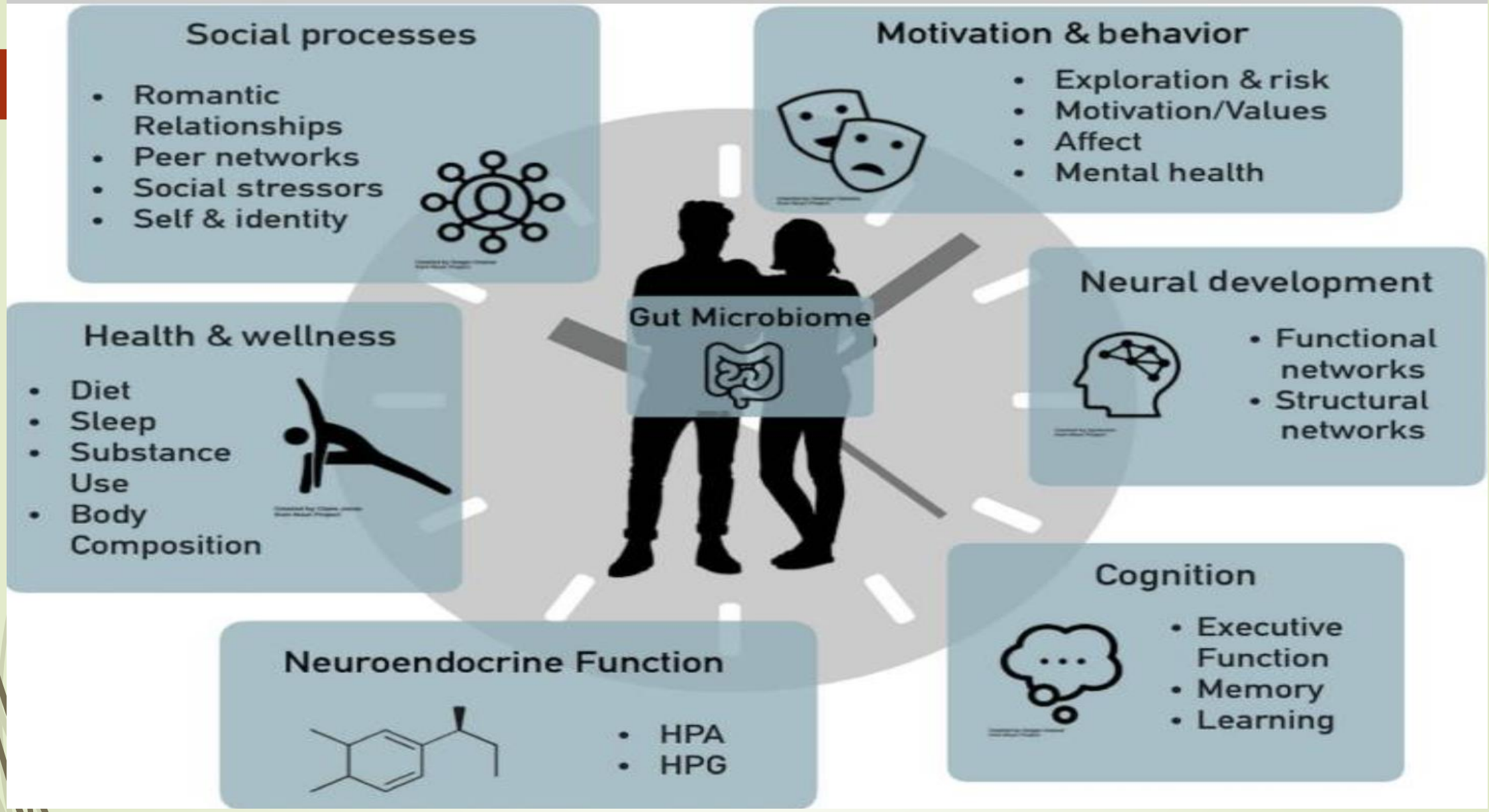
Adolescent microbiome change



https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6776431/bin/nihms-1044067-f0001.jpg

