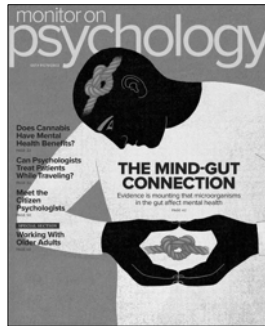


The Mind-Gut Connection: How Healing the Gut Improves Mental and Neurological Health



Tieraona Low Dog, MD

Chair: US Pharmacopeia Dietary Supplement Admissions, Evaluation and Labeling Expert Committee

Clinical Assoc. Professor of Medicine
University of Arizona (retired)

Guiding Teacher: NY Zen Center Fellowship in
Contemplative Medicine

National Geographic's
Life Is Your Best Medicine
Healthy At Home
Fortify Your Life
Guide to Medicinal Herbs

www.DrLowDog.com

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Cognition



- The process in which **one learns about the world**, and the **relationship between self and one's place in the world**.
- Ability to **learn and understand experiences**; acquire and **retain knowledge, respond** to situations and solve problems.
- Cognitive processes include **attention, perception, memory, reasoning, planning, language, problem solving**.

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Mental Health

- Refers to our **emotional, psychological, and social well-being**. It affects how **we think, feel, and act**. Helps determine **how we handle stress, relate to others**, and make **healthy choices**.
- When **demands** placed on us **exceed our resources** and coping abilities, our **mental health** can be impacted. If someone is **working long hours, caring** for a relative, or experiencing **economic hardship**, they **may** experience **poor mental health**.
- **Poor mental health** and **mental illness** *are not the same*. A person can experience poor mental health and not be diagnosed with a mental illness. Someone with a mental illness can have periods of mental, physical, social wellbeing.

<https://www.cdc.gov/mentalhealth/learn/index.htm>

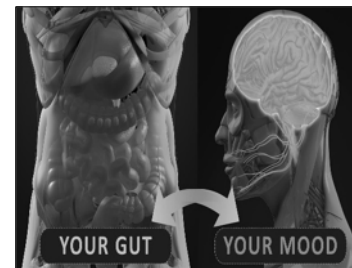
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Enteric Nervous System (ENS): The Second Brain



- **100 million nerve cells** from esophagus to rectum. **Anatomical and physiologic** two-way communication between the gut and brain via **vagus nerve**.
- **Gut-brain axis** offers us a greater understanding of connection between the **gut, diet and disease**, including depression and anxiety.

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Gut-Brain Communication



- Gut bacteria produce neurotransmitters: **dopamine, serotonin, norepinephrine, GABA, acetylcholine, melatonin**; critical for mood, sleep, anxiety, concentration, reward, and motivation.
- Serotonin associated with **depression and happiness** - **90%** is made in the digestive tract - not the brain.
 - Most common side effects of SSRIs are gut-related (e.g., nausea, diarrhea).
- Gut microbiota can **change** how our brains react to events/stressors.

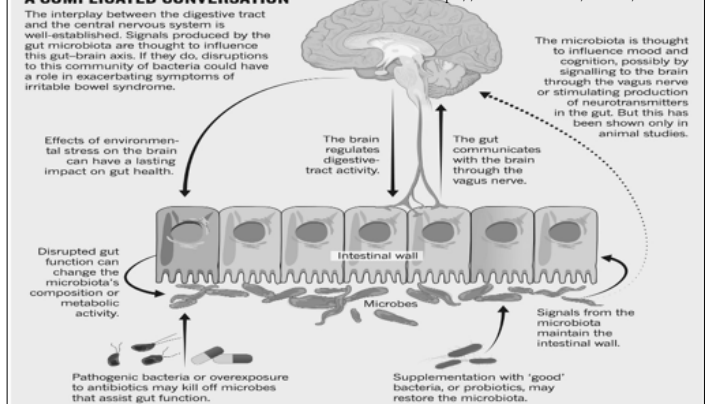
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A COMPLICATED CONVERSATION

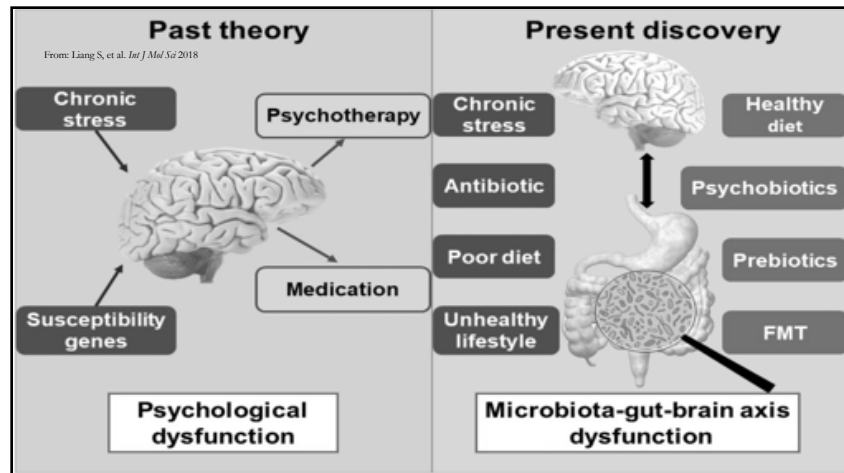
The interplay between the digestive tract and the central nervous system is well-established. Signals produced by the gut microbiota are thought to influence this gut-brain axis. If they do, disruptions to this community of bacteria could have a role in exacerbating symptoms of irritable bowel syndrome.

<https://www.nature.com/articles/533S104a>



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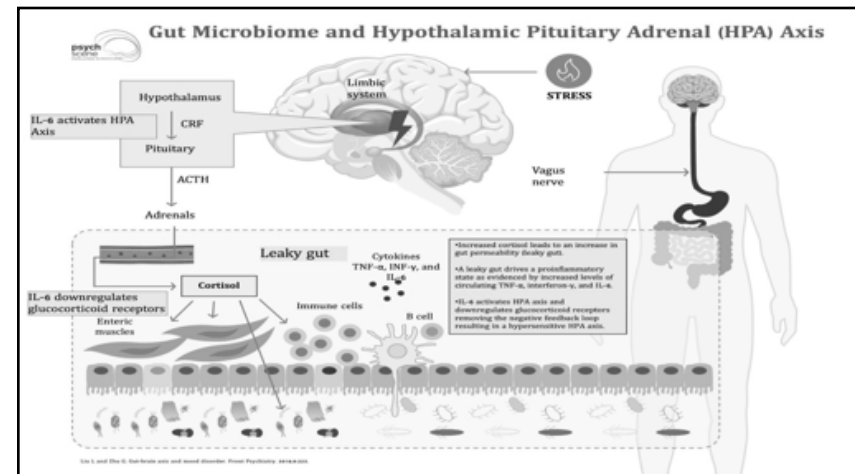
Two Bugs Noticeably Absent

- **Gut microbial diversity** has been shown to be **lower** in those with depression.
- **Flemish Gut Flora Project (1054 healthy adults):** 173 diagnosed with depression or poor quality-of-life intake; research team compared their microbiomes with those of other participants.
- **Two kinds of microbes, *Coprococcus* and *Dialister*, missing from microbiomes of depressed subjects,** but not those with a high quality of life. Findings true, even after age, sex, or antidepressant use, all of which influence the microbiome, were accounted for.
- **1064 Dutch people:** researchers found **same two species missing** among those who were depressed but not in those with high quality of life.
- **Intriguing.....**

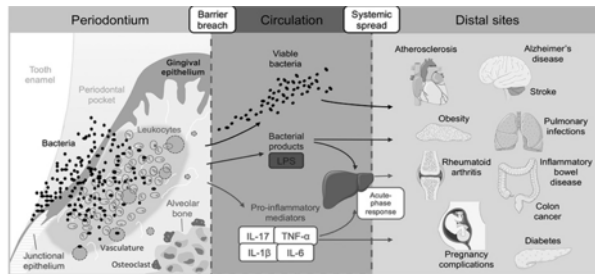
Valles-Colomer M, et al. The neuroactive potential of the human gut microbiota in quality of life and depression. *Nature Microbiology* 2019; 4: 623–632

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- Severe periodontitis affects 743 million people worldwide.
- Bacteria can enter bloodstream and translocate to extra-oral tissue: **lung, heart, gut, placenta, brain inflamed joints, etc.** Study found **100%** of patients with CVD had *P. gingivalis* arterial colonization, found in **brains** of those with AD.

