

Integrative Medicine: *It's Not Alternative Anymore*



Tieraona Low Dog, M.D.

Author of National Geographic's
"Fortify Your Life" "Healthy At Home"
and "Life Is Your Best Medicine"

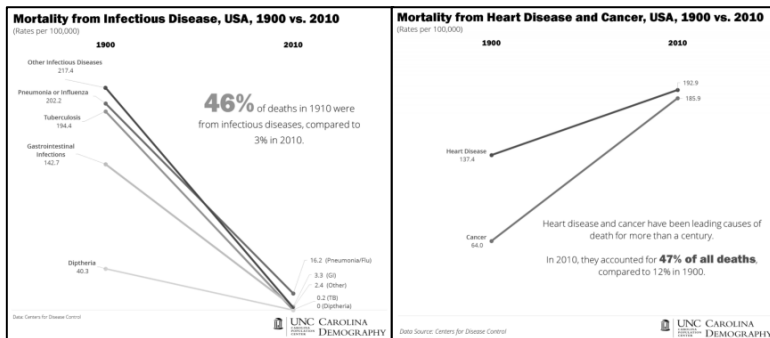
www.DrLowDog.com

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The Times They Are A-Changing



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Epigenetics



- The mapping of **human genome** was one of the greatest scientific undertakings of past century, **detailing with incredible accuracy the blueprint of our species.**
- It also paved the way for field of **epigenetics**, which has shown that when it comes to our genes, **nurture is inextricably linked with nature.**
- That it is the **way we live our lives - from the moment of conception to our last breath - that influences the expression of our genes.**

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• If the American public embraced a healthier lifestyle:

- **no smoking**
- **no or moderate alcohol consumption**
- **limited or no exposure to toxic chemicals**
- **healthy nutrition**
- **balance of exercise and rest**
- **stress management**
- **and healthy social networks**

93% of diabetes, 81% of heart attacks, 50% of strokes, and 36% of all cancers could be prevented.

Ford, et al *Arch Intern Med.* 2009; 169(15):1355-62.

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Complexity of the Unhealthy Lifestyle

- Poor diet, nutrient deficiencies
- Sedentary, high stress lifestyles
- Poor sleep, too much screen time
- Inadequate social support
- Strong emphasis on “knowing” and “having”

Much of what is making us sick cannot be fixed with more and more pills.....

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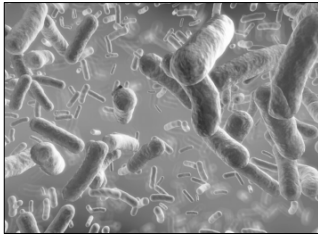
The Future

- It is increasingly clear that much of the modern burden of disease stems from lifestyle behaviors.
- Our health care system must expand its focus to **incorporate nutrition, exercise, environmental health, stress management, dietary supplements, motivational interviewing and more.**



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Vaccine Adjuvant



Lei WT, et al. Effect of Probiotics and Prebiotics on Immune Response to Influenza Vaccination in Adults: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. *Nutrients*. 2017 Oct 27;9(11).

- Systematic review 20 studies concluded that “supplementation of influenza vaccines with probiotics or prebiotics before vaccination increased the immunogenicity to specific influenza viral strains, including the H1N1, H3N2, and B strains.”
- Higher seroprotection and seroconversion rates against the H1N1, H3N2, and B strains were noted compared to the control groups.
- Longer duration of pre-supplementation, the greater the response. The older the adult, the more protection offered.
- Strains most active were *L. casei*, *L. paracasei*, and *B. longum*.

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"THE FOOD YOU EAT
CAN BE EITHER
THE SAFEST
&
MOST POWERFUL
FORM OF MEDICINE
OR
THE SLOWEST
FORM OF POISON."

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Nutritional Guidance



- Despite overwhelming evidence that **relatively small dietary changes** can significantly improve health, **clinicians seldom discuss** nutrition with patients.
- Poor nutritional intake and nutrition-related health conditions (cardiovascular disease, diabetes, obesity, hypertension, and certain cancers) are highly prevalent in US, yet **only 12% of office visits include dietary counseling**.

Kahan S, et al. Nutrition Counseling in Clinical Practice: How Clinicians Can Do Better. *JAMA*. 2017;318(12):1101-1102.

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"A medical doctor uninterested in nutrition, in agriculture, in the wholesomeness of mind and spirit, is as absurd as a farmer who is uninterested in health."