Critical Hubs of Microbiome-Gut-Brain - axis

- Bi-directional pathway between the brain and gut
- Social
- Behavioral
- Adaptation
- Emotional
- Motivation
- Influences the development of hypothalamus, hippocampus and amygdala



https://www.ncbi.nlm.nih.gov/corecgi/tileshop/tileshop.fcgi?p=PMC3&id=21457&s=93&r=1&c=1

Translated to clinical medicine

- Adverse Childhood experience
- IBS and mood disorders respond to probiotics, https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6776431/#R83
- https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6776431/#R56

What are other associations with microbiota?

- **Firmicutes**: This phylum includes many bacterial species that play vital roles in digesting dietary fibers and producing **short-chain fatty acids**, which provide energy to gut cells and have anti-inflammatory effects. Some notable genera within this group include *Lactobacillus*, *Clostridium*, and *Ruminococcus*.
- **Bacteroidetes**: These bacteria also play essential roles in carbohydrate metabolism. The balance between Firmicutes and Bacteroidetes has been of interest in research related to obesity and metabolic health. Within this phylum, *Bacteroides* is a particularly prevalent genus.
- **Actinobacteria**: This phylum includes the *Bifidobacterium* genus, which is often associated with beneficial effects on gut health, especially in the context of probiotics.
- **Proteobacteria**: This phylum includes a diverse group of bacteria, some of which can be pathogenic. However, they are a normal part of a healthy gut microbiome in low abundances. Common genera from this group include *Escherichia* and *Helicobacter*.
- **Verrucomicrobia**: This is generally less abundant than the phyla mentioned above, but it's often present. The most well-known genus within this phylum is *Akkermansia*, which has gained interest due to its potential beneficial roles in metabolic health

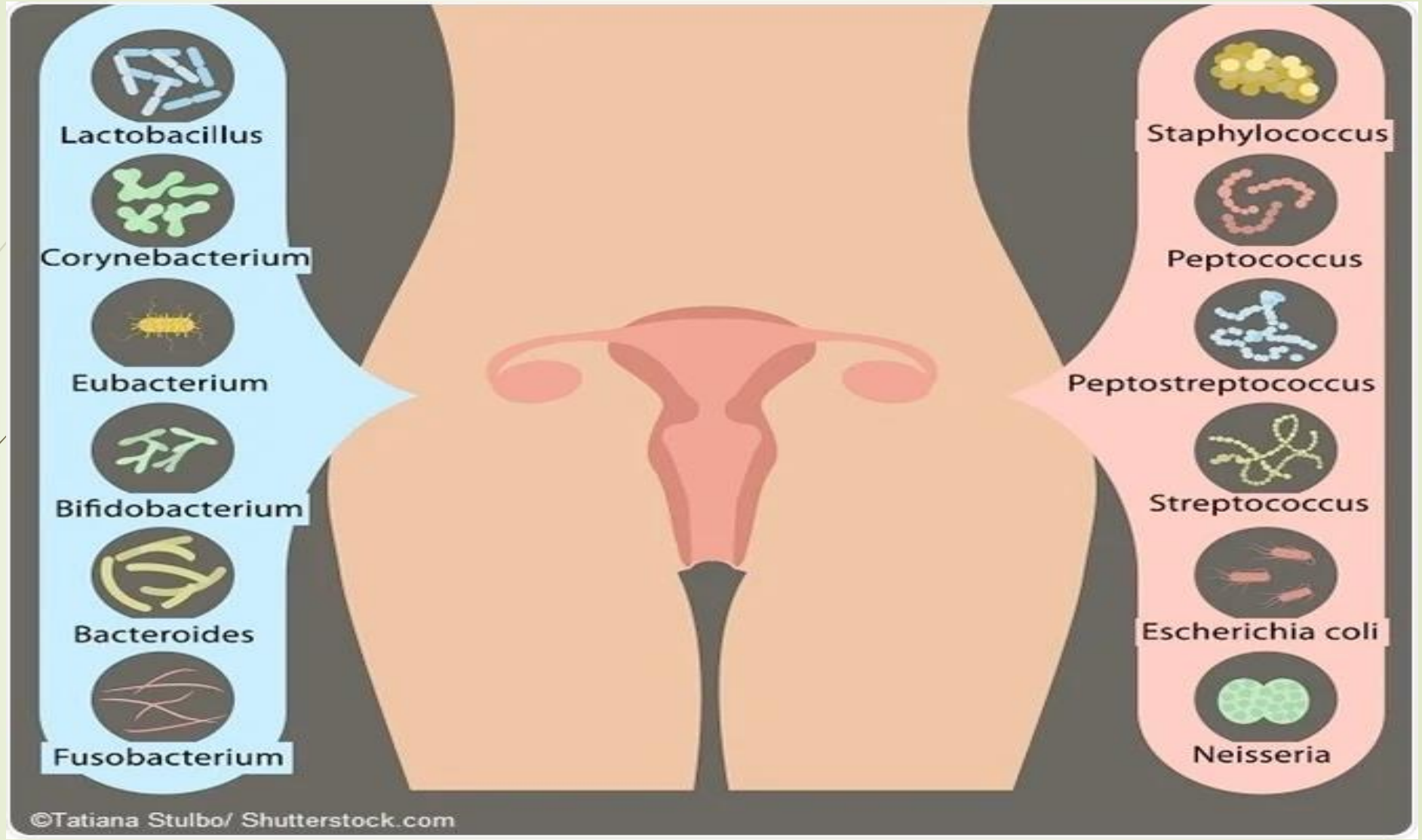
Brain Structure and Response to Emotional Stimuli as Related to Gut Microbial Profiles in Healthy Women

