



Autoimmune Disease

Dr. Joseph Pizzorno, ND

Editor-in-Chief, *Integrative Medicine: A Clinician's Journal*

Chair, IFM Board of Trustees

Founding President, Bastyr University

President, SaluGenecists, Inc.

Chair, Scientific Advisory Board, Bioclinic Naturals

mail2@DrPizzorno.com

Copyright © 2020

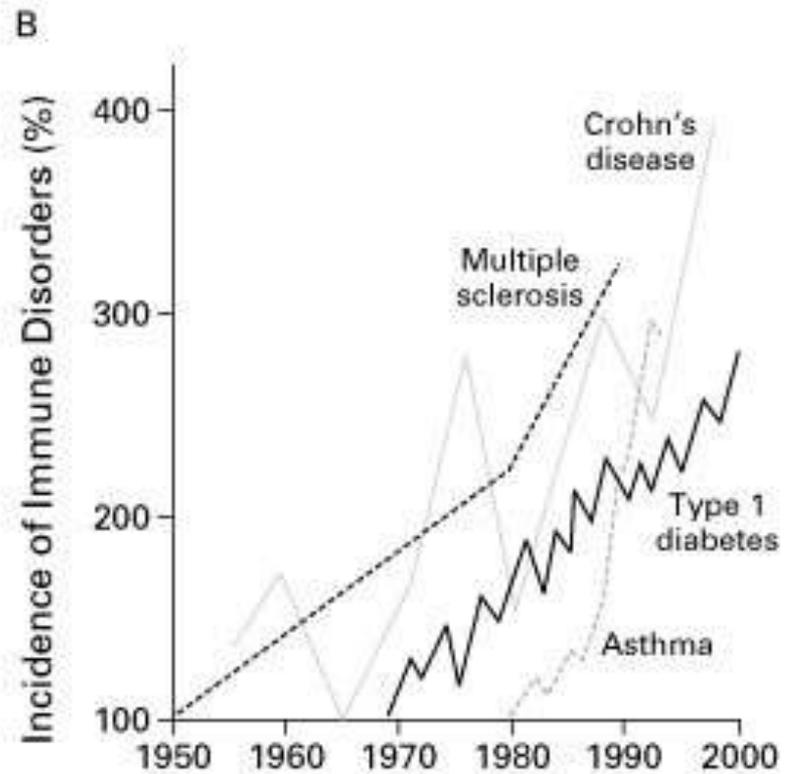
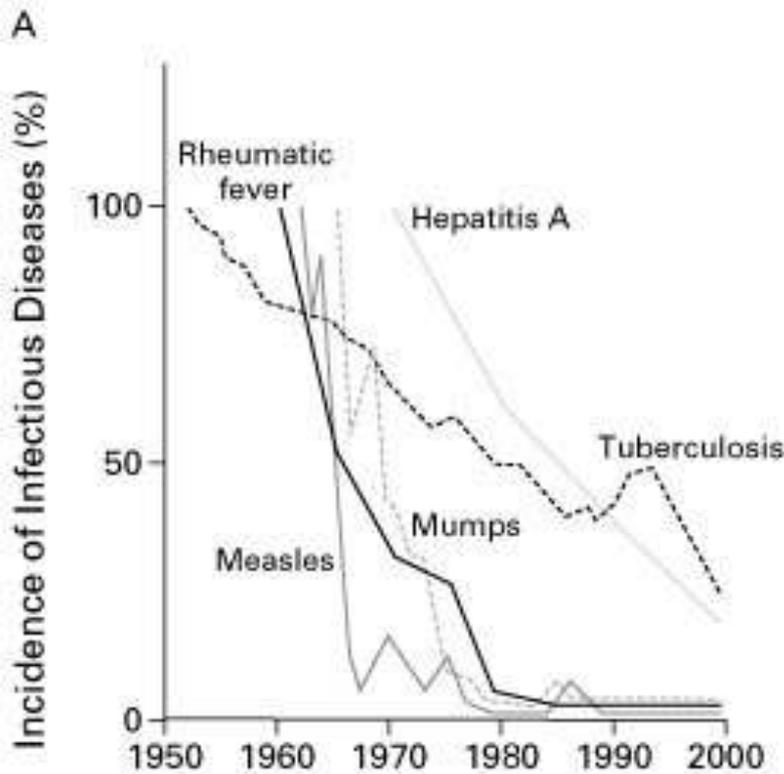


Overview

- Worldwide Epidemic of Immune Disorders
- Key Concepts
- Condition-Specific Protocols
 - Asthma
 - Atopic Conditions
 - Diabetes, Type 1
 - Hashimoto's Thyroiditis
 - Multiple Sclerosis
 - Rheumatoid Arthritis
 - Systemic Lupus Erythematosus
 - Urticaria
- Systemic Approaches



Autoimmune Disease Increasing Relentlessly





Worldwide: Type 1 Diabetes

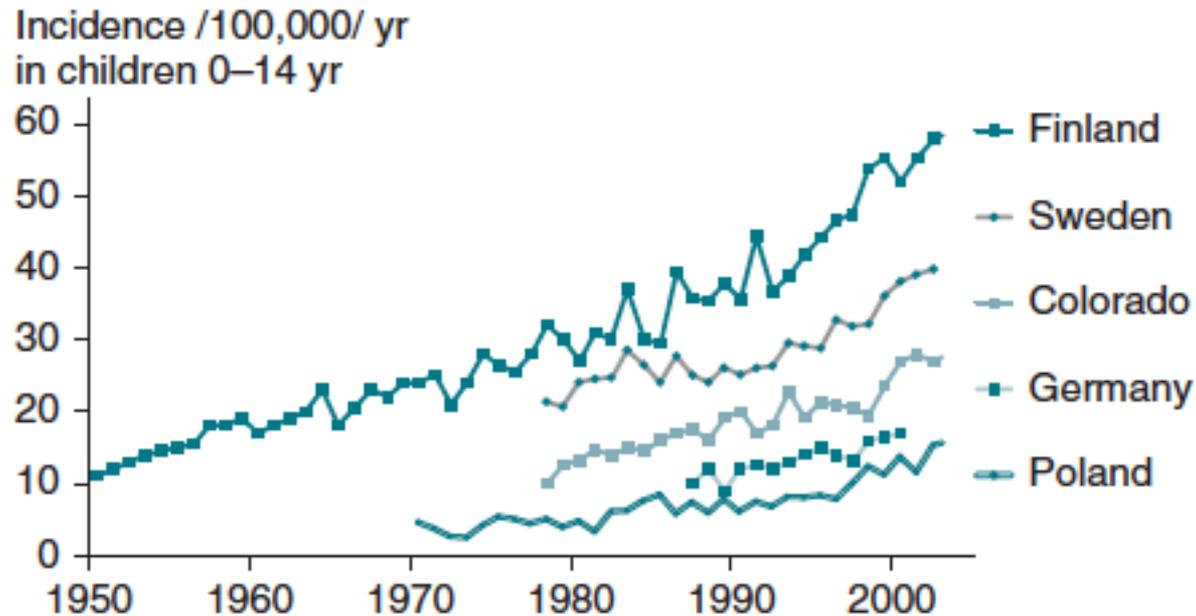


Figure 2.1 Increasing incidence of T1DM. Source: Adapted from The Environmental Determinants of Diabetes in the Young (TEDDY) Study. *Annals of the N Y Academy of Sciences* 2008. Reproduced with permission of John Wiley.



Key Concepts in Autoimmune Disease

1. Vitamin D deficiency very common
 - Causes loss of immune modulation
2. Food allergy/intolerance very common
 - Causes uncontrolled gut permeability
 - Increases circulating immune complexes
3. Excessive inflammatory response very common
4. Metals and chemicals binding to “self” molecules making them “non-self” which induces immune response and cross reactivity with normal tissues



Disease Incidence Prevention by Serum 25(OH)D Level

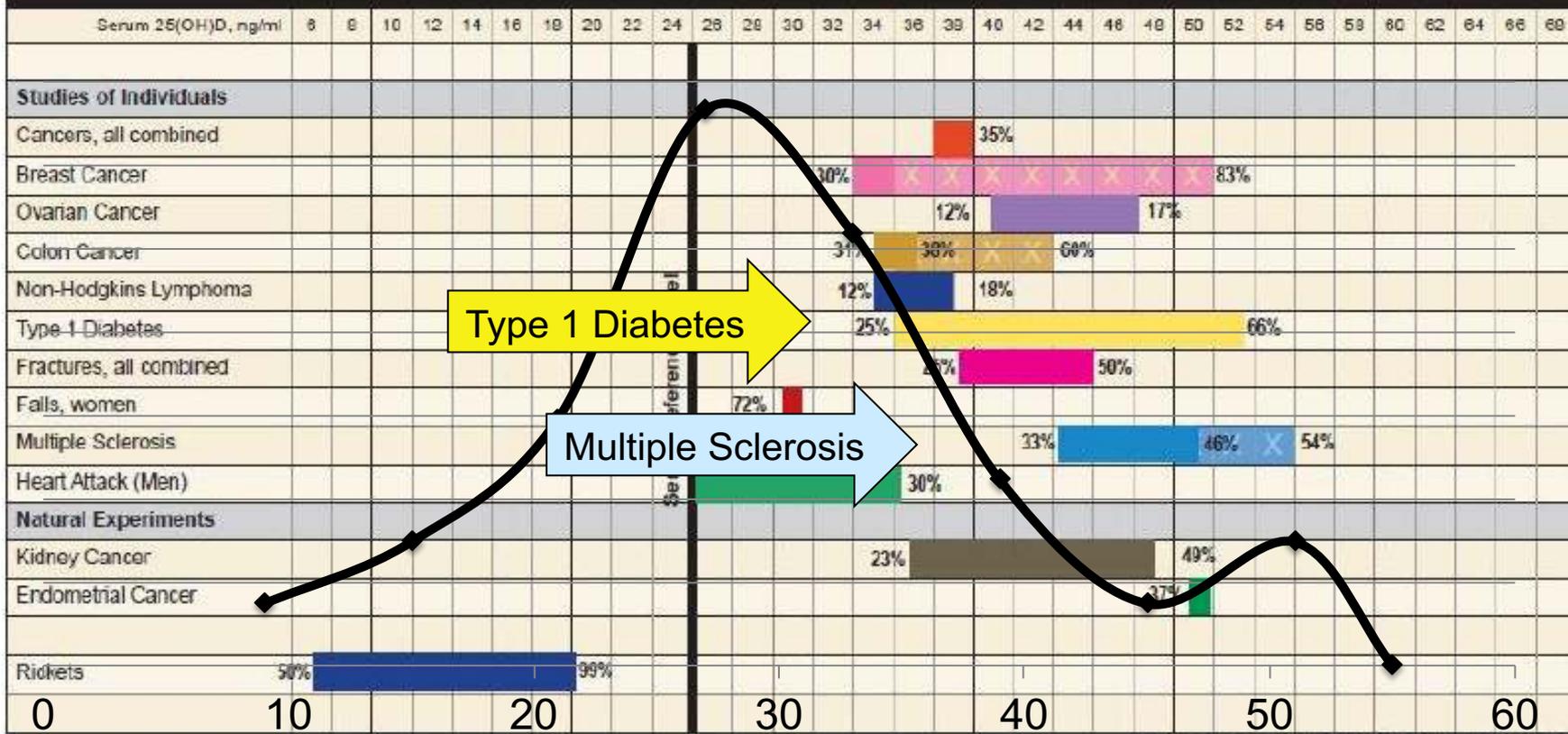


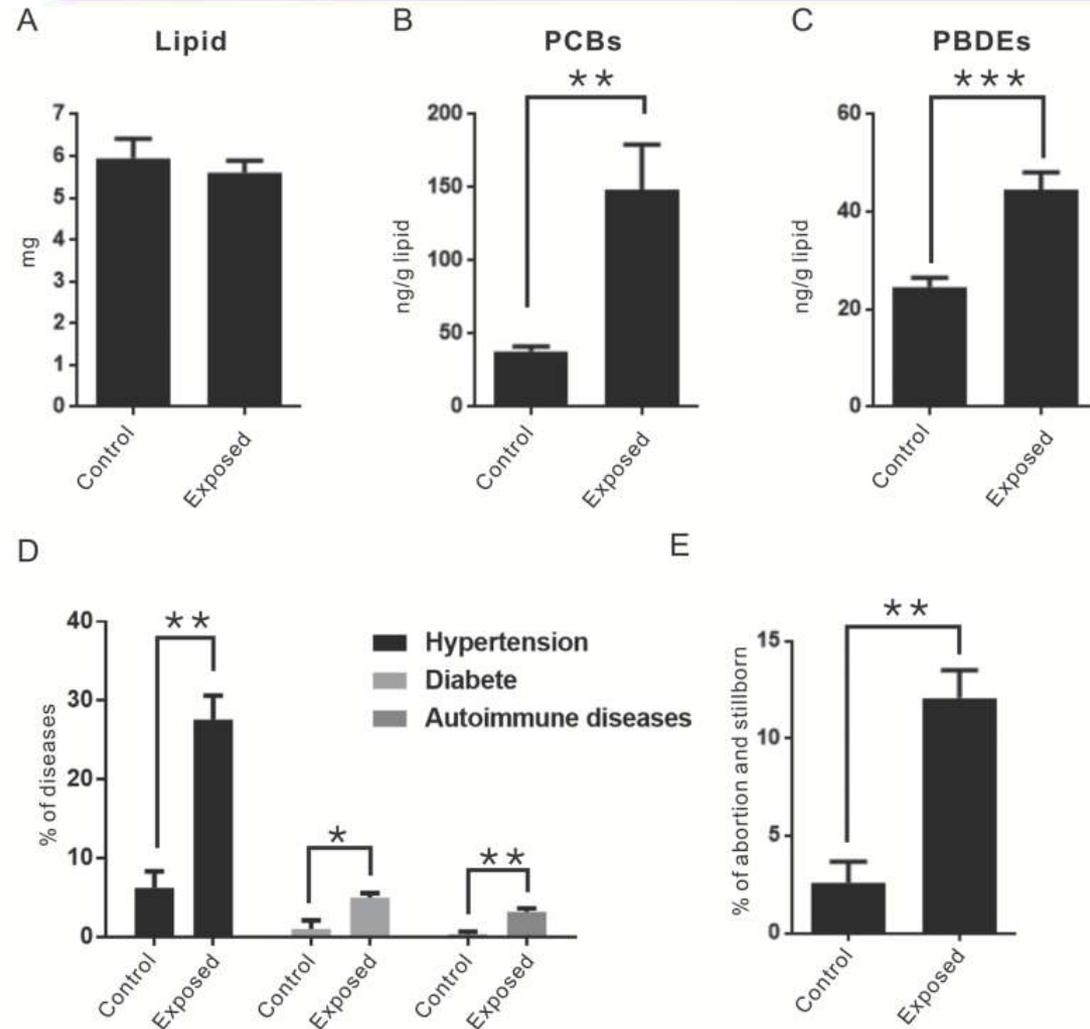
Chart prepared by: Garland CF, Baggerly CA

Legend:
 All percentages reference a common baseline of 25 ng/ml as shown on the chart.
 %'s reflect the disease prevention % at the beginning and ending of available data. Example: Breast cancer incidence is reduced by 30% when the serum level is 34 ng/ml vs the baseline of 25 ng/ml. There is an 83% reduction in incidence when the serum level is 50 ng/ml vs the baseline of 25 ng/ml.
 The 'x's in the bars indicate 'reasonable extrapolations' from the data but are beyond existing data.

