NeuroRegeneration

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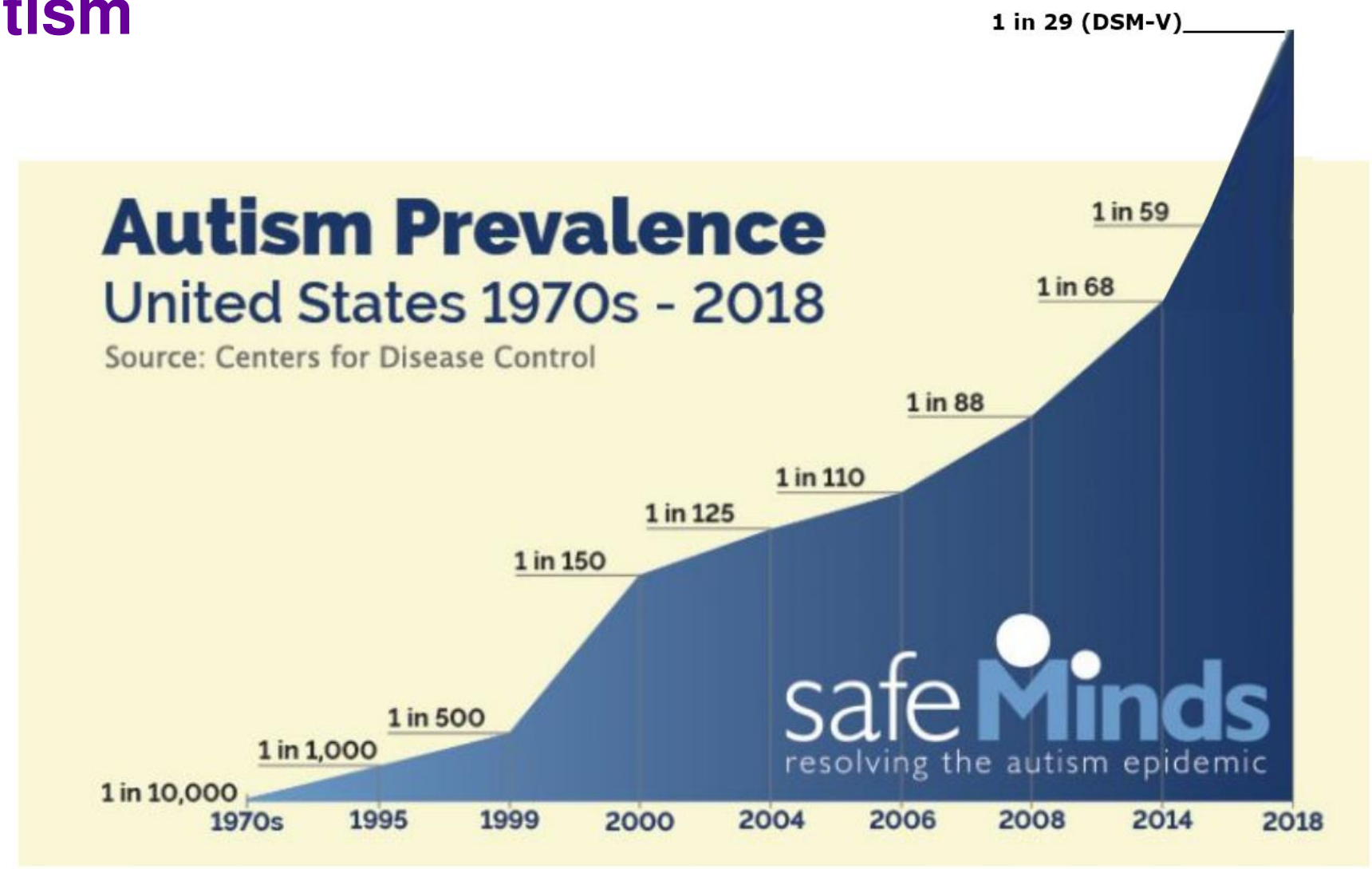
Overview

1. Worldwide Epidemic of Brain Disorders
2. Stop the Damage
   - Neurotoxic Metals and Chemicals in Environment
   - Loss of Blood Sugar Control
   - Mitochondrial Dysfunction
   - Neuroinflammation
3. Protect From Damage
   - Antioxidants
   - Glutathione
4. Support Normal Function
   - Nutritional Deficiencies/Excesses are Rampant
5. Facilitate Regeneration
6. Condition-Specific Protocols

WORLDWIDE EPIDEMIC OF NEUROLOGICAL DISORDERS

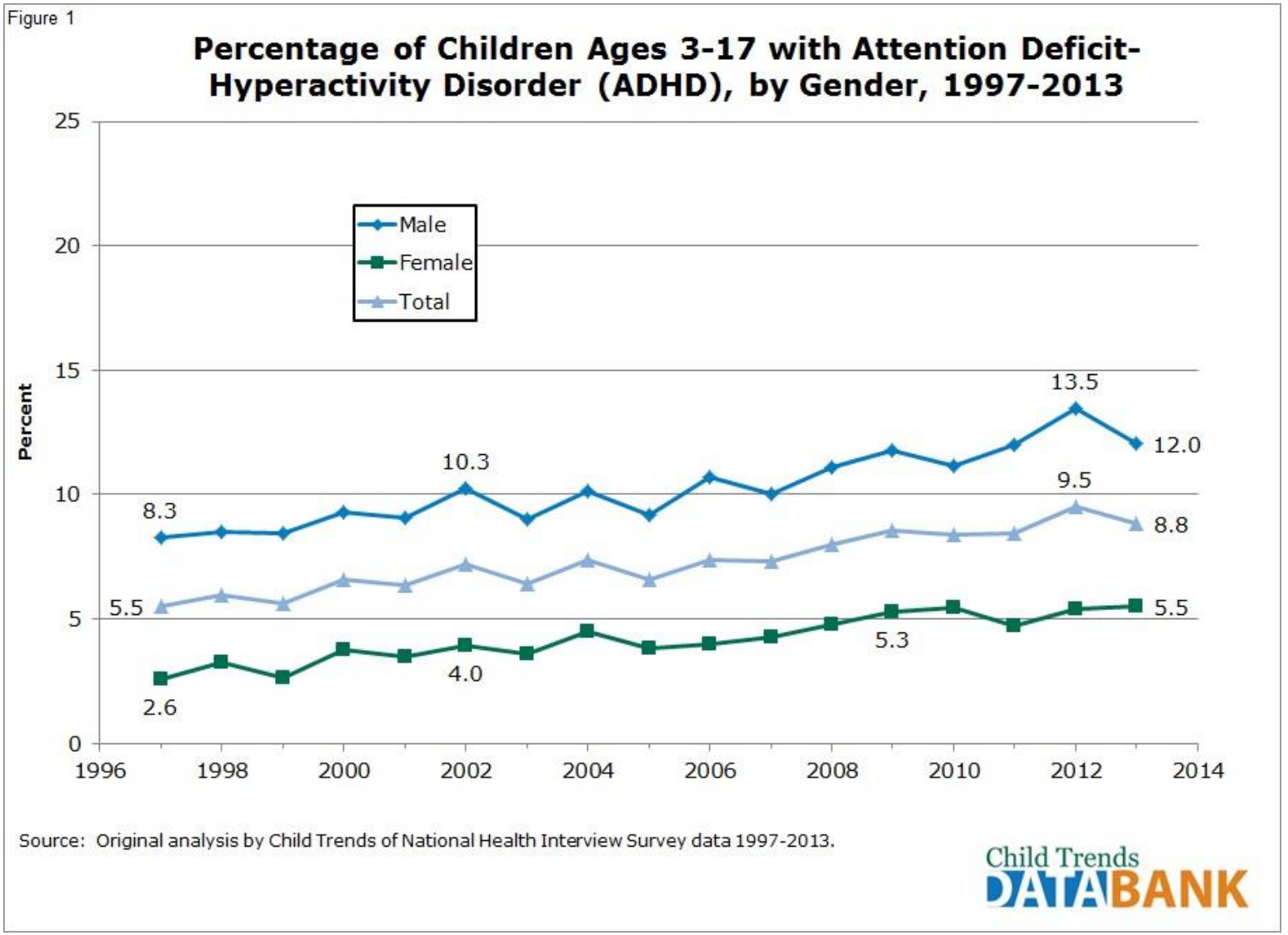
Autism



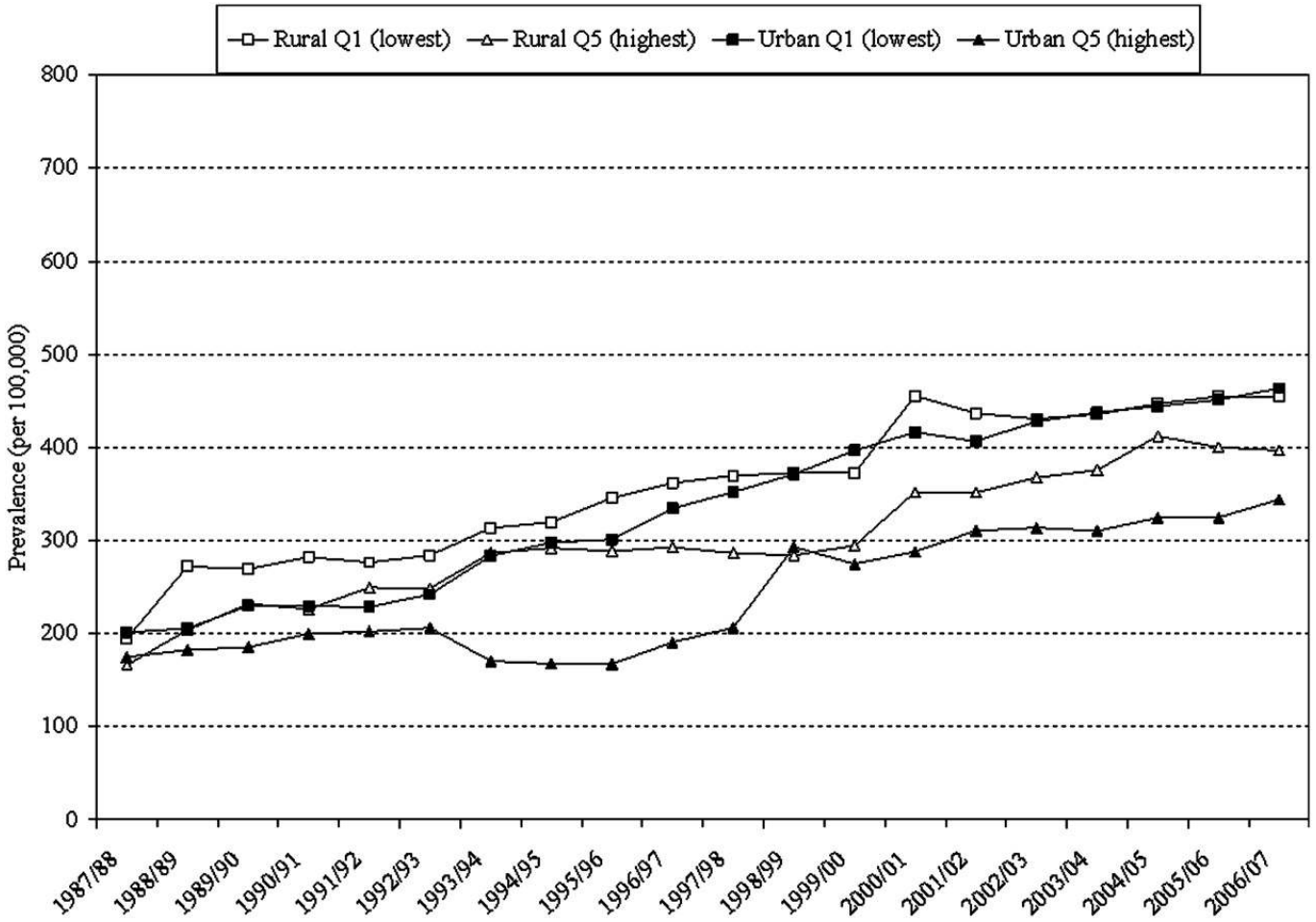
https://www.cdc.gov/ncbddd/autism/data.html (CDC data from 2000 to 2014)

ADHD

Figure 1

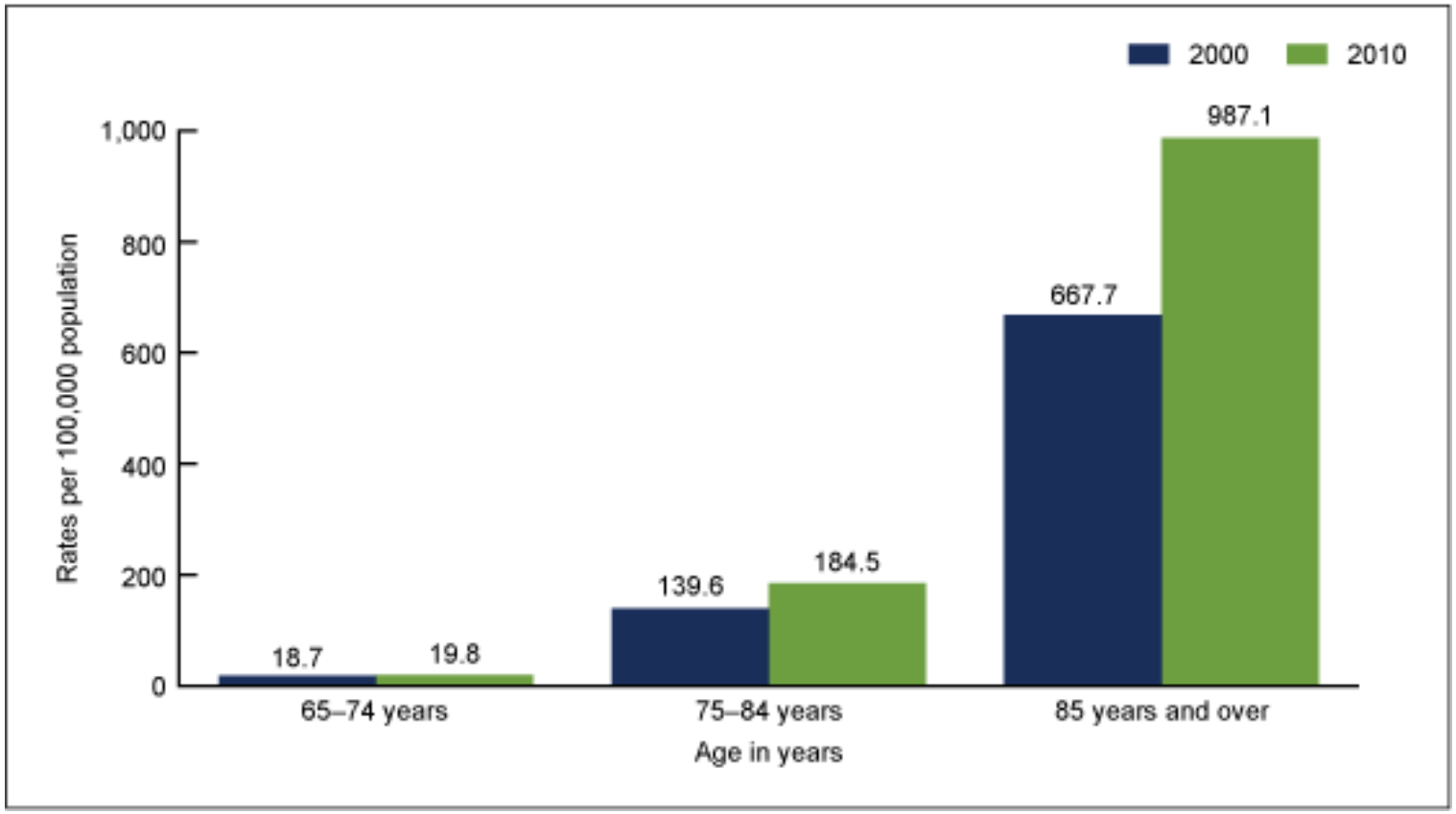


Parkinson's Disease



Lix LM, Hobson DE, Azimaee M, et al. Socioeconomic variations in the prevalence and incidence of Parkinson's disease: a population-based analysis. J Epidemiol Community Health. 2010 Apr;64(4):335-40

Alzheimer's Disease



https://www.cdc.gov/nchs/products/databriefs/db116.htm (Accessed July 2019)

Virtually every disease and clinical condition caused by neurological damage has increased in every age group the past 50 years

WHY?

Neurotoxins
Nutritional Deficiencies
Depletion of Key Molecules in Food Supply
Nutritional Excesses
Loss of Blood Sugar Control
Decreased Brain Regeneration
Genomic Susceptibility

CAUSES OF NEURODEGENERATION EPIDEMIC

Neurological Degeneration

Basic Mechanisms

- Microglia overactivation
- Mitochondrial damage
- Inflammation
- Oxidative stress
- Mis-folded proteins

Common Etiologies

- APOE e4 allele
- Lack of sleep
- Hyperhomocysteinemia
- Functional B12 deficiency
- Sugar dysregulation
- **Commonly prescribed drugs**
- Hypoxia
- Psychological stress
- Animal product consumption?
- **Environmental neurotoxins**

Microglia overactivation
Neurotoxic Metals and Chemicals in Environment
Loss of Blood Sugar Control
Loss of Mitochondrial Function
Neuroinflammation

STOP THE DAMAGE

Significant Clinical and/or Epidemiological Research Support for Neurotoxin Damage

Diseases

- Attention deficit hyperactive disorder (ADHD)
- Autism spectrum disorder (ASD)
- Amyotrophic lateral sclerosis (ALS)
- Alzheimer's disease (AD)
- Parkinson's disease (PD)

Conditions

- Cognitive decline
- Dementia
- Headache
- IQ loss (esp children)
- Mood disorders
- Motor neuron disorders

Crinnion W, Pizzorno J. Neurotoxicity in, *Clinical Environmental Medicine*. Elsevier, 2018

The Worst Neurotoxins(?)