Wendell Berry, *The Unsettling of America*

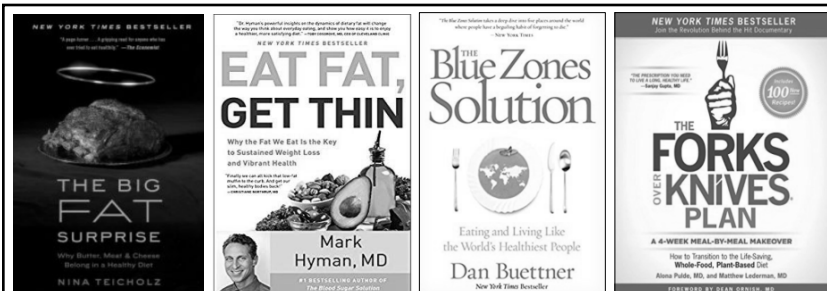
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The Questions are Endless



•Should my 4 year old eat fish? What kind? Should I give him cod liver oil? Will eliminating milk help eczema? What kind of probiotics should we use? Is organic produce really better? What is BPA? Do vegans really need a multivitamin? How can I lose weight? What about paleo? Should I go gluten free? Do you think coconut oil is better than olive oil? What about GMO foods?

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Is it any wonder that people are confused?

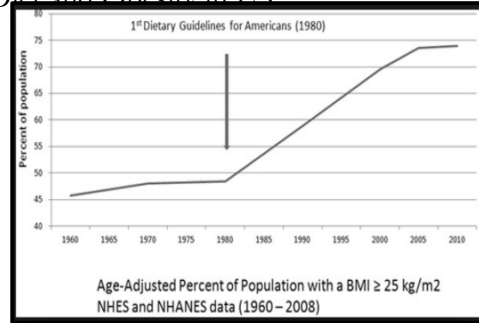
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Nutrition in the 21st Century



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Diet and Obesity in US



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Results show that <18% of adults consume the recommended amount of fruit and <14% consume the recommended amount of vegetables per day.

www.cdc.gov/mmwr/preview/mmwrhtml/mm6426a1.htm Accessed January 3, 2018

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SCIENTIFIC
AMERICAN

PUBLIC HEALTH

The Hunger Gains: Extreme Calorie-Restriction Diet Shows Anti-Aging Results

A new study shows five days of hunger a month may reduce risk factors for aging and age-related diseases

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Caloric Restriction?



Canto is 27 year old monkey on CR diet, Owen is 29 year old on unrestricted diet.

news.wisc.edu/monkey-caloric-restriction-study-shows-big-benefit-contradicts-earlier-study/
Ravussin E, et al.: A 2-Year Randomized Controlled Trial of Human Caloric Restriction: Feasibility and Effects on Predictors of Health Span and Longevity. *J Gerontol A Biol Sci Med Sci*. 2015;70(9):1097–104

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- 25 year study University of Wisconsin: **76 rhesus monkeys ages 7-14 years**, fed a diet reduced in calories by 30%.
- **Disease was 3 fold greater in control group.** No evidence of diabetes in any caloric-restricted animal.
- **NIA 2-year** study randomized 218 non-obese people to current diet or 25% caloric restriction (**11.7%** on average).
- **Statistically significant reduction in inflammatory markers, weight loss, improved mood, sleep duration, etc.**

Fasting-Mimicking Diets



Wei M, et al. Fasting-mimicking diet and markers/risk factors for aging, diabetes, cancer, and cardiovascular disease. *Sci Transl Med* 2017; 9(377).

- USC study **100 healthy people** randomized into 2 study arms to test effects of FMD done 5 consecutive days each month for 3 months.
 - **1100 calorie first day, 700 calories for 4 days (plant based, multivitamin).** Ate whatever they wanted rest of the month.
- Three cycles reduced **body weight, total body fat; lowered blood pressure, cholesterol, triglycerides and IGF-1.**
- Note: **25% drop-out rate**
- Effects still noted 3 months **AFTER** study ended.

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Lack of Sleep



- **1 in 3 Americans** do not get sufficient sleep. Research shows chronic sleep problems can lead to **weight gain, obesity, diabetes** (33% increased risk type 2 DM), and **heart disease**.
- **Biological clock** most important regulator of the sleep wake cycle. Responsible for 24 hour fluctuations in hormone secretion, body temperature and other bodily functions.
- **Lack of exposure to sunlight** and use of **bright lights at night** increases the likelihood of disordered circadian clock. Consider **dawn simulation device/app**, use **blue light blocking glasses** at night with technology.
- **Controlled release melatonin** now first line therapy for those older than 60 (**2 mg**)

Shan Z, et al. *Diabetes Care* 2015;38(3):529-37
Matheson E, et al. *Insomnia: Pharmacologic Therapy. Am Fam Physician* 2017; Jul 1;96(1):29-35.

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Cognitive Behavioral Therapy

- CBT has emerged as a **recommended first-line therapy non pharmaceutical approach for insomnia**. Digital CBT has been shown to be effective for improving sleep, as well as mental health and well-being.
- CBT-I typically consists of:
 - Psychoeducation about sleep and insomnia
 - Stimulus control
 - Sleep restriction
 - Sleep hygiene
 - Relaxation training
 - Cognitive therapy



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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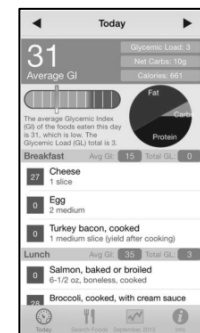
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Glycemic Index/Load

- **Glycemic load** measurement of impact of carbohydrates on blood sugar/insulin.
- International **consensus** conference concluded that given the **consistency of the scientific evidence**, diets **low in glycemic index/load** should be promoted in the **prevention and management of diabetes and coronary heart disease**, and are **particularly important in individuals with insulin resistance**.