- Women in the microbial cluster predominated by *Prevotella* (vs. *Bacteroides*) had decreased hippocampal activity and increased functional brain connectivity between brain regions involved in emotional and attentional sensory processing.
- What does decreased hippocampal activity mean?
- Reduced hippocampal volumes were associated with **deficits in visual and verbal memory performance**. Conclusions. Although reduced hippocampal volumes are most pronounced in late-onset depression, older people with early-onset disorders also display volume changes and memory loss.
- https://www.cambridge.org/core/journals/the-british-journal-of-psychiatry/article/reduced-hippocampal-volumes-and-memory-loss-in-patients-with-early-and-lateonset-depression/2A7269A56BAABE79F0B715794F5B4DD5

- https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6776431/#R107
- http://www.ncbi.nlm.nih.gov/pmc/articles/pmc6089374/

Childbearing years and the microbiome

- Pregnancy and changes in the microbiome
- The importance of nutrition



https://www.google.com/url?sa=i&url=https%3A%2F%2Fwww.news-medical.net%2Flife-sciences%2FUterine-Microbiome.aspx&psig=AOvVaw1453REANvsKOXWfBvMwlHS&ust=1697598176818000&source=images&cd=vfe&opi=89978449&ved=0CBAQjRxqFwoTCMiknZSM_IEDFQAAAAAdAAAAABAS

Vaginal Microbiome:

- The vaginal microbiome plays a significant role in reproductive health.
- A healthy vaginal microbiome is typically dominated by *Lactobacillus* species. These bacteria produce lactic acid, creating an acidic environment that protects against pathogenic microbes.
- Imbalances in the vaginal microbiome (dysbiosis) can lead to bacterial vaginosis (BV). BV has been associated with miscarriage, preterm birth, and increased risk of acquiring sexually transmitted infections, all of which can indirectly influence infertility.