Prenatal

- Methylmercury
- Organophosphate pesticides
- PCBs
- Phthalates
- Polyfluoroalkyl chemicals

Postnatal

- Arsenic
- Cadmium
- DDT/DDE
- Lead
- Mercury
- OCPs
- PCBs
- Particulate matter (Vehicular exhaust)
- Solvents

Primary Mechanisms of Neuron Damage

1. Direct neurotoxicity
2. Oxidative stress
3. Inappropriate microglial activation
4. Mitochondrial damage
5. Methyl group depletion
6. Decreased production of BDNF
7. Impairment of microcirculation

SOURCES OF NEUROTOXINS

Sources of Neurotoxins

- Farmed fish (POPs)
- Large fish (Hg)
- Chemically-grown foods (pesticides, Cd)
- Food storage (BPA, phthalates)
- Amalgam fillings (hg)
- Arsenic in water
- PM in air (PMs carry VOCs)
- Lead in water, paint
- Mold? (mycotoxins)
- Common prescription drugs

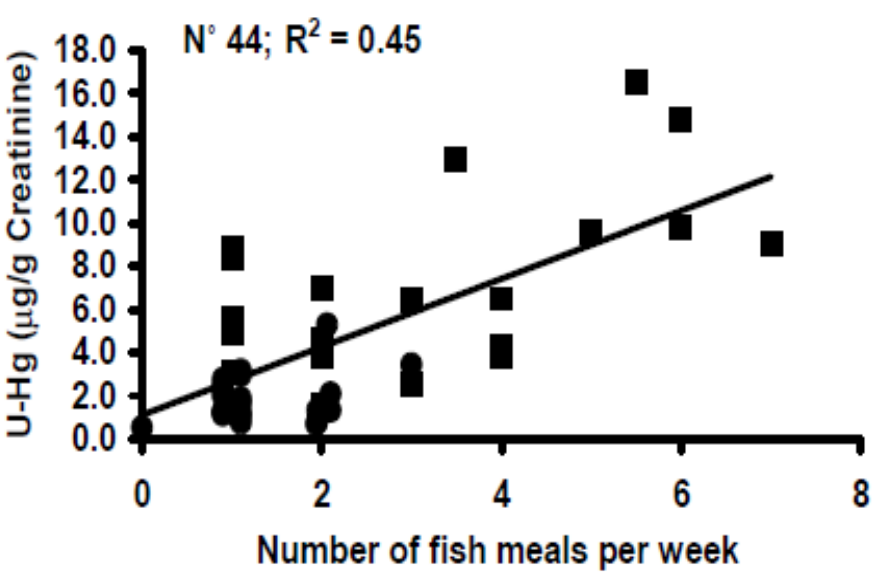
Mercury Exposure Common

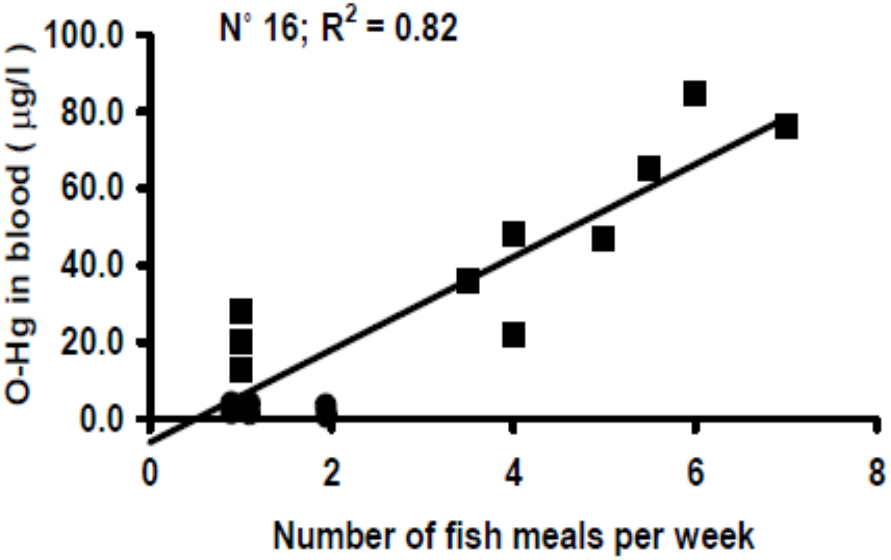
- Average exposure in non-industrial populations
  - Amalgams: 10 ug/d
  - Fish: 2.3 ug/d
  - Water: 0.3 ug/d
  - Air
  - Vaccinations
- Industrial

Vimy, M.J., and Lorscheider, F.L (1990) Dental amalgam mercury daily dose estimated from intra-oral vapor measurements: A predictor of mercury accumulation in human tissues.]. Trace Elem. Exp. Med 3, 111-123

Hg From Fish

- **Total Hg urinary excretion proportional to amount of fish eaten**
- **Impaired psychomotor performance**
  - R = 0.38 blood
  - R = 0.77 urine
- Huge variation in amount of Hg in fish

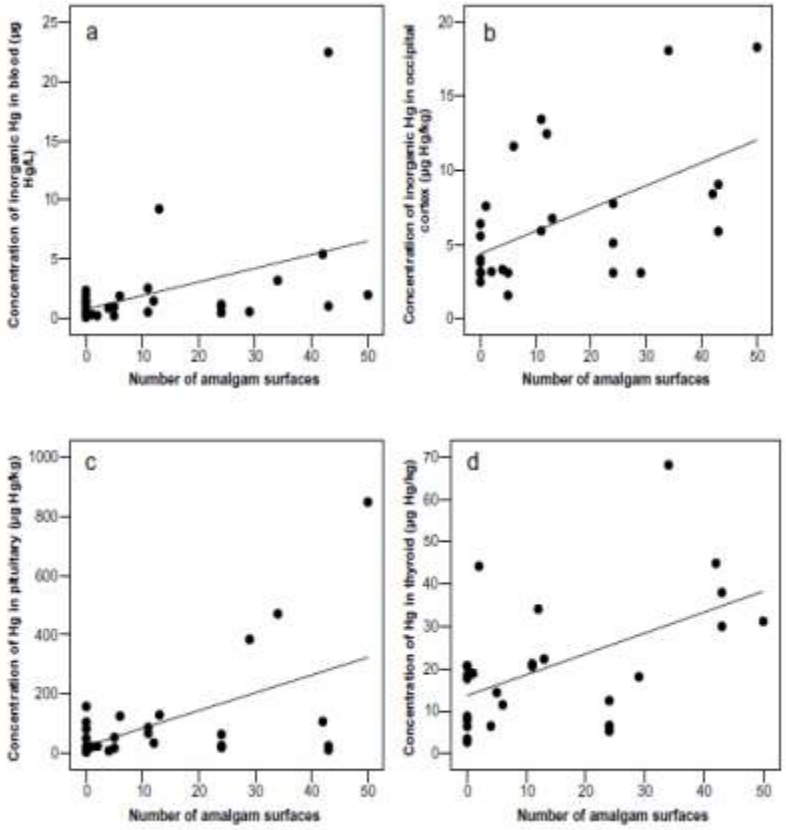




Apostoli P, ICortesi I, Mangili A, et al. Assessment of reference values for mercury in urine: the results of an Italian polycentric study. The Science of the Total Environment 289 (2002)13-24
Carta P, et al. Sub-clinical neurobehavioral abnormalities associated with low level of mercury exposure through fish consumption. NeuroToxicology 24 (2003) 617–623

Amalgams Put Mercury Into the Brain

- **Mercury accumulates in the brain in proportion to surface area of amalgams**
- Study of 18 cadavers
  - Hg in brain, thyroid and kidneys proportional to the number of amalgam surfaces
  - For those with more than 12, Hg in brain disproportionately higher
  - Suggests that at higher levels of exposure the brain's mercury excretion pathways become overloaded.

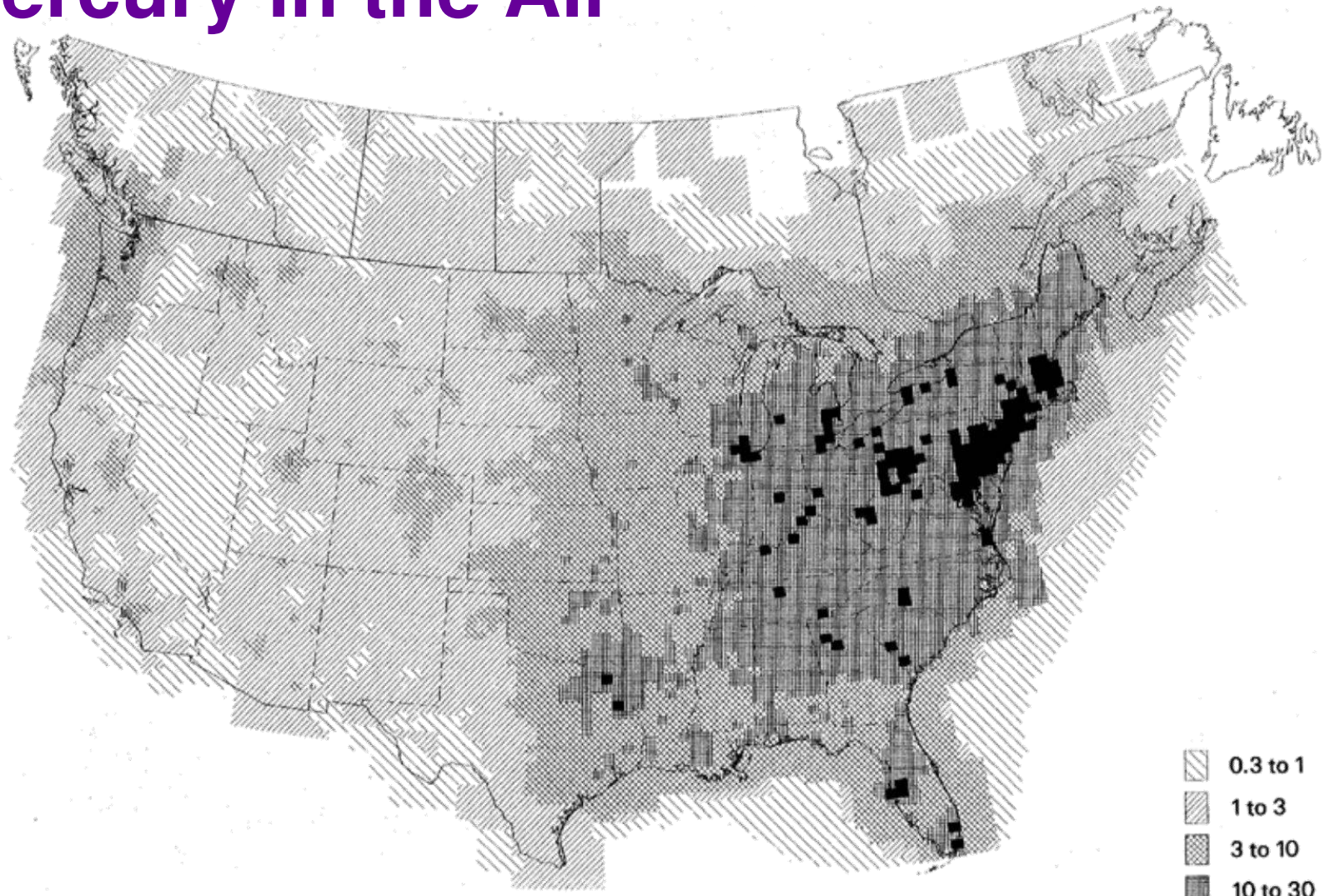


Guzzi 2006

Reinhardt JW. Side-Effects: Mercury contribution to body burden from dental amalgam. Adv Dent Res. 1992;6: 110

Guzzi G, et al. Dental amalgam and mercury levels in autopsy tissues. Am J Forensic Med Pathol. 2006 Mar;27(1):42-5

Mercury in the Air



EPA-452/R-97-003 December 1997

Neurological disorders associated with lipophilic chemical exposures.

	POPS				PLASTIC EXUDATES		HYDROCARBONS	
	PCBs	**OCs**	**PBDEs**	**Dioxins/Furans**	**phthalates**	**BPA**	**PAHs**	**LMWHCs**
NI								
Cognitive effects	*	*	*	*	*	*	*	*
Motor deficits	*	*	*		*		*	*
Sensory deficits	*	*	*	*			*	*
Peripheral NS effects	*	*		*			*	*
NDD								
Autism	*	*	*		*	*	*	
ADHD	*	*	*	*	*	*	*	
NDG								
Alzheimer's disease		*		*	**	**	*	
Parkinson's disease	*	*	*	*	**	**	*	*
ALS		*		*				

*Established relationship
**Suspected relationship

Daily Exposure to Neurotoxins

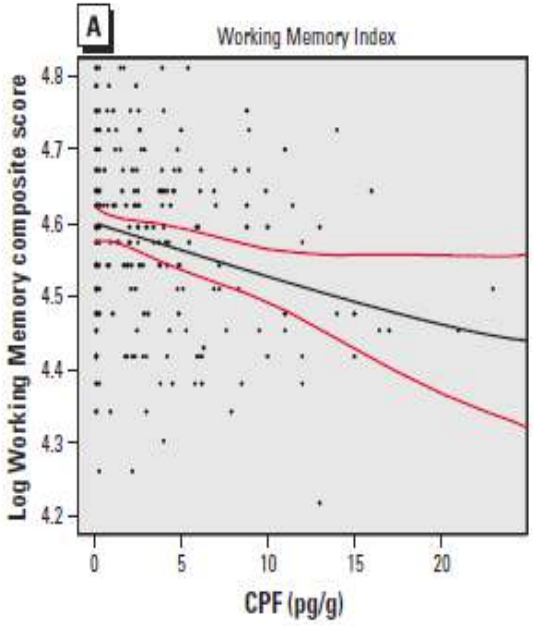
Zeliger HI. Exposure to lipophilic chemicals as a cause of neurological impairments, neurodevelopmental disorders and neurodegenerative diseases. Interdiscip Toxicol. 2013 Sep;6(3):103-10 PMID: 24678247

NEUROTOXICITY

FETUS AND CHILDREN

Prenatal Effects - Organophosphates

- Prenatal exposure particularly harmful
- Higher levels = poorer cognitive scores, (memory, processing speed, comprehension, and reasoning).
- **7-point lower IQ (highest-lowest quintile)**
- **25% of pregnant US women have levels exceeding the median in this study**
- Children with higher levels of OP metabolites had up to **2x increased risk for ADHD**, and the levels associated with risk were commonly found in the US population among children



Rauh et al. 2011

Bouchard MF, et al. Prenatal Exposure to Organophosphate Pesticides and IQ in 7-Year Old Children. Environ Health Perspect. 2011 Aug;119(8):1189-95

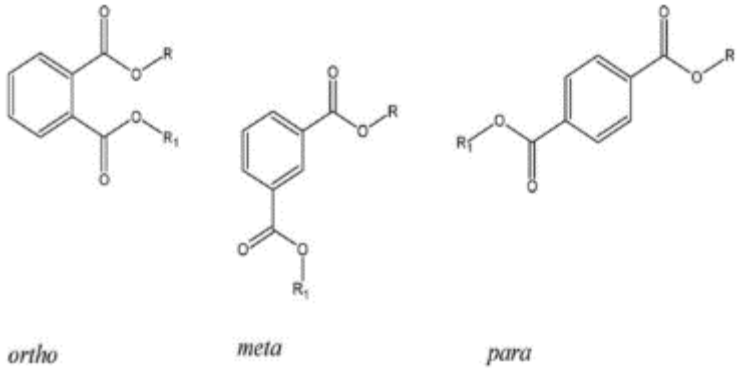
Rauh V, et al. 7-Year Neurodevelopmental Scores and Prenatal Exposure to Chlorpyrifos, a Common Agricultural Pesticide. Environ Health Perspect. 2011 Apr 21.

Bouchard MF,et al. Attention-deficit/hyperactivity disorder and urinary metabolites of organophosphate pesticides. Pediatrics. 2010 Jun;125(6):e1270-7

Polyfluoroalkyl Chemicals - Children

- **Developmental neurotoxicants**
- Associated with ADHD in children age 12-15
- **Eliminated very slowly from the body – serum ½ life of 2 to 8.5 years**
- **Gore-Tex, Scotchgard and STAINMASTER** all PFCs
- Serum levels directly associated with income (opposite of BPA, with higher levels seen in lower income)

Hoffman K, et al. Exposure to polyfluoroalkyl chemicals and attention deficit/hyperactivity disorder in U.S. children 12-15 years of age. Environ Health Perspect. 2010 Dec;118(12):1762-7.
Nelson JW, et al. Social disparities in exposures to bisphenol A and polyfluoroalkyl chemicals: a cross-sectional study within NHANES 2003-2006. Environ Health. 2012 Mar 6;11:10.