References:
 All Cancers: Lappe JM, et al. Am J Clin Nutr. 2007;85:1586-91. Breast: Garland CF, Gorham ED, Mohr SB, Grant WB, Garland FC. Breast cancer risk according to serum 25-Hydroxyvitamin D: Meta-analysis of Dose-Response (abstract). American Association for Cancer Research Annual Meeting, 2008. Reference serum 25(OH)D was 5 ng/ml.
 Garland, CF, et al. Amer Assoc Cancer Research Annual Mtg. April 2008. Colon: Gorham ED, et al. Am J Prev Med. 2007;32:210-6. Diabetes: Hyppönen E, et al. Lancet 2001;358:1500-3. Endometrium: Mohr SE, et al. Prev Med. 2007;45:323-4. Falls: Brøe KE, et al. J Am Geriatr Soc. 2007;55:234-9. Fractures: Bischoff-Ferrari HA, et al. JAMA. 2005;293:2257-64. Heart Attack: Giovannucci et al. Arch Intern Med/Vol 168 (No 11) June 9, 2008. Multiple Sclerosis: Munger KL, et al. JAMA. 2006;296:2832-8. Non-Hodgkin's Lymphoma: Purdue MP, et al. Cancer Causes Control. 2007;18:989-99. Ovary: Tworoger SS, et al. Cancer Epidemiol Biomarkers Prev. 2007;16:783-8. Renal: Mohr SB, et al. Int J Cancer. 2006;110:2705-9. Rickets: Amdur SB, et al. JAMA. 1981;245:1061-4.
 Copyright GrassrootsHealth, 10/16/08 www.grassrootshealth.org



Toxin Load Correlates with Autoimmune Disease



Yuan J, Liu Y, Wang J, et al. Long-term Persistent Organic Pollutants Exposure Induced Telomere Dysfunction and Senescence-Associated Secretary Phenotype. *J Gerontol A Biol Sci Med Sci*. 2018;73(8):1027-1035



Ways Toxins Cause Autoimmunity

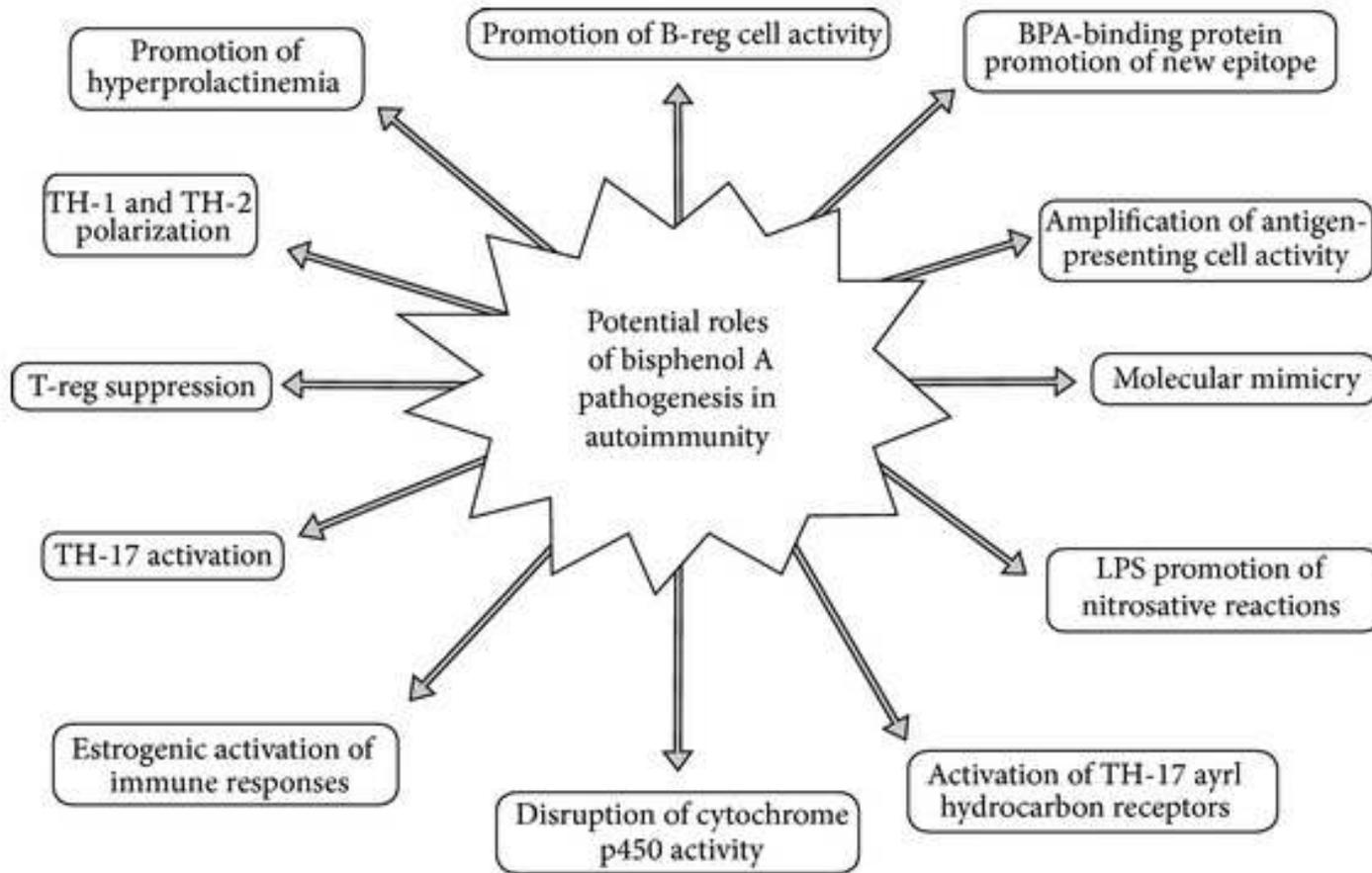
Toxin	Mechanism	Diseases
Silica/Asbestos	Adjuvant effect ↑ Inflammation set point	SLE, RA, vasculitis
Heavy metals (Hg, Ag, Au)	↓ T cell activation threshold ↑ Inflammation set point	Nephropathy, SLE, ANA
Drugs (procainamide)	↓ T cell activation threshold	SLE
Dioxins	↓ T cell activation threshold ↓ Central tolerance	Anti-nuclear autoantibodies
Fungicides (hexachlorobenzene)	Adjuvant effect	SLE
Trichloroethylene (TCE)		Scleroderma
BPA	Binds to proteins, receptor sites and enzymes	Many autoimmune

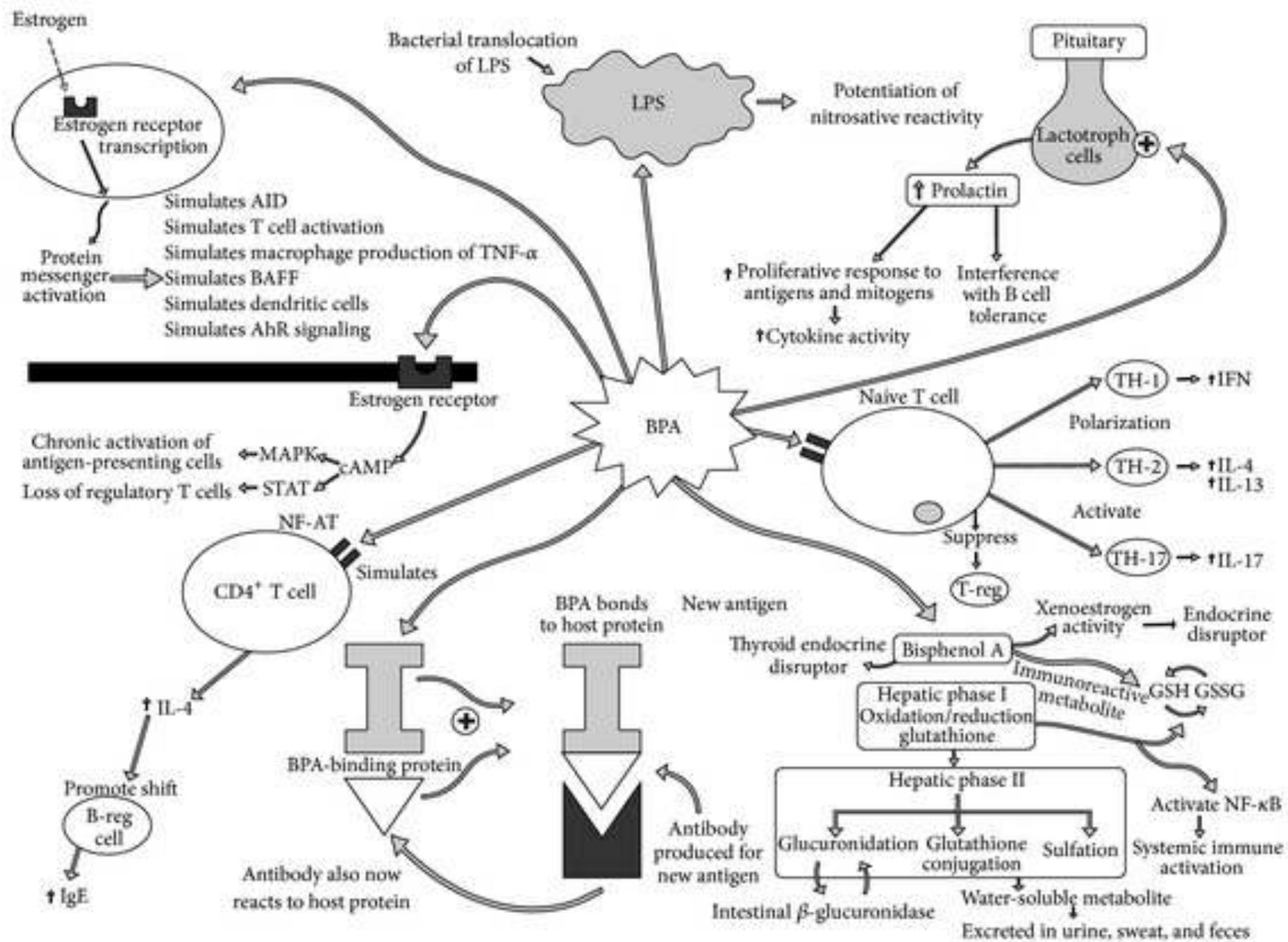
Pollard KM, Hultman P, Kono DH. Toxicology of autoimmune diseases. *Chem Res Toxicol*. 2010 Mar 15;23(3):455-66

Vojdani A, Kharrazian D, Mukherjee PS. Elevated levels of antibodies against xenobiotics in a subgroup of healthy subjects. *J Appl Toxicol*. 2015 Apr;35(4):383-97



Many Mechanisms: BPA Example







% OF CHRONIC DISEASE DUE TO TOXINS



Converting Disease Risk to % Caused: Attributable Fraction Calculation

$$AF = \frac{p(rr-1)}{p(rr-1) + 1}$$

p = underlying prevalence of risk factor in the population

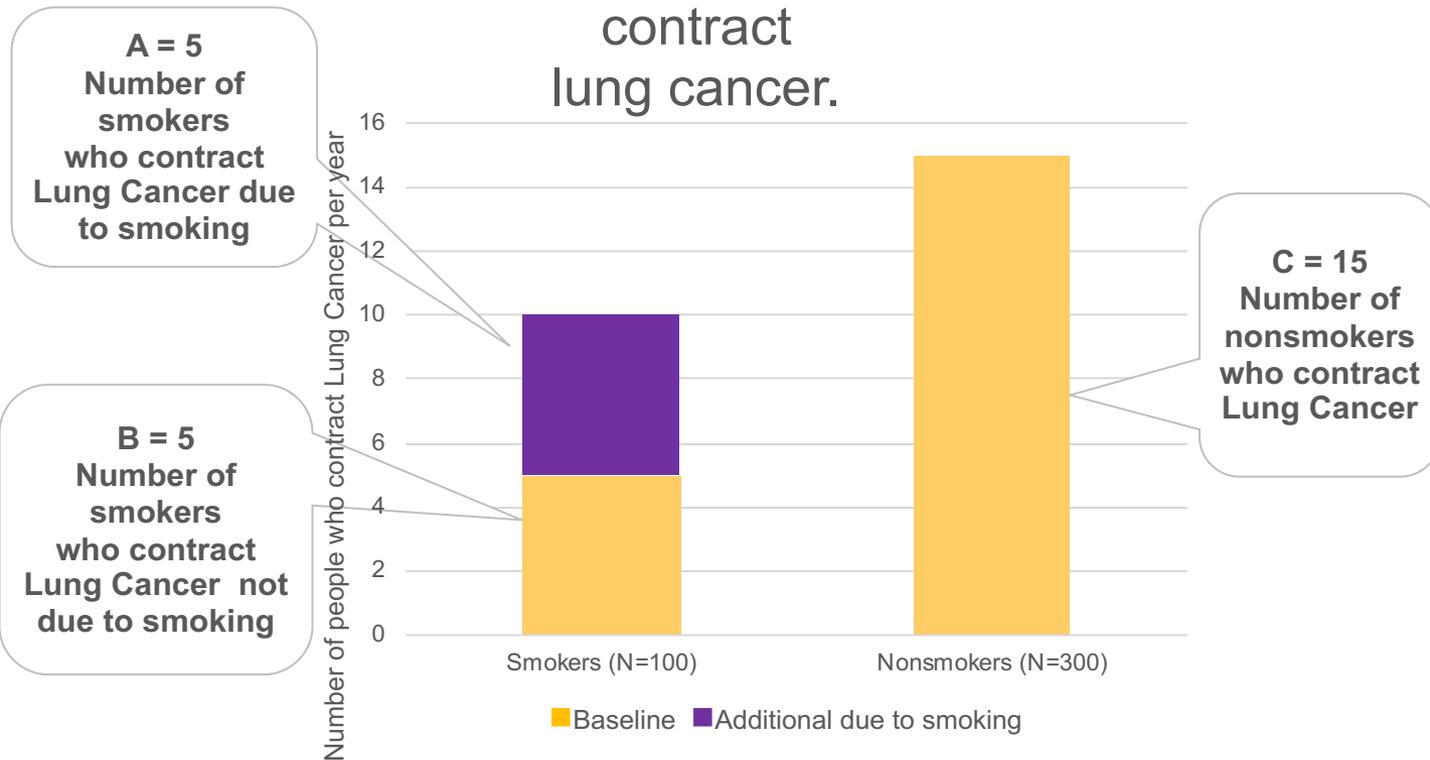
rr = relative risk (risk of contracting a disease in an exposed population divided by the risk of contracting the disease in an unexposed population)