Lactobacilli

- restoration of normal vaginal microflora through *Lactobacilli* supplementation is considered to be a viable adjunctive strategy for the treatment or prevention of BV
- The route of administration of probiotics was coded as either oral or vaginal
- women of different ethnicity had differential vaginal pH levels, which were lowest in White, followed by Asian, Black, and Hispanic study subjects. These findings thus suggested that different populations may have incongruous probiotic efficacy against BV
- https://www.frontiersin.org/articles/10.3389/fnut.2022.938838/full#supplementary-material
- https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9530327/

Endometrium

- The endometrium, or lining of the uterus, was once thought to be sterile. However, recent studies have identified a unique endometrial microbiome.
- A balanced endometrial microbiome may be essential for embryo implantation.
- A study found that a non- *Lactobacillus* dominated microbiome in the endometrium could be linked to recurrent implantation failure in in-vitro fertilization (IVF) procedures.
- *Lactobacilli* play an important role in maintenance of vaginal bacterial communities through production of bacteriocins, hydrogen peroxide, and lactic acid, which decreases the vaginal pH and impairs growth of pathogenic bacteria.
  https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8745284/

Endometrium

- Inflammatory responses to bacterial modifications might also be related to infertility, as proinflammatory microenvironments occur in different gynecological and obstetrical diseases.
- Increasing evidence demonstrates the impact of variations in the FGT microbiota on overall female health
- *Gardnerella vaginalis*, *Atopobium vaginae*, and *Prevotella bivia*—are associated with the occurrence of chronic endometritis and pelvic inflammatory disease
- https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8745284/

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Gut hormone connection

- **Gut Microbiome and Hormonal Balance**: The gut microbiome can influence the metabolism and recycling of estrogens. Dysbiosis in the gut microbiome can disrupt these processes, potentially leading to conditions like polycystic ovary syndrome (PCOS), which is a common cause of infertility in women.
- **Inflammation**: Chronic inflammation, which can result from gut microbiome dysbiosis, has been implicated in various conditions that can influence fertility, such as endometriosis and PCOS.
- **Immune Modulation**: The microbiome plays a role in training and regulating the immune system. An imbalanced microbiome might lead to immune responses that are unfavorable for implantation and early fetal development.

PCOS continued

- many microbiome-related diseases have a sex bias, some of which have been shown to be associated with sex hormones
- Polycystic ovary syndrome (PCOS) is a multifactorial disorder with various genetic, endocrine and environmental abnormalities. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10405626/

Pre-menstrual & Menopause Microbiome

- Changes leading to menopause
- How the microbiome adjusts and its effects on health
- The microbiome may play a role in body weight. Some studies have shown that transplanting the microbiome from an obese mouse to a lean one can cause the lean mouse to gain weight.
- research suggests that menopause is associated with lower gut microbiome diversity and a shift toward greater similarity to the male gut microbiomehttps://www.ncbi.nlm.nih.gov/pmc/articles/PMC9379122/

Aging, Longevity, & the Microbiome

- How a healthy microbiome can promote longevity
- Nutrition and the exposome in old age
- **Brain Connection**: The gut microbiome and the brain communicate, often referred to as the "gut-brain axis." Certain gut bacteria can produce neurotransmitters, potentially influencing mood and behavior.

Prevotella and emotion

- Women in the microbial cluster predominated by *Prevotella* (vs. *Bacteroides*) had decreased hippocampal activity and increased functional brain connectivity between brain regions involved in emotional and attentional sensory processing.
- https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6776431/#R107

Healthy microbiome and healthy poops: How to be a 3 on the Bristol Stool scale

- Eat whole foods
- Understand the clean 15 and dirty dozen
- 30 grams of fiber a day
- Increase omega 3
- Preserve your digestive system from the lips to the anus

Why do we need a healthy poop?

Synthesis of Vitamins

- Role of the microbiome in vitamin production
- Importance for overall health at all stages
- Some gut bacteria are able to synthesize essential vitamins that the human body can't produce on its own, like vitamin K and some B vitamins.