From: Konkel JE, et al. Distal Consequences of Oral Inflammation *Front. Immunol* 2019; <https://doi.org/10.3389/fimmu.2019.01403>

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The Who's Who of Brain Cells

Glial cells outnumber neurons by 9 to 1. Once thought of as mere helper cells, glia are now known to play key roles in shaping brain circuitry and controlling neurons' behavior.

Neuron
Forms networks with other neurons and transmits messages through rapid electrochemical signals across connections known as synapses.

Astrocyte
Provides structural support, nutrients and oxygen to neurons. Enables synapse formation and prunes weak synapses. Can help heal — or destroy — injured or diseased neurons.

Microglia
Prunes excess synapses in developing nervous system. Removes molecular debris. During infections, gobbles up invading pathogens. May also prune functional synapses in cases of neurodegenerative disease.

Oligodendrocyte
Insulates axons (nerve fibers) with myelin, improving transmission of nerve impulses. Damage to oligodendrocytes leads to demyelination, implicated in neurological disorders such as multiple sclerosis and Charcot-Marie-Tooth disease. —S.M.

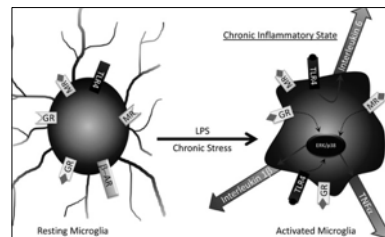
From: <https://www.discovermagazine.com/mind/the-brain-of-ben-barres>

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Stress and Microglia

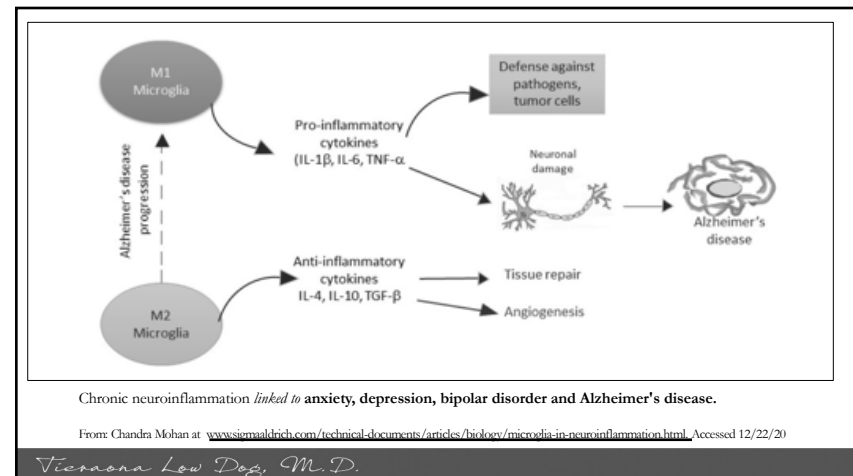
- **Microglia** constant surveillance mode; biosensors for **stressors** in CNS.
- Mouse study: repeated **unpredictable stress** caused microglia in prefrontal cortex to **remodel neural circuits**. *All animals* showed signs of **anxiety and depression**.¹
- Microglia hold “**memories**” of stress and have **larger** and **more rapid response** when exposed to future stressors.²



1. Wohleb ES, et al. *Biol Psychiatry* 2018; 83(1): 38-49
2. Weber MD, et al. *Biol Psychiatry* 2019; 85(5): 667-678

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LPS and Neuroinflammation

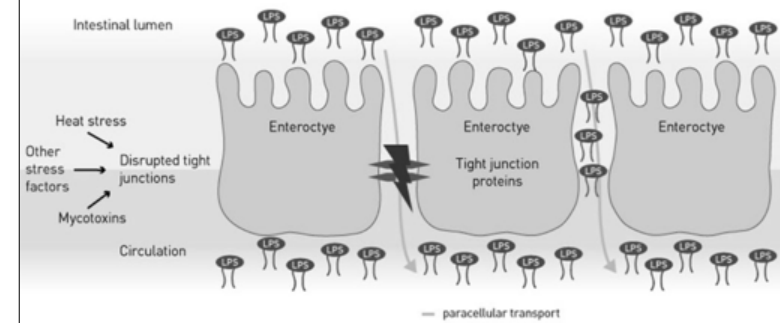
- LPS enter circulation from decreased intestinal barrier function, bind TLR-4.
- Triggers **systemic inflammation** degrades **intestinal/blood brain barriers**.
- TLR-4 is expressed on cells in the brain and nervous system - **once activated, they stimulate release of pro-inflammatory cytokines**.
- LPS induce **cognitive impairment, anxiety, depression** in animal models.
- **Systemic inflammation** can **change microglial phenotype** and **disrupt blood brain barrier** in absence of precipitating neuronal damage/infection.

Zhao J, et al. *Sci Rep* 2019; 9:5790 doi:10.1038/s41598-019-42286-8
Kure C, et al. *Front Pharmacol* 2017; doi.org/10.3389/fphar.2017.00117

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Impaired gut barrier



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Human Microbiome Project

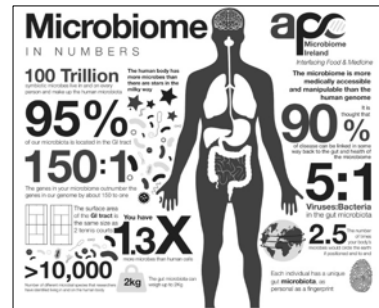
- **Massive NIH research initiative** cataloging microorganisms living in and on our body launched in 2007.
- Led to *rapidly growing appreciation* for **incredible and diverse impact** these organisms have on our **health and well-being**.
- Gut bacteria: produce **vitamins**, break down food; their presence OR absence linked to **obesity, IBD, IBS, anxiety, depression, food allergies, neuroinflammation, GI infections, high blood pressure, diabetes, metabolic syndrome, and more**.
- **Our resiliency**, our ability to recover quickly from stressors, may be a function of *which bacteria inhabit or don't inhabit our gut*.

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Definitions

- **Microbiome**— all genetic material of microorganisms in particular environment
- **Microbiota**— the microorganisms.
- **Dysbiosis** (microbial imbalance); lower diversity associated with autoimmune disease, obesity, and metabolic conditions.
- **Probiotics**: live microorganisms when administered in adequate amounts confer a health benefit to the host.



Valdes AM, et al. *BMJ* 2018;361:k2179

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Birth

- Babies born **vaginally** covered in microbial film as they pass through birth canal.
- Babies born by **C-section** colonized by skin microbes—very different species.
- Babies **acquire microbes from everyone and everything they touch**.
- **Where** the baby is born, what type of **delivery**, if **breastfed or bottle fed** – all these impact the microbiome for **months or years after birth**.
- **Controversy**: are babies colonized in-utero? Most evidence supports **sterile womb theory**.



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Neonatal Microbiome



- Differences in microbial species observed between C-section- and vaginally delivered babies *up to 7 years after birth*.¹
- Intrapartum antibiotics associated with **lower abundance of good bacteria (*Lactobacilli* and *Bifidobacterium*)** in neonatal gut.²
- Formula feeding associated with **increased** prevalence of pathogenic bacteria (*C. difficile*, *Bacteroides fragilis*, *E. coli*) and **decreased** prevalence of *Bifidobacterium*.³

1. Salminen S, et al. *Gut*. 2004;53:1388–1389; 2. Aloisio I, et al. *Appl Microbiol Biotechnol*. 2014;98:6051–6060.
3. Mueller NT, et al. *Trends Mol Med* 2015; 21(2): 109-17

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Probiotics and Birth Mode

- **Mothers given probiotic** or placebo during pregnancy and then **infants** given same.¹
 - **Placebo group**: birth mode and/or antibiotics significantly altered microbiota composition and function, reducing *Bifidobacterium*.
 - **Probiotic group**: effects of birth mode and/or antibiotics either *completely eliminated or dramatically reduced*.