AF = % of disease due to the identified cause



Example: Smoking and Lung Cancer

Number of smokers and nonsmokers who contract lung cancer.



$$AF = \frac{A}{A + B + C}$$



Our Process In Summary

1. Determine incidence of disease in “unexposed” population
2. Determine threshold for increased disease risk
3. Determine % of population above threshold
4. Determine incidence of disease (OR) in those above threshold
5. Calculate AF, i.e., % of disease

Whole population is exposed, so probably UNDERESTIMATES % of disease.

However, independence almost impossible, so OVERESTIMATES as well.



How to Interpret the Toxin/Disease Slides

- **Threshold:** Threshold exposure at which there is an increased risk of disease outcome
- **% Above Threshold:** Percentage of the population with higher exposure than the threshold
- **Odds Ratio:** Increased disease risk in those above threshold
- **% of Dz:** Percent contribution of the toxin to that disease presence
- **Insufficient Data:** Studies too small or contradictory
- **NAD:** Could not find good data
- **Blank:** Not studied yet



CONDITION-SPECIFIC PROTOCOLS



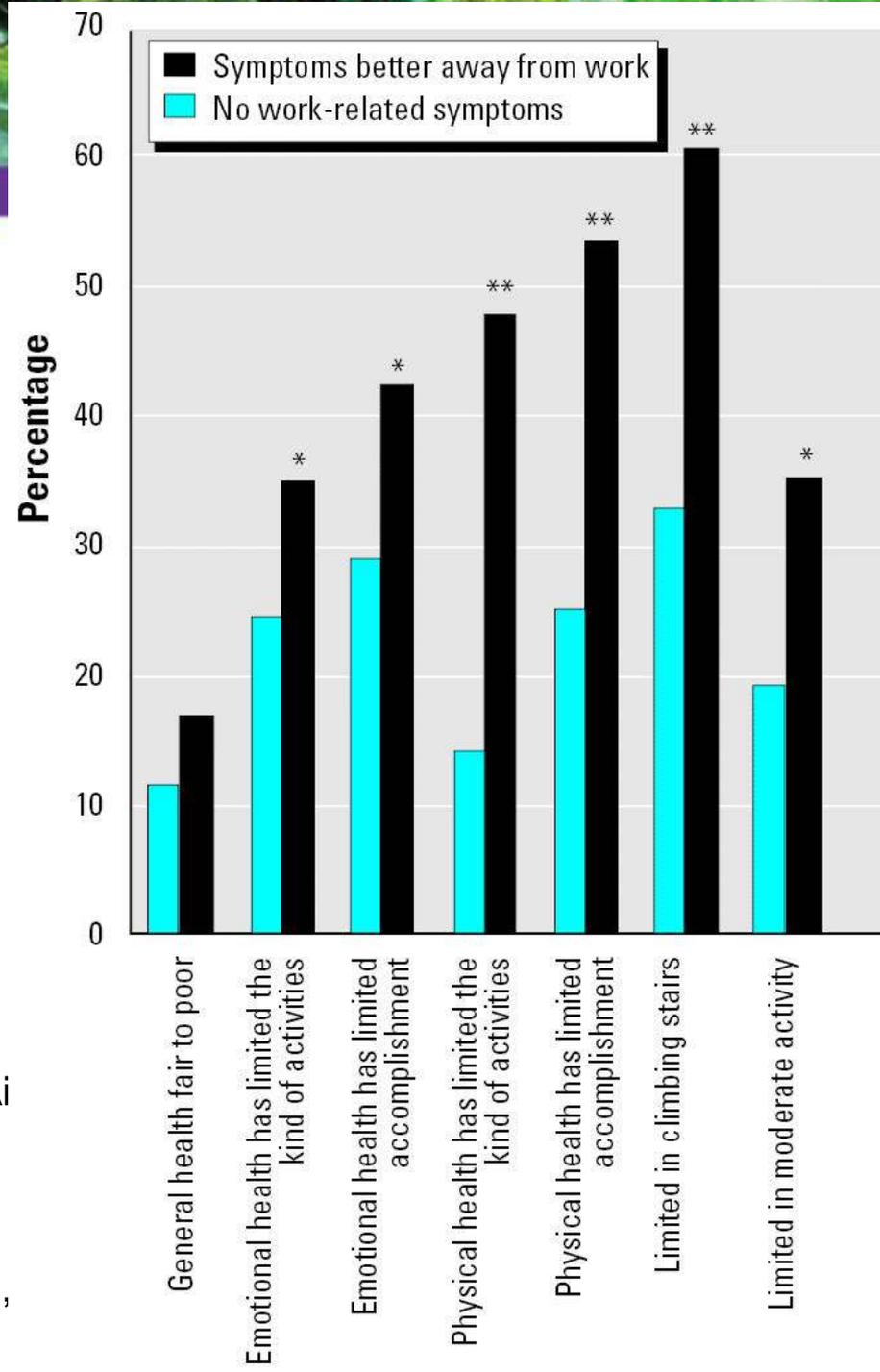
Asthma

- Worst toxins: sulfites, air pollution, mold, drugs
- Key nutrient deficiencies: omega-3 FA
- Key interventions:
 - If sulfite sensitive, molybdenum : 500 ug/d (IV faster)
 - If hypochlorhydria, HCl: see protocol
 - Omega-3 FA: 2-4 g/d
 - Vitamin C: 500 mg bid
 - Vitamin D: 2,000-8,000 iu/d (measure!)
 - Quercetin: 500 mg/d (use more absorbable forms)
 - Nebulized Mg during attack



Mold

- 21% of asthma
- 67% if adult onset



Fisk WJ, Lei-Gomez Q, Mendell MJ. (2007). Meta-analyses of the associations of respiratory health effects with dampness and mold in homes. *Indoor Air* 17(4), 284-96. PubMed PMID: 17661925

Cox-Ganser JM, White SK, Jones R, et al. (2005). Respiratory morbidity in office workers in a water-damaged building. *Environ Health Perspect.*, 113(4), 485-490 PubMed PMID: 15811840



Drugs (Prescription and OTC)

- Aspirin/NSAIDs: 2% to 25%
- Drugs shown to cause bronchial spasm:
 - Angiotensin-converting enzyme (ACE) inhibitors
 - Cholinergic agonists
 - Cholinomimetic alkaloids
 - Chemotherapeutic agents
 - Diuretics
 - Corticosteroids
 - Antibiotics
 - Radiocontrast dyes

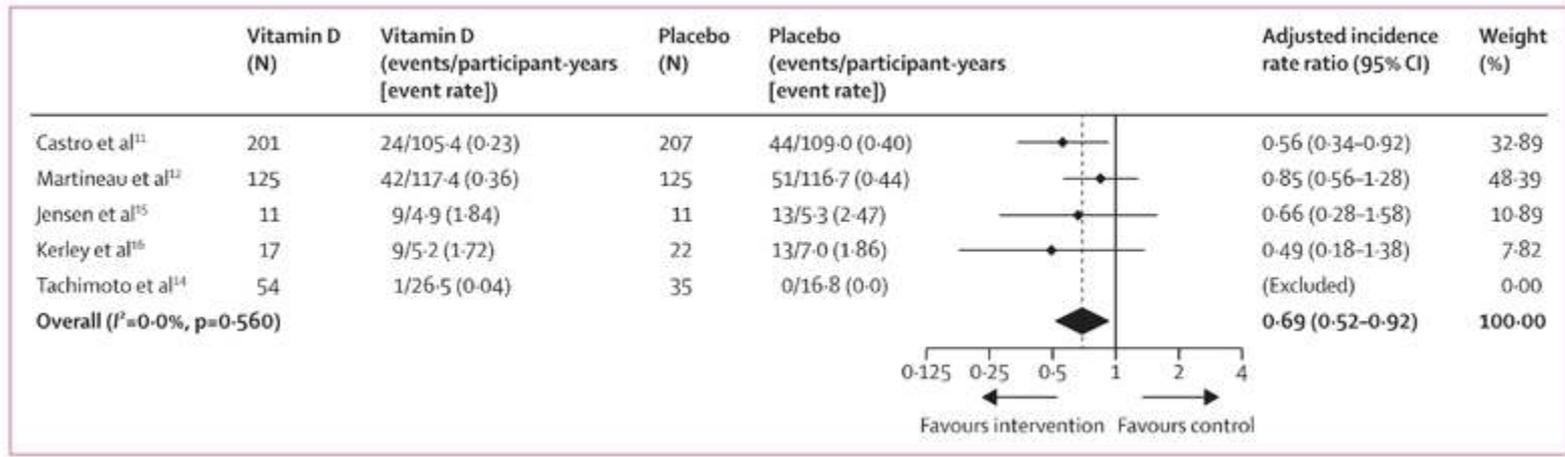
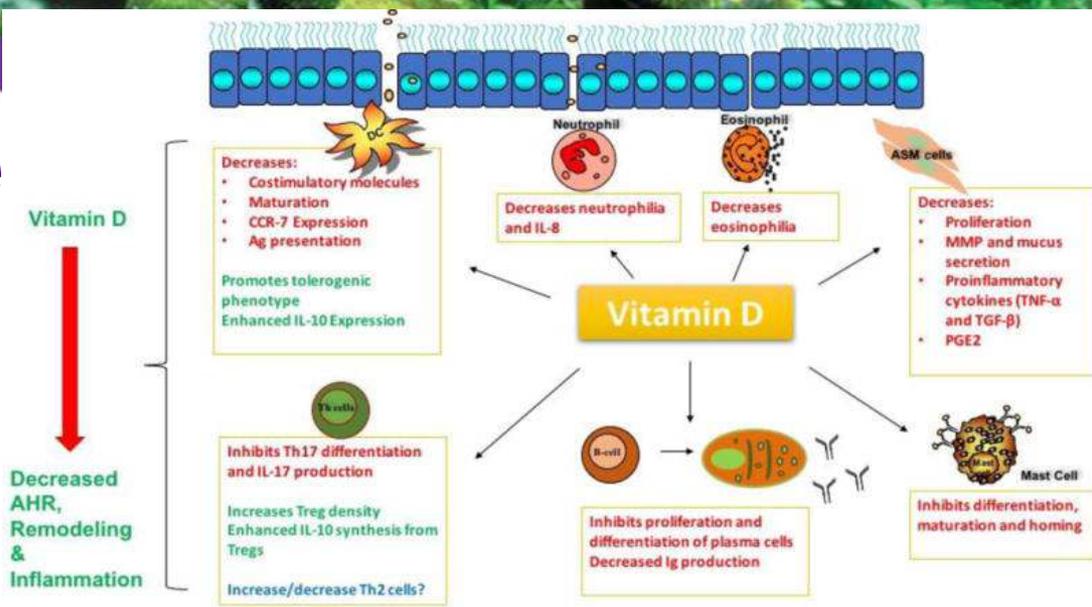
Ledford DK, Wenzel SE, Lockey RF. (2014). Aspirin or other nonsteroidal inflammatory agent exacerbated asthma. *J Allergy Clin Immunol Pract.*, 2(6), 653-7. PubMed PMID: 25439353

Covar RA, Macomber BA, Szeffler SJ. (2005). Medications as asthma triggers. *Immunol Allergy Clin North Am.*, 25(1), 169-90. PubMed PMID: 15579370



Hard to Overstate Importance of Vitamin D

- Prevention AND treatment



Hall SC, Agrawal DK. Vitamin D and Bronchial Asthma: An Overview of Data From the Past 5 Years. Clin Ther. 2017;39(5):917–929

Jolliffe DA, Greenberg L, Hooper RL, et al. Vitamin D supplementation to prevent asthma exacerbations: a systematic review and meta-analysis of individual participant data [correction appears in Lancet Respir Med. 2018 Jun;6(6):e27]. Lancet Respir Med. 2017;5(11):881–90



Sulfite Sensitivity

- Found in 10% of patients with asthma
- Sulfite sensitivity causes bronchial spasm
- Daily consumption of sulfites surprisingly high:
 - Average person: 2-3 mg/d
 - Wine and beer drinkers: additional 5-10 mg/d
 - Restaurant meal: 25-100 mg of metabisulfites
- Increased urinary sulfite/sulfate ratio
- Usually respond to molybdenum, but:
 - Very poor absorption \Rightarrow IV recommended

Stevenson DD. Simon R.A. Sensitivity to ingested metabisulfites in asthmatic subjects. *J Allergy Clin Immunol* (1981) 68 26–32.