Fabjan et al. 2006
(17050082)

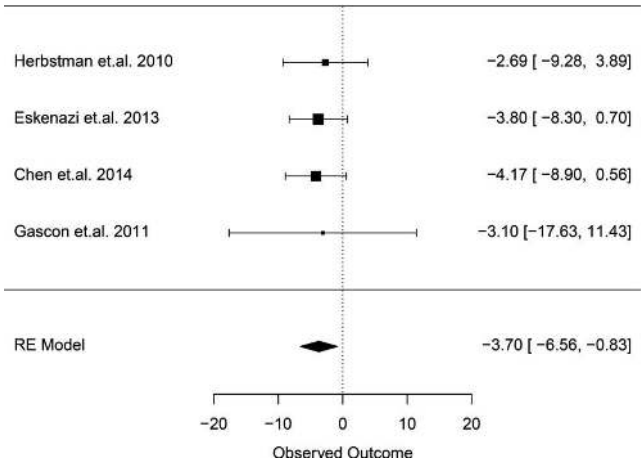
Phthalates

- Prenatal exposure associated with **conduct & attention disorders**
- Found in building materials, **personal cosmetics, pharmaceuticals, nutritional supplements**, solvents, adhesives, paints, lacquers, insecticides, air fresheners, shampoos, cleaning materials, **children's toys**, and **food packaging**
- May be listed as "**fragrance**"
- Dietary sources – chickens and eggs had DEHP metabolites, suggesting **chickens** (vs. packaging) are contaminated

Engel SM, et al. Prenatal phthalate exposure is associated with childhood behavior and executive functioning. Environ Health Perspect. 2010 Apr;118(4):565-71
Schettler T. Human exposure to phthalates via consumer products. Int J Androl. 2006 Feb;29(1):134-9;

PBDE – Less Burns, BUT: Less IQ, More ADHD

- Polybrominated diphenyl ethers
- **Prenatal exposure linked to lower IQ**, and lower scores on tests of physical and mental development at 12-28, and 72 months
- **Postnatal exposure linked to poor social competence and attention deficit** in 4 year old children



She J, et al. Polybrominated diphenyl ethers (PBDEs) and polychlorinated biphenyls (PCBs) in breast milk from the Pacific Northwest. Chemosphere. 2007 Apr;67(9):S307-17

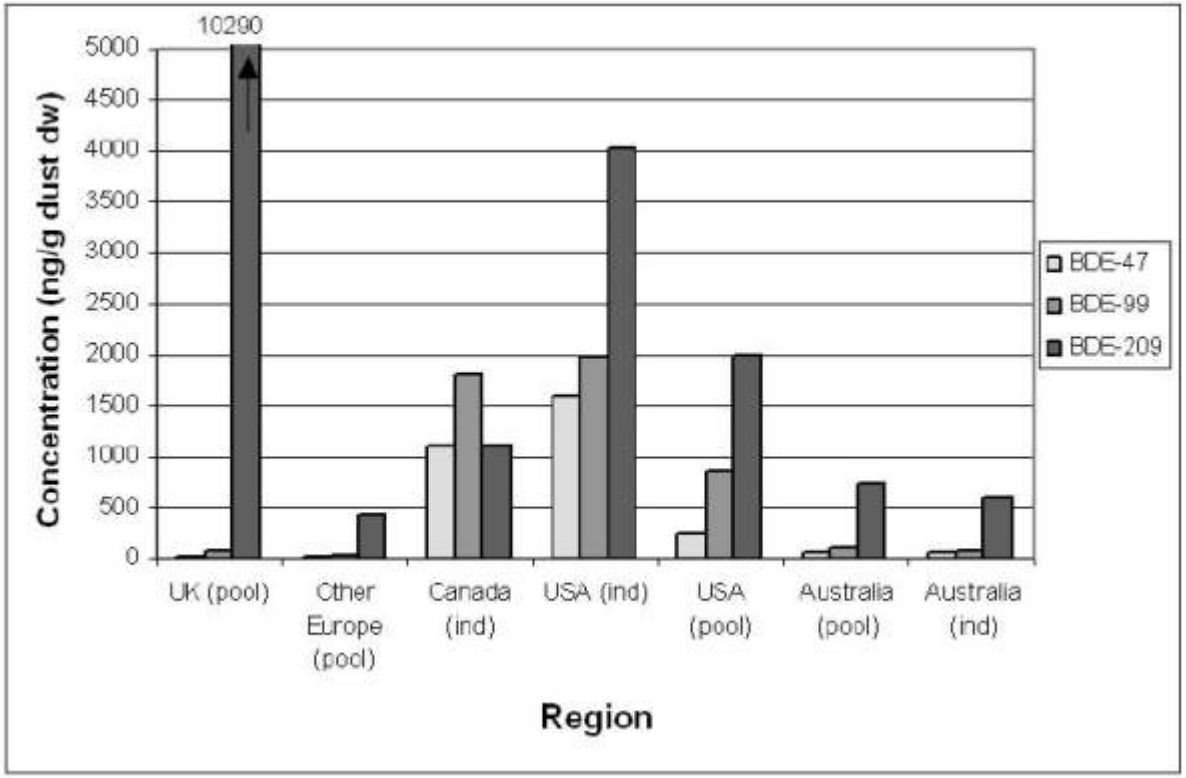
Gascon M, et al. Effects of pre and postnatal exposure to low levels of polybromodiphenyl ethers on neurodevelopment and thyroid hormone levels at 4 years of age. Environ Int. 2011 Apr;37(3):605-11.

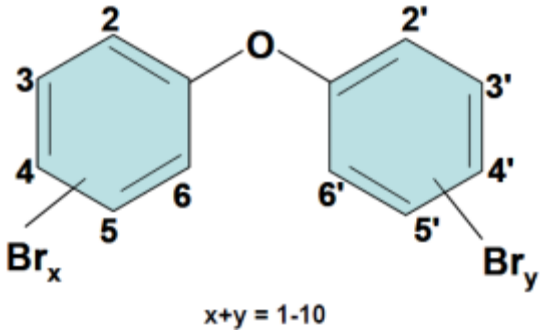
Herbstman JB, et al. Prenatal exposure to PBDEs and neurodevelopment. Environ Health Perspect. 2010 May;118(5):712-9

Lam J, Lanphear BP, Bellinger D, et al. Developmental PBDE Exposure and IQ/ADHD in Childhood: A Systematic Review and Meta-analysis. Environ Health Perspect. 2017 Aug 3;125(8):086001

PBDEs in Dust World-Wide

- Polybrominated diphenylethers
- Flame retardants
- Presence in dust
- UK especially high



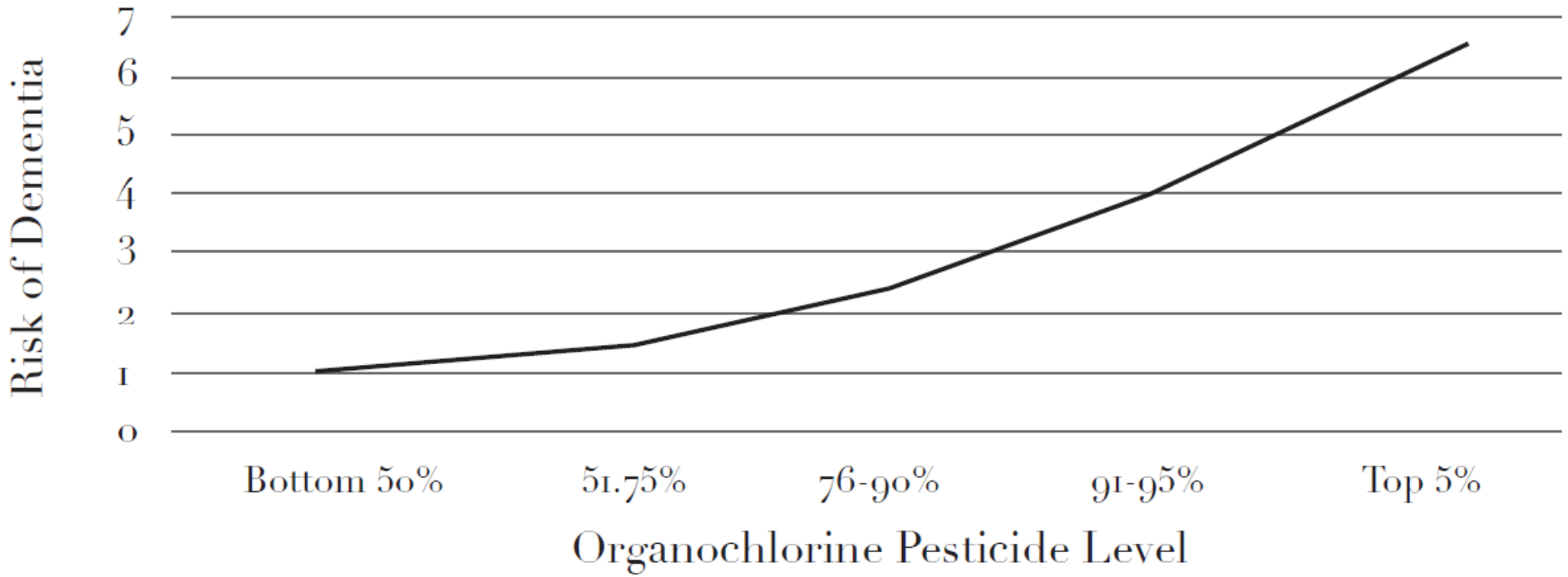


Aust Gov. Interim public health risk assessment of certain PBDE congeners. March 2007

NEUROTOXICITY

ADULTS

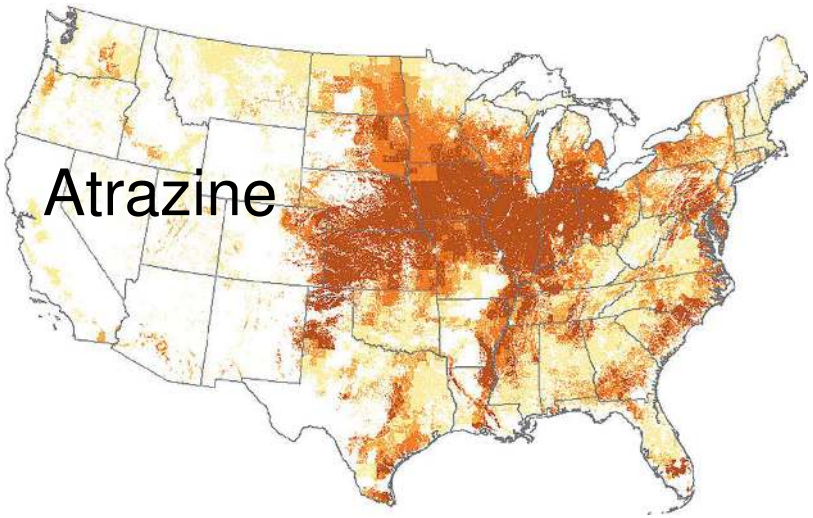
Organochlorine Pesticides and Dementia

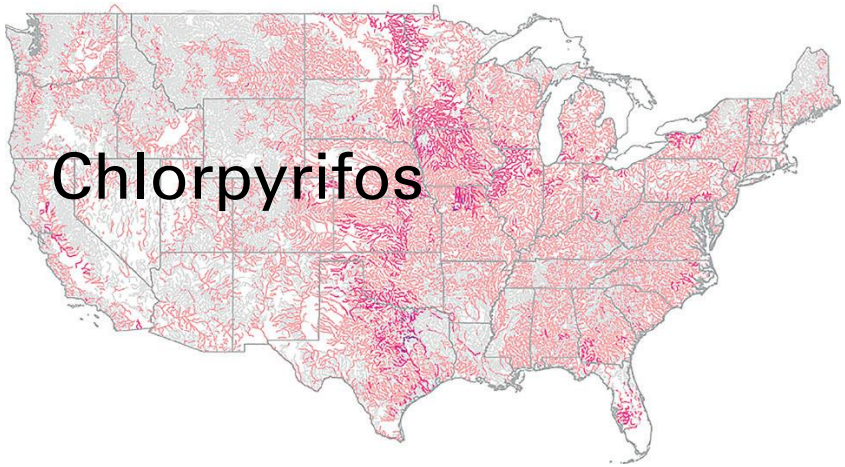


Kim KS, Lee YM, Lee HW, et al. Associations between organochlorine pesticides and cognition in U.S. elders: National Health and Nutrition Examination Survey 1999–2002. Environment International 2015;75: 87–92

Parkinson's Disease

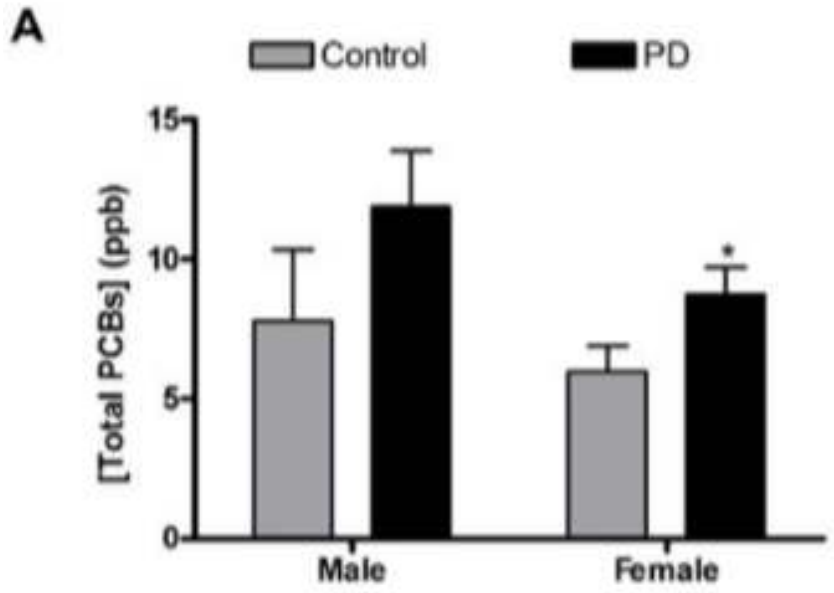
- Measured atrazine, simazine, alachlor, and metolachlor in 286 well water samples
- For every 1.0 µg/L of total pesticide in groundwater, the risk of PD increased by 3%

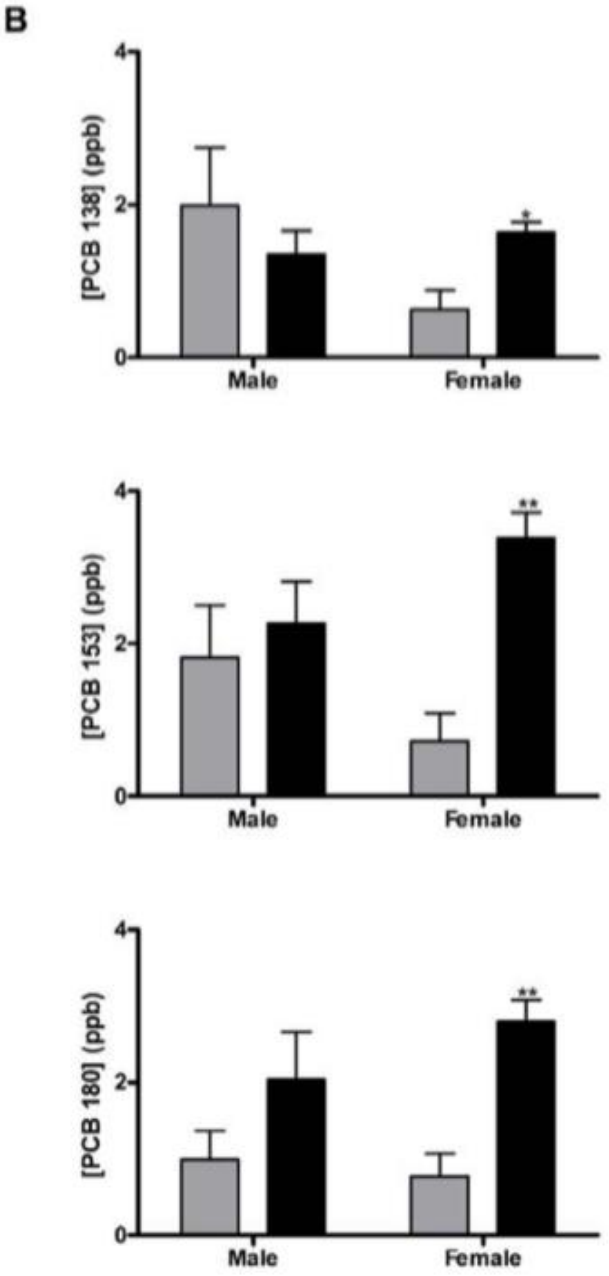




James KA, Hall DA. Groundwater pesticide levels and the association with Parkinson disease. Int J Toxicol. 2015 May-Jun;34(3):266-73

PCB Levels Correlate with Parkinson's Disease





Hatcher-Martin JM, Gearing M, Steenland K, et al. Association between polychlorinated biphenyls and Parkinson's disease neuropathology. Neurotoxicology. 2012 Oct;33(5):1298-304. PMID: 22906799

Solvents Impair Neurological and Psychological Function

- Compared auto repair workers exposed 2.3 hr/day to those exposed most of day to toluene
- All wore face masks and protective gear
- **Impairment of sympathetic nerves** (OR = 4.1)
- **Impairment of peripheral nerves** (OR = 6.9)
- Positive relationship between **neurological abnormalities** and a self-reported **neuropsychiatric** measurement (r = 0.35-0.66)

Shih HT, et al. Subclinical abnormalities in workers with continuous low-level toluene exposure. Toxicol Ind Health. 2011 Sep;27(8):691-9

Commonly Prescribed Drugs

- Cognitive Damage
  - Anti-cholinergics
  - Anti-depressants
  - Antimicrobials
  - PPIs
  - Statins
  - Z Drugs and Sleep Meds
  - Polypharmacy/PIP
- Neurological Damage
  - Peripheral Neuropathy
  - Cerebellar & Ototoxicity
  - Medication induced headaches
  - Pro-arrhythmia meds
  - Homocysteine-inducing drugs

Antibiotics Poison Mitochondria

After 4 days	Ciplofloxan	Ampicillin	Kanamycin	Tetracycline
ATP Production	-90%	-75%	-80%	-20%
ROS	+250%	+200%	+240%	+40%
MDA	+90%	+80%	+75%	+20%
8-OHdG	+100%	+720%	+400%	230%

Mitochondrial DNA damage is permanent

- Cell study, reproduced in animals
- Damage decreased 50% with NAC supplementation

Kalghatgi S, et al. Bactericidal antibiotics induce mitochondrial dysfunction and oxidative damage in Mammalian cells. Sci Transl Med. 2013 Jul 3;5(192):192

Loss of Blood Sugar Control
Mitochondrial Dysfunction
Stress and Glucocorticoids
Neuroinflammation
Inadequate Sleep
Vitamin D Deficiency
Vitamin B12 Deficiency
Iron Overload

MANY COMMON CAUSES OF NEUROLOGICAL DAMAGE

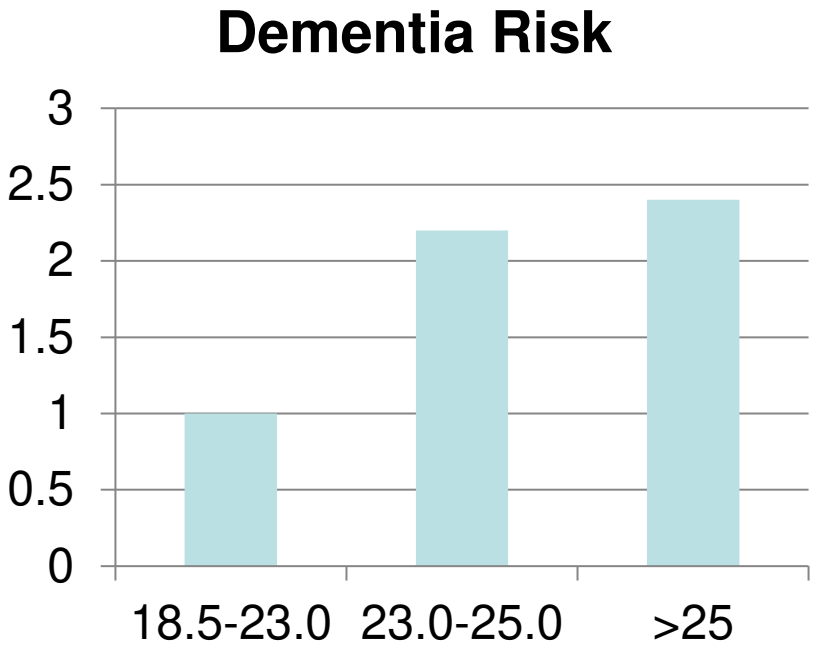
Hyperglycemia is a Huge Risk Factor For Neurodegeneration

- Prospective study of over 6000 participants
- Diabetes was found to almost double the risk of dementia
- Those being treated with insulin had more than quadruple the risk
- Diabetes may account for nearly 10% of the population with dementia
- Having diabetes & APOE 4 (e4) allele nearly 5-fold risk for AD compared to having neither
  - apoE4 recently shown to bind to mitochondrial complex III and complex IV, inhibiting their activity

Ott A, et al. Diabetes mellitus and the risk of dementia: The Rotterdam Study. Neurology. 1999 Dec 10;53(9):1937-42.
Irie F, et al. Enhanced risk for Alzheimer disease in persons with type 2 diabetes and APOE epsilon4: the Cardiovascular Health Study Cognition Study. Arch Neurol. 2008 Jan;65(1):89-93
Nakamura et al. Apolipoprotein E4 (1-272) fragment is associated with mitochondrial proteins and affects mitochondrial function in neuronal cells. Mol Neurodegener. 2009 Aug 20;4:35.