(Probiotic: *Bifidobacterium breve*, *Propionibacterium freudenreichii* subsp. *shermanii* JS, *Lactobacillus rhamnosus* Lc705, and *L. rhamnosus* GG)

1. Korpela K, et al. Probiotic Supplementation Restores Normal Microbiota Composition and Function in Antibiotic-Treated and in Caesarean-Born Infants. *Microbiome* 2018; 6(1): 182



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Birth to 3 Years

- Within weeks, **microbial specialization** occurs.
- Microbial populations in infant are **similar to the people they live with**.
- Microbiota dramatically altered by **antibiotics, PPI use, etc.**
- **Number and type of species increase and change with age.**
 - Example: babies have more folate *producing* microbes – adults have more folate *harvesting* microbes.



Azad MB, et al. Gut microbiota of healthy Canadian infants: profiles by mode of delivery and infant diet at 4 months. *Can Medical Association Journal*, 2013; 185(5), 385-394.

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Probiotics: Long Term Follow-Up of Moms and Infants

- **316 mother infant pairs: *L. rhamnosus* HN001 (6 billion cfu) or placebo**
- Pregnant mothers supplemented **from 35 weeks gestation to 6 months post-partum** if nursing. **Infants supplemented from birth until 2 years old.**
- At **2, 4 and 6 years of age**, prevalence of **eczema and allergic sensitization** determined by clinical diagnosis and skin prick (results following slide)¹
- **Prevalence at 11 years follow-up:**²
 - **29% reduced risk of atopic sensitization**
 - **42% reduced risk of eczema**
 - **24% reduced risk of wheeze**

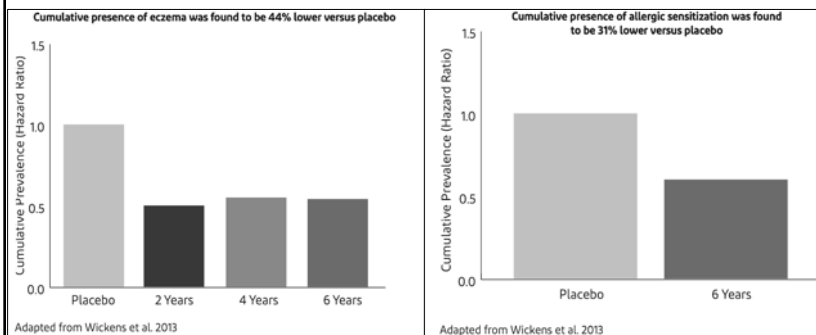


1. Wickens K, et al. *Clin Exp Allergy* 2013; 43(9):1048-57.
2. Wickens K, et al. *Pediatr Allergy Immunol* 2018; 29(8): 808-14

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Impact of Probiotics at 2, 4 and 6 Years on Eczema and Allergic Sensitization



Wickens K, et al. *Clin Exp Allergy* 2013; 43(9):1048-57.

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Are Probiotics and Prebiotics Safe for Use during Pregnancy and Lactation? A Systematic Review and Meta-Analysis

- **11 of 100 eligible studies** reported adverse effects and were eligible for inclusion in quantitative analysis.
- Adverse effects associated with probiotic and prebiotic use **do not pose any serious health concerns to mother or infant. Authors concluded:** Probiotic and prebiotic products **safe for use during pregnancy and lactation.**

Sheyholislami H, et al. *Nutrients* 2021; Jul 13;13(7):2382.



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Age 3 to Old Age

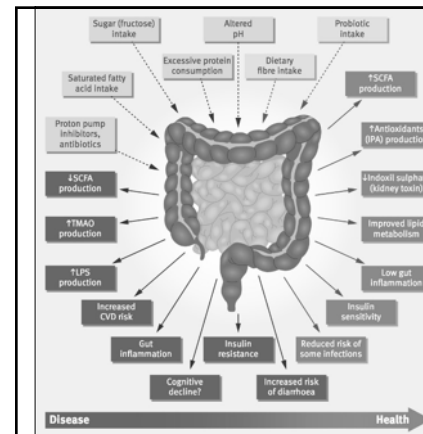
- Throughout the human life span, gut microbiome follows some predictable patterns, with **rapid change from infancy to age three, stability up until middle age, and then accelerated change starting in late adulthood.**
- Diets rich in **salty, sugary, fatty processed foods may damage aging gut**, while higher **fiber foods like fruits, vegetables, seeds, beans, and nuts** combined with **exercise** help protect healthy gut microbiome as we age.

Wilmanski, T et al. Gut microbiome pattern reflects healthy ageing and predicts survival in humans. *Nature Metabolism* 2021; 3(2): 274-286.



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- Many dietary, lifestyle and medications can **dramatically impact** the microbiome and ultimately impact human health.
- Dietary fiber and probiotics are **SO important** for gut health.

From: Valdes AM, et al. Role of gut microbiota in nutrition and health. *British Medical Journal* 2018;361:j2179

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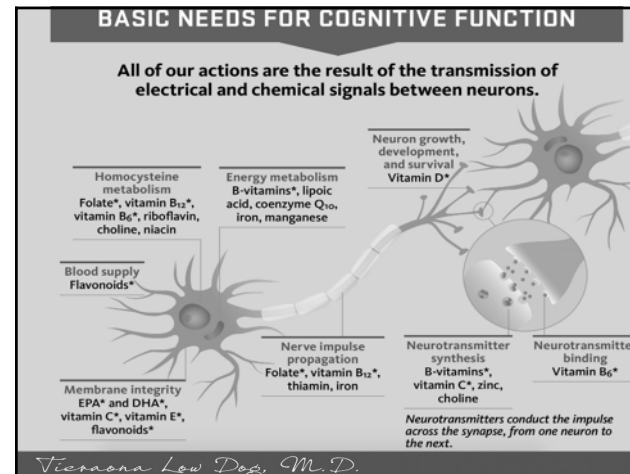
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Brain and Nutrition

- Your brain is always on - managing** thoughts, movements, breathing, heartbeat, all of your senses —24/7.
- Your brain requires **constant supply of fuel** from the food we eat. And what we eat directly affects **structure and function of brain and mood.**
- If brain is deprived of good-quality nutrition, or damaging inflammatory cells circulate within the **brain's enclosed space, negative consequences can happen.**
- Emerging field of **nutritional psychiatry** highlights the **impact of food on the gut microbiome and the impact of the microbiome on mood.**

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From: Nutrition and Cognitive Function

Linus Pauling Institute Oregon State University

<https://lpi.oregonstate.edu/sites/lpi.oregonstate.edu/files/lpi-cognition-infographic.pdf>

Accessed 12/15/20

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Take an Age/Gender Appropriate Multi

- **90 million** Americans are **vitamin D** deficient (using Endocrine Society guidelines < 20ng/mL)
- **30 million** are deficient in **vitamin B6** (mostly women)
- **18 million** people have **B12** deficiency (mostly > 50 yrs.)
- ~**21 million** Americans have serious **vitamin C** deficiency, **66 million** are *at risk* for deficiency
- **13% Latinas** and **16% African American**, and **8% white women** (ages 12–49) are **iron** deficient
- Women 25–39 overall have **borderline iodine** insufficiency



CDC: 2nd National Report on the Biochemical Indicators of Diet and Nutrition in the U.S. population

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Twelve Antidepressant Nutrients

- Food is **modifiable determinant** of **systemic inflammation**, which has been described as a **major cause and consequence** of **depression**.
- **Folate, iron, EPA and DHA, magnesium, potassium, selenium, thiamin, vitamins A, B6, B12, C; and zinc.**
- Highest scoring foods were bivalves (oysters, mussels), seafoods, and **organ meats** for animal foods.
- Highest scoring **plant** foods were **leafy greens, lettuces, peppers, and cruciferous vegetables.**

Kiecolt-Glaser JK, et al. Inflammation: depression fans the flames and feasts on the heat. *Am J Psychiatry*. 2015;172:1075–1091.