Papaioannou R. Pfeiffer CC. Sulfite sensitivity—unrecognized threat. Is molybdenum deficiency the cause? *J Orthomol Psych* (1984) 13 105–110.



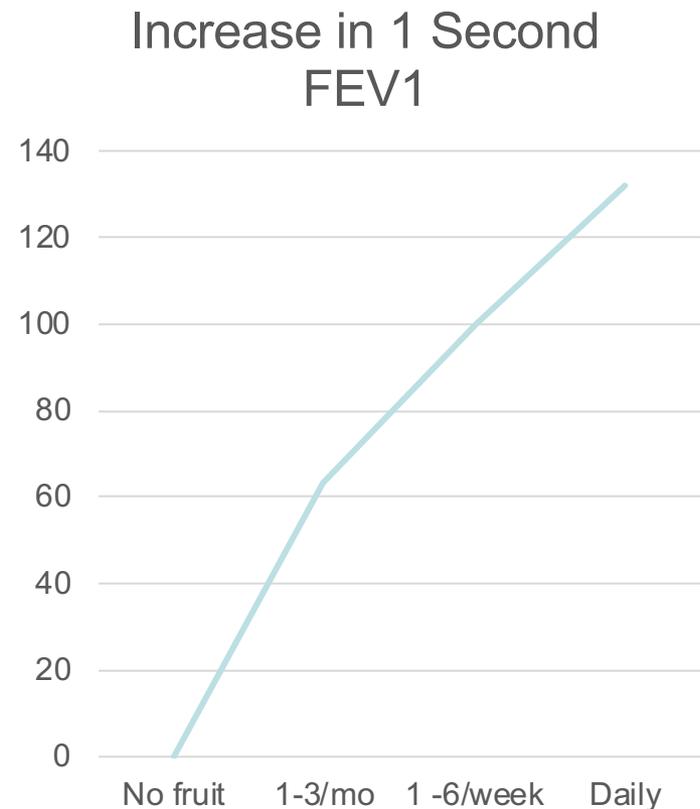
Diet Extremely Important

- Food allergy/intolerance almost always present
- Importance of fruit
- High omega-3 fish (small, low mercury)



Simply Eating More Fruit Improves Lung Function in Asthma

- Eating more fruits, vegetables and fish improves respiratory function





Most Common Food Allergies in Asthma



Peanuts
(includes peanut butter
and many candies)



Gluten
(includes flour, wheat,
and more)



Tree Nuts
(includes almonds, hazelnuts,
walnuts, pecans, cashews,
and more)



Dairy
(includes milk, cheese,
yogurt, and more)

Foods Cross-React

If Allergic to:	Risk of Reaction to at Least One:	Risk:
A legume* peanut 	Other legumes peas  lentils  beans 	5% 
A tree nut walnut 	Other tree nuts brazil  cashew  hazelnut 	37% 
A fish* salmon 	Other fish swordfish  sole 	50% 
A shellfish shrimp 	Other shellfish crab  lobster 	75% 
A grain* wheat 	Other grains barley  rye 	20% 
Cow's milk* 	Beef hamburger 	10% 
Cow's milk* 	Goat's milk goat 	92% 
Cow's milk* 	Mare's milk horse 	4% 
Pollen birch  ragweed 	Fruits/vegetables apple  peach  honeydew 	55% 
Peach* 	Other Rosaceae plum  pear  apple  cherry 	55% 
Melon* cantaloupe 	Other fruits watermelon  banana  avocado 	92% 
Latex* latex glove 	Fruits kiwi  banana  avocado 	35% 
Fruits kiwi  avocado  banana 	Latex latex glove 	11% 

<https://asthmaallergyclinic.in/allergy/food-allergy/>

(accessed 2020-04-30)



Hypochlorhydria

- 80% of children with asthma have hypochlorhydria
 - Discovered in 1931!
- Greatly increases risk of:
 - Food allergy
 - Increased gut permeability
 - Decreased absorption of many nutrients
- Be sure to treat *H. pylori*
- HCl supplementation protocol



Hypochlorhydria Common

Acne

Addison's disease

Asthma

Autoimmune disorders

Celiac disease

Chronic candidiasis

Dermatitis herpetiformis

Diabetes mellitus

Eczema

Gallbladder disease

Graves' disease

Hepatitis

Hives (chronic)

Hyperthyroidism/hypothyroidism

Myasthenia gravis

Osteoporosis

Pernicious anemia

Psoriasis

Rheumatoid arthritis

Rosacea

Sjögren's syndrome

Systemic lupus erythematosus

Thyrotoxicosis

Vitiligo



Hypochlorhydria Signs & Symptoms

Bloating, belching,
burning, and flatulence
immediately after meals

Chronic intestinal
parasites or abnormal
flora

Dilated blood vessels in
the cheeks and nose

Fullness after eating

Indigestion, diarrhea, or
constipation

Iron deficiency

Itching around the rectum

Multiple food allergies

Nausea after taking
supplements

Undigested food in stool

Upper digestive tract
gassiness

Weak, peeling, and
cracked fingernails



HCl Patient Protocol

1. Take 1 HCl capsule (10 grains) at next large meal.
2. At every meal after that of same size, take 1 more capsule.
3. Continue to increase the dose until you reach any of:
 - a. 7 capsules
 - b. Feel a warmth in your stomach
 - c. Maldigestion symptoms ameliorate
4. After determining the dose, maintain that dose at all meals of similar size. Take fewer capsules with smaller meals.
5. Best to take capsules throughout the meal rather than all at once
6. As your stomach begins to produce HCl again, you will notice the warm feeling again. Start decreasing the dose level.
7. Every 3 days, decrease by 1 capsule per meal. If the warmth continues, decrease more rapidly. If maldigestion symptoms return, add capsules back until digestion improves again.



Atopic Conditions

- Worst toxins: PAHs
- Key nutrient deficiencies: Vitamin D
- Key interventions:
 - Omega-3 FA: 2,000-4,000 mg/d
 - Vitamin D: 2,000-6,000 IU/d
 - Zinc: 25 mg/d

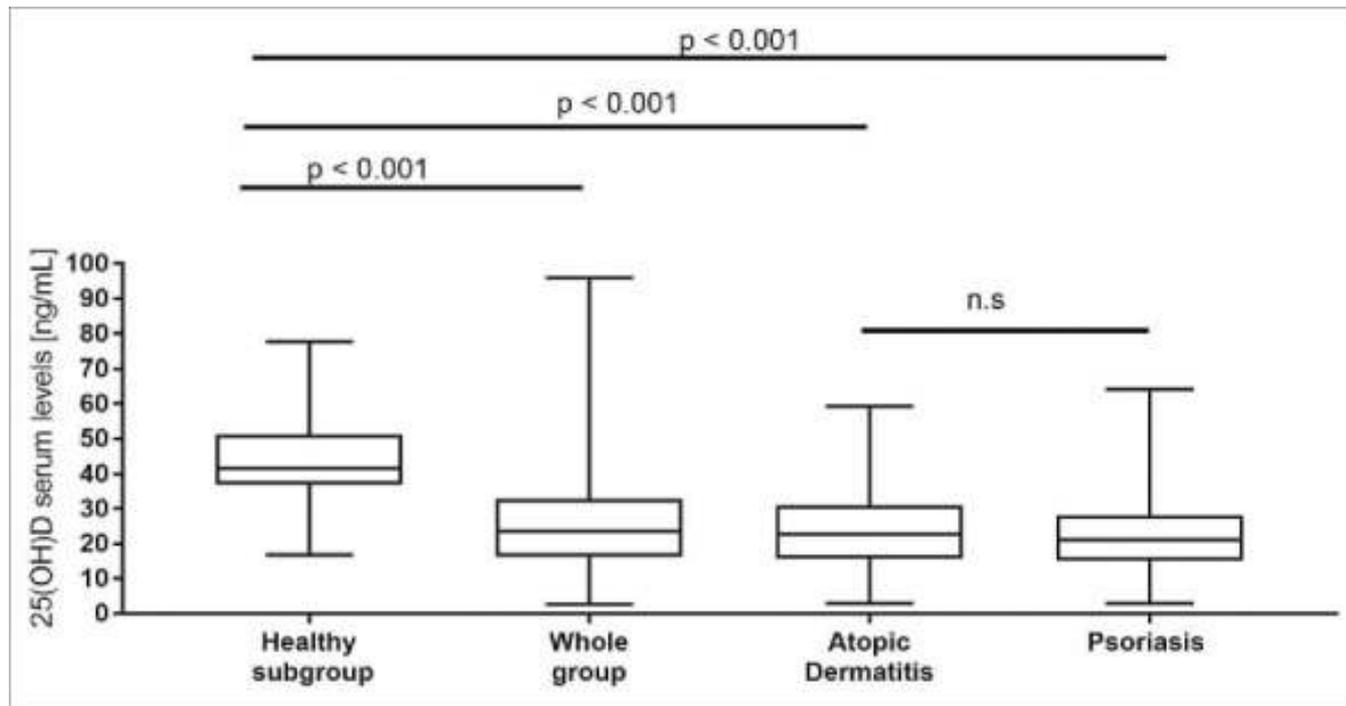


Atopic Conditions

Toxin	Threshold	% Above Threshold	Odds Ratio	% of Disease	Example PMID
PAHs	Maternal 2.41 ng/m ³		3.9	19%	19221603
BPA			1.3		26765087



Low Vitamin D Associated with Common Skin Disorders

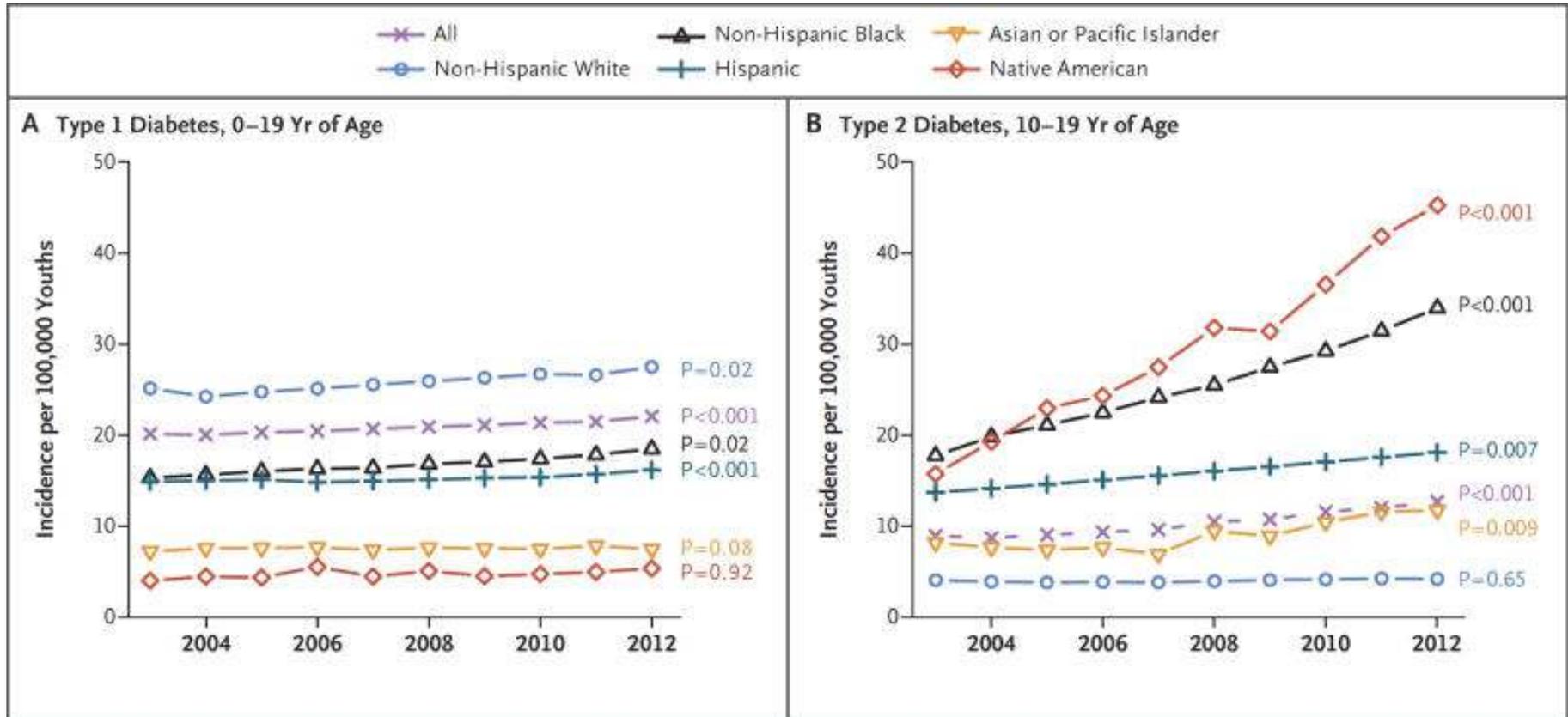




Type 1 Diabetes

- Worst toxins:
- Key nutrient deficiencies: Vitamin D
- Key interventions:
 - Niacinamide (only for early stage)
 - Vitamin D: titrate to serum 25(OH)D₃ >40 ng/mL
 - Fish oil: 150 mg of EPA and DHA/kg body weight

We Have a Serious Problem



Mayer-Davis EJ, Lawrence JM, Dabelea D, et al. Incidence Trends of Type 1 and Type 2 Diabetes among Youths, 2002-2012. *N Engl J Med.* 2017;376(15):1419-1429.