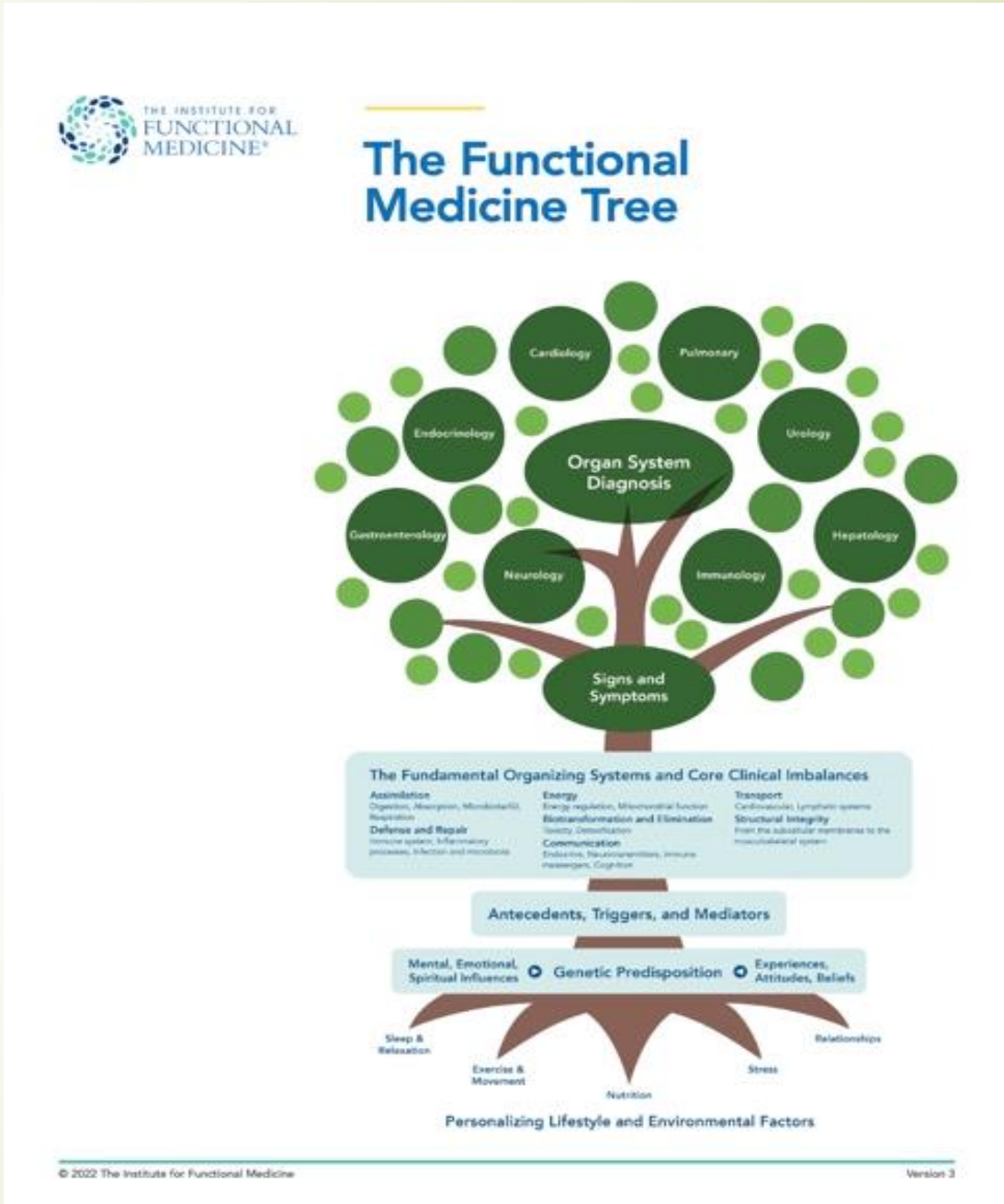
Nutrition, Exposome, & Epigenetics

Conclusions

Woman's life unfolds,

Microbes change with each new phase,

Health's balance they hold.



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