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European Union: My New Gut Project

- Initiative focused on understanding and **promoting health** by **targeting the gut microbiome**.
- Dietary recommendation intended to improve **major depressive symptoms** by targeting the gut microbiome: **increase consumption of fiber and fish.**
- Average annual seafood intake for Americans is 14.6 pounds, and the USDA estimates that **80-90 percent of the population fails to meet the recommendation of two servings of seafood per week**

Dinan TG, et al. Feeding melancholic microbes: MyNewGut recommendations on diet and mood. *Clin Nutr* 2019;38:1995–2001
Bliss RM. Consumers Missing Out on Seafood Benefits.
Available: <https://search.proquest.com/openview/bdc2156f62c34a381e42b25b3249a11f/1?pq-origsite=scholarlink&42132>

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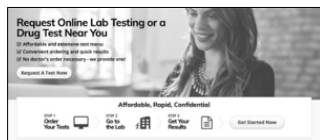
Global Omega-3 Status Map shows low levels for most of the world



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Where Can You Get Tested?

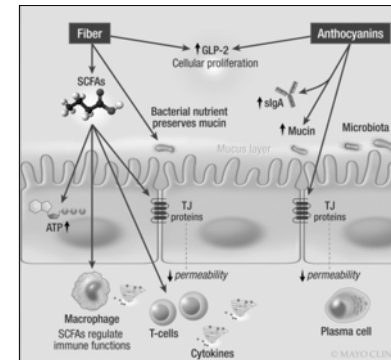
- Talk to your health care practitioner about potential concerns around micronutrient deficiencies.
- Most lab tests are readily available through LabCorp or Quest.
- If you order your own tests, www.requestatest.com, Vibrant America, EveryWell, and SpectraCell are commonly used.



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Eat More Fiber and Colorful Plants



- Diets **high in fiber and anthocyanins** (purple, black, blue or red pigments in plants) **strengthen intestinal barrier**, preventing toxins from passing through intestinal wall into bloodstream.

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Fruits	Serving size	Total fiber (grams)*
Raspberries	1 cup	8.0
Pear	1 medium	5.5
Apple, with skin	1 medium	4.5
Banana	1 medium	3.0
Orange	1 medium	3.0
Strawberries	1 cup	3.0

Vegetables	Serving size	Total fiber (grams)*
Green peas, boiled	1 cup	9.0
Broccoli, boiled	1 cup chopped	5.0
Turnip greens, boiled	1 cup	5.0
Brussels sprouts, boiled	1 cup	4.0
Potato, with skin, baked	1 medium	4.0
Sweet corn, boiled	1 cup	3.5
Cauliflower, raw	1 cup chopped	2.0
Carrot, raw	1 medium	1.5

<https://www.mayoclinic.org/healthy-lifestyle/nutrition-and-healthy-eating/in-depth/high-fiber-foods/art-20050948>

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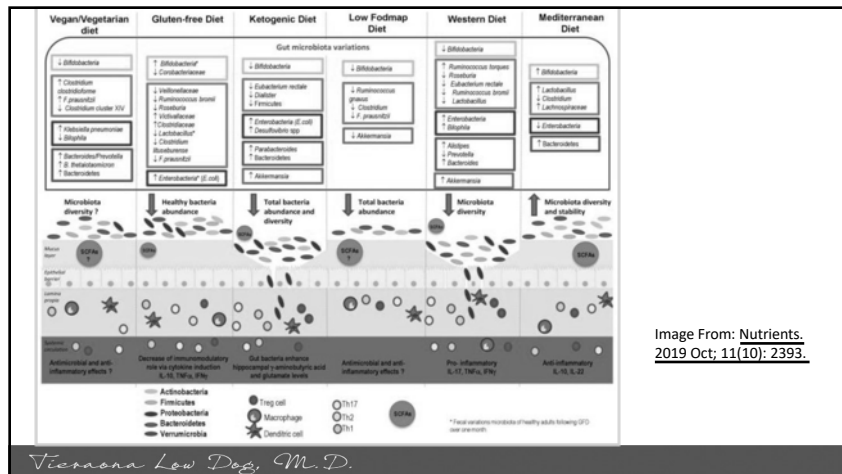
Grains	Serving size	Total fiber (grams)*
Spaghetti, whole-wheat, cooked	1 cup	6.0
Barley, pearled, cooked	1 cup	6.0
Bran flakes	3/4 cup	5.5
Quinoa, cooked	1 cup	5.0
Oat bran muffin	1 medium	5.0
Oatmeal, instant, cooked	1 cup	5.0
Popcorn, air-popped	3 cups	3.5
Brown rice, cooked	1 cup	3.5
Bread, whole-wheat	1 slice	2.0

Legumes, nuts and seeds	Serving size	Total fiber (grams)*
Split peas, boiled	1 cup	16.0
Lentils, boiled	1 cup	15.5
Black beans, boiled	1 cup	15.0
Baked beans, canned	1 cup	10.0
Chia seeds	1 ounce	10.0
Almonds	1 ounce (23 nuts)	3.5
Pistachios	1 ounce (49 nuts)	3.0
Sunflower kernels	1 ounce	3.0

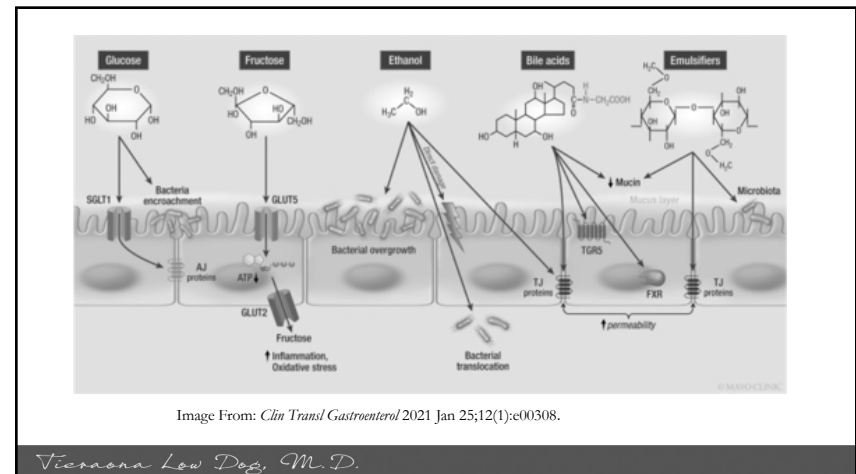
<https://www.mayoclinic.org/healthy-lifestyle/nutrition-and-healthy-eating/in-depth/high-fiber-foods/art-20050948>

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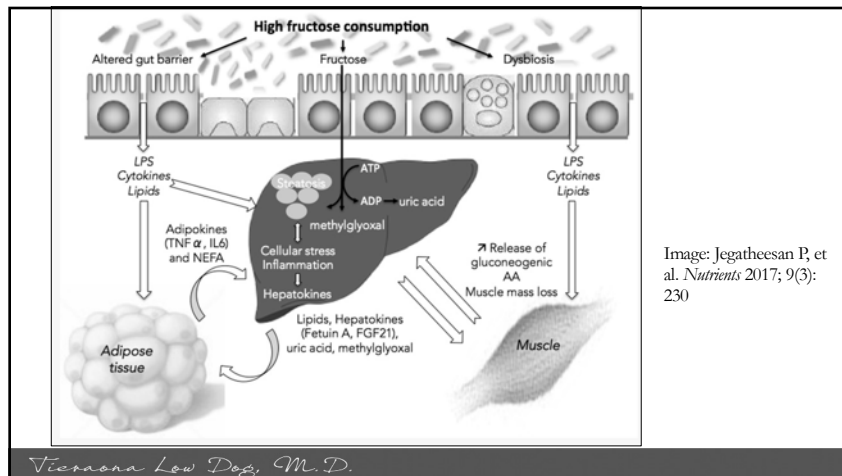
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Glycemic Load and Mood

- 82 healthy weight and healthy overweight or obese adults enrolled in randomized, crossover controlled feeding study.
- Compared to a low GL diet, consumption of high GL diet resulted in:
 - 38% higher score for **depressive symptoms** (P = 0.002)
 - 55% higher score for **total mood disorder** (P = 0.05)
 - 26% higher score for **fatigue/inertia** (P = 0.04), compared to low GL diet.