Augustin LS, et al. Glycemic index, glycemic load and glycemic response: An International Scientific Consensus Summit from the International Carbohydrate Quality Consortium (ICQC). *Nutr Metab Cardiovasc Dis* 2015 Sep;25(9):795-815.

Low GI Diet Tracker
App: \$3.99



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Sugars



- Americans consume primarily: **table sugar** and **high-fructose corn syrup**.
- Table sugar (sucrose): bond between **one glucose** and **one fructose** molecule
- High fructose corn syrup: **55% fructose**, **42% glucose** and 3% other sugars.
- Every cell in our body readily converts **glucose into energy**.
- Liver cells** are one of few types of cells that **can convert fructose to energy**.
- Soda floods liver with large amounts of **free floating fructose** versus the **fiber in an apple** slows down digestion, making the **fructose slowly enter the liver**.
- Large amounts of **“free” fructose taxes the liver** and increases fatty liver disease.
- Fructose raises levels of the hormone **ghrelin**, which stimulates hunger, and suppresses **leptin**, the hormone that makes you feel full.

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SUGAR COATING

43 DIFFERENT NAMES FOR 'ADDED SUGAR'

- | | | |
|---------------------------|------------------------------|--------------------|
| 1. AGAVE NECTAR/SYRUP | 16. EVAPORATED CANE JUICE | 29. WHITE SUGAR |
| 2. BARLEY MALT | 17. FRUCTOSE | 30. MALTOSE |
| 3. BEET SUGAR | 18. FRUIT JUICE | 31. MAPLE SYRUP |
| 4. BLACKSTRAP MOLASSES | 19. FRUIT JUICE CONCENTRATE | 32. MOLASSES |
| 5. BROWN SUGAR | 20. GLUCOSE | 33. MUSCOVADO |
| 6. CANE SUGAR | 21. GOLDEN SYRUP | 34. PALM SUGAR |
| 7. CAROB SYRUP | 22. GRAPE SUGAR/SYRUP | 35. PANELA |
| 8. CASTER SUGAR | 23. HONEY | 36. POWDERED SUGAR |
| 9. COCONUT SUGAR | 24. HIGH-FRUCTOSE CORN SYRUP | 37. RAPADURA |
| 10. COFFEE SUGAR CRYSTALS | 25. ICING SUGAR | 38. RAW SUGAR |
| 11. CONFECTIONER'S SUGAR | 26. INVERT SUGAR | 39. RICE SYRUP |
| 12. CORN SYRUP | 27. LACTOSE | 40. SUCROSE |
| 13. DATE SUGAR/SYRUP | 28. MALT | 41. SUGAR |
| 14. DEMERARA | | 42. TREACLE |
| 15. DEXTROSE | | 43. TURBINADO |

choice
ENDICE.COM/US

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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.



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

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Glycemic Load

Individual Food Portion

Whole Day

Low	0-10	Low	< 80
Moderate	11-19	Moderate	80-120
High	20+	High	>120

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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 Turkey breast	6 inch	17
Carrots	1 large	5	Butter pecan ice cream	5.5 ounces (small)	22
Orange	1 medium	6	Vanilla ice cream cone	4.5 ounces (small)	19
Sweet potato	1 cup	17	Potato chips, fat free	1 bag (8 ounces)	49
Baked potato	1 medium	28	Tortilla chips, white corn	3.5 ounces	38
French fries	1 medium serving	26	White bread	1 slice	10
Snickers	1 bar	35	White rice	1 cup	33
Reese's cup	1 miniature	2	Brown rice	1 cup	23
White table wine	5 ounces	1	Spaghetti	1 cup	38
Red table wine	5 ounces	1			
Grape juice	6 ounces	12			

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Low/High GI Meals

GI = 80 GL = 32

GI = 61 GL = 12

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Dietary Inflammatory Index (DII)

- Inflammation often driven by dietary patterns. An anti-inflammatory diet may reduce **sub-chronic inflammation** and improve **cardiovascular, metabolic, and neurologic parameters**.
- The **Dietary Inflammatory Index** is based on measuring inflammation in the body in response to specific foods (many clinical trials).
- You can take the test by **downloading the app for Dietary Inflammatory Index** (iTunes: DII Screener)

Cancel Question #1 Next

What was your average intake of bananas over the last year?