Obesity Associated w Dementia

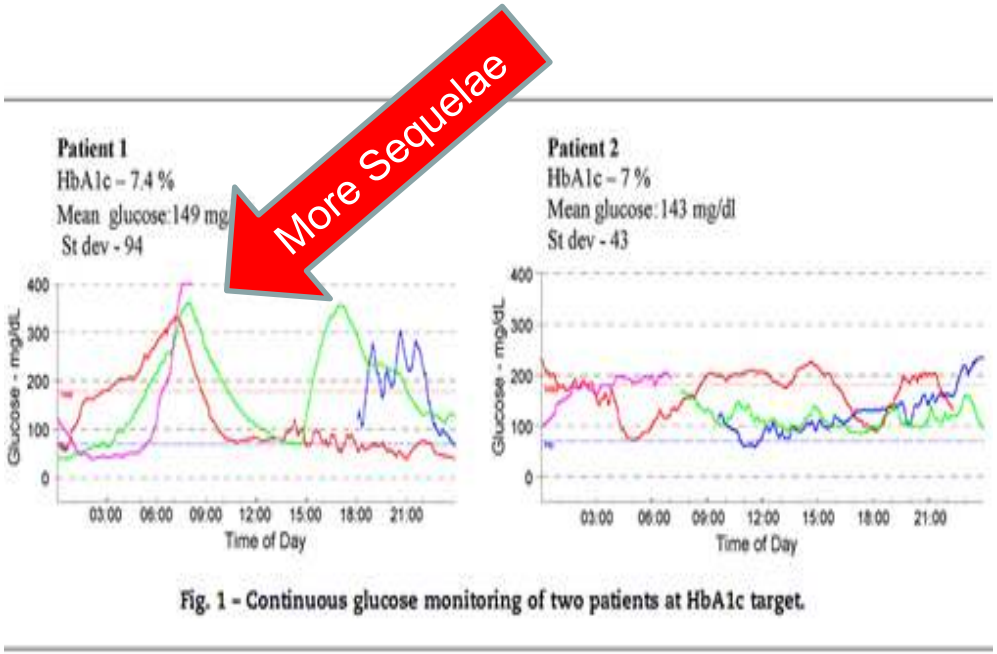
- Direct association between excessive weight and dementia
- **Weight loss in obese older adults improves cognitive function**



Chang WS, Won KH, Lee JY, et al. The Relationship between Obesity and the High Probability of Dementia Based on the Body Mass Index and Waist Circumference. Korean J Fam Med. 2012 Jan;33(1):17-24
Siervo M, Nasti G, Stephan BC, et al. Effects of intentional weight loss on physical and cognitive function in middle-aged and older obese participants: a pilot study. J Am Coll Nutr. 2012 Apr;31(2):79-86

Hemoglobin A1c

- HbA1c is the standard, but:
- Not just average—the peaks are what cause the damage!
- However, misses daily fluctuations such as postprandial hyperglycemia, which can be detected with continuous glucose monitoring



19027978

Executive summary: standards of medical care in diabetes--2011. Diabetes Care. 2011 Jan;34 Suppl 1:S4-10
Hoeks LB, et al. Real-time continuous glucose monitoring system for treatment of diabetes: a systematic review. Diabet Med. 2011 Apr;28(4):386-94.

Peak Sugar Levels Much More Damaging than Average Blood Sugar

- Polyol and glycation activation greatly increased at higher glucose levels which results in the sequelae of diabetes
- MANY plant “Unimportant” plant constituents:
  - Decrease peak sugar
  - Inhibit polyol pathway
  - Inhibit glycation of proteins, enzymes, etc.

Chlorophyll

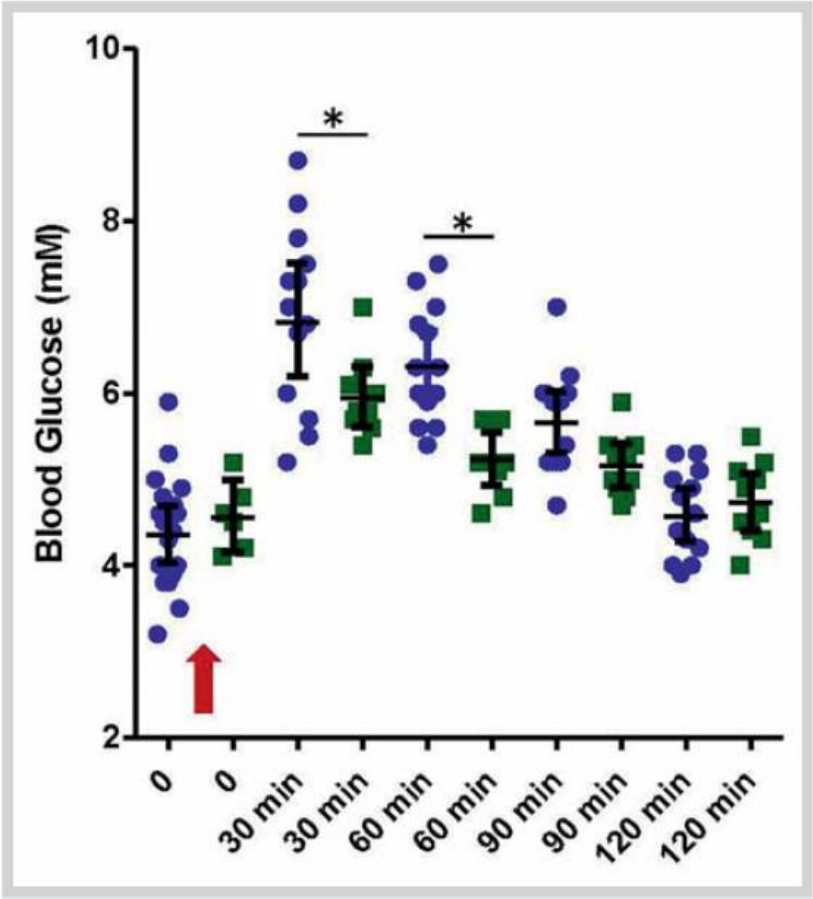
Concept: Whole foods, plant-based diet (organically grown, of course) has many constituents with unexpected health benefits

☼ Blue dots: 75 g glucose only

Green dots: Plus 1 g chlorophyll

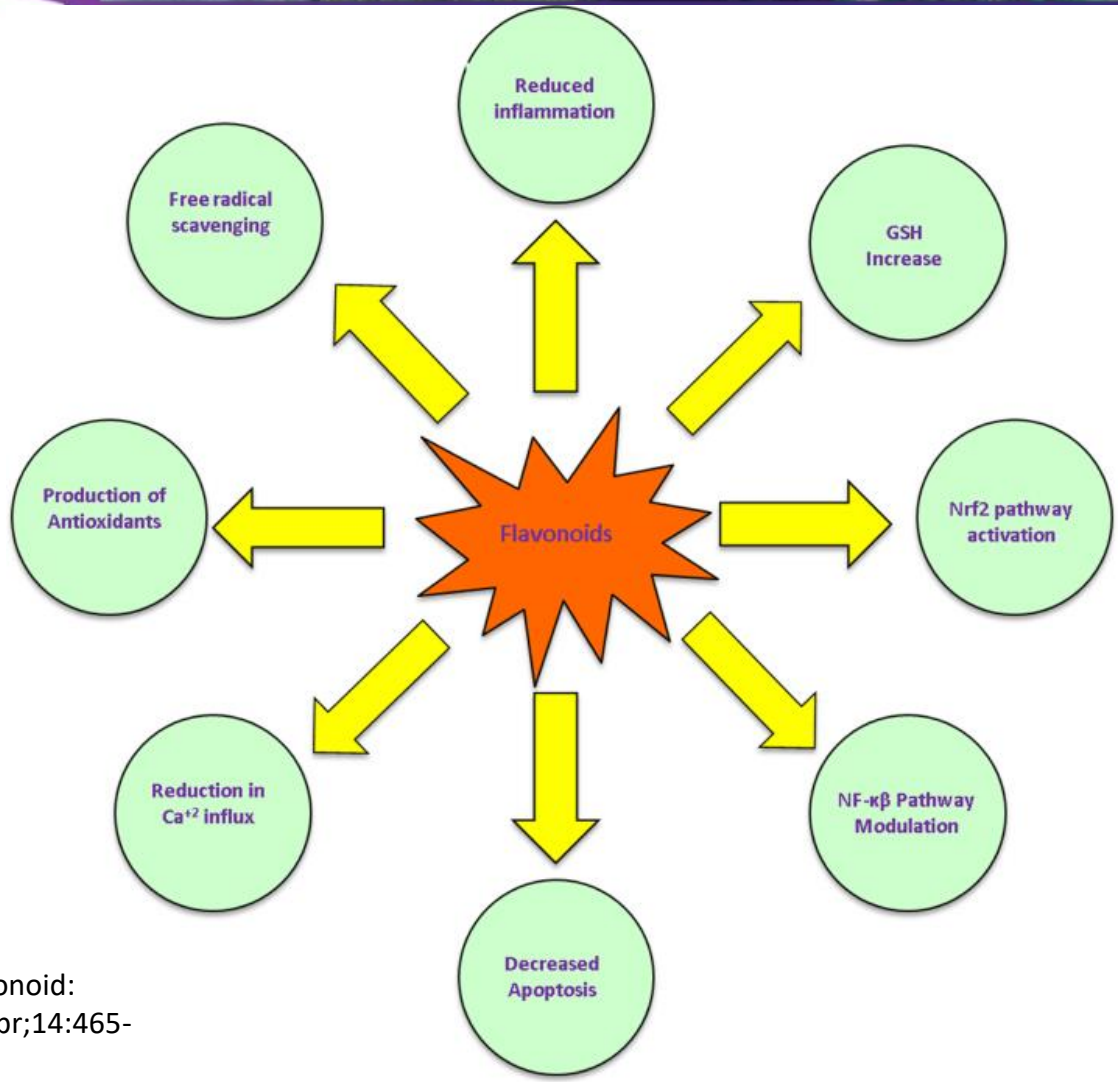
Remember, it is the glucose spikes that cause the most damage

Include the fiber slides



Gertsch J. The Metabolic Plant Feedback Hypothesis: How Plant Secondary Metabolites Nonspecifically Impact Human Health. Planta Med. 2016 Jul;82(11-12):920-9 PMID: 27286339

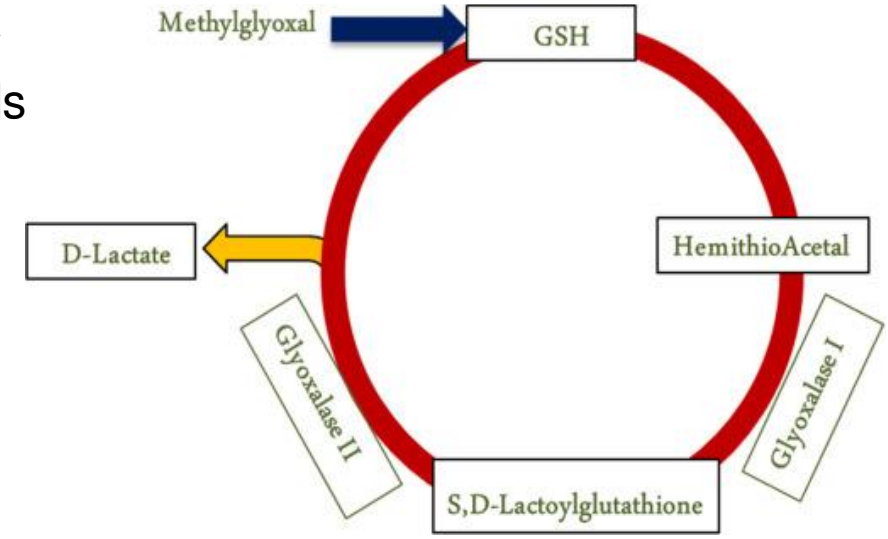
Flavonoids Critical For Health



Frandsen JR, Narayanasamy P. Neuroprotection through flavonoid: Enhancement of the glyoxalase pathway. Redox Biol. 2018 Apr;14:465-473 PMID: 29080525

Keeping Our Brains

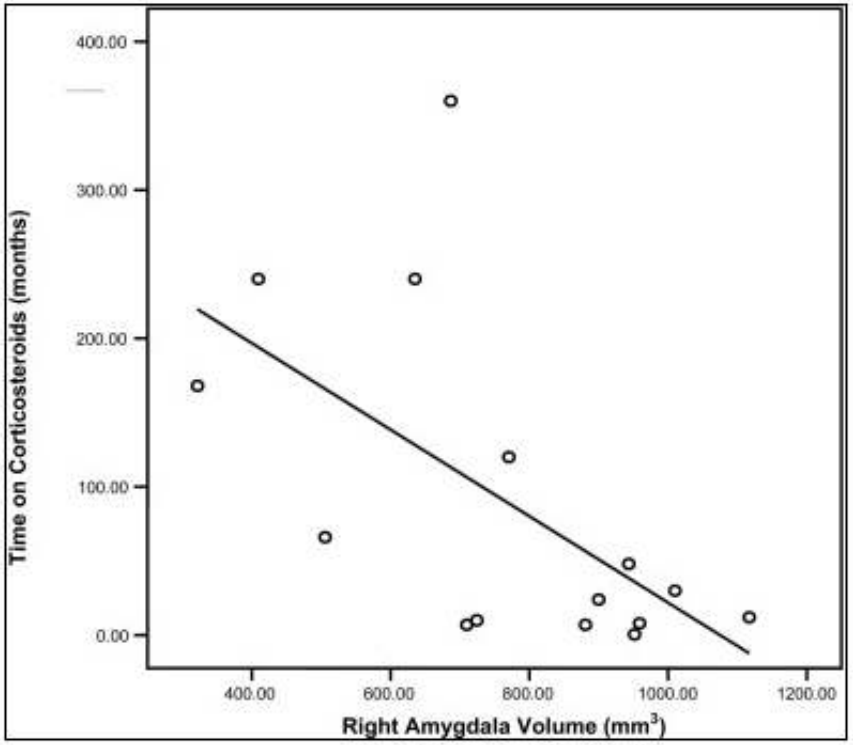
- Flavonoids enhance glyoxalase pathway
- Detoxifies reactive dicarbonyl compounds esp. methylglyoxal
- Critical antioxidant neuron protection
- Decreases risk for:
  - Alzheimer's
  - Parkinson's
  - Aging
  - Autism Spectrum Disorder

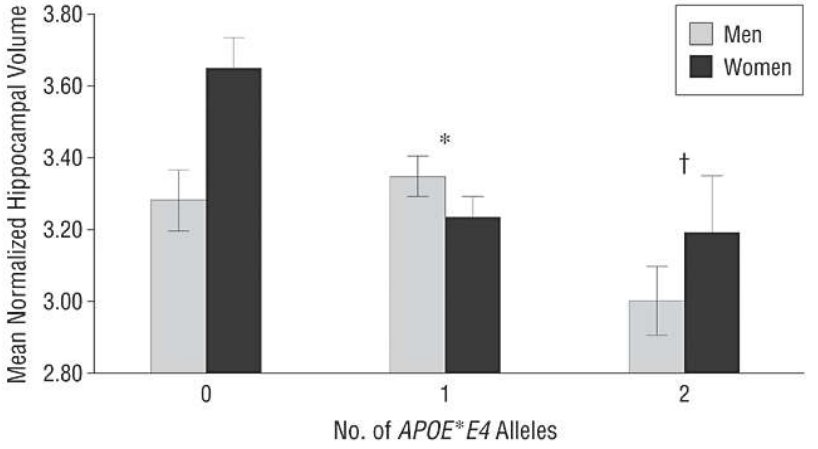


Frandsen JR, Narayanasamy P. Neuroprotection through flavonoid: Enhancement of the glyoxalase pathway. Redox Biol. 2018 Apr;14:465-473
PMID: 29080525

Glucocorticoids/Stress Damage Neurons

- Hippocampus role in cognition and memory
- Damaged by stress/glucocorticoids
- Worse with APOE*E4
- Decrease in brain volume!