Diabetes, Type 1

Toxin	Threshold	% Above Threshold	Odds Ratio	% of Disease	Example PMID
Air pollution	Tertial	33%	1.04		26527558
Arsenic	Water concentration	Positive correlation			29527309
Fluoride	Water concentration	Positive correlation			29527309
Glyphosate					NAD
Cadmium					NAD
Trihalomethane					NAD



Vitamin D

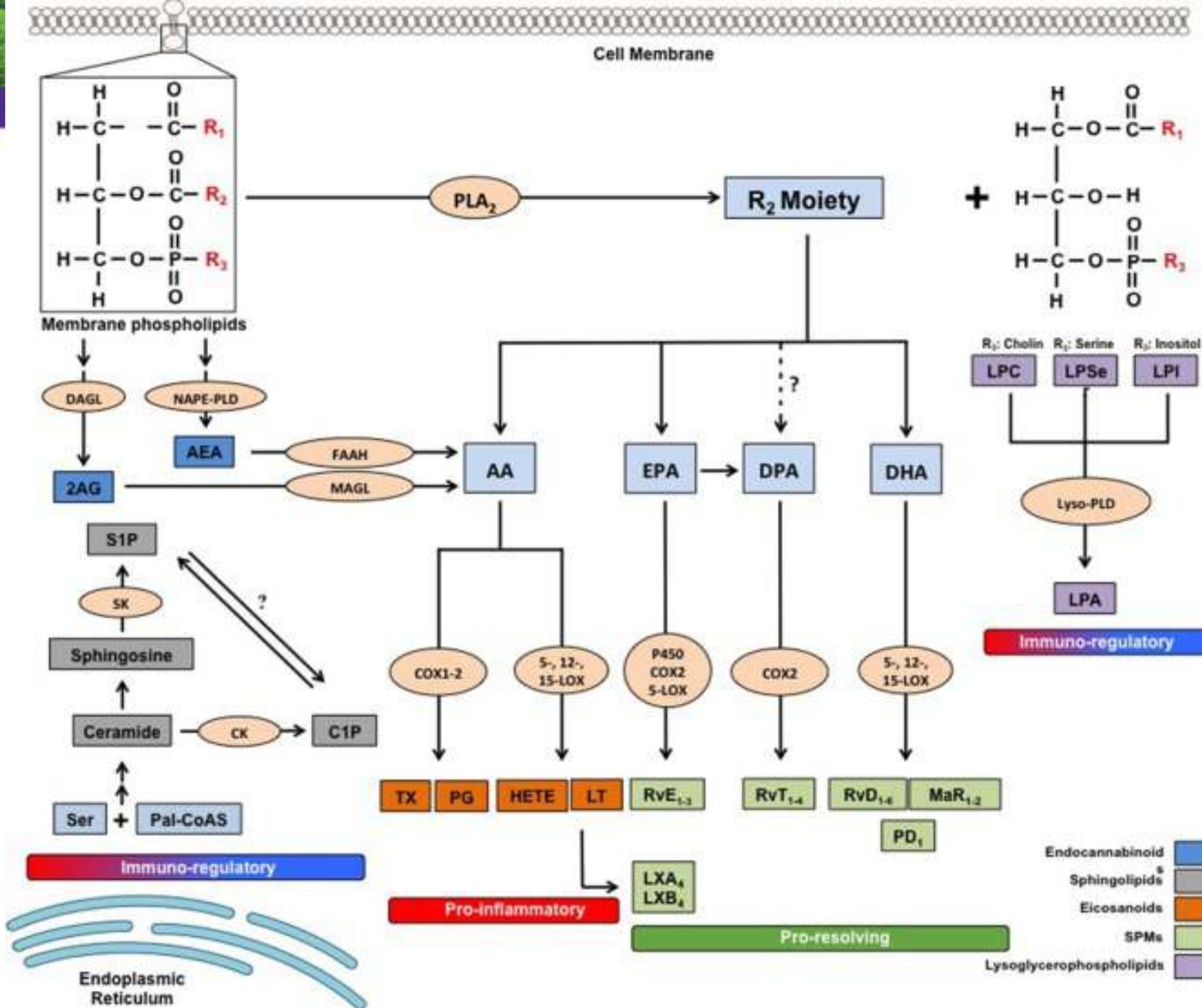
- Hard to overstate importance
- Clearly major role in prevention
 - Deficiency greatly increases risk
 - VDR polymorphisms greatly impact risk
- Limited benefit after full development of disease



Vitamin D + SPMs (Specialized Pro-Resolving Lipid Mediators)

- Show benefit even after disease developed—**but only if some beta-cells still alive**
- Halts autoimmunity and preserves beta-cell function in pediatric and adult subjects with new-onset and established T1D

Resolvins (SPMs)





Hashimoto's Thyroiditis

- Worst toxins: Hg, PCBs
- Key nutrient deficiencies: Se, vitamin D
- Key interventions:
 - Avoid all sources of gluten
 - Selenium: 500 **ug**/d
 - Vitamin D: 2,000-6,000 IU/d (always balance with A and K2)
 - Use both!

Liontiris MI, Mazokopakis EE. A concise review of Hashimoto thyroiditis (HT) and the importance of iodine, selenium, vitamin D and gluten on the autoimmunity and dietary management of HT patients. Points that need more investigation. Hell J Nucl Med. 2017;20(1):51-56



Hashimoto's Thyroiditis

Toxin	Threshold	% Above Threshold	Odds Ratio	% of Disease	Example PMID
Mercury	Blood 1.8 ug/L	20%	2.2	20.0%	22280926
PCBs	Non-Linear	2 nd quintile	Significant		19856712



Trace and Toxic Minerals Significant

The obtained values for the trace elements in control and HT blood samples (ng/g).

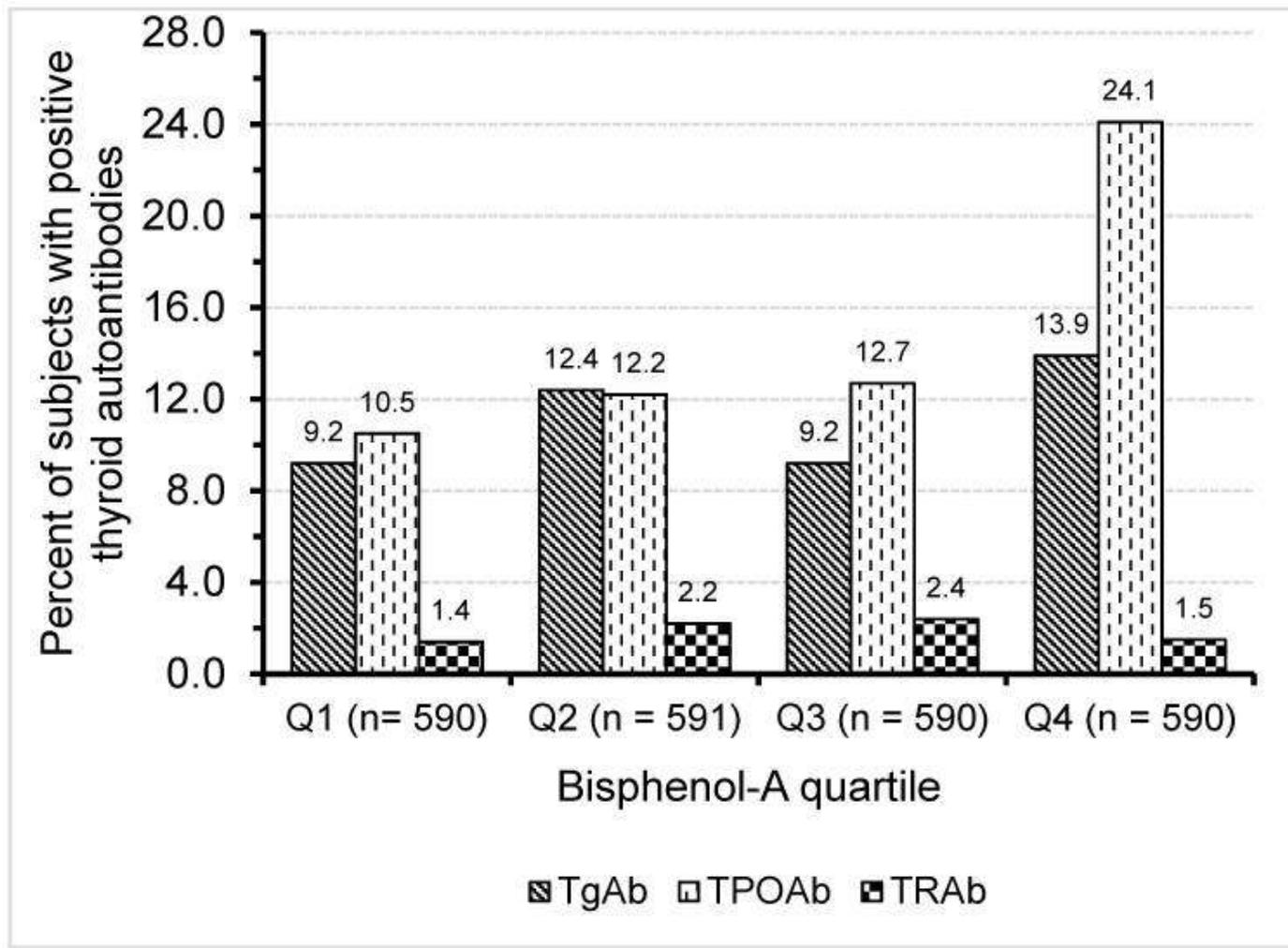
		Mn	Ni	Cu	Zn	As	Se	Cd	Pb	U
Control	mean	14.4	3.35	965	4801	0.69	95.4	0.77	12.3	0.04
HT	mean	16.5	21.4	545	1707	1.89	84.2	0.25	24.2	0.06
<i>U</i> test	P-value	.2076	< .0001	< .0001	< .0001	< .0001	.0147	< .0001	< .0001	.030

- Toxins higher in HT: As, Ni, Pb
- Nutrients lower in HT: Cu, Se, Zn

Stojsavljević A, Rovčanin B, Jagodić J, et al. Significance of arsenic and lead in Hashimoto's thyroiditis demonstrated on thyroid tissue, blood, and urine samples [published online ahead of print, 2020 Apr 18]. *Environ Res.* 2020;186:109538. doi:10.1016/j.envres.2020.109538



BPA and Thyroid Antibodies





Multiple Sclerosis

- Worst toxins: BPA, smoking, benzene, animal fat (arachidonic acid, not saturated)
- Key nutrient deficiencies: Vitamin D, omega-3 EFAs
- Key interventions:
 - Omega-3 FA: 2-6 g/d
 - Vitamin D: 5,000 iu/d
 - Biotin: 100 mg/d

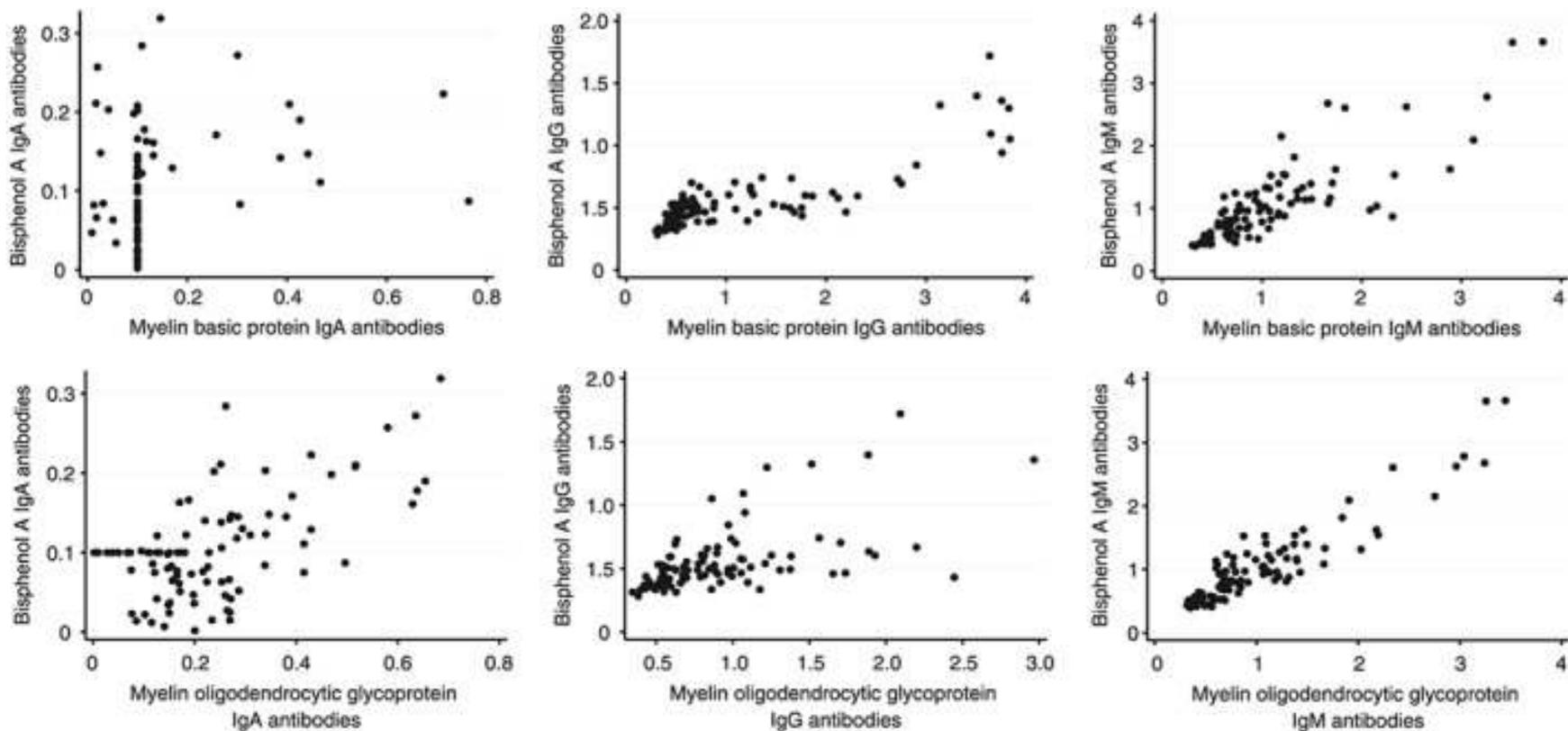


Multiple Sclerosis

Toxin	Threshold	% Above Threshold	Odds Ratio	% of Disease	Example PMID
Smoking	Y/N	(Spouse control)	1.3	20.4%?	23455932
BPA			Large		
Benzene			1.7-2.6		24734319
Air pollution	Quartiles	25%	1.4		26624240
Dioxins	High vs low exposure		1.2		24137524