1 banana 1 cup banana

Small Medium Large

Never

1 Per Month

2-3 Per Month

1 Per Week

2 Per Week

3-4 Per Week

5-6 Per Week

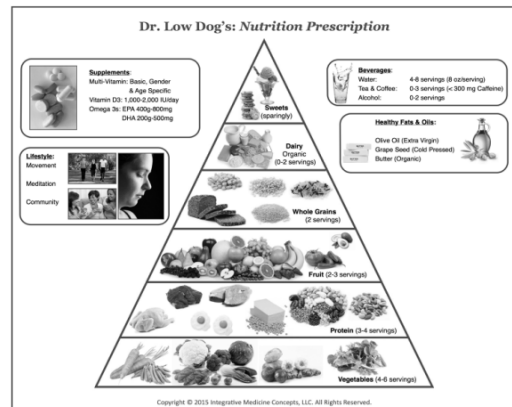
1 Per Day

2+ Per Day

Inflammatory Food Ratings

200 or higher	Strongly anti-inflammatory
101 to 200	Moderately anti-inflammatory
0 to 100	Mildly anti-inflammatory
-1 to -100	Mildly inflammatory
-101 to 200	Moderately inflammatory
-201 or lower	Strongly inflammatory

FOOD	SERVING SIZE	SERVING SIZE (GRAMS)	IF RATING
AGAVE NECTAR	1 TBSP	21	-74
ALMOND BUTTER	¼ CUP	64	100
CHEESE, CHEDDAR	1 OUNCE	28.35	-20
CHICKEN BREAST, RSTD	3 OUNCES	85	-19
MILK, WHOLE	1 CUP	246	-46
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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Meds and ADHD

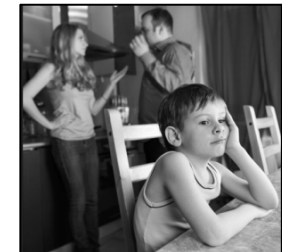


- 11% of US school aged kids have ADHD diagnosis.
- 87% of children with ADHD are prescribed medication, mostly methylphenidates (Ritalin) and amphetamines (such as Adderall).
 - (15 have been approved for children)
- Meds can cause liver toxicity, weight loss, sleep problems, mood swings, and even thoughts of suicide. They can also interfere with growth.
- Between \$320- \$500 million spent annually in U.S. on medications for those *inappropriately diagnosed with ADHD*.

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Other Causes?

- **Environmental toxins**
- **Lack of key nutrients during pregnancy**
- **High carb, low nutrient diet**
- **Less effective parenting**
- **Everyone more stressed**
- **Higher demands on children**



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• **Meditation interventions** are being increasingly implemented among youth in school, community, and clinic based settings

• **Review of 16 studies** found that **meditation can be an effective intervention for psychosocial, and behavioral problems among children and adolescents.**

Black DS, et al. *Pediatrics* 2009; 124(3):e532-41

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*Where Would You
Want to Play?*



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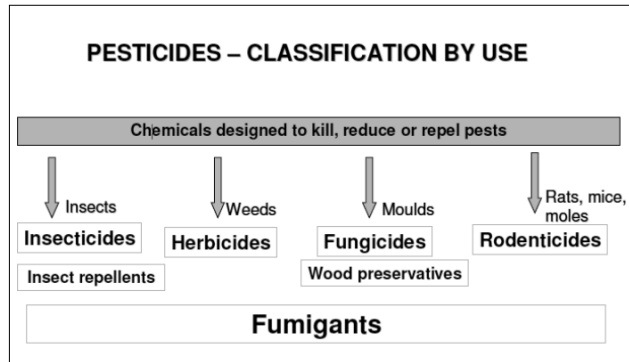


*Where Would You
Want to Learn?*



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Neurofeedback



- **104 children (7-11 years)** with ADHD randomly assigned to receive **40 in school sessions: neurofeedback, cognitive training, or control condition** and evaluated six months post-intervention.
- **Neurofeedback participants** made more prompt and **greater improvements in ADHD symptoms**, which were sustained at the 6-month follow-up. **CT and control groups** both had increased med dosing during follow up.

Steiner NJ, et al. *Pediatrics* 2014; 133(3):483-92

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Pesticide Exposure and ADHD

- Pound for pound, children drink 2.5 times more water, eat 3-4 times more food, and breathe 2 times more air. They are exposed to more pesticide.
- Using data from NHANES – children with **typical levels of pesticide exposure from eating pesticide-treated fruits/vegetables**, have **higher risk of developing ADHD**.
- Children ages 8-15 with **higher urinary levels of pesticide metabolites**, had **twice the odds of ADHD when compared with children with low or undetectable levels**.
- Organophosphate exposure, at levels common in US children, contributes to **ADHD prevalence**.

Kuehn BM. *JAMA*. 2010 Jul 7;304(1):27-8.

Bouchard, et al. *Pediatrics*. 2010 Jun;125(6):e1270-7.

Wagner-Schuman M, et al. *Environ Health* 2015; May 28;14:44.

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Pesticides and Organic Produce



- **Consumption of an organic diet for one week** significantly reduced **organophosphate pesticide exposure in adults and children as measured by urinary metabolites**.
- Mean total OP metabolites in the organic phase were **89% lower than when eating conventional foods**.
- Unfortunately, organic produce is often more expensive than conventionally grown, making it out of reach for some of our most at risk patients.