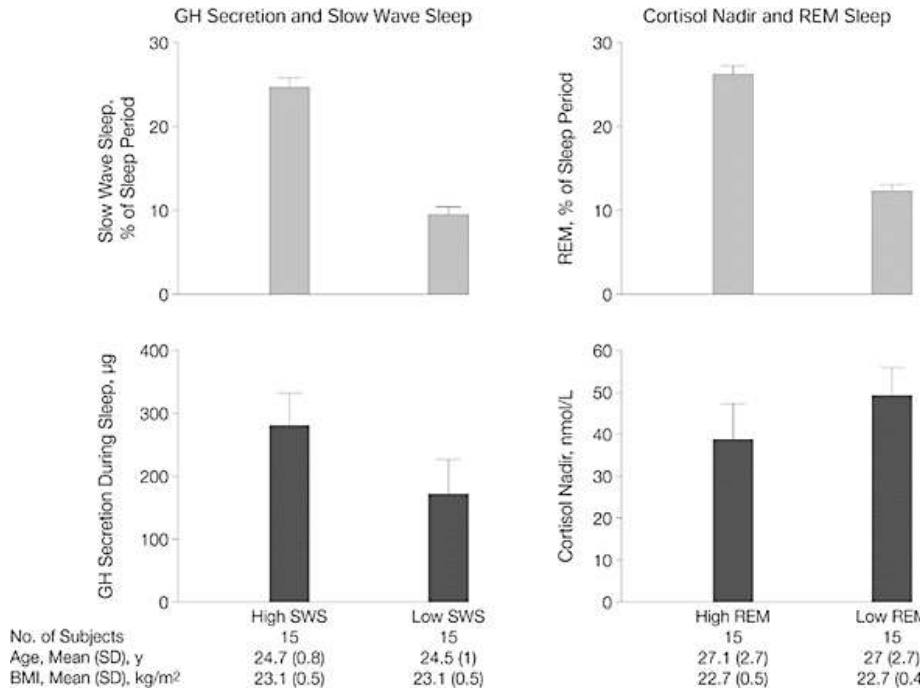
Brown ES, et al. Amygdala volume in patients receiving chronic corticosteroid therapy. Biol Psychiatry. 2008;63:705-9

Fleisher A, et al. Sex, apolipoprotein E epsilon 4 status, and hippocampal volume in mild cognitive impairment. Arch Neurol 2005;62:953-7

Sleep Deprivation Increases Cortisol and Damages Neurons

- Age related increases in cortisol are directly related to sleep fragmentation and reduction of REM sleep
- "Elevated evening cortisol levels in late life probably reflect an impairment of the negative feedback control of the HPA axis in aging.

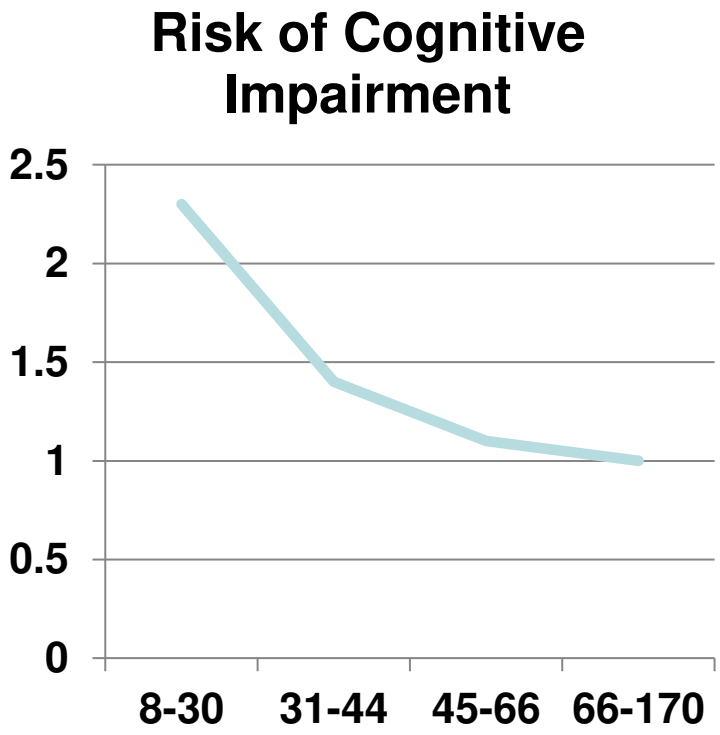
  Our analysis suggests that there is a relationship between this alteration of HPA function and decreased amounts of REM sleep that is independent of age."



Van Couter, E., et al. Age-related changes in slow wave sleep and REM sleep and relationship with growth hormone and cortisol levels in healthy men. JAMA 2000;284: 861-8

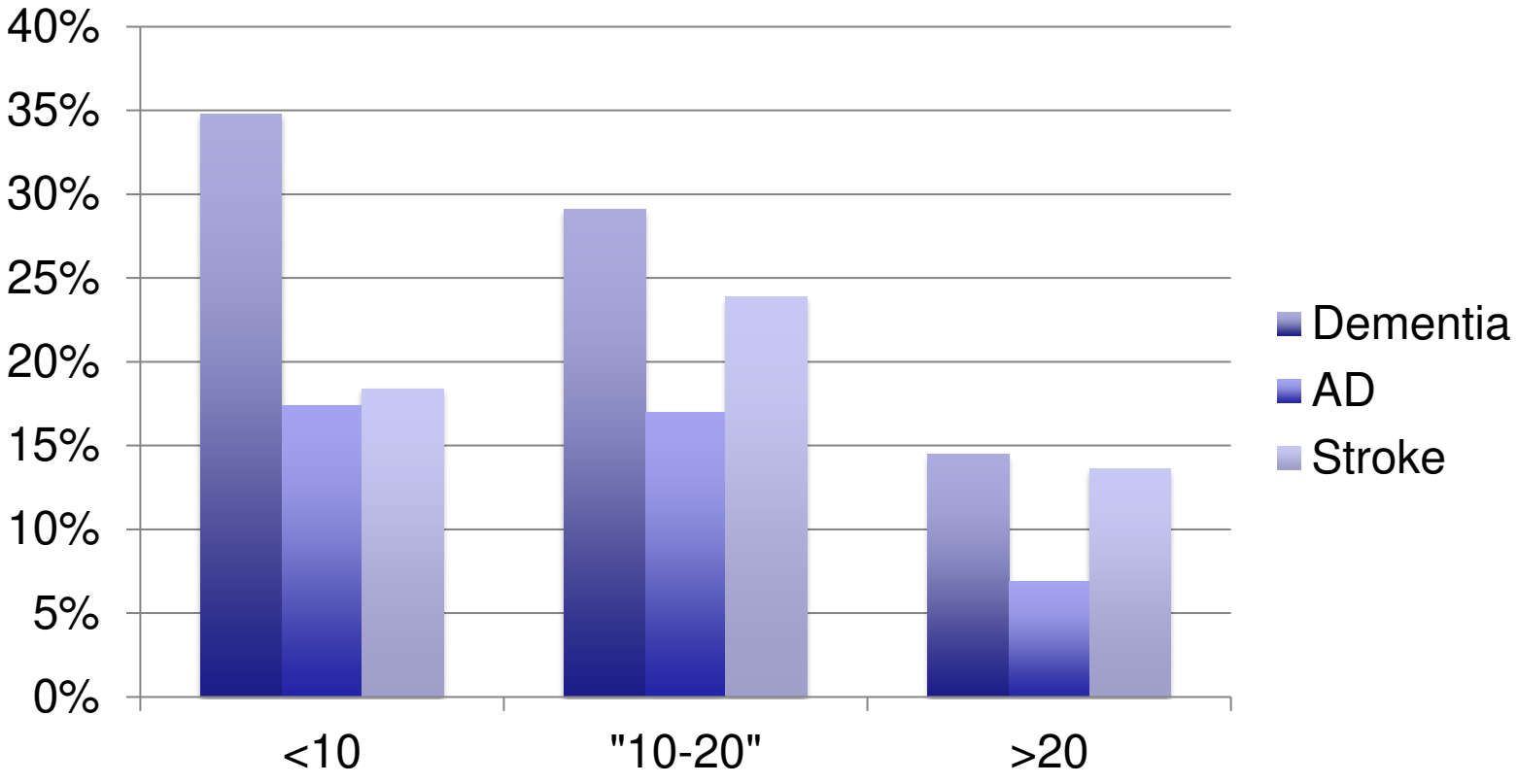
Vitamin D & Cognitive Decline

- 1,766 adults >65 yo in England
- Worse in black Americans:
  - 45.0 nmol/L vs. 63.0 nmol/L
  - 40% worse cognitive impairment
- In those >65, <50 nmol/l = 11.7 odds ratio of active mood disorder



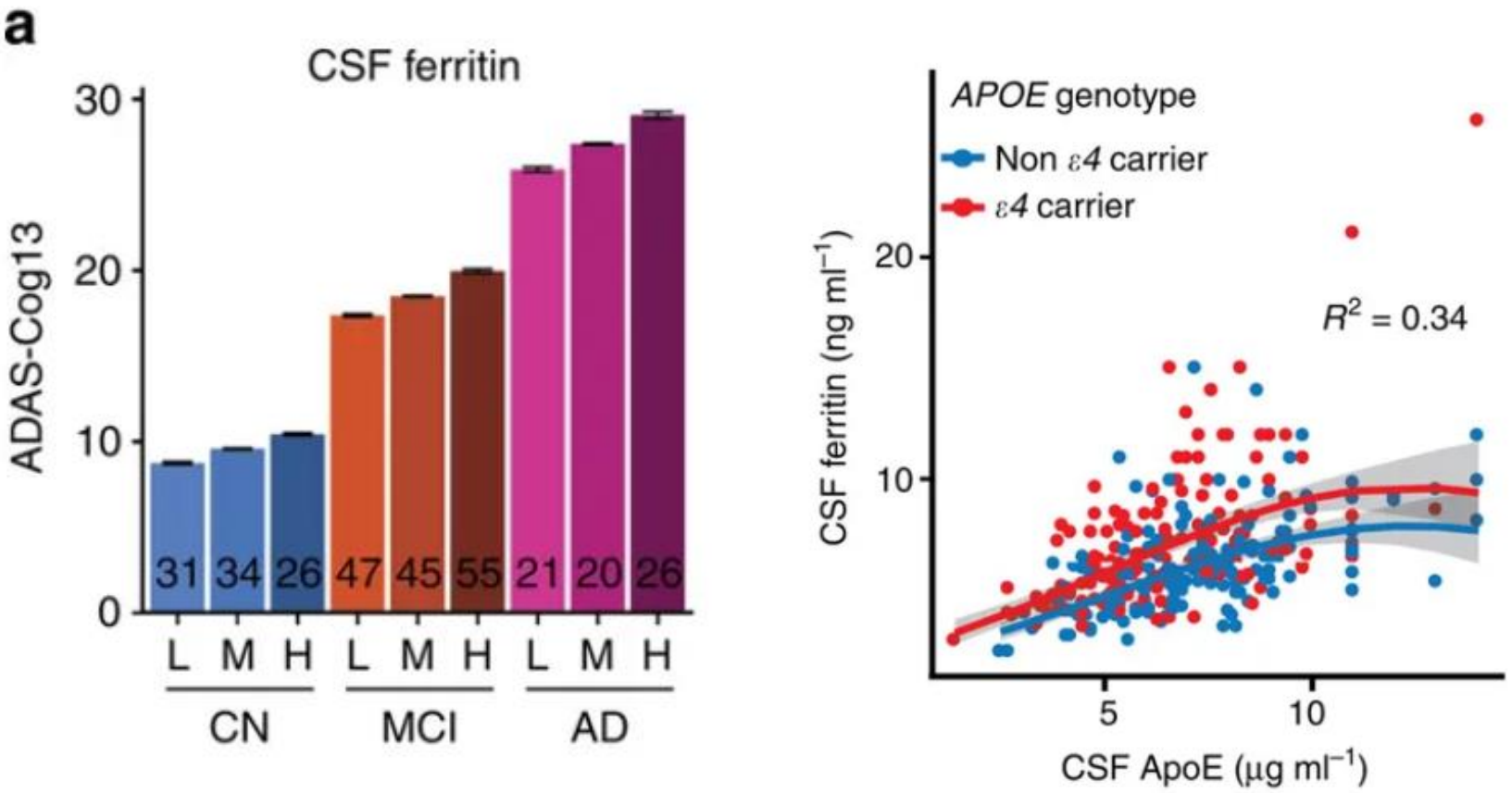
Llewellyn DJ, Langa K, Lang I. Serum 25-Hydroxyvitamin D Concentration and Cognitive Impairment. J Geriatr Psychiatry Neurol. 2009 Feb 4.
Wilkins CH, Birge SJ, Sheline YI, Morris JC. Vitamin D deficiency is associated with worse cognitive performance and lower bone density in older African Americans. J Natl Med Assoc. 2009 Apr;101(4):349-54
Wilkins CH, Sheline YI, Roe CM, et al. Vitamin D deficiency is associated with low mood and worse cognitive performance in older adults. Am J Geriatr Psychiatry. 2006 Dec;14(12):1032-40

Vitamin D Critical for Brain Health



Buell JS, Dawson-Hughes B, Scott TM. 25-Hydroxyvitamin D, dementia, and cerebrovascular pathology in elders receiving home services. Neurology. 2010 January 5; 74(1): 18–26

Iron Overload Damages Neurons

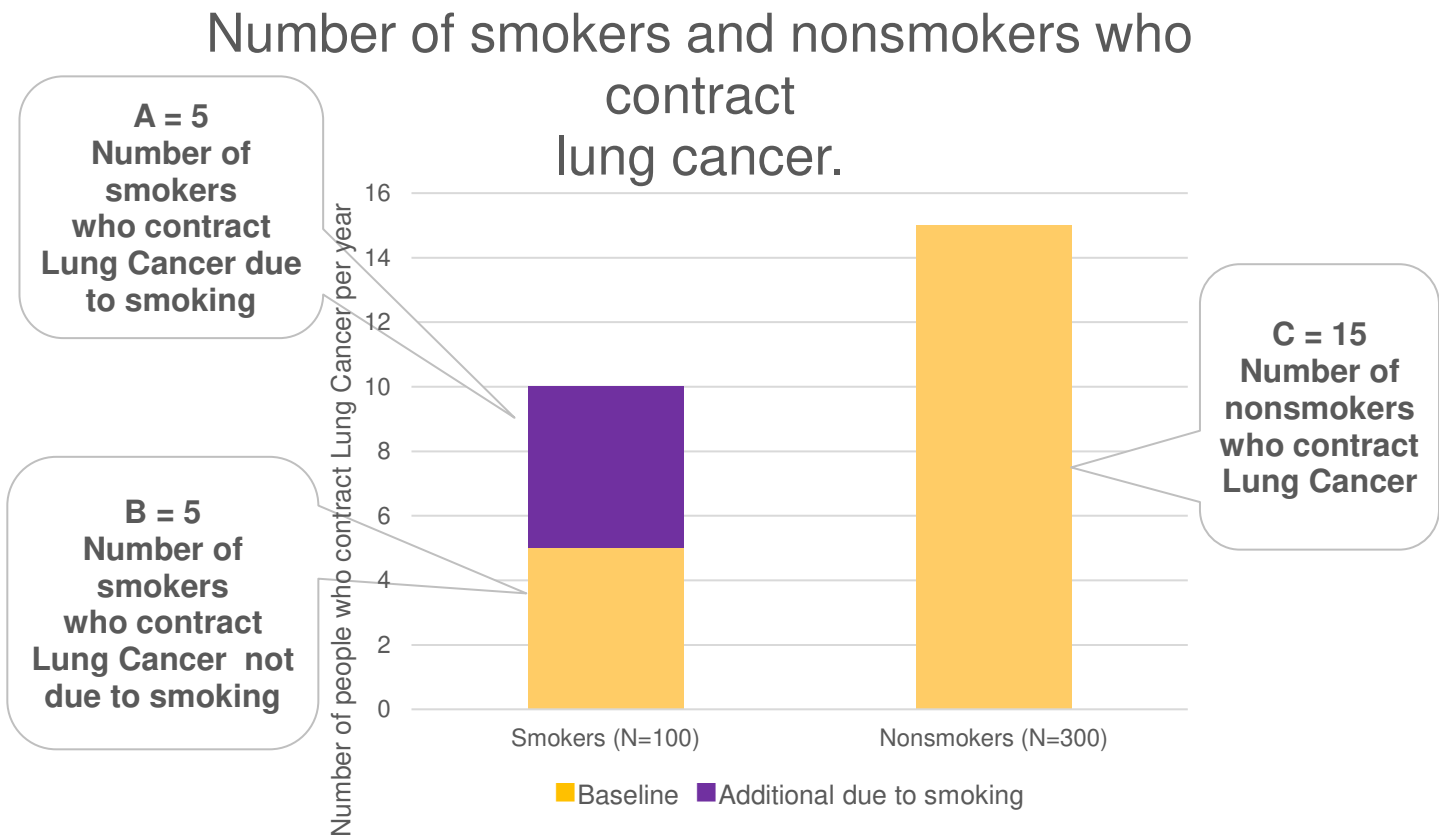


Ayton S, Faux NG, Bush AI. Et al. Ferritin levels in the cerebrospinal fluid predict Alzheimer's disease outcomes and are regulated by APOE. Nat Commun. 2015; 6: 6760 PMC4479012

% OF NEURODEGENERATION DISEASES DUE TO NEUROTOXINS

Example: Smoking and Lung Cancer

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



Rosen L. An Intuitive Approach to Understanding the Attributable Fraction of Disease Due to a Risk Factor: The Case of Smoking. Int. J. Environ. Res. Public Health 2013, 10, 2932-2943

How to Interpret the Following 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

Attention Deficit Hyperactivity Disorder

Toxin	Threshold	% Above Threshold	Odds Ratio	% of Disease	Example PMID
PAHs	2.27 ng/m^3	94.0%	1.25	19.0%	22440811
DDT	1.26 ng/g serum (p,p'-DDE)	25.0%	1.8	16.6%	20106937
PCBs	1.04 ng/g serum (50 PCBs)	25.0%	1.76	16.0%	20106937
Phthalates	Depends on phthalate	Depends on phthalate	2.1-12.7	>5.2%	24267794
Mercury	~3.5ug/dL maternal blood	, ~8-9%	1.6	Difficult to determine, 3.2%	24952233
Lead	2.3 ug/dL	1.3%	2.54	2.0%	27659349
Organophosphate pesticides	~413nm/L		1.6		20478945

Juvenile IQ

Toxin	Threshold	% Above Threshold	Odds Ratio	IQ Change	Example PMID
Arsenic	>50ug/L urine	~5%		0.5 point decrease	23570911
Fluoride	0.7mg/L urine	NAD		0.59 point decrease per 1mg/mL fluoride	21237562
Lead	5-10ug/dL	~5%		4.9 point decrease	21450073
Mercury	≥7.5 µg/L cord	83%!!?	>7.5 = 4x risk <80 IQ	4.8 point decrease	25757069
Organophosphates	75nmol/L	NAD		5.6 point decrease	21507776
PAHs	17.96ng/m3	NAD		3.8 point decrease	20406721
Phthalates	19.4 5.0 ug/L (MnBP/MiBP)	~41% ~57%		6.7-7.6 point decrease	25493564