Bresneyer KL, et al. *Appetite* 2016; Dec 1;107:253-259.

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Food	Serving Size	Glycemic Load	Food	Serving Size	Glycemic Load
Grapefruit	½ large	3	Asparagus	½ cup	2
Apple	1 medium	6	Broccoli	1 cup	4
Banana	1 large	14	Green beans	1 cup	3
Raisins	1 small box	20	Tomato	1 medium	2
Watermelon	1 cup	8	Subway sandwich	6 inch	17
Carrots	1 large	5	Turkey breast		
Orange	1 medium	6	Butter pecan ice cream	5.5 ounces (small)	22
Sweet potato	1 cup	17	Vanilla ice cream cone	4.5 ounces (small)	19
Baked potato	1 medium	28	Potato chips, fat free	1 bag (8 ounces)	49
French fries	1 medium serving	26	Tortilla chips, white corn	3.5 ounces	38
Snickers	1 bar	35	White bread	1 slice	10
Reese's cup	1 miniature	2	White rice	1 cup	33
White table wine	5 ounces	1	Brown rice	1 cup	23
Red table wine	5 ounces	1	Spaghetti	1 cup	38
Grape juice	6 ounces	12			

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Inflammatory Food Ratings		FOOD	SERVING SIZE	SERVING SIZE (GRAMS)	IF RATING
200 or higher	Strongly anti-inflammatory	AGAVE NECTAR	1 TBSP	21	-74
101 to 200	Moderately anti-inflammatory	ALMOND BUTTER	¼ CUP	64	100
0 to 100	Mildly anti-inflammatory	CHEESE, CHEDDAR	1 OUNCE	28.35	-20
-1 to -100	Mildly inflammatory	CHICKEN BREAST, RSTD	3 OUNCES	85	-19
-101 to 200	Moderately inflammatory	MILK, WHOLE	1 CUP	246	-46
-201 or lower	Strongly inflammatory	OLIVE OIL	1 TBSP	14	74
		ONIONS, COOKED	½ CUP	105	240
		RICE, WHITE	1 CUP	158	-153
		SPINACH	1 CUP	30	75
		SALMON, SOHO BAKED	3 OUNCES	85	450
		TURMERIC	½ TSP	1.5	338

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Table 1 Examples of foods, nutrients, and dietary patterns that influence human health linked to their effects		
Dietary element	Effect on gut microbiome	Effect on health outcomes mediated by gut microbiome
Low FODMAP diet	Low FODMAP diet increased Actinobacteria; high FODMAP diet decreased abundance of bacteria involved in gas consumption ⁵⁸	Reduced symptoms of irritable bowel syndrome ⁵⁶
Cheese	Increased <i>Bifidobacteria</i> , ^{97,98} which are known for their positive health benefits to their host through their metabolic activities, ⁹⁹ Decrease in <i>Bacteroides</i> and <i>Clostridia</i> , some strains of which are associated with intestinal infections ⁹⁸	Potential protection against pathogens, ¹⁰⁰ Increased production of SCFA and reduced production of TMAO ⁹⁹
Fibre and prebiotics	Increased microbiota diversity and SCFA production ^{102,101,102}	Reduced type 2 diabetes ¹⁰² and cardiovascular disease ¹⁰³
Artificial sweeteners	Overgrowth of Proteobacteria and <i>Escherichia coli</i> , ¹⁰⁴ <i>Bacteroides</i> , <i>Clostridia</i> , and total aerobic bacteria were significantly lower, and faecal pH was significantly higher ⁴⁷	Induced glucose intolerance ¹⁰⁵
Polyphenols (eg, from tea, coffee, berries, and vegetables such as artichokes, olives, and asparagus)	Increased intestinal barrier protectors (<i>Bifidobacteria</i> and <i>Lactobacillus</i>), butyrate producing bacteria (<i>Faecalibacterium prausnitzii</i> and <i>Roseburia</i>) and <i>Bacteroides vulgatus</i> and <i>Akkermansia muciniphila</i> , ¹⁰⁷ Decreased lipopolysaccharide producers (<i>E coli</i> and <i>Enterobacter cloacae</i>) ¹⁰⁶	Gut micro-organisms alter polyphenol bioavailability resulting in reduction of metabolic syndrome markers and cardiovascular risk markers ¹⁰⁸
Vegan	Very modest differences in composition and diversity in humans and strong differences in metabolomic profile compared with omnivore diet in humans ⁵⁰	Some studies show benefit of vegetarian over omnivore diet, ¹⁰⁹ others fail to find a difference ¹¹⁰

Valdes AM, et al. Role of gut microbiota in nutrition and health. *British Medical Journal* 2018;361:j2179

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Sugar Substitutes



- Sugar substitutes frequently **1000 times sweeter** than sucrose.
- Dan have negative effects** on gut microbiota.
- Sucralose, saccharin and stevia all shown to disrupt balance and diversity** of gut microbiota.
- Erythritol, mannitol and sorbitol have no effect** on gut microbiota.
- Isomaltose and maltitol, increase bifidobacteria** and may have **prebiotic actions**

Neukam JE, et al. Reshaping the gut microbiome: Impact of low-calorie sweeteners and the link to insulin resistance? *Physiol Behav* 2016;164(Pt B):488-93.
Raza-Ojeda EJ, et al. Effects of Sweeteners on the Gut Microbiota: A Review of Experimental Studies and Clinical Trials. *Adv Nutr* 2019; 10(1): S31-48

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Obesity and Microbiota?

- Diets high in sugar, simple carbs, and saturated fat encourages growth of microbes better at **extracting** energy from food, signaling body to **store energy as fat**.
- Early disruption of gut microbiota leads to low levels *Bifidobacteria* and obesity.
- Obesity during middle age (40 -60 years) consistently associated with higher risk of dementia later in life.

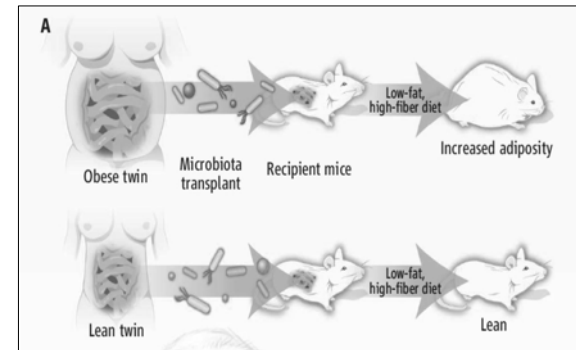
Federico A, et al. Gut microbiota, obesity and metabolic disorders. *Minerva Gastroenterol Dietol* 2017;63(4):337-344



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Ridaura, V.K., et al., *Gut microbiota from twins discordant for obesity modulate metabolism in mice*. Science, 2013.



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Antibiotics and Obesity



- American children on *average*:
 - 0 to 2 years age: 3 full doses of antibiotics
 - Up to 10 years: 10 full doses of antibiotics
 - By age 20: 17 full doses of antibiotics
- Four or more courses of antibiotics given before 3 years of age independently associated with obesity at age 5.

Cox LM. Antibiotics in early life and obesity. *Nat. Rev. Endocrinol* 2015; 11, 182-190.

Kelly D, et al. Antibiotic use in early childhood and risk of obesity: longitudinal analysis of a national cohort. *World J Pediatrics* 2019;15(4):390-397.