Oates L, et al. *Environ Res* 2014; 132:105-11

Bradman A, et al. *Environ Health Perspect* 2015; 123(10):1086-93

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Insecticides and Cancer

- Meta-analysis of **16 studies** found childhood **exposure to indoor residential insecticides associated with a significant increased risk of childhood leukemia and lymphomas.**
- Positive but not statistically significant association also found for childhood brain tumors.

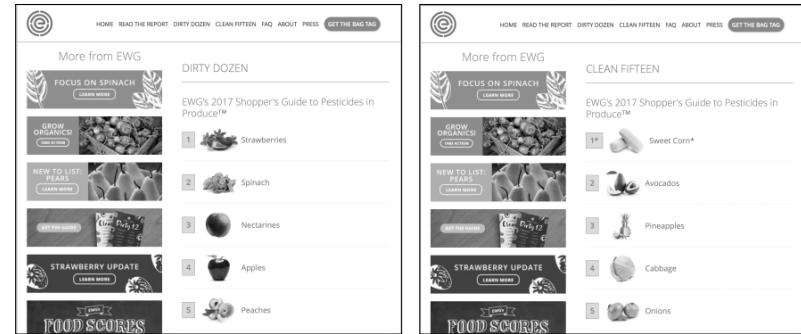


Chen M, et al. *Pediatrics* 2015; 136(4):719-29.

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www.ewg.org/foodnews/index.php



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"If we are going to live so intimately with these [agricultural] chemicals--eating and drinking them--taking them into the very marrow of our bones—we had better know something about their nature and their power."



Rachel Carson
Silent Spring

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Iron

- Iron deficiency most common nutrient deficiency in world.**
- Low iron** levels most common cause of anemia in adolescent girls; very detrimental to **mood, cognition, physical well-being.**
- Iron deficiency anemia accounts for 20% of all global maternal deaths.
 - If mother is anemic, increases **risk baby born prematurely with lower birth weight and poor neurocognitive development.**



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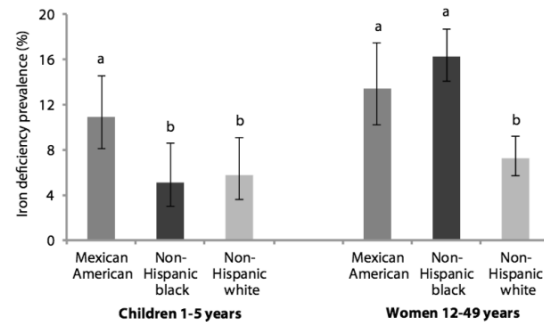


Figure H.3.a. Age-adjusted prevalence estimates of low body iron stores (<0 mg/kg) in U.S. children and women by race/ethnicity, National Health and Nutrition Examination Survey, 2003-2006.

Error bars represent 95% of confidence intervals. Bars not sharing a common letter differ within children and women ($p < 0.05$). Age adjustment was done using direct standardization.

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Iodine in Pregnancy

- Many reproductive aged women in US have marginal iodine status; **salt in processed foods is not iodized.**
- Deficiency associated with **pregnancy loss and prematurity, and neurocognitive defects in baby.**
- Iodine deficiency now accepted as the most common cause of **preventable brain damage** in the world.
- Mild to moderate iodine deficiency associated with higher incidence of **ADHD and lower IQ** in the baby.
- American Thyroid Association recommends pregnant/lactating women supplement: **150 mcg/d potassium iodide.**



Council on Environmental Health, et al. *Pediatrics* 2014; 133(6):1163-6
Perrine CG, et al. NHANES data: Some subgroups of reproductive age women in the United States may be at risk for iodine deficiency. *J Nutr* 2010; 140:1489-1494, 2010. PMID: 20554903

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Iodine Intake Pregnancy and Breastfeeding

- Data from National Health and Nutrition Examination Survey 2011-2014 found that the **use of iodine containing dietary supplements among pregnant and lactating women remains low** in contrast with current recommendations.
- Among **pregnant** women, 72.2% used any dietary supplement; however, **only 17.8% used a dietary supplement with iodine.**
- Among **lactating** women, 75.0% used a dietary supplement; however, **only 19.0% used a dietary supplement with iodine.**

Gupta PM, et al. Use of Iodine-Containing Dietary Supplements Remains Low among Women of Reproductive Age in the United States: NHANES 2011-2014. *Nutrients* 2018 Mar 29;10(4). pii: E422

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Research

Maternal choline supplementation during the third trimester of pregnancy improves infant information processing speed: a randomized, double-blind, controlled feeding study

Marie A. Caudill, Barbara J. Strupp, Laura Muscalu, Julie E. H. Nevins, and Richard L. Canfield

Published Online: 29 Mar 2018 | <https://doi.org/10.1096/fj.201700692RR>

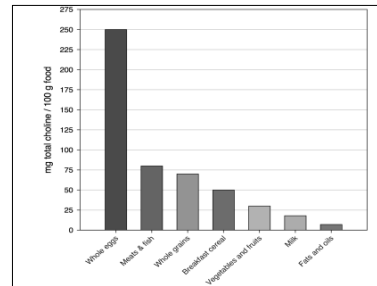
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Choline

- Choline critical during fetal development, influencing mood regulation, cognitive development, stress regulation and lifelong memory function.
- Only 8-10% of adults or pregnant women meet adequate intake levels. Those eating eggs had highest levels.
- Look for prenatal with 200-300 mg.