Alzheimer's Disease

Toxin	Threshold	% Above Threshold	Odds Ratio	% of Disease	Example PMID
Aluminum (water)	0.1 mg/L drinking water	2.3%	3.0	1/3 above 0.1 develop AZ	10901330
Aluminum (dust)	Ever exposed		1.4		24142983
Aluminum (food)	Grains, additives		2.0-8.6		10350420
Arsenic					Theoretical
Lead					Insufficient data
Mercury					Insufficient data
Ozone	10.9 ppb		2.1/10.9 ppb		25310992
$PM_{2.5}$	4.34µg/m3		1.4		25310992
VOC (solvents)	Exposure		2.3 (6.0 men)		7771442

Alzheimer's Disease

Toxin	Threshold	% Above Threshold	Odds Ratio	% of Disease	Example PMID
Total pesticides	High vs Low exposure	43.6%	2.1	32%	21601587
Total pesticides	Occupationally exposed (when young)		2.4		12615605
β-HCH & Dieldrin			2.8 & 2.3		25654508
DDT	1.66 ng/mg cholesterol	6%	3.4	12.6%	24473795
Organophosphate pesticides		18.5%	1.4		20458069
Fumigants & Defoliants	Exposed		4.4		11416089

Amyotrophic Lateral Sclerosis (ALS)

Toxin	Threshold	% Above Threshold	Odds Ratio	% of Disease	Example PMID
Aluminum					Insufficient data
DDT	Any exposure	5%	2.1	Unknown at this time	PMC3358481
Lead	2.38 ug/dL blood	33%	1.81	6.2%	25479292
Mercury					Insufficient data
Organophosphate pesticides					Insufficient data
PAHs					NAD
PCBs					NAD

Brain Cancer

Toxin	Threshold	% Above Threshold	Odds Ratio	% of Disease	Example PMID
Lead	0.005 ug/dL	14%	1.9	~50.0%??	17164378
Pyrethroid pesticides	3.02 ug/g creatinine	19%	1.8	13.6%	27593355
PCBs	Industrial exposure		1.8		PMC1128926

Multiple Sclerosis

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

Parkinson's Disease

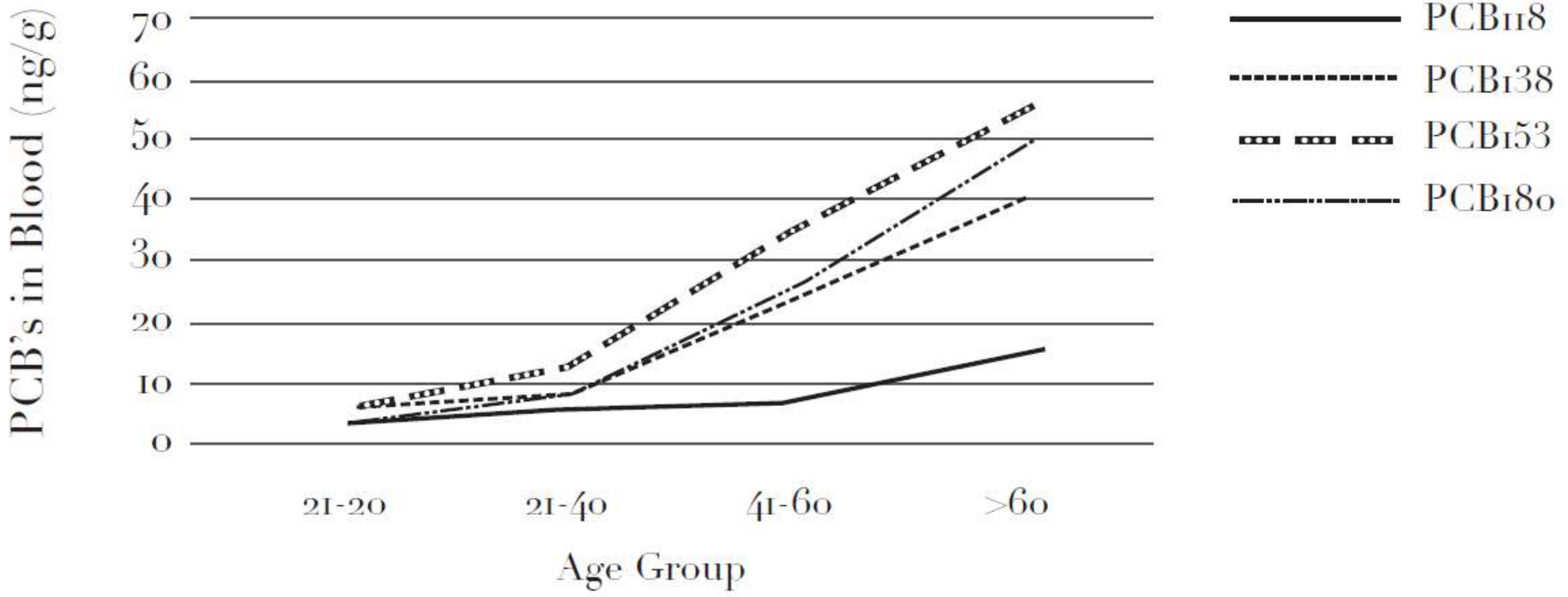
Toxin	Threshold	% Above Threshold	Odds Ratio	% of Disease	Example PMID
Organophosphate pesticides	Household use		1.5 (any use) 1.7 (32/year)		24057998
Pyrethroid pesticides	Depends on HLA		2.5		27148593
Trichloroethylene (TCE--solvent)	Exposure, twin study		6.1		22083847

Applying Same AF Formula to AD for "Conventional" Risk Factors

RISK FACTOR	POPULATION PREVALENCE	RELATIVE RISK (95% CI)	PAR% (Confidence Range)
Physical inactivity	32.5%	1.82 (1.19, 2.78)	21.0% (5.8%, 36.6%)
Depression	19.2%	1.90 (1.55, 2.33)	14.7% (9.6%, 20.3%)
Smoking	20.6%	1.59 (1.15, 2.20)	10.8% (3.0%, 19.8%)
Mid-life hypertension	14.3%	1.61 (1.16, 2.24)	8.0% (2.2%, 15.1%)
Mid-life obesity	13.1%	1.60 (1.34, 1.92)	7.3% (4.3%, 10.8%)
Low education	13.3%	1.59 (1.35, 1.86)	7.3% (4.4%, 10.3%)
Diabetes	8.7%	1.39 (1.17, 1.66)	3.3% (1.5%, 5.4%)
Combined			30.8% - 54.1%

Barnes DE, Yaffe K. The projected effect of risk factor reduction on Alzheimer's disease prevalence. Lancet Neurol. 2011 Sep;10(9):819-28.

Bioaccumulation of Neurotoxins



DDT banned in 1972 PCBs banned in 1977

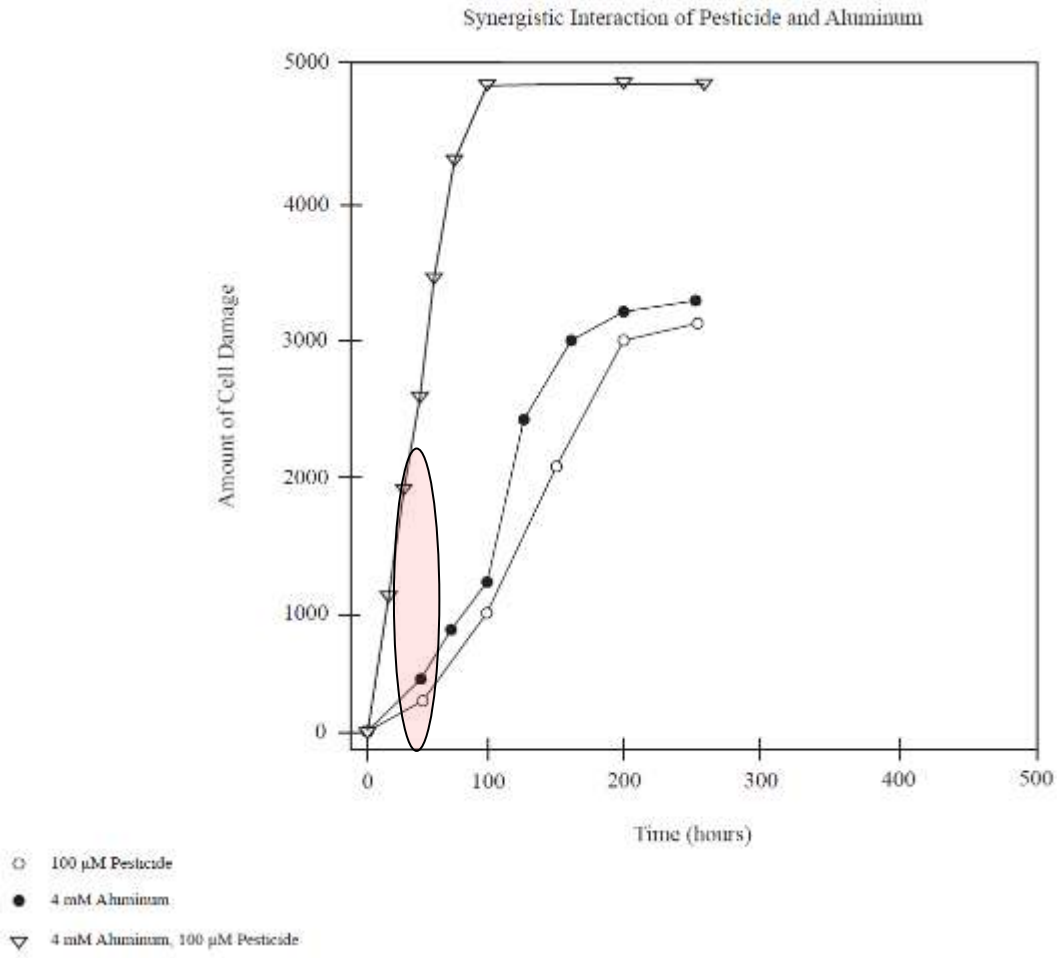
Serdar B, et al. Potential effects of polychlorinated biphenyls (PCBs) and selected organochlorine pesticides (OCPs) on immune cells and blood biochemistry measures: a cross-sectional assessment of the NHANES 2003-2004 data. *Environ Health*. 2014;13:114.

Neurotoxin Synergy

- Neuron cell study
- Damage (units):
  - 400 (OCP)

    +
  - 600 (AL)

    =
  - **2,000**



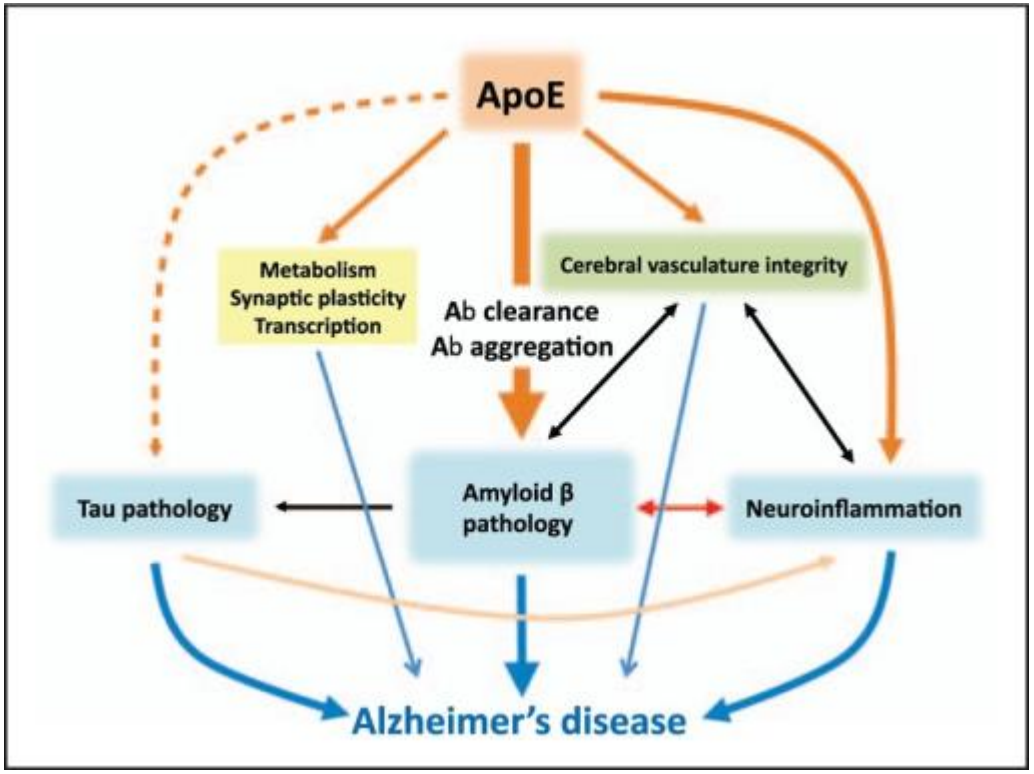
Uversky VN. Synergistic effects of pesticides and metals on the fibrillation of alpha-synuclein: implications for Parkinson's disease. Neurotoxicology. 2002;Oct;23(4-5):527-36.

ApoE
PONs

GENETICS OF NEURODEGENERATION

ApoE4 Increases Risk of Dementia

- Accounts for 13-20% of dementia
- Heterozygous, onset 5-10 years earlier
- Homozygous, onset 10-20 years earlier



Yoon, H., & Kim, J. (2017). Apolipoprotein E metabolism and functions in brain and its role in Alzheimer's disease. Current Opinion in Lipidology, 28(1), 60-67. PubMed PMID: 27922847

PON1, Organophosphates and Parkinson's Disease

- Paraoxonase (PON1)
  - Hydrolyzes organophosphate pesticides and nerve gasses
  - Only present in mammals
  - Activity greatly impacted by genomics
- Those exposed to organophosphate pesticides **AT RESIDENCES** PD risk:
  - Slow version: 1.2-1.4
  - Fast version: 1.8-2.5

Lee PC, Rhodes SL, Sinsheimer JS, et al. Functional paraoxonase 1 variants modify the risk of Parkinson's disease due to organophosphate exposure. Environ Int. 2013 Jun;56:42-7. PMID 23602893

Eliminate Neurotoxin Exposure
Facilitate Neurotoxin Excretion
Optimize B12, Folate and B6 Status

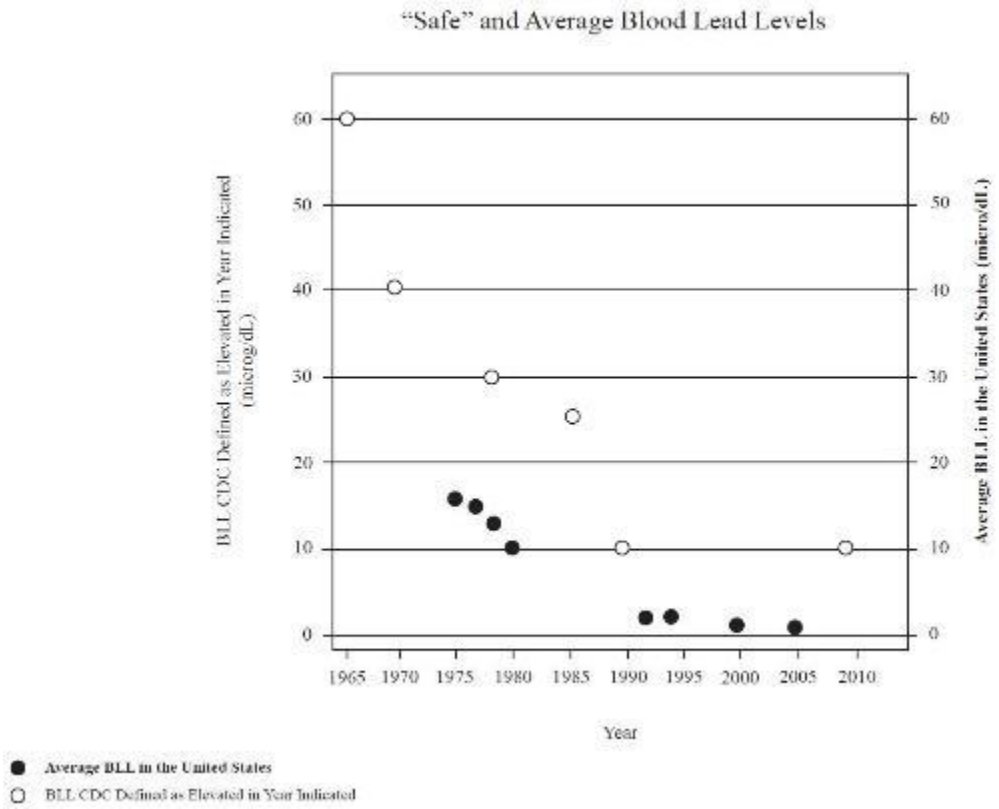
INTERVENTION

Neurotoxin Elimination

- Avoidance, AVIODANCE, **AVOIDANCE**
- Facilitate detoxification
- Increase excretion

Public Health Can Decrease Toxic Load

- Banning lead in gasoline and paint worked—blood levels down dramatically.
- No threshold for safety –
  - **Children who had whole blood lead concentrations of <5 µg/dL (supposedly safe) associated with decreased IQ**
  - **2.4 million children at levels between 5 and 9.9 ug/dL**
- July 2012: CDC changed recommended level to intervene in children from 10 to 5.0 ug/dL. Eliminated term “level of concern”, to avoid false sense of safety.