Strong Correlation Between BPA and Myelin Antibodies



Kharrazian D, Vojdani A. Correlation between antibodies to bisphenol A, its target enzyme protein disulfide isomerase and antibodies to neuron-specific antigens. J Appl Toxicol. 2017 Apr;37(4):479-484



Dietary Interventions

- Swank diet
 - 1948
 - Low saturated fat, high fish/fish oil
 - Uncontrolled studies show benefit
- McDougall diet
 - Very low-fat, strictly plant-based
 - Improvement in health parameters, but only slight NS MS
- Caloric restriction
 - 1700-1800 kcal
 - Small studies show benefit



Terry Wahls, MD Protocol

- Personal experience with MS
- Followed a typical natural medicine protocol and totally reversed
- Key components:
 - Modified Paleo diet
 - Non-domesticated lean meats
 - Plant-based foods except fruits, nuts, roots, and legumes
 - 3 cups of green leafy vegetables, 3 cups of sulfur-rich vegetables, and 3 cups of intensely colored vegetables daily
- Small studies show benefit

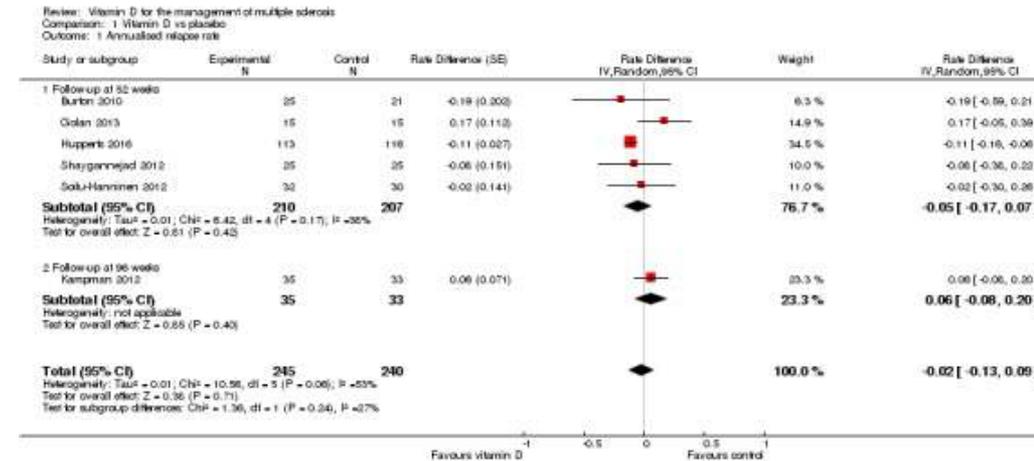
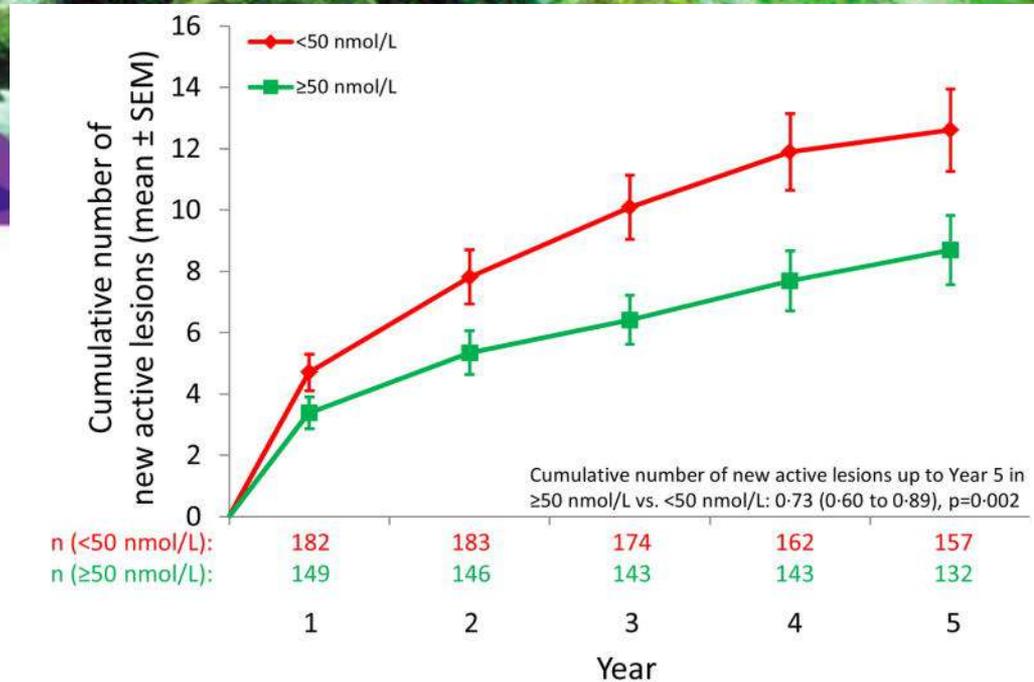


Omega-3 Fatty Acids

- Significant reduction in inflammatory markers
- Modest clinical improvement
- Decreasing omega-6 FA likely improves results

Vitamin D

- Deficiency huge risk factor for MS:
 - Initiation and progression
- Inexplicably, intervention trials mixed
 - Decreases many inflammation markers
 - Many confounding factors
 - VDR status
 - Trigger likely different from progression



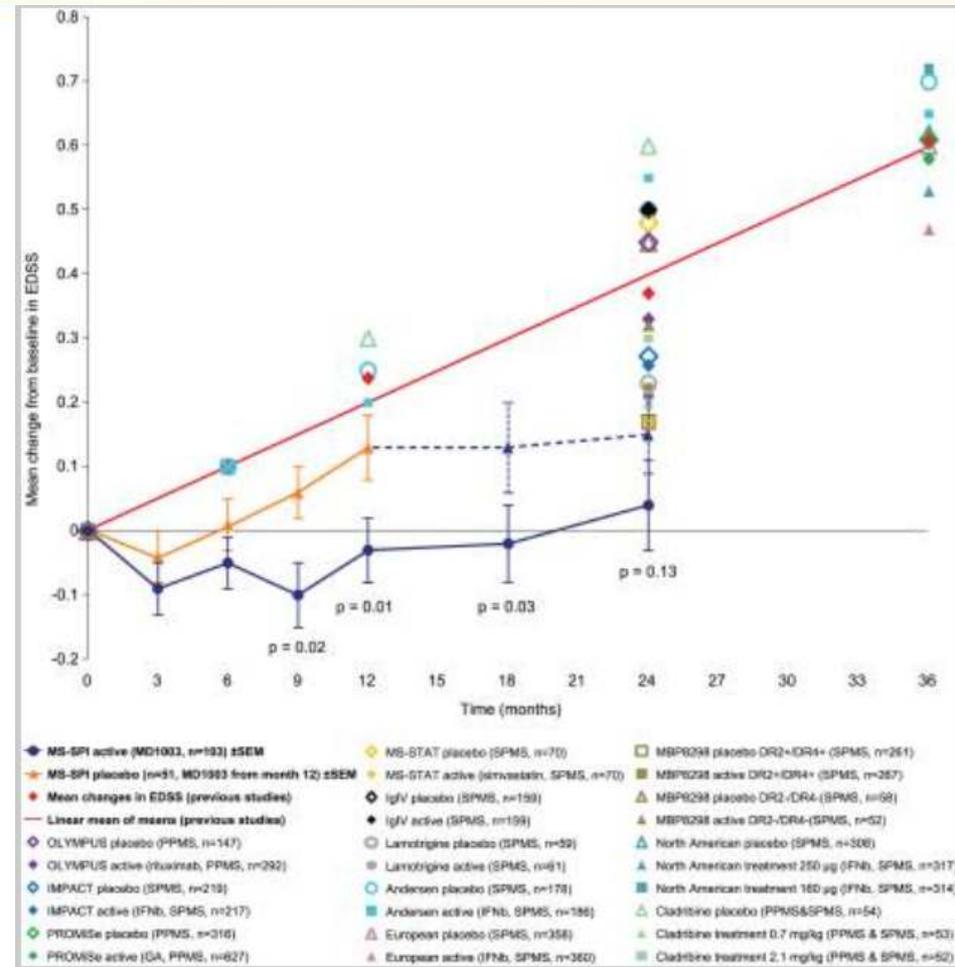
Ascherio A, Munger KL, White R, et al. Vitamin D as an early predictor of multiple sclerosis activity and progression. *JAMA Neurol.* 2014;71(3):306–314

Jagannath VA, Filippini G, Di Pietrantonj C, et al. Vitamin D for the management of multiple sclerosis. *Cochrane Database Syst Rev.* 2018;9(9):CD008422



Biotin?

- Limited number of studies, but encouraging
- Hypothesis: activates carboxylases to support myelin repair
- 100 mg/d (RDI 30 ug/d)



Tourbah A, Lebrun-Frenay C, Edan G, et al. MD1003 (high-dose biotin) for the treatment of progressive multiple sclerosis: A randomised, double-blind, placebo-controlled study. *Mult Scler.* 2016;22(13):1719–1731



Rheumatoid Arthritis

- Worst toxins: PCBs, pesticides, benzene
- Key nutrient deficiencies: Omega-3 FA
- Key interventions:
 - Restoration of health gut flora
 - Elimination of food allergies/intolerances (esp. wheat)
 - Fasting: water fast, 3-5 days
 - Fish oil: 3 g/d
 - Curcumin: 400 mg tid between meals (Meriva, Theracumin)
 - Ginger: 8-10 g of dried ginger standardized to contain 20% gingerol and shogaol tid



Rheumatoid Arthritis

Toxin	Threshold	% Above Threshold	Odds Ratio	% of Disease	Example PMID
PCBs	Quartiles	25%	Dioxin type 2.9 Non-dioxin type 2.2	23%	17589595
Pesticide exposure	Agricultural or spouse		1.4	2.4-17.6%	27285288
Benzene	Exposed	18.9%	1.6	10.6%	27285288
Silica			2.7		10086214
Glyphosate			1.4		27285288



Gut Dysbiosis

- Decreased *Bifidobacteria sp.*, *Bacteroides-Porphyromonas-Prevotella sp.*
- 51% SIBO—dose-dependent relationship

Rashid T.; Jayakumar K.S.; Binder A.; et al. Rheumatoid arthritis patients have elevated antibodies to cross-reactive and non cross-reactive proteus microbes. *Clin Exp Rheumatol* (2007) 25:259–67.

Hooper L.V.; Wong M.H.; Thelin A.; et al. Olecular analysis of commensal host-microbial relationships in the intestine. *Science* (2001 Feb 2) 291 (5505) 881–884.

Henriksson A.E.; Blomquist L.; Nord C.E.; et al. Small intestinal bacterial overgrowth in patients with rheumatoid arthritis. *Ann Rheum Dis* (1993 Jul) 52 (7) 503–510.

Henriksson AE, Blomquist L, Nord CE, Midtvedt T, Uribe A. Small intestinal bacterial overgrowth in patients with rheumatoid arthritis. *Ann Rheum Dis*. 1993 Jul;52(7):503-10. PubMed PMID: 8346978.



Food Allergy/Intolerance

- Multiple mechanisms of damage:
 - Inflammatory reaction at enterocytes causing loss of gut permeability control
 - Cross reactivity of food antibodies with normal proteins
- 20-40% have demonstrated food reactions
- Jejunal IgA, IgG, & IgM elevated against nearly all food antigens; substantially cross-reactive



Food Reactions

- Most common
 - Corn (56%), wheat (54%), rye (34%), oats (37%), malt (27%)
 - Bacon/pork (39%), beef (32%), lamb (17%)
 - Oranges (39%), grapefruit (24%)
 - Milk (37%), cheese (24%)
 - Egg (32%)
 - Tomato (22%)
 - Peanuts (20%)
- 19% symptom- and drug-free at 5-year follow-up



Wheat!!

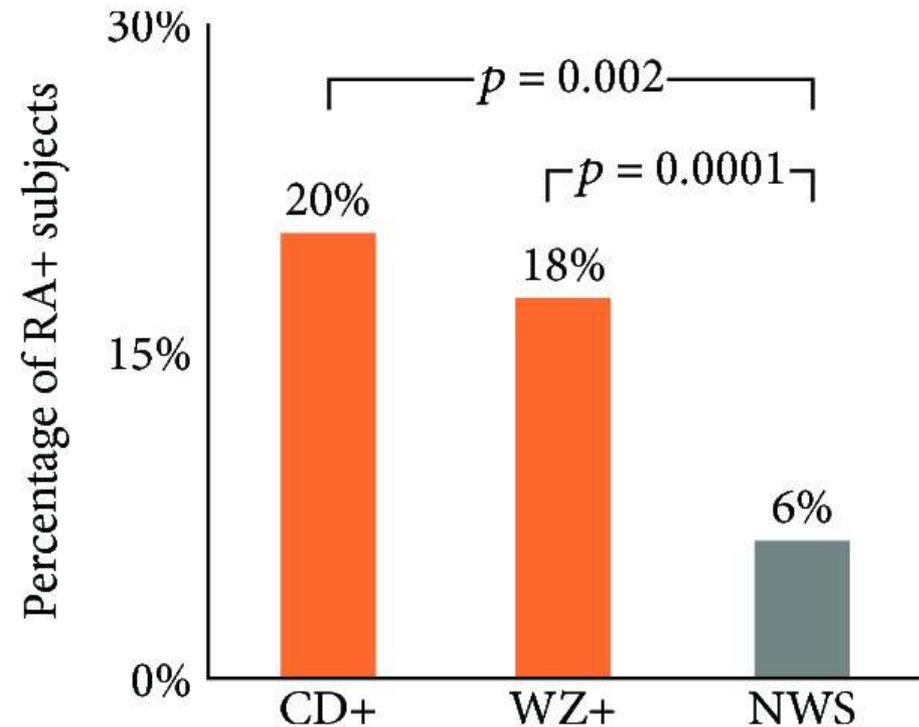
- Hard to overstate contribution of wheat to RA
- Gliadin (from gluten) causes release of zonulin
- Zonulin increases gut permeability
- Multiple constituents increase inflammation

- Personal clinical experience: 50% of patients with ANY chronic inflammatory disease improve—some even to cure—by carefully avoiding gluten AND all grains