Blusztajn JK, et al. Neuroprotective actions of dietary choline *Nutrients* 2017; Jul 28;9(8). pii: E815.
Wallace TC, et al. *Nutrients* 2017 Aug 5;9(8). pii: E839.

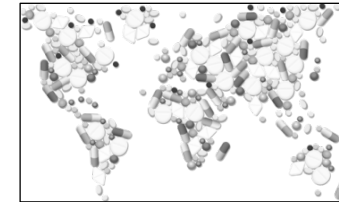


Choline in Foods: <http://naldc.nal.usda.gov/download/47335/PDF>

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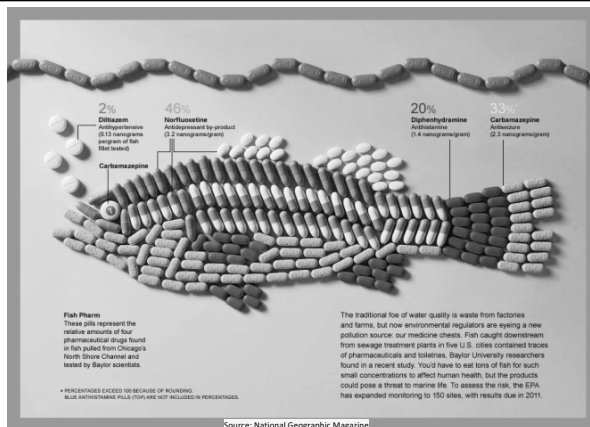
Pharmaceuticals in the Environment

Over 200 different pharmaceutical agents, including antibiotics, NSAIDs, analgesics, lipid-lowering drugs, estrogens, anti-depressants and others, have been detected in aquatic and terrestrial environments around the world, including areas as remote as the Antarctic.



Murdoch K. www.ntn.org.au/wp-content/uploads/2015/05/NTN-Pharmaceutical-Pollution-in-the-Environment-2015-05.pdf Accessed September 12, 2016

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Neurodevelopment ????

- Animal studies suggest psychoactive pharmaceuticals at environmentally relevant concentrations found in drinking water alter genes that regulate the development and function of the nervous system.



Kaushik G, et al. *Biochem Biophys Res Commun* 2016; 474(2):291-5.

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Antibiotic Resistance: Global Problem

- Emergence and rapid spread of **antibiotic resistant bacteria** has led to **increasing concerns about the potential environmental and public health risks.**
- In US, at **least 2 million people** become infected with **antibiotic resistant organisms** and **23,000 people die each year** as a direct result (CDC)
- **480 000 new cases of multidrug-resistant tuberculosis**
- Cambodia-Thailand border malaria is resistant to almost all available medicines

Bouki C. et al. *Ecotoxicology and Environmental Safety*, Volume 91, 1 May 2013, Pages 1-9.
Centres for Disease Control and Prevention, *Antibiotic Resistant threats in the United States*, 2013,
US Department of Health and Human Services.
Smith R, Coast J. *BMJ*, 2013, 346, f1493
Belinda H, et al. *Science of The Total Environment*, Volumes 456-457, 1 July 2013, Pages 161-170.



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The Need for Other Solutions

- **High killing potential** of current drugs is one of the strongest sources of selection exerted on pathogens, **as evidenced by the rapid and consistent evolution of antibiotic resistance**
- In addition to **using antibiotics far more judiciously**, removing them from **non-medical use in animals**, and **continuing to expand our pipeline (which is running dry)** - a broader way of thinking is necessary.
- Exploring **natural strategies for enhancing host resistance** should be a **high priority for both clinicians and researchers.**
- **New rapid testing to determine when antibiotics are necessary.**

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“The lesson from both our agricultural and medical experience is remarkable for its consistency: Ignoring the evolutionary attributes of biological systems can only be done at the peril of ecological catastrophe.”

Marc Lappe, When Antibiotics Fail

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CDC Guidance for Influenza 2017-18

- Caused by RNA viruses **resulting in fever/myalgia in infected people.**
- Seasonal influenza leads to **three to five million severe illness cases and around 250,000 to 500,000 deaths in the world yearly.**
- Flu viruses most common in US during **fall/winter months**, increasing in Oct/Nov, **peaking between December and February** and can last until May.
- CDC recommends annual flu vaccine for everyone 6 months and older. **Optimal timing is October** but recommend through end of January. ~2 weeks for antibodies to develop.

<https://www.cdc.gov/flu/about/season/flu-season-2017-2018.htm> Accessed January 2, 2018; Copyright © Integrated Medicine Center, LLC. All Rights Reserved.
Wei Te Lei, et al. Nutrients 2017 Nov; 9(11):1175

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Flu Vaccine Effectiveness

- Frequent alterations in antigenic structures of respiratory viruses, pose difficulties in production of effective vaccines. Estimates range from 10% (early data from Australia) to 38% efficacy for 2017-18 flu vaccine.