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Title of the study	Year	Subjects of the study	Final result(s) gathered	Reference
Childhood overweight after establishment of the gut microbiota: the role of delivery mode, pre-pregnancy weight and early administration of antibiotics.	2011	28354 mother-child	Antibiotics in infancy influences the risk of overweight in later childhood	Aplev et al., 2011
Infant antibiotic exposures and early-life body mass.	2013	11532 children	Exposure to antibiotics during the first 6 months of life was associated with increases in body mass.	Trasande et al., 2013
Antibiotic treatment during infancy and increased body mass index in boys: an international cross-sectional study.	2014	74946 children	Exposure to antibiotics during the first 12 months of life is associated with a small increase in BMI in boys aged 5-8 years	Murphy et al., 2014
Infant antibiotic exposure and the development of childhood overweight and central adiposity	2014	1047 children	Antibiotic use in the first year of life was associated with overweight	Azad et al., 2014
Association of antibiotics in infancy with early childhood obesity.	2014	64580 children	Repeated exposure to broad-spectrum antibiotics was associated with early childhood obesity	Bailey et al., 2014
Prenatal exposure to antibiotics, cesarean section and risk of childhood obesity.	2015	436 mother-child dyads	Exposure to antibiotics in the second or third trimester of pregnancy were associated with higher risk of childhood obesity.	Mueller et al., 2015
Prenatal exposure to systemic antibacterials and overweight and obesity in Danish schoolchildren: a prevalence study.	2015	9686 children	Prenatal exposure to systemic antibacterials was associated with an increased risk of overweight and obesity at school age	Mor et al., 2015
Antibiotic exposure in infancy and risk of being overweight in the first 24 months of life.	2015	6114 boys and 5948 girls	Antibiotic exposure before 6 months was associated with increased body mass	Saari et al., 2015
Early Life Antibiotic Exposure and Weight Development in Children.	2016	979 children	Repeated exposure to antibiotics early in life, especially β -lactam agents, is associated with increased weight and height.	Mbakwa et al., 2016
Antibiotic Use and Childhood Body Mass Index Trajectory.	2016	142824 children	Body Mass Index increase	Schwartz et al., 2016
Administration of Antibiotics to Children Before Age 2 Years Increases Risk for Childhood Obesity.	2016	21714 children	Administration of 3 or more courses of antibiotics before age of 2 years was associated with an increased risk of early childhood obesity	Scott et al., 2016

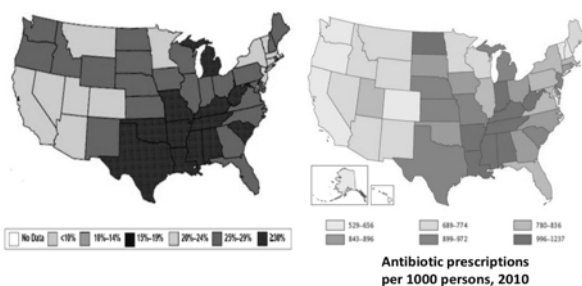
Del Fiol FS, et al. Obesity: A new adverse effect of antibiotics? *Front Pharmacol* 2018

doi.org/10.3389/fphar.2018.01408

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Comparisons between the geography of obesity and antibiotic use, 2010



L Segal & MJ Blaser, *Ann Am Thor Soc* 2014

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Probiotics

- **Regulate/modulate immune functions**, reduce risk intestinal infection.
- Improve **intestinal barrier functions**, reduces endotoxemia.
- Induce hypo-responsiveness to **food antigens**.
- Improve glucose control and **reduce inflammatory cytokines**.
- Inhibit tumorigenesis and **may inhibit cancer progression**.
- 81 obese postmenopausal women randomized to high or low dose multi-strain probiotics or placebo for 12 weeks. *Statistically significant differences in LPS, uric acid, glucose, insulin* found for both doses compared to placebo.

Gianotti L. et al. *World J Gastroenterol*. 2010;16:167-175

Szulinska M, et al. *Nutrients* 2018, 10(6), 773; <https://doi.org/10.3390/nu10060773>

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Probiotics Quiet the Brain

- UCLA study: **women** with no GI or psychiatric problems randomly assigned to one of **three groups for four weeks**:
 - Fermented milk (**yogurt**) with **5 strains of probiotics** twice daily
 - **Non-fermented milk product** (control group) twice daily
 - No intervention group
- Researchers did **functional brain MRI** before and after intervention to look for brain changes in response to an emotional attention task.
- Group consuming fermented milk had calmer brains during emotional task. Other groups showed opposite trend, more brain hyperactivity.

Tillisch, K. et al. Consumption of fermented milk product with probiotic modulates brain activity. *Gastroenterology* 2013; 144(7), 1394-1401.e14014.

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PPIs, Dysbiosis, and Infection

- Stomach acid **directly destroys harmful pathogens**.
- When **acid is shut down**, ~**50% of salivary and ingested bacteria survive** by slipping past this “gastric acid trap.”
- **Translocated bacteria** disrupt gut microbiota, leading to **dysbiosis, SIBO, and dyspepsia**.
- **70% of immune system resides in GI tract: critical line of defense**.
- By **altering balance between beneficial and pathogenic microbes**, the **risk for infection** is increased.



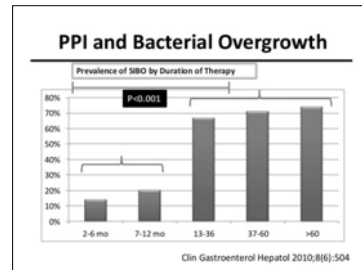
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Dysbiosis & SIBO

- Meta analysis 19 studies (n=7055): **statistically significant association between increased risk of SIBO and PPI use (OR 1.71).**¹
- Dysbiosis and SIBO increase **intestinal permeability**, allowing **bacteria** and other substances to pass directly through the intestinal mucosa **into the blood stream**.
- PPIs may have more prominent effect on microbiota composition on population basis than any other drug.²



1. Su T, et al. *J Gastroenterol* 2018; Jan;53(1):27-36
 2. Imhann F, et al. *Gut*. 2016; 65: 740-748

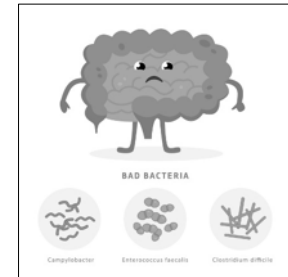
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PPI and *C. difficile* Infection

- FDA warning 2012: PPIs increase risk of *C. diff* infection (CDI) which can cause life-threatening inflammation of the colon and diarrhea.
- Review 56 studies (n=356,000): **double the odds of CDI** if taking PPIs, compared to non-users.



Trifan A, et al. *World J Gastroenterology* 2017

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Probiotics for Preventing *C. difficile*: Adults and Children

Outcome	Risk with Control	Risk with Probiotics (95% CI)	Relative Effect (95% CI)	Number of Participants (studies)	Certainty of Evidence
Antibiotic Associated Diarrhea in Children	271 per 1000	103 per 1000 (79-133)	RR: 0.38 (0.29-0.49)	1141 (6 RCTs)	Moderate
Benefits in NNT		Harms in NNT			
1 in 42 for preventing <i>C. difficile</i> -associated diarrhea (1 in 12 in high risk patients)		No significant harm			

From: Goldenberg JZ, et al. *Probiotics for the prevention of Clostridium difficile-associated diarrhea in adults and children. Cochrane Database Syst Rev* 2017 Dec; 2017(12): CD006095

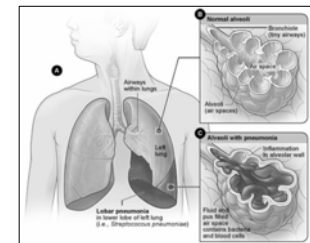
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PPI and Community Acquired Pneumonia

- Without adequate stomach acid, there can be **overgrowth of oropharyngeal bacteria**, which can increase the risk for infection.
- Review of 26 studies: 1.5-fold increase in risk for community-acquired pneumonia, with the highest risk occurring within 30 days of starting PPI.