Iqbal S, et al. Estimated burden of blood lead levels 5 microg/dl in 1999-2002 and declines from 1988 to 1994. Environ Res. 2008
http://www.cdc.gov/nceh/lead/acclpp/cdc_response_lead_exposure_recs.pdf
http://www.environment.ucla.edu/reportcard/article3772.html

Mercury In Fish

- 10-fold variation from lowest to highest
- All fish contain some mercury
- Pick those with highest omega-3 and lowest Hg:
  - Sardines
  - Anchovies
  - Small salmon

Guide to mercury levels in different varieties of fish and shellfish

LOW-MERCURY FISH AND SHELLFISH

VERY LOW	BELOW AVERAGE
Shrimp	Pollock
Sardines	Atlantic Mackerel
Tilapia	Anchovies, Herring & Shad
Oysters & Mussels	Flounder, Sole & Plaice
Clams	Crabs
Scallops	Pike
Salmon	Butterfish
Crayfish	Catfish
Freshwater Trout	Squid
Ocean Perch & Mullet	Atlantic Croaker
	Whitefish

MODERATE-MERCURY FISH AND SHELLFISH

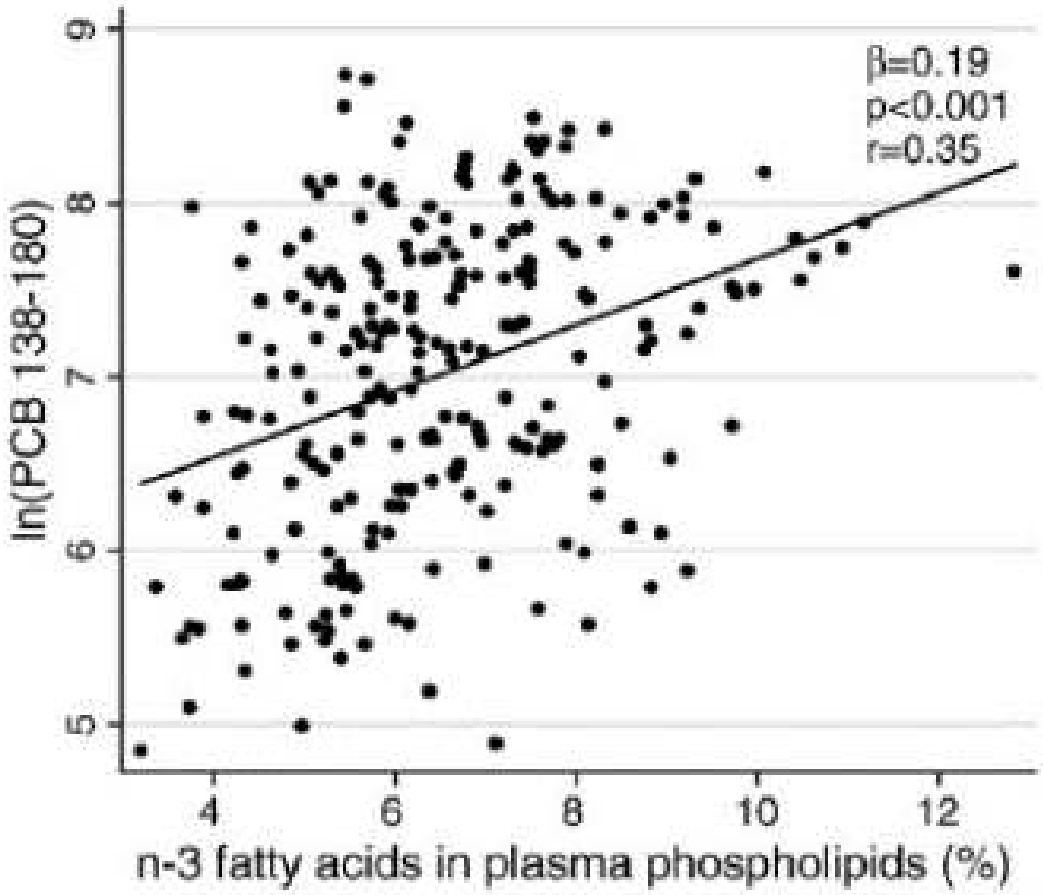
ABOVE AVERAGE	MODERATELY HIGH
Pacific Mackerel (Chub)	Carp & Buffalofish
Smelt	Halibut
Atlantic Tilefish	Sea Trout
Cod	Sablefish
Caned Light Tuna	Lingcod & Scorpionfish
Spiny Lobster	Sea Bass
Snapper, Porgy, Sheepshead	Pacific Croaker
Skate	American Lobster
Freshwater Perch	Freshwater Bass
Haddock, Hake, Monkfish	Bluefish

HIGH-MERCURY FISH

HIGH	VERY HIGH
Canned Albacore Tuna	King Mackerel
Spanish Mackerel	Swordfish
Fresh/Frozen Tuna	Shark
Grouper	Gulf Tilefish
Marlin	Tuna Sushi/Bluefin Tuna
Orange Roughy	

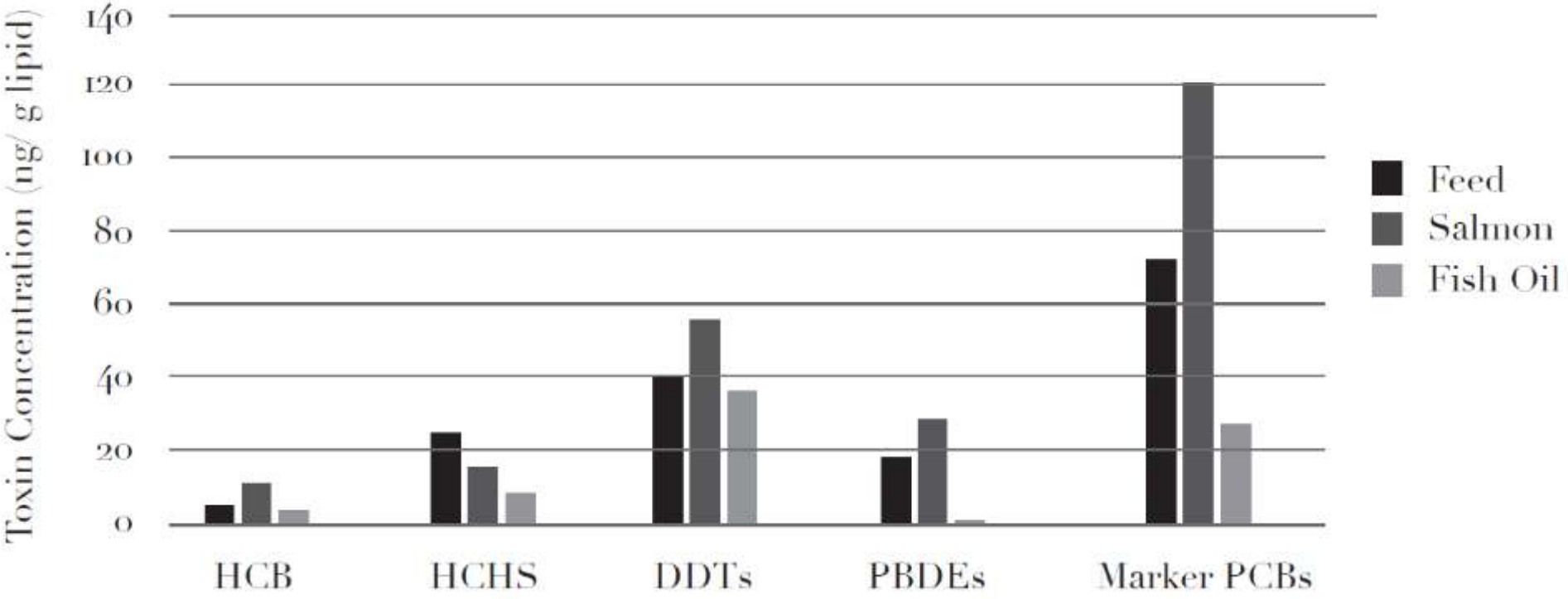
Source: http://www.fda.gov/Food/FoodSafety/Product-SpecificInformation/Seafood/FoodbornePathogensContaminants/Methylmercury/ucm115644.htm

Fish (esp farmed) a Significant Source of POPs



Bjermo H, et al. Fish intake and breastfeeding time are associated with serum concentrations of organochlorines in a Swedish population. Environ Int. 2013 Jan;51:88-96

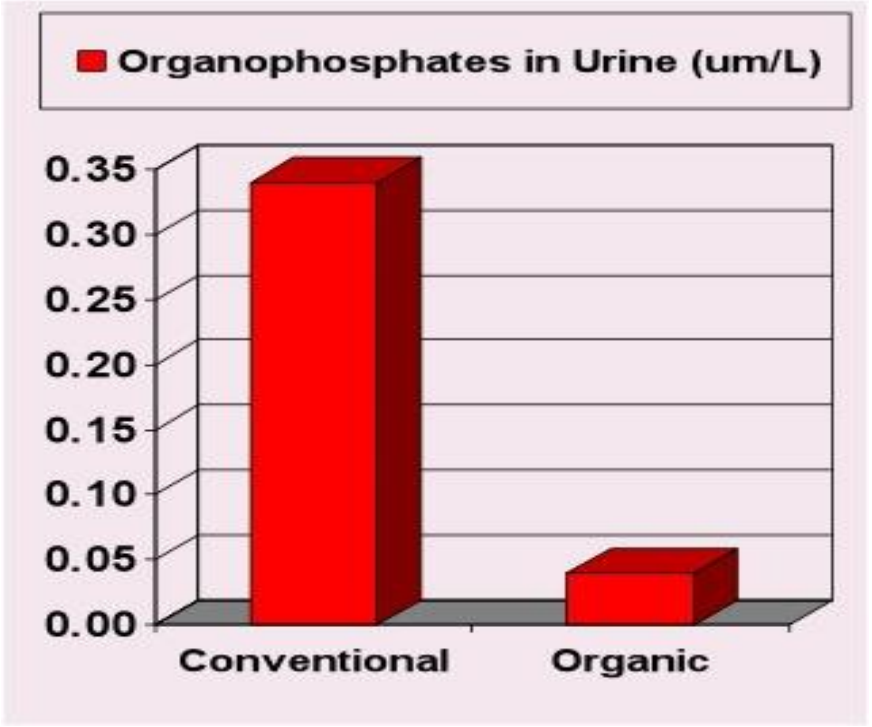
PCBs in Farmed Fish



Jacobs MN, Covaci A, Schepens P. Investigation of selected persistent organic pollutants in farmed Atlantic salmon (Salmo salar), salmon aquaculture feed, and fish oil components of the feed. Environmental Science & Technology 2002;36: 2797–805

Eating Organically Grown Foods Dramatically Decreases Neurotoxins

- Study done in Seattle children
- 10-fold increase in POPs doubles ADHD
- **Blood levels drop measurably within 3 days of eating only organically grown foods**



Curl CL, et al. Organophosphorus pesticide exposure of urban and suburban preschool children with organic and conventional diets. Env Health Perspect. 2003;111:377-82
Bouchard MF, et al. Attention-deficit/hyperactivity disorder and urinary metabolites of organophosphate pesticides. Pediatrics. 2010 Jun;125(6):e1270-7

FACILITATE DETOXIFICATION AND EXCRETION

Fiber Decreases POPs

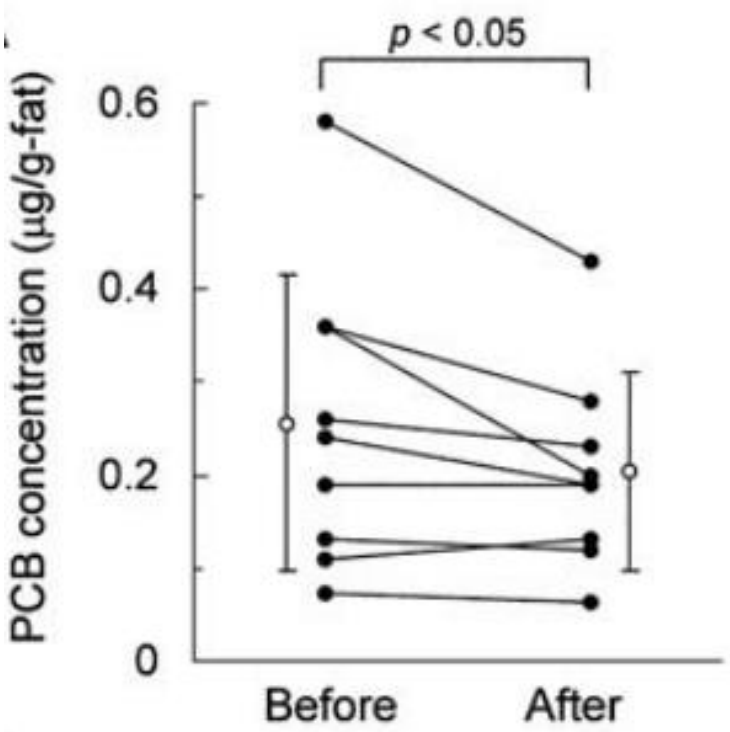
- Fiber
  - Rice bran (PCBs, PCDFs, dioxins)
  - Wheat bran (PCBs)
  - 5g/day
  - Slow!!
- Bile sequestrants
  - Cholestamide, Cholestyramine, Olestra

Sera N, et al. Binding effect of polychlorinated compounds and environmental carcinogens on rice bran fiber. J Nutr Biochem. 2005 Jan;16(1):50-8

Genuis SJ, Birkholz D, Ralitsch M, Thibault N. Human detoxification of perfluorinated compounds. Public Health, 2010; 124:367–75

Colestimide Reduces PCBs

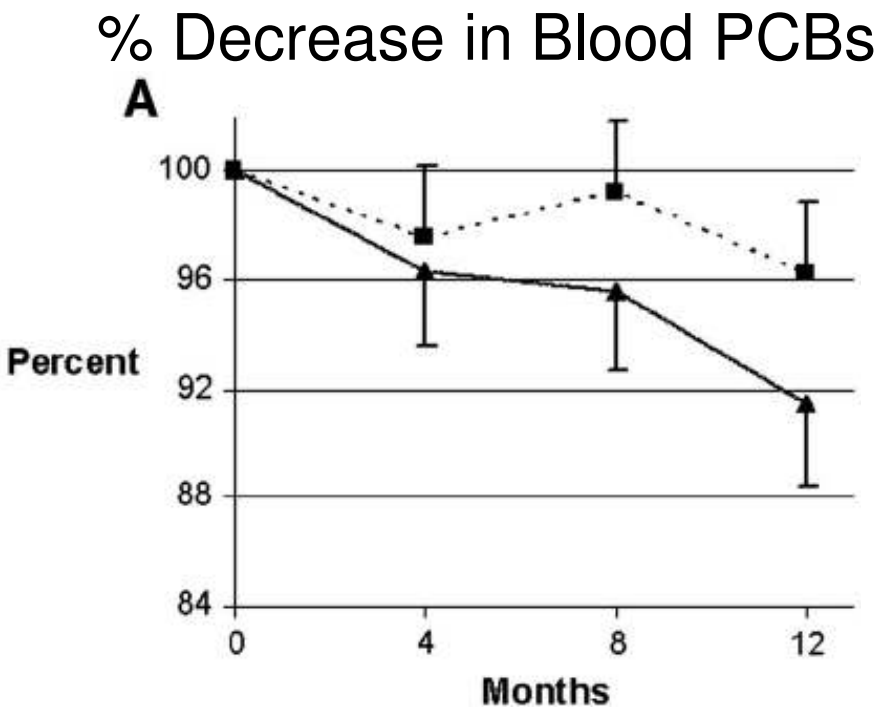
- 5 g/d (?)
- 6 months
- Average reduction 23%
- Those who did not take increased 24%



Sakurai K, Fukata H, Todaka E, et al. Colestimide reduces blood polychlorinated biphenyl (PCB) levels. Intern Med. 2006;45(5):327-8

Olestra Decreases PCBs and DDE

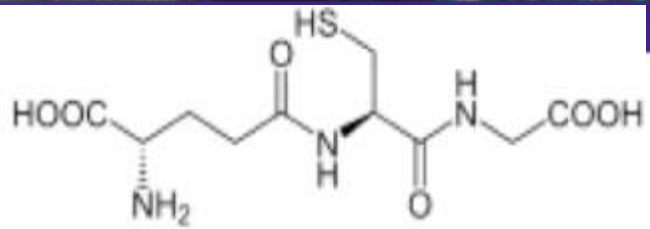
- Potato chips made with olestra or vegetable oil
- 12 months
- 15 g of olestra per day
  - 22 Pringles Light crisps
- No change in diet
- Higher body fat = lower % decrease
- 25% loose stools



½ life decreased from 20+ years to 8.5 years

Jandacek RJ, Heubi JE, Buckley DB, et al. Reduction of the body burden of PCBs and DDE by dietary intervention in a randomized trial. J Nutr Biochem, 2014;25 483–488

Glutathione: Critical



- **Difficult to overstate its importance in brain health**
- Most important intracellular and intra-mitochondrial antioxidant
- Binds and transports mercury out of cells and brain
- Irreversibly(?) binds to mercury in the brain
- Neutralizes oxidative damage from mercury and POPs
- Facilitates detoxification of POPs
- Depleted by oxidative stress, metals, alcohol
- Even predictor of healthy aging!

Baker, SM. The Metaphor of Oceanic Disease. IMCJ February, 2008;7:1.
Mosharov, E., Cranford, M.R., Baneriee, R. The Quantitatively Important Relationship between Homocysteine Metabolism and Glutathione Synthesis by the Transsulfuration Pathway and Its Regulation by Redox Changes. Biochemistry. 2000 Sept;39:13005-13011.