2010-11	Treanor 2011	WI, MI, NY, TN	4757	60	53, 66
2011-12	Ohmit 2014	WI, MI, PA, TX, WA	4771	47	36, 56
2012-13	McLean 2014	WI, MI, PA, TX, WA	6452	49	43, 55
2013-14	Gagliardi 2016	WI, MI, PA, TX, WA	5999	52	44, 59
2014-15	Zimmerman 2016	WI, MI, PA, TX, WA	9311	19	10, 27
2015-16*	Jackson 2017	WI, MI, PA, TX, WA	6879	48*	41, 55*
2016-17**	ACIP presentation, Ferdinando [743 KB, 19 pages]	WI, MI, PA, TX, WA	7410	39**	32, 46

*Estimate from Nov 2, 2015–April 15, 2016.

**Unpublished final estimates

<https://www.cdc.gov/flu/professionals/vaccination/effectiveness-studies.htm> Accessed January 2, 2018

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CDC Guidance, continued

- **Most people with the flu have mild illness and do not need medical care or antiviral drugs.** “If you get sick with flu symptoms, in most cases, you should stay home and avoid contact with other people except to get medical care.”
- Antiviral drugs can be used to treat flu illness in those at risk for serious flu complications (i.e., **children younger than 5, adults 65 and older, pregnant women, people with long-term medical conditions, residents of nursing homes/long-term care facilities**) and people who are hospitalized for flu.
- Three FDA approved antivirals: **oseltamivir (generic and Tamiflu®), zanamivir (Relenza®), and peramivir (Rapivab®).**

<https://www.cdc.gov/flu/about/season/flu-season-2017-2018.htm> Accessed January 2, 2018

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Tamiflu Derived from Star Anise



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Tamiflu

- In 2009, widespread concern about a new flu pandemic, caused billions to be spent stockpiling Tamiflu globally. Sales that year hit \$3 billion.
- WHO recommends Tamiflu, but did not vet data.
- EMA approved Tamiflu, but did not review the full Tamiflu dataset.
- CDC and ECDC encourage the use and stockpiling of Tamiflu, but did not vet the Tamiflu data.
- The majority of Roche's Phase III treatment trials remain unpublished over a decade after completion.
- In 2009, scientists requested Roche to hand over data for evaluation.....

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Stocks of the antiviral drug Tamiflu at an undisclosed location in the United Kingdom.

Jefferson T, et al. *British Medical Journal* 2014; 348: g2545.

In October 2013, Cochrane reviewers received 107 full clinical study reports from Roche and GlaxoSmithKline.

- Reduction in time to **first alleviation of symptoms: from 7 to 6.3 days** compared to control group.
- **No evidence oseltamivir reduces hospitalizations or complications of flu: pneumonia, bronchitis, sinusitis, ear infections in adults or kids**
- In prophylaxis trials, **reduced flu-like symptoms in adults; did not prevent person-to-person spread.**
- **Increased risk of vomiting, headaches, psychiatric syndromes and a statistically significant increase in adverse kidney events.**

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Concluding Thoughts in BMJ

- The stated intentions of governments to distribute Tamiflu to healthy people to prevent complications and interrupt transmission of influenza on the basis of a published evidence base that has been affected by reporting bias, ghost authorship, and poor methods is worrisome.
- *"We believe these findings provide reason to question the stockpiling of oseltamivir, its inclusion on the WHO list of essential drugs, and its use in clinical practice as an anti-influenza drug."*

Jefferson T, et al. *British Medical Journal* 2014; 348: g2545.

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2016 Meta-Analysis Update

- Oseltamivir and zanamivir **cause small reductions in time to first alleviation of influenza symptoms in adults.**
- Oseltamivir **increases risk of nausea, vomiting, psychiatric events in adults and vomiting in children and has no protective effect on mortality among patients with 2009A/H1N1 influenza.**
- Prophylaxis with either drug may reduce symptomatic influenza in individuals and in households.
- The balance between benefits and harms should be considered when making decisions about use of antiviralC for either prophylaxis or treatment of influenza.

Heneghan CJ, et al. *Health Technol Assess* 2016; 20(42):1-242.

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Elder berry *Sambucus nigra*

- Long ethnobotanical history across many disparate cultures as a treatment for **viral infections**.
- Numerous compounds thought active for **antiviral and immune priming effects**.
- Possesses antimicrobial activity against Gram-positive bacteria *Streptococcus pyogenes* and group C and G Streptococci, and the Gram-negative bacterium *Branhamella catarrhalis*.



Porter RS, et al. A Review of the Antiviral Properties of Black Elder (*Sambucus nigra* L.) Products. *Phytother Res* 2017 Apr;31(4):533-554.