Lambert AA, et al. *PLoS One* 2015

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PPI and SARS-CoV-2

- **GI tract** significant portal of entry for virus. Bind to widely expressed **ACE-2 receptors** in intestine, replicating rapidly.
- **No stomach acid means no viral inactivation.**
- Korean study: **current use of PPIs** conferred 79% greater risk of **severe clinical outcomes**; risk climbed to **90% if PPI use started within 30 days** of confirmed Covid 19 infection.¹
- US study: **mortality** from COVID-19 was **2.3 times higher in PPI users**, compared to non-users.²

1. Lee SW, et al. *Gut* 2021

2. Ramachandran P, et al. *Eur J Gastroenterol Hepatol* 2021

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PPI and Infection Risk in Children



- **Review 14 studies:** significant association between acid-suppressive therapies and risk of **GI infection, sepsis, and pneumonia** in infants.¹
- **~70–85 % infants** experience regurgitation/reflux within first two months of life; **resolves on its own in 95 % of babies** by 1st birthday.²
- Pediatric GI guidelines strongly recommend **against acid suppression** for **GER**. (*2-4 weeks elimination of cow's milk dramatically reduces reflux~ 42-58% of infants with GERD).²

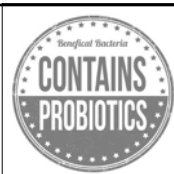
1. Chung EY, et al, *Hospital Pediatrics* 2013; 2. Czinn SJ, et al. *Pediatr Drugs* 2013

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PPI + Probiotics in Children



- 128 children with GERD randomized to **12 weeks PPI** (esomeprazole 1 mg/kg/d; max 40 mg) **plus probiotics** (*Lactobacillus reuteri* DM 17938) or identical **placebo**. Control: 120 healthy age-matched children.
- After 12 weeks, **dysbiosis** occurred in **56.2%** of group receiving **placebo** versus **6.2%** of those taking **probiotics** ($p < 0.001$).
- Probiotics + PPI significantly **decreased prevalence of small intestinal bacterial overgrowth (SIBO)**, compared to PPI and placebo ($P < 0.001$).

Belei O, et al. *J Neurogastroenterol Motil*. 2018 Jan 30;24(1):51-57.

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Summary of Systematic Review Analyzing the Role of Probiotics on Clinical Outcomes

Outcome	Reference	No of studies/ participants	Evidence of benefit?
Prevention and treatment of Clostridium difficile associated diarrhea in adults and children	Goldenberg et al (2017) ¹¹	39/9955	Yes
Necrotizing enterocolitis	Al Faleh et al (2014) ¹² Rees et al (2017) ¹³	17/5338	Yes
Antibiotic associated diarrhea in children	Goldenberg et al (2015) ¹⁴	26/3898	Yes
Probiotics for preventing acute upper respiratory tract infections	Hao et al (2015) ¹⁵	12/3720	Yes
Urinary tract infections	Schwenger et al (2015) ¹⁶	9/735	No
Prevention of asthma and wheeze in infants	Azad et al (2013) ¹⁷	6/1364	No
Prevention of eczema in infants and children	Mansfield et al (2014)	16/2797	Yes
Prevention of invasive fungal infections in preterm neonates	Agrawal et al (2015) ¹⁸	19/4912	Unclear
Prevention of nosocomial infections	Manzanares et al (2015) ¹⁹	30/2972	Yes
Treatment of rotavirus diarrhea in infants and children	Ahmadi et al (2015) ²⁰	14/1149	Yes
Prevention and treatment of Crohn's disease and ulcerative colitis	Saez Lara et al (2015) ²¹	14/821 ulcerative colitis 8/374 Crohn's disease	Yes
Pulmonary exacerbations in children with cystic fibrosis	Ananthan et al (2016) ²²	9/275	Yes
Type 2 diabetes (fasting glucose, glycated haemoglobin test)	Akbari et al (2016) ²³	13/805	Yes
Type 2 diabetes (insulin resistance, insulin levels)	Zhang et al (2016) ²⁴	7/425	Yes
Necrotizing enterocolitis in pre-term neonates with focus on Lactobacillus reuteri	Athalye-Jape et al (2016) ²⁵	6/1778	Yes
Reduction of serum concentration of C reactive protein	Mazidi et al (2017) ²⁶	19/935	Yes
Cardiovascular risk factors in patients with type 2 diabetes	Hendijani et al (2017) ²⁷	11/641	Yes
Reduction of total cholesterol and low density lipoprotein cholesterol	Wu et al (2017) ²⁸	15/976	Yes
Depressive symptoms	Wallace and Milev (2017) ^{29,30}	6/1080	Yes
Vulvovaginal candidiasis in non-pregnant women	Xie et al (2018) ³¹	10/1656	Yes

From: Valdes AM, et al. Role of gut microbiota in nutrition and health. *BMJ* 2018;361:2179

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Clinical Resource Tool: www.usprobioticguide.com

AEProBio		Clinical Guide to Probiotic Products Available in USA Indications, Dosage Forms and Clinical Evidence to Date - 2019 Edition				
INDICATIONS FOR PEDIATRIC HEALTH						
Search	entries					
	Brand Name	Probiotic Strain	Dosage Form	OTC/Pres	No. of Doses/Day	Indications (Level of Evidence)
⊕	Bio-Kult Infant [®]	L. casei PDSM 32™ L. rhamnosus PDSM 34™ Bifidobacterium infantis PDSM 36™ L. rhamnosus PDSM 37™ L. reuteri PDSM 38™ B. infantis PDSM 39™	Sachet	18 Sachet	1/1 sachet	CDAD - Childhood-onset necrotizing enteritis (2) Colic - Colic (2) HPI - Infantile colic - Adjust to standard eradication therapy (2)
⊕	BiDough Probiotic Baby Drops with Vitamin D [®]	L. reuteri DSM 17928	Drops	100mg/5mL	5 drops	AAD - Antibiotic-associated diarrhea - Prevention (2) C - Constipation (2) CDAD - Childhood-onset necrotizing enteritis (2) CD - Common infectious diseases - community acquired (2) Colic - Colic (2) IBS/FA - Irritable bowel syndrome/functional abdominal pain (2) O - Infectious diarrhea (2) Regurg (2) - Mild - Reduce regurgitation/improve gastrointestinal motility (2)
⊕	BiDough Probiotic [®]	L. reuteri DSM 17928	Chewable Mints	100mg/5mL	1 tab 5 drops	AAD - Antibiotic-associated diarrhea - Prevention (2) C - Constipation (2) CDAD - Childhood-onset necrotizing enteritis (2) CD - Common infectious diseases - community acquired (2) Colic - Colic (2) IBS/FA - Irritable bowel syndrome/functional abdominal pain (2) O - Infectious diarrhea (2) Regurg (2) - Mild - Reduce regurgitation/improve gastrointestinal motility (2)
⊕	Gerber Good Start Soothe Powder Infant Formula [®]	L. reuteri DSM 17928	Powder	14g/14g	1/14g	AAD - Antibiotic-associated diarrhea - Prevention (2) C - Constipation (2) CDAD - Childhood-onset necrotizing enteritis (2) Colic - Colic (2) IBS/FA - Irritable bowel syndrome/functional abdominal pain (2) Regurg (2) - Mild - Reduce regurgitation/improve gastrointestinal motility (2)
⊕	Gerber Soothe Probiotic Cuts (Drops) [®]	L. reuteri DSM 17928	Drops	100mg/5mL	5 drops	AAD - Antibiotic-associated diarrhea - Prevention (2) C - Constipation (2) CDAD - Childhood-onset necrotizing enteritis (2) CD - Common infectious diseases - community acquired (2) Colic - Colic (2) IBS/FA - Irritable bowel syndrome/functional abdominal pain (2) O - Infectious diarrhea (2) Regurg (2) - Mild - Reduce regurgitation/improve gastrointestinal motility (2)

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Level 1 Evidence for Probiotics in Adults