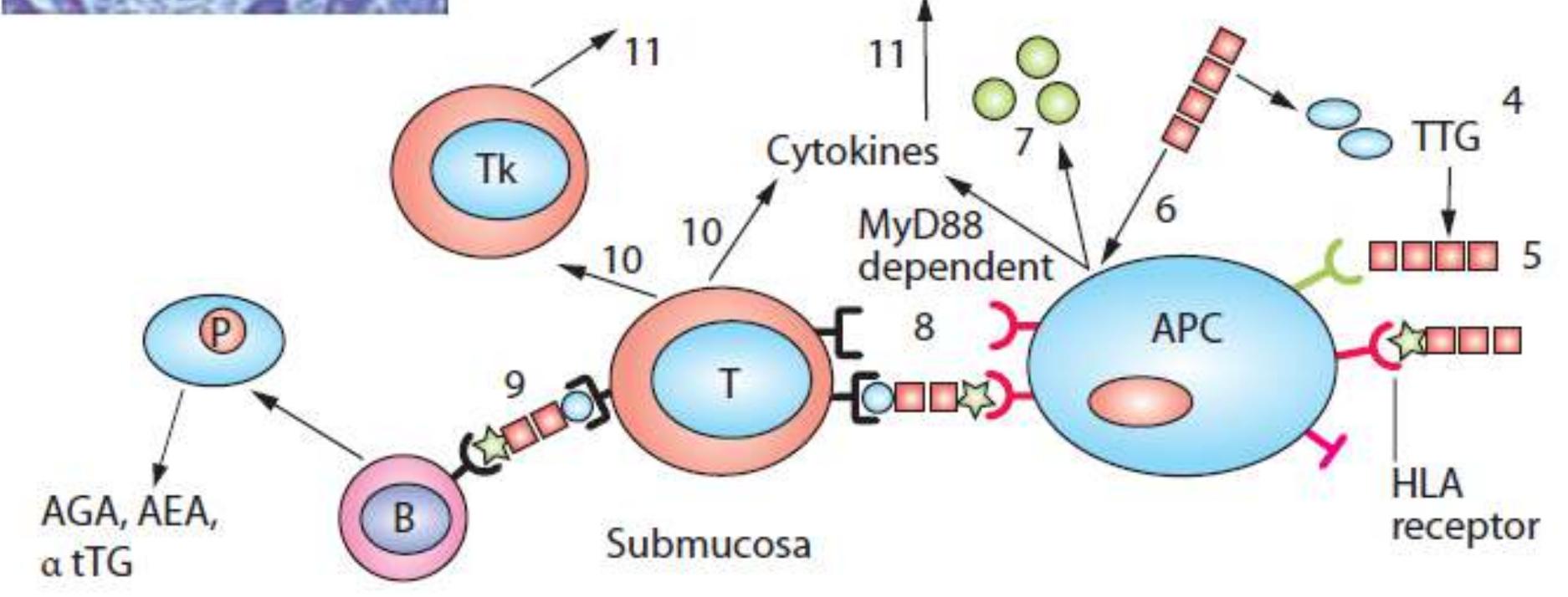
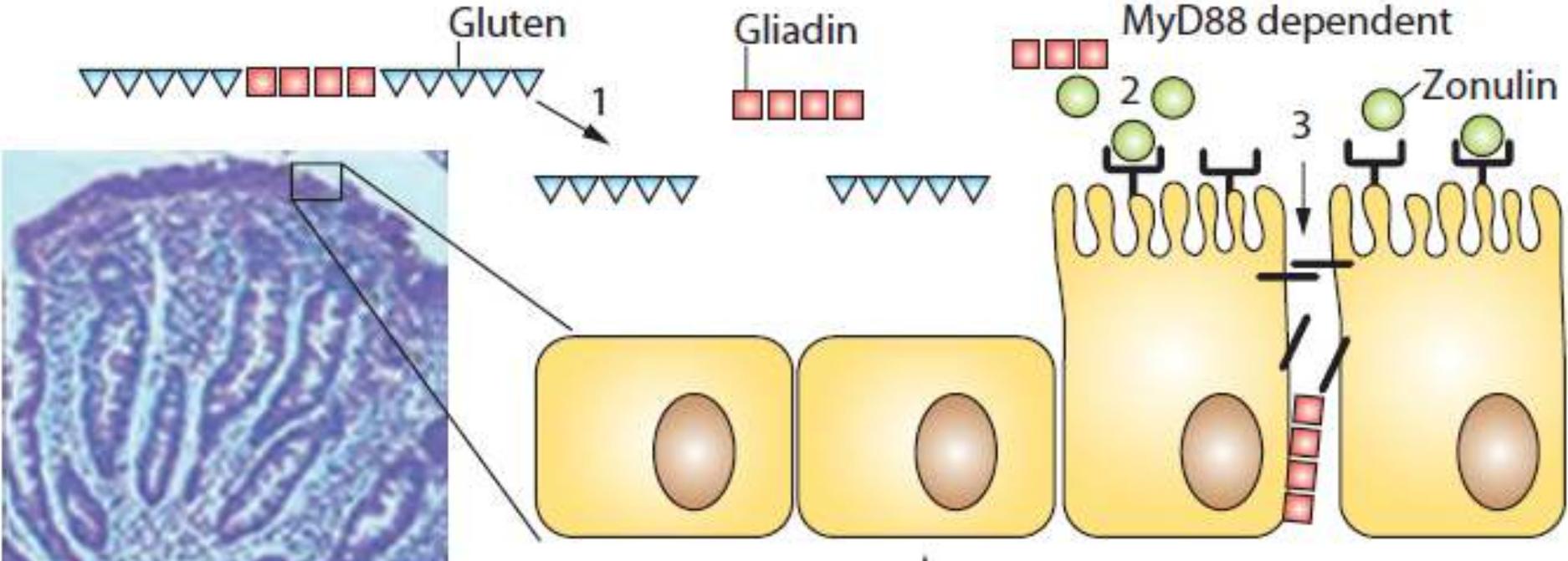
Celiac Disease and Wheat Antibodies Common in RA

- Zonulin high in patients with RA



Yang Y, Deshpande P, Krishna K, et al. Overlap of characteristic serological antibodies in rheumatoid arthritis and wheat-related disorders. *Dis Markers*. 2019;2019:4089178.

Fasano A. Zonulin and its regulation of intestinal barrier function: the biological door to inflammation, autoimmunity, and cancer. *Physiol Rev*. 2011 Jan;91(1):151-75.



Zonulin Only Found in Humans

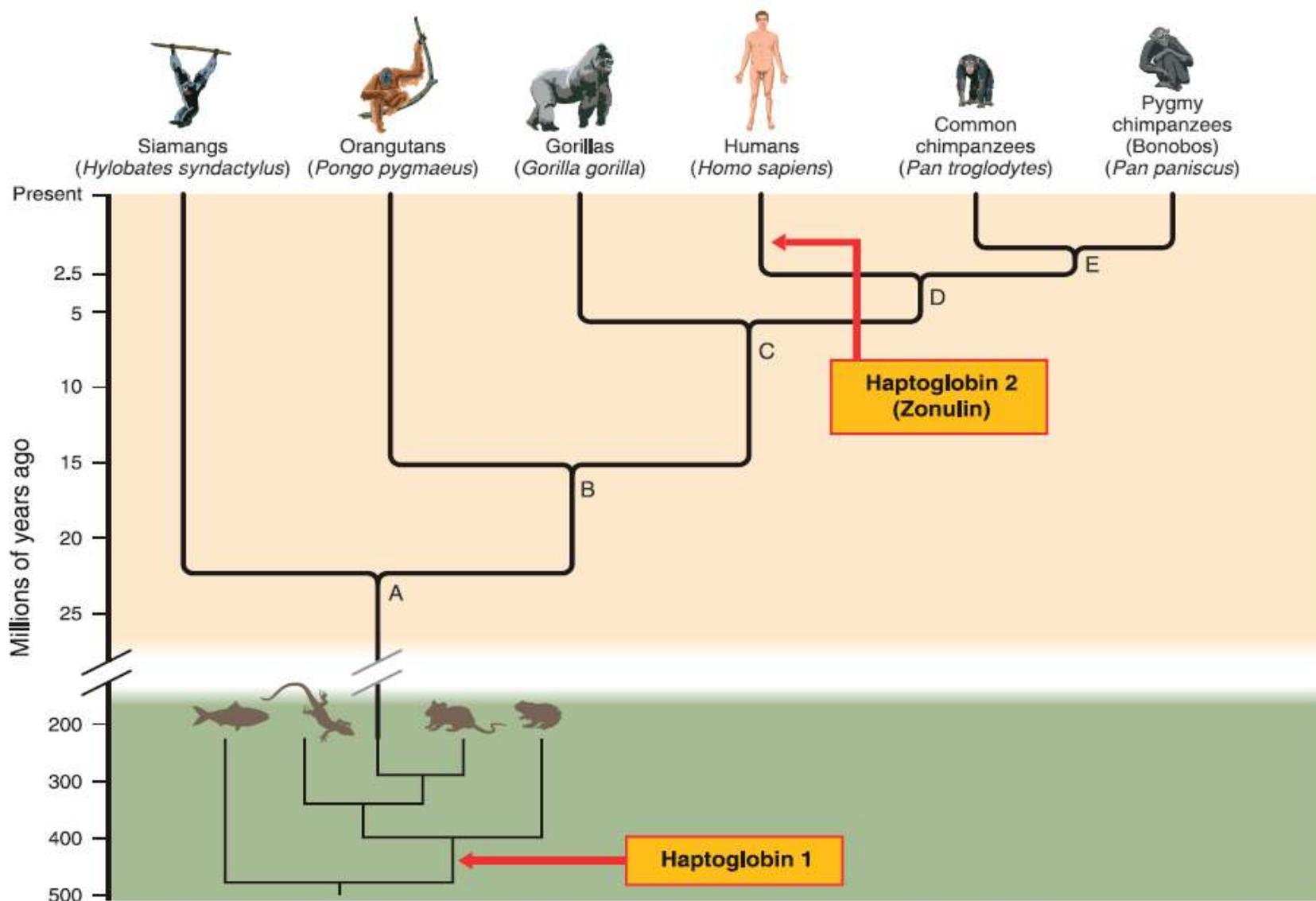


FIG. 2. Evolutionary tree of HP gene. The appearance of the gene encoding HP1 has been mapped ~450 millions years ago, soon after the split between bony fish, reptiles, and mammals. HP2 appeared much later, 500, 000 years after, then chimpanzee and human split 2.5 millions years ago.

- Zonulin is the precursor to haptoglobin 2
- Haptoglobins scavenge iron when tissues are damaged and blood is released



Recommendations

Response to Wheat	% Pop.	Characteristics	Intervention
Safe	34%	HP1-1; no grain antibodies	None needed
Inconsistent, dose-dependent response (some research is labeling severe form non-celiac gluten sensitivity—NCGS)	43%	HP1-2; low to elevated blood zonulin	Limit wheat, rye, barley; optimize protein digestion; reseed with <u>Bifidobacteria</u> and other healthy gut bacteria
Immune reactions to grains	15%	Antibodies to some grain proteins	Avoid all grains
Celiac disease	3%	HP1-2 or HP2-2; elevated antibodies to gliadin; HLA-DQ2 or DQ8	Strictly avoid wheat, rye, barley; may need to avoid other grains as well
Autoimmune disease	5%	HP1-2 or HP2-2; elevated anti-self antibodies	Strictly avoid all allergens; DHEA, vitamin D, etc.



Water Fasting

- **Water** fasts of 3-5 days—some studies to 10 days
- Substantial reduction of joint pain, swelling, morning stiffness
- Increases serum DHEA-S
- Decreases serum IL-6, CRP, ESR, and disease activity
- Improved intestinal permeability control

Fraser D.A.; Thoen J.; Djøseland O.; et al. Serum levels of interleukin-6 and dehydroepiandrosterone sulphate in response to either fasting or a ketogenic diet in rheumatoid arthritis patients. *Clin Exp Rheumatol* (2000 May-Jun) 18 (3) 357–362

Udén, A. M., Trang, L., Venizelos, N. & Palmblad, J. Neutrophil functions and clinical performance after total fasting in patients with rheumatoid arthritis. *Ann Rheum Dis* 42, 45-51 (1983)



Fish Oil

- Many studies on omega-3 FA, but fish oil more effective
- Inhibits COX-2 and increases anti-inflammatory eicosanoids
- Reduces morning stiffness, swollen joints, joint pain, fatigue
- Reduces markers of inflammation: CRP, IL-1 β , TNF- α and LTB₄
- Minimum 3 g/d for 12 weeks to see clinical results
- Decreases need for RA drugs

Ariza-Ariza R.; Mestanza-Peralta M.; Cardiel M.H.. Omega-3 fatty acids in rheumatoid arthritis: an overview. *Semin Arthritis Rheum* (1998) 27 366–370