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Table 3. Human clinical studies on the effects of various *Sambucus nigra* treatments against influenza

Study	Treatment	dosage	n	Results	p
Zakay-Rones et al., 1995	Sambucol®	4 tsp (all adults) once daily for 2 days 4 tsp (adults) or 2 tsp (children) once daily for 2 days	25 27	Absence of side-effects in healthy adults Recovery from fever in 4 days instead of 6 or more days Symptomatic improvement in 2 days instead of 5 or more days Complete recovery in 2-3 days instead of 5 or more days	<.0.01 <.0.001 <.0.001 <.0.001
Konlee, 1998 Zakay-Rones et al., 2004	Sambucol® Sambucol®	15 mL four times daily for 5 days	60	Lessened duration of illness All individual symptoms relieved in 2-4 days instead of 7-8 days Global assessment showed pronounced improvement after 3 days instead of 7 days Less use of rescue medication than control Absence of side-effects in patients	<.0.001 <.0.001 <.0.001 <.0.001
Kong, 2009	Elderberry extract lozenge from HerbalScience Singapore Pte. Ltd.	4 lozenges daily for 2 days	64	24 h: significant improvement in all symptoms except coughing and mucus discharge 48 h: significant improvement in all symptoms 48 h: complete eradication of all symptoms in 28% of treatment group and 0% of control group	<.0.0001 <.0.0001
Tiralongo et al., 2016	Rubini capsules	2 capsules/day priming (9 days), then 3 capsules/day (6 days)	29 312	Absence of side effects in patients Lessened symptom severity Lessened illness duration No significant difference in use of rescue medications Less occurrence of illness in treatment group (not significant)	0.06 0.02 0.9 0.2

All studies were randomized, double-blinded, and placebo-controlled, with acceptable patient compliance.

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Phytother. Res. 31: 533-554 (2017)

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- **Safety is good** when the fruit is thoroughly cooked. No adverse effects from elder flowers.
- **Cost is good** for elderberry fruit extracts in the marketplace. Given the complexity of the antiviral activity, resistance is unlikely to occur.
- Take elderberry extracts as instructed on label (crude equivalent 5000-6000 mg) every 4 hours at first sign of infection.



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Echinacea and Elderberry

- *Echinacea purpurea* has **demonstrated strong activity against influenza virus strains**.
- **473 patients with flu symptoms less than 48 hours randomized to 240 mg echinacea herb/root extract + elderberry fruit (Vogel Bioforce) or tamiflu.**
- **No difference between recovery rates, antibiotic use, intermediate doctor visits, use of over-the-counter medications for symptoms, “ability to return to normal daily activities,” or physician- and patient-reported efficacy of the treatments.**

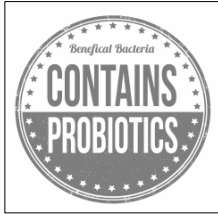


Rauti K, et al. *Curr Ther Res*. 2015 Dec; 77: 66-72.

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Probiotics and Prebiotics



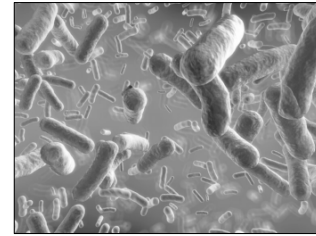
Hao Q, Dong BB, Wu T. Probiotics for preventing acute upper respiratory tract infections. *Cochrane Database Syst Rev*. 2015 Feb 3;(2):CD006895.

- Probiotics **modulate innate and adaptive immunity** in elders and **reduce duration of respiratory/flu infection in children and adults**
- Review of **12 studies** with 3720 participants including children, adults, and elders not at high risk for upper respiratory tract infection (URTI).
 - Moderate-quality evidence **shows fewer people develop URTI when taking probiotics**
 - Moderate quality evidence probiotics probably **reduces duration of a URTI by approximately 2 days.**

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Vaccine Adjuvant



Lei WT, et al. Effect of Probiotics and Prebiotics on Immune Response to Influenza Vaccination in Adults: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. *Nutrients*. 2017 Oct 27;9(11).

- 20 studies found “supplementation of influenza vaccines with **probiotics or prebiotics before vaccination** increased the immunogenicity to specific influenza viral strains, including the H1N1, H3N2, and B strains.”
- **Longer duration of pre-supplementation, the greater the response.** The older the adult, the more protection offered.
- Strains most active were *L. casei*, *L. paracasei*, and *B. longum*.

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Vitamin D and Respiratory Infection



Martineau AR, et al. Vitamin D supplementation to prevent acute respiratory tract infections: systematic review and meta-analysis of individual participant data. *BMJ* 2017; 356: i6583.

- Acute respiratory infection kills ~2.65 million people/year.
- 25 randomized controlled trials (n=10,933, aged 0-95 years).
- Vitamin D supplementation **reduced risk of acute respiratory infection among all participants and those who were vitamin D deficient experienced the most benefit (NNT=4)**

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Patient: Doctor, I don't feel well and I'm not sure why.



Doctor: I want you to meditate for 20 minutes, twice a day, exercise for at least 30 minutes a day, avoid processed foods, eat plenty of organic fruit and veg, spend more time in nature and less indoors, stop worrying about things you can't control and ditch your T.V. Come back in 3 weeks.

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