- **Antibiotic Associated Diarrhea/C. diff Prevention**
 - Bio-K, Culturelle, Dan Active Actimel, Florastor and FlorastorMax, Schiff Digestive Advantage Advanced Probiotics, Ultra Flora Restore
- **Constipation**
 - Activia, Bio-Gaia Protectis (*also for GERD*)
- **IBS**
 - Activia, Align, Bio-K, BioKult, GoodBelly (*also for GERD*), Ideal Bowel Support, Ultra Flora Intensive Care (*also for GERD*)

http://usprobioticguide.com/PBCAdultHealth.html?utm_source=adult_ind&utm_medium=civ&utm_campaign=USA_CHART

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Level 1 Evidence for Probiotics in Children

- **Antibiotic Associated Diarrhea/C. diff Prevention**
 - BioGaia® Protectis, Culturelle Kids, FlorastorKids, Gerber Good Start Grow Toddler Probiotic + Gentle Infant Formula + Soothe Vitamin D and Probiotic Drops, Pedia-Lax® Probiotic Yums
- **Constipation**
 - BioGaia® Protectis, Gerber Good Start Grow Toddler Probiotic + Gentle Infant Formula + Soothe Vitamin D and Probiotic Drops, Pedia-Lax® Probiotic Yums
- **IBS/Functional Abdominal Pain**
 - BioGaia® Protectis, Culturelle Kids, Gerber Good Start Grow Toddler Probiotic + Gentle Infant Formula + Soothe Vitamin D and Probiotic Drops, Pedia-Lax® Probiotic Yums, Visbiome + Extra Strength

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Circadian Rhythms

- The microbiota modulates circadian rhythm and circadian disruptions can affect the intestinal microbiota. **Microbes and humans share circadian clock.**
- More than **90 million Americans struggle** with getting regular, restful sleep.
- Major depressive disorder is often associated with a **dysregulation of the circadian clock.**



Farré N, et al. Sleep and circadian alterations and the gut microbiome: associations or causality. *Current Sleep Med Reports* 2018; 4(1):50-57
Li, Y, et al. The role of microbiome in insomnia, circadian disturbance and depression. *Front Psychiatry* 2018; doi: 10.3389/fpsy.2018.00669

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To Sleep is to Heal



1. Make your bedroom dark, quiet, and cool. Invest in *good mattress and pillows*.
2. Turn off **TV, computers, tablets, and smart phones** 1 hour before bedtime
3. **Avoid caffeine** after 12:00 PM (e.g., coffee, tea, soda, chocolate).
4. **Limit alcohol intake and don't drink** within 2-3 hours of bedtime
5. Try not to exercise within 2 hours of bedtime.
6. Consider a hot bath 1-2 hours before bedtime.
7. Try to not to eat right before bed. A glass of warm milk, bowl of cereal okay.
8. **Keep same sleep schedule** 7 days a week.
9. Get **sleep evaluation** if sleep disruption and/or daytime fatigue continues.

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Cognitive Behavioral Therapy for Insomnia

- American College of Physicians officially endorsed what multiple meta-analyses have found: **CBT for insomnia**, or CBT-I, is best treatment for chronic insomnia and should be **first line of treatment**.
- **Sleepio, Somly, Calm Sleep School** provide in-person/on-line.
- There are purely digital programs if therapist not available.
- To find trained sleep specialist,
<https://behavioralsleep.org/index.php/directory/north-america/united-states>



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Ashwagandha Root (*Withania somnifera* (L.) Dunal.)



- Modulates GABA, key target for drugs designed to treat anxiety.
- Restores/maintains blood brain barrier
- Human trials show it **reduces stress, lowers cortisol** (biomarker of stress), **relieves anxiety and promotes sleep over time** (does not make you drowsy), improves executive function and cognition.
- Very good safety profile.
- Dose most common in studies: **300 mg 2 x day extracts standardized 2.5-5% withanolides**

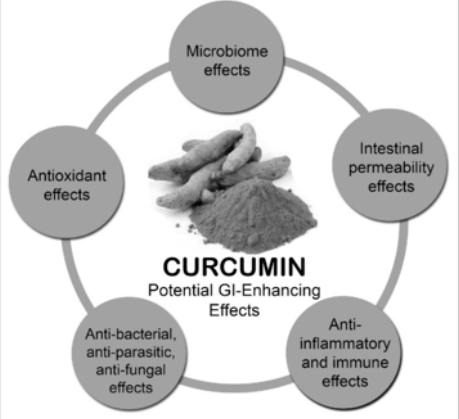
Chandrasekhar K, et al. *Indian J Psychol Med.* 2012;34(3):255-62.
Lopresti AL, et al. *Medicine* 2019 Sep;98(37):e17186.
Kelgane SB, et al. *Cortex* 2020 Feb 23;122(2):7083.
Langade D, et al. *J Ethnopharmacol* 2021 Jan 10;264:113276.

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CURCUMIN
Potential GI-Enhancing Effects

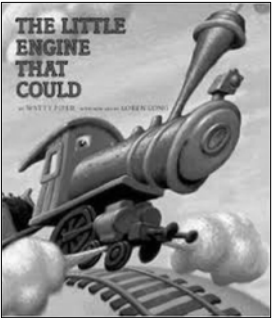
Dose: 1000-1200 mg per day of standardized extract (95% curcumin). May contain piperine or be liposomal bound: Meriva.
Do NOT exceed 20 mg per day of piperine if taking prescription drugs.

From: Lopresti A. The Problem of Curcumin and Its Bioavailability: Could Its Gastrointestinal Influence Contribute to Its Overall Health-Enhancing Effects? *Adv Nutr* 2018 Jan; 9(1): 41–50.

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What We Think Matters



- Is it a challenge or a threat?
- Do I have the resources to handle it?
- Are my thoughts helpful or dysfunctional?

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Resources for Stress Reduction

- **Calm** – great app for guided meditation, bedtime stories, breathing exercises (free to \$60 annual subscription)
- **Insight Timer** – ~4,000 guided meditations >1,000 teachers (self-compassion, nature, stress, podcasts). Music tracks (free to \$5/mo)
- **Headspace** – meditation, videos, meditations music (free basic course, \$12.99 mo, \$95/year)
- **10% Happier** – performance enhancement. Busy people, stressed lives. (Free one week intro, then \$100 per year)
- **Buddhify** – for the more advanced meditator. Can sort by location, activity and/or emotion. (small monthly fee, premium is \$30/yr)

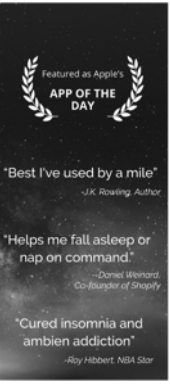
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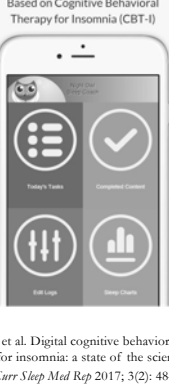
Calm App



Pzizz App



Based on Cognitive Behavioral Therapy for Insomnia (CBT-I)



Luik AI, et al. Digital cognitive behavioral therapy for insomnia: a state of the science review. *Curr Sleep Med Rep* 2017; 3(2): 48–56

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Loneliness, Social Isolation & Your Health

- Poor social relationships associated with **29% increase in risk of heart disease** and **32% increased risk of stroke**.
- **148 studies** on the effects of social isolation on health found it is:
 - = **to smoking** 15 cigarettes a day
 - As dangerous as being an **alcoholic**
 - As harmful as **never exercising**
 - Twice as dangerous as being **obese**



- Valtorta NK, et al. Loneliness and social isolation as risk factors for coronary heart disease and stroke: systematic review and meta-analysis of longitudinal observational studies. *Heart*. 2016 Jul 1;102(13):1009-16.
- Cacioppo JT, et al. *Ann NY Acad Sci* 2011; 1231:17-22

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Meaning and Purpose

- What truly gives a person a sense of *meaning and purpose* in life?
- How does one feel the oneness, find the *holy and sacred* in the mundane?
- “If I only had one day left to live, I’d want to _____.”

Listen.
Are you
breathing
just a little
and calling
it a life?

~ Mary Oliver

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