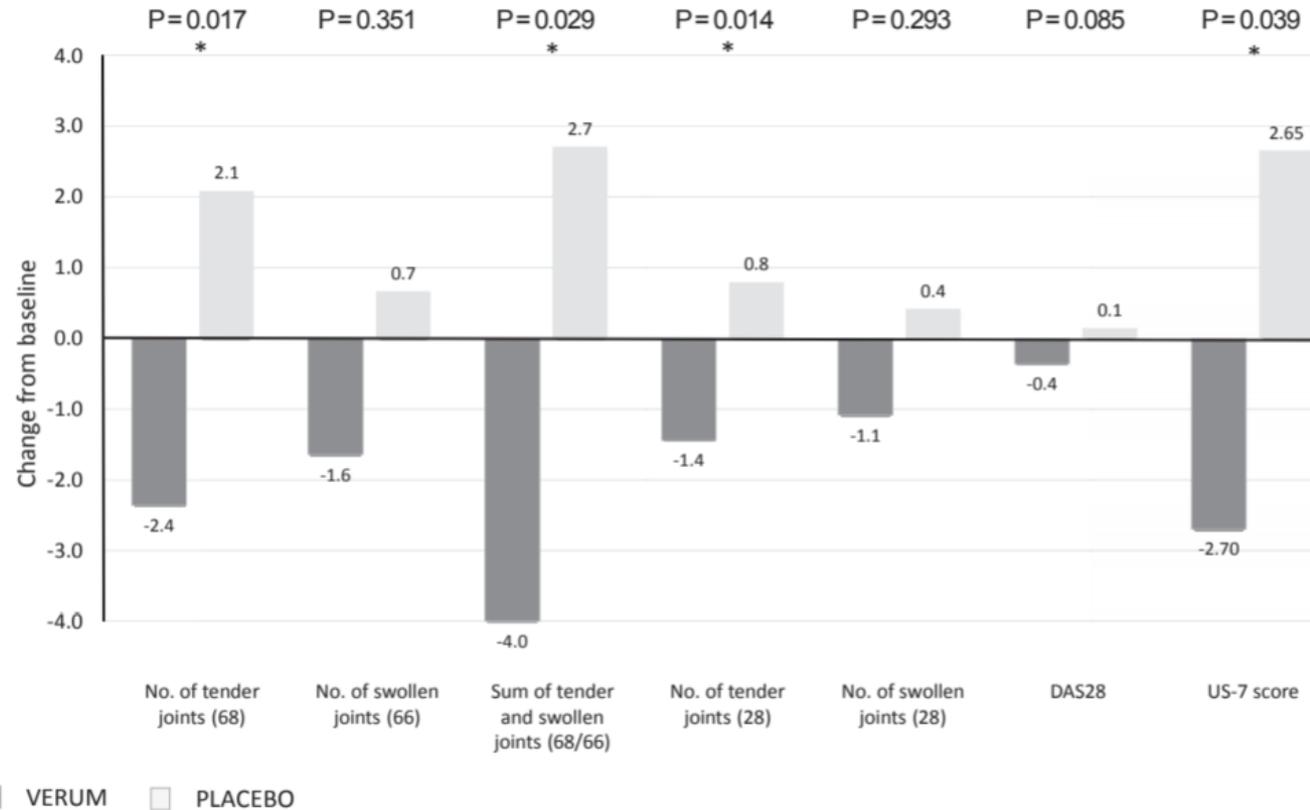
Galli C.; Calder P.C.. Effects of fat and fatty acid intake on inflammatory and immune responses: a critical review. *Ann Nutr Metab* (2009) 55 123–139

Proudman SM, James MJ, Spargo LD, et al. Fish oil in recent onset rheumatoid arthritis: a randomised, double-blind controlled trial within algorithm-based drug use. *Ann Rheum Dis*. 2015;74(1):89–95



DHA Improves RA Symptoms and Labs

- 8 g algae oil
 - = 2.1 g DHA
- Sunflower oil control
- High fat diet

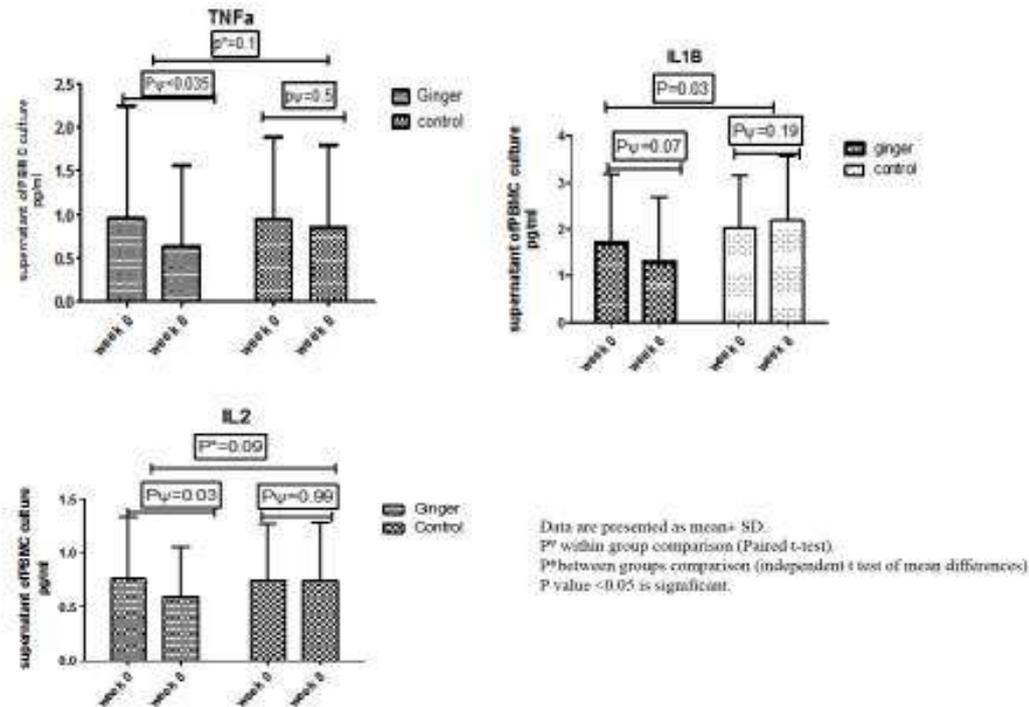


Dawczynski C, Dittrich M, Neumann T, et al. Docosahexaenoic acid in the treatment of rheumatoid arthritis: A double-blind, placebo-controlled, randomized cross-over study with microalgae vs. sunflower oil. Clin Nutr. 2018;37(2):494-504.



Zingiber officinalis (Ginger)

- Many herbal medicines have shown some benefit in RA:
 - Curcumin, ginger, *Tripterygium wilfordii* Hook F, *Valeriana officinalis*
- Helpful, but not likely curative





Systemic Lupus Erythematosus

- Worst toxins: air pollution, mercury, PCBs
- Key nutrient deficiencies: omega-3 FA
- Key interventions:
 - DHEA: 100+ mg/d
 - Vitamin D: 5,000 iu/d (target 40-75 ng/dL)
 - Fish oil: 3-5 g/d



Systemic Lupus Erythematosus

Toxin	Threshold	% Above Threshold	Odds Ratio	% of Disease	Example PMID
Air pollution	43.9 ug/m ³	25%	1.7	19.2%	26724462
Silica	Exposure	12.8%	1.6 >1 yr 4.3	7.2%	20675707
Mercury	Air 24.2 ng/m³		19.3		17316448
PCBs	Exposure (women)		14.7		17257654
Smoking			3.6-6.7		11708417
Pesticides	Exposure		1.9 Farm history 2.7		20740609



Vitamin D

- Daily supplementation! NOT weekly or monthly.
 - Primary reason for studies showing limited benefit
- Most likely effective at early stages rather than later after significant pathology
 - Good results in juvenile SLE
 - Limited results in adults
- Typically most effective in those with lowest serum 25(OH)D₃

Lima GL, Paupitz J, Aikawa NE, Takayama L, Bonfa E, Pereira RM. Vitamin D Supplementation in Adolescents and Young Adults With Juvenile Systemic Lupus Erythematosus for Improvement in Disease Activity and Fatigue Scores: A Randomized, Double-Blind, Placebo-Controlled Trial. *Arthritis Care Res (Hoboken)*. 2016;68(1):91-98

Zheng R, Gonzalez A, Yue J, et al. Efficacy and Safety of Vitamin D Supplementation in Patients With Systemic Lupus Erythematosus: A Meta-analysis of Randomized Controlled Trials. *Am J Med Sci*. 2019;358(2):104-114



DHEA

- Decreases production of proinflammatory cytokines, such as IL-6, IL-10, and cytokine-mediated antibodies
- Clinical studies show modest benefit
- Decrease need for corticosteroids
- 50 to 200 mg/day
- Main ADRs: androgenic effects in women

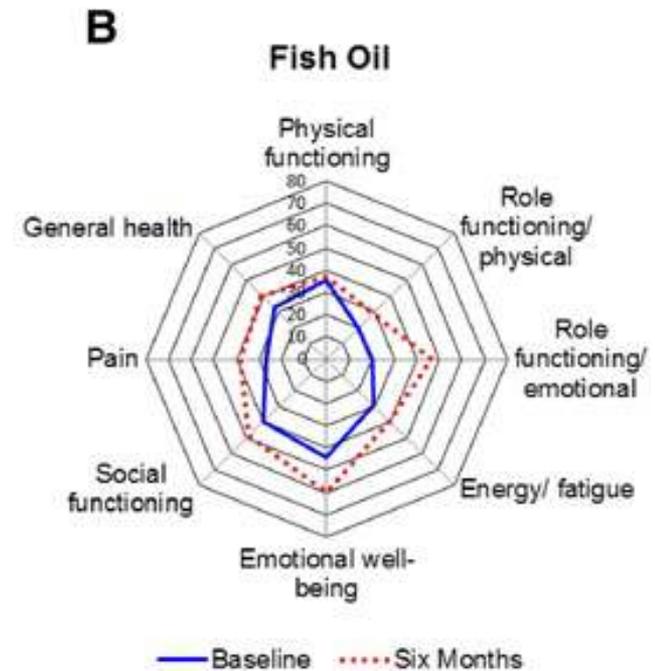
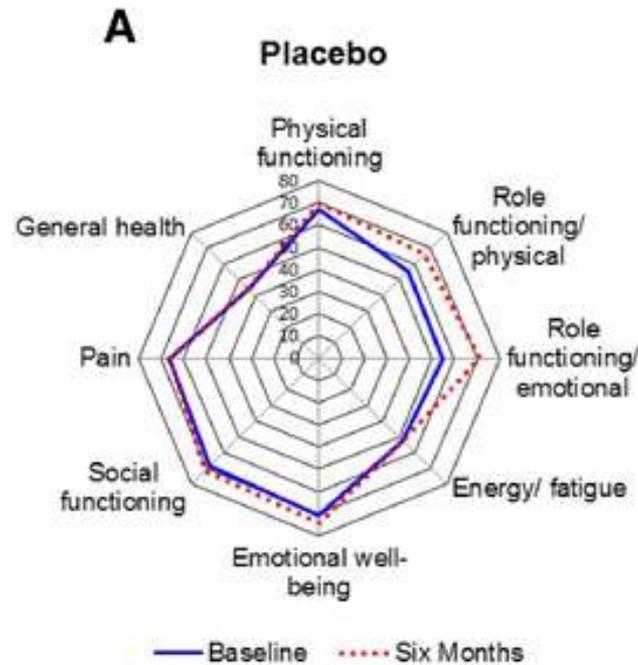
Chang DM, Chu SJ, Chen HC, et al. Dehydroepiandrosterone suppresses interleukin 10 synthesis in women with systemic lupus erythematosus. *Annals of the Rheumatic Diseases* (2004) 63:1623-6

Ronald F van Vollenhoven. Dehydroepiandrosterone for the treatment of systemic lupus erythematosus. *Expert Opinion on Pharmacotherapy* (2002) 3:1, 23-31.



Fish Oil

- 50 patients
- 2.25 g EPA & 2.25 g DHA
- Olive oil placebo!
- 6 mo





Urticaria

- Worst toxins: nickel, air pollution
- Key nutrient deficiencies: vitamin D, omega-3 FA
- Key interventions:
 - Identify and eliminate food/food additive reactions
 - Restore stomach acid if low
 - Quercetin: 500 mg/d
 - Fish oil: 3 g/d



Toxins

- Nickel
 - Contact dermatitis in areas of jewelry
 - Patch testing
- Topical insect repellants
- Air pollution
 - Ozone, nitrogen dioxide, particulate matter (PM_{2.5})

Kousha, T, & Valacchi, G. (2015). The air quality health index and emergency department visits for urticaria in Windsor, Canada. *J Toxicol Environ Health A*, 78(8), 524-33. PubMed PMID: 25849769

Shutty, B., Swender, D., Chernin, L., Tcheurekdjian, H., & Hostoffer, R. (2013). Insect repellants and contact urticaria: differential response to DEET and picaridin. *Cutis*, 91(6), 280-2. PubMed PMID: 23837149



Food Reactions and Food Additives

- Most common immune reactions: milk, fish, meat, eggs, beans, nuts
- Non-immune reactions: tomatoes, wine, and culinary herbs (basil, fenugreek, cumin, dill, ginger, coriander, caraway, turmeric, parsley, pepper, rosemary, and thyme)
- Additives: colorants (azo dyes), flavorings (salicylates, aspartame), preservatives (benzoates, nitrites, sorbic acid), antioxidants (hydroxytoluene, sulfite, gallate), emulsifiers-stabilizers (polysorbates, vegetable gums)



SYSTEMIC APPROACHES



Fasting

- Repeated water fasts of at least 4 days
- Example mechanisms
 - Promotes autophagy
 - Lowers circulating immune complexes
 - Facilitates removal of inappropriately activated or improperly targeting immune cells
- Improves many measures associated with autoimmune disease
 - Decreased erythrocyte sedimentation rate



Fasting

- Research-documented clinical benefits
 - Glomerulonephritis
 - Mixed connective disease
 - Rheumatoid arthritis
 - Systemic lupus erythematosus
 - Urticaria

Okamoto, O., Murakami, I., Itami, S. & Takayasu, S. Fasting diet therapy for chronic urticaria: report of a case. *The Journal of Dermatology* 19, 428-431 (1992).

Fuhrman, J., Sarter, B. & Calabro, D. J. Brief case reports of medically supervised, water-only fasting associated with remission of autoimmune disease. *Alternative Therapies in Health and Medicine* 8, 112, 110-111 (2002).

Brod, J., Pavkova, L., Fencel, V., Hejl, Z. & Kratkova, E. Influence of fasting on the immunological reactions and course of acute glomerulonephritis. *Lancet* (London, England) 1, 760-763 (1958).



“The definitive book linking the exploding burden of environmental toxins to chronic diseases, including autoimmunity, obesity, and cancer.”

—MARK HYMAN, MD

THE TOXIN SOLUTION

How Hidden Poisons in the Air, Water, Food, and
Products We Use Are Destroying Our Health—
AND WHAT WE CAN DO TO FIX IT



DR. JOSEPH PIZZORNO

CRINNION
PIZZORNO

Clinical Environmental Medicine

Identification and Natural Treatment of
Disease Caused by Common Pollutants

Clinical Environmental Medicine
Identification and Natural Treatment of Disease Caused by Common Pollutants



WALTER J. CRINNION • JOSEPH E. PIZZORNO

ELSEVIER

ELSEVIER