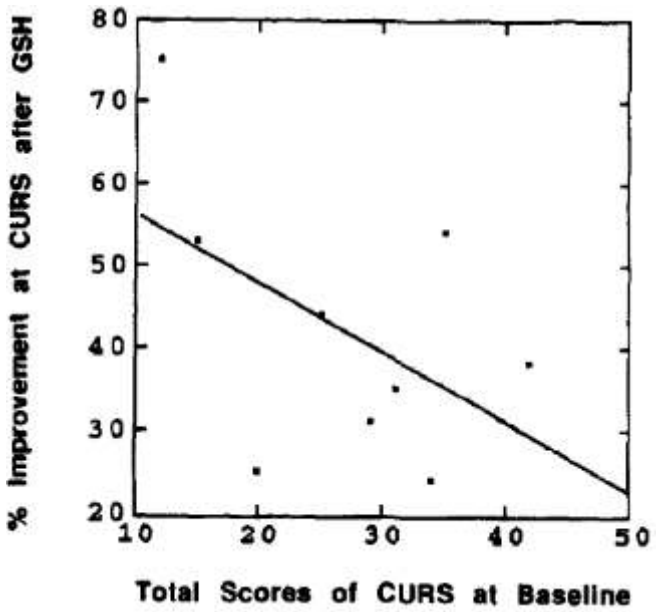
Depleted GSH Common in Neurodegeneration

- Alzheimer’s disease
- Amyotrophic lateral sclerosis
- Dementia
- Friedreich's ataxia
- Huntington's disease
- Parkinson’s disease

Ballatori N, Krance SM, Notenboom S, Shi S, Tieu K, Hammond CL. Glutathione dysregulation and the etiology and progression of human diseases. Biol Chem. 2009 Mar;390(3):191-214

Glutathione Protects Neurons

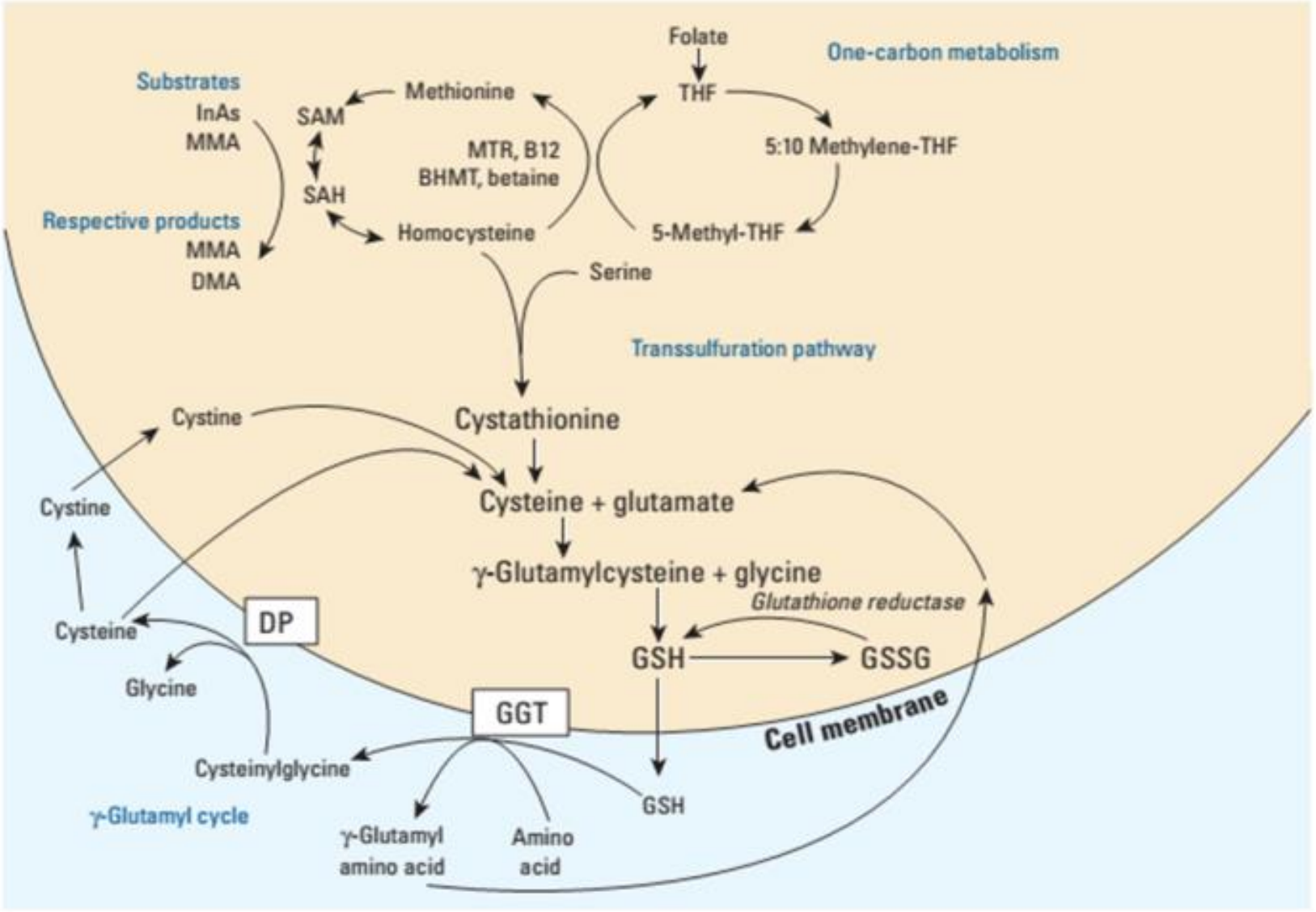
- 50% less glutathione (GSH) in the substantia nigra of Parkinson's patients
- But not in other parts of brain => used up in neutralization of local toxins
- GSH 600 mg IV bid x 30 days
  - 42 % decline in disability
  - Lasted 2-4 months after stopped
- **Protects both telomeres and mtDNA**



Perry TL, et al. Idiopathic Parkinson's disease: A disorder due to nigral glutathione deficiency. Neuroscience Letter 1986;67:269-74

Sechi G, et al. Reduced intravenous glutathione in the treatment of early Parkinson's disease. Prog Neuropsychopharmacol Biol Psychiatry 1996;20:1159-70

Synthesis, Regeneration and Recycling



Hall MN, Niedzwiecki M, Liu X, et al. Chronic arsenic exposure and blood glutathione and glutathione disulfide concentrations in bangladeshi adults. Environ Health Perspect. 2013 Sep;121(9):1068-74

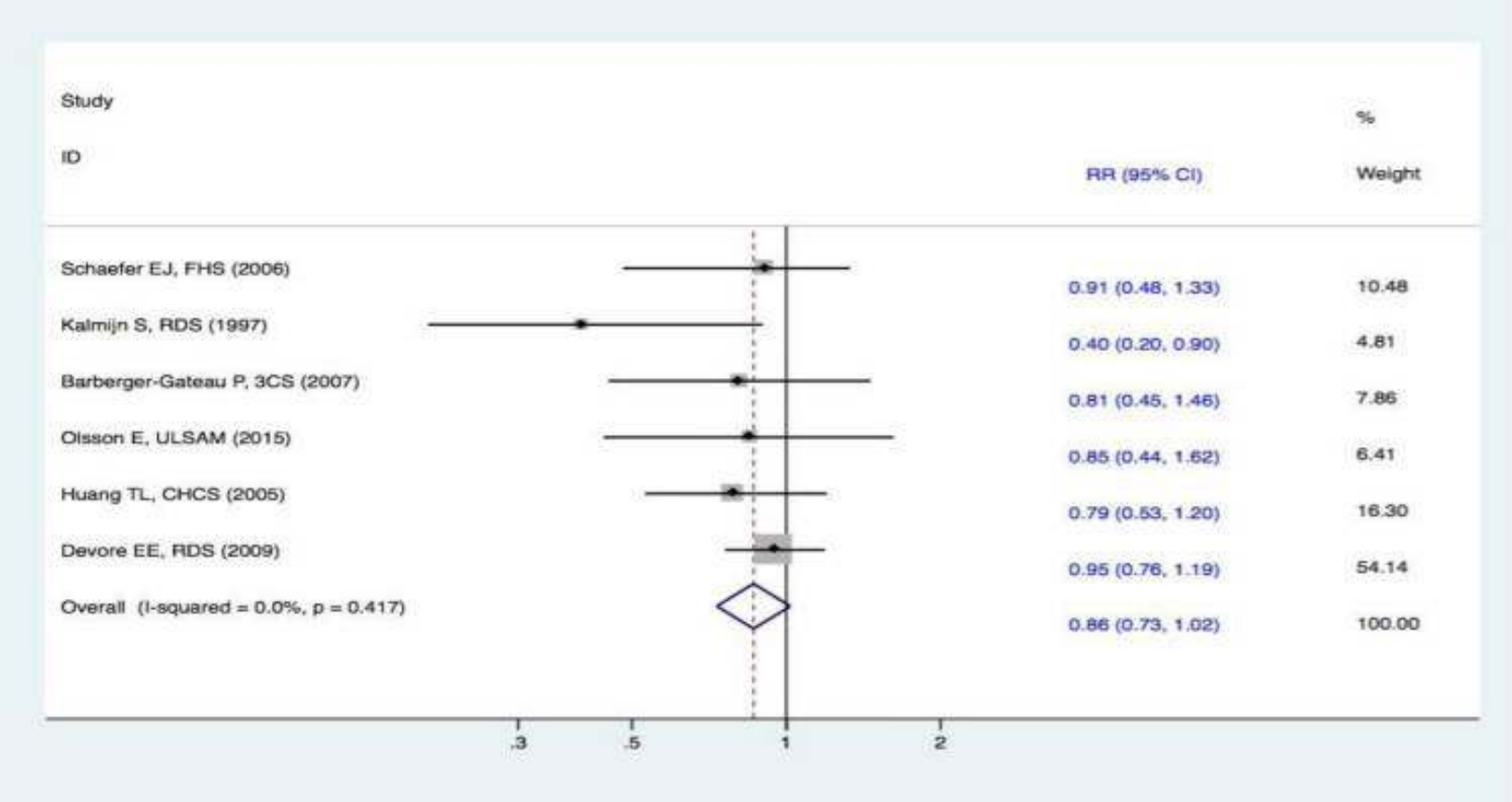
SUPPORT NORMAL FUNCTION

Mediterranean Diet Slows Aging and Prevents Neurological disease

- Those following most closely this dietary pattern have a longer lifespan and a **reduced risk of neurodegenerative disease, including Alzheimer's**
- Review of all prospective cohort studies (nearly 600,000 subjects)
- Greater adherence to a Mediterranean diet is associated with a significant reduction in:
  - Overall mortality (-8%),
  - Mortality/incidence of cardiovascular diseases (-10%),
  - Incidence of or mortality from cancer (-6%),
  - **Incidence of Parkinson's disease and Alzheimer's disease (-13%)**

Pérez-López FR, Chedraui P, Haya J, Cuadros JL. Effects of the Mediterranean diet on longevity and age-related morbid conditions. Maturitas. 2009 Oct 20;64(2):67-79. Epub 2009 Aug 31.
Sofi F, et al. Adherence to Mediterranean diet and health status: meta-analysis. Am J Clin Nutr. 2010 Nov;92(5):1189-96.

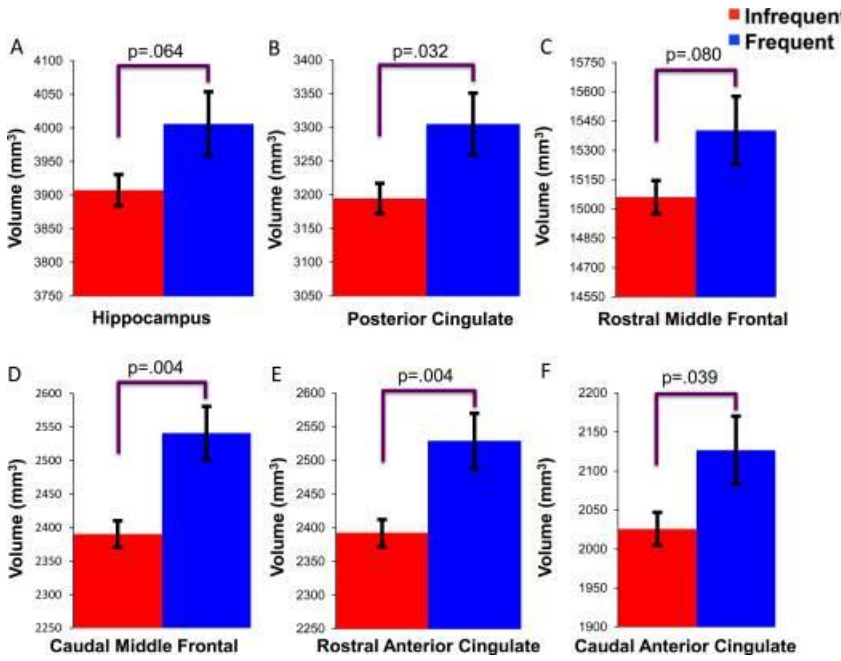
Fish Consumption Decreases Dementia



Zeng LF, Cao Y, Liang WX, et al. An exploration of the role of a fish-oriented diet in cognitive decline: a systematic review of the literature. Oncotarget. 2017 Jun 13;8(24):39877-3989 PMID: 28418899

Use It or Lose It!

- Playing games, especially strategy types, has many documented benefits
  - Correlative and intervention
- Playing chess several times a week: OR 0.65
- Being taught a new game improves all measures in frequency-dosage manner
- Even increases brain volume!

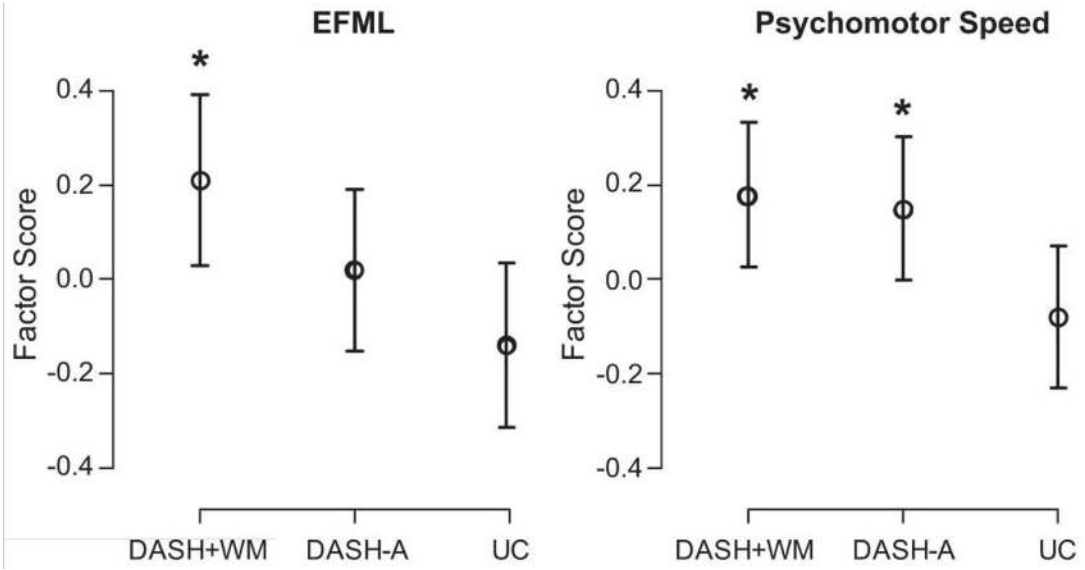


Lillo-Crespo M, Forner-Ruiz M, Riquelme-Galindo J, et al. Chess Practice as a Protective Factor in Dementia. Int J Environ Res Public Health. 2019 Jun 14;16(12) PMID: 31207926

Schultz SA, Larson J, Oh J, et al. Participation in cognitively-stimulating activities is associated with brain structure and cognitive function in preclinical Alzheimer's disease. Brain Imaging Behav. 2015 Dec;9(4):729-36 PMID: 25358750

Caloric Restriction + Exercise

- Overweight with high blood pressure
- DASH diet alone or with weight loss and exercise
- 30-min supervised aerobic exercise 3 times per week



Smith PJ, Blumenthal JA, Babyak MA, et al. Effects of the dietary approaches to stop hypertension diet, exercise, and caloric restriction on neurocognition in overweight adults with high blood pressure. Hypertension. 2010 Jun;55(6):1331-8. PMID: 20305128

ADHD
Alzheimer's Disease/Dementia
Parkinson's Disease

CONDITION-SPECIFIC PROTOCOLS

For All Patients with Neurodegeneration

1. Identify and eliminate all neurotoxins
2. Identify and replenish all nutrient deficiencies
3. Exercise—both aerobic and anaerobic
4. Optimize blood sugar control
5. Optimize mitochondrial function
6. Healthy Mediterranean diet
7. Increase fish consumption (small, cold water)
8. Decrease iron load (ferritin should be 50-75)

ADHD

- Worst neurotoxins: BPA, PBDEs, PFOS, lead, organophosphate pesticides
- Main nutrient deficiencies: Omega-3 fatty acids, magnesium, zinc, iron, vitamin D
- Key interventions:
  - Food intolerance: strict elimination diet benefited 64%

Pelsser LM1, Frankena K, Toorman J, et al. Effects of a restricted elimination diet on the behaviour of children with attention-deficit hyperactivity disorder (INCA study): a randomised controlled trial. Lancet. 2011 Feb 5;377(9764):494-503. PMID: 21296237)

Alzheimer's Disease/Dementia

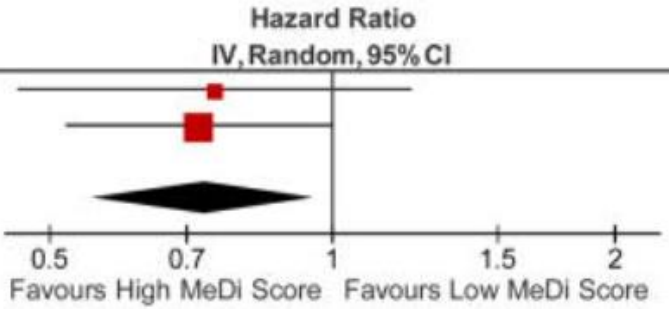
- Worst neurotoxins: PM, organophosphates, organochlorine pesticides
- Main nutrient deficiencies: Activated B12,vitamin D
- Key interventions:
  - Mediterranean diet: reduction MCI 27%, AD 36%
  - Methyl and adenosyl B12
  - Multiple natural therapies have shown benefit (see last slide)

Mediterranean Diet Critical for Brain Health

- Meta-analysis of **prospective** studies

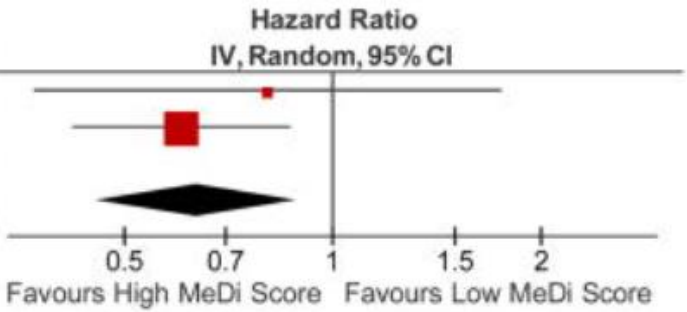
Study or Subgroup	log[Hazard Ratio]	SE	MCI Total	CN Total	Weight	Hazard Ratio IV, Random, 95% CI
Roberts 2010	-0.2889	0.2467	93	1141	31.4%	0.75 [0.46, 1.21]
Scarmeas 2009 MCI	-0.3285	0.1668	241	1199	68.6%	0.72 [0.52, 1.00]
Total (95% CI)			**334**	**2340**	**100.0%**	**0.73 [0.56, 0.96]**

Heterogeneity: Tau² = 0.00; Chi² = 0.02, df = 1 (P = 0.89); I² = 0%
Test for overall effect: Z = 2.29 (P = 0.02)



Study or Subgroup	log[Hazard Ratio]	SE	AD Total	CN Total	Weight	Hazard Ratio IV, Random, 95% CI
Feart 2009	-0.2169	0.3966	51	1410	18.0%	0.81 [0.37, 1.75]
Scarmeas 2006	-0.5034	0.1858	219	1759	82.0%	0.60 [0.42, 0.87]
Total (95% CI)			**270**	**3169**	**100.0%**	**0.64 [0.46, 0.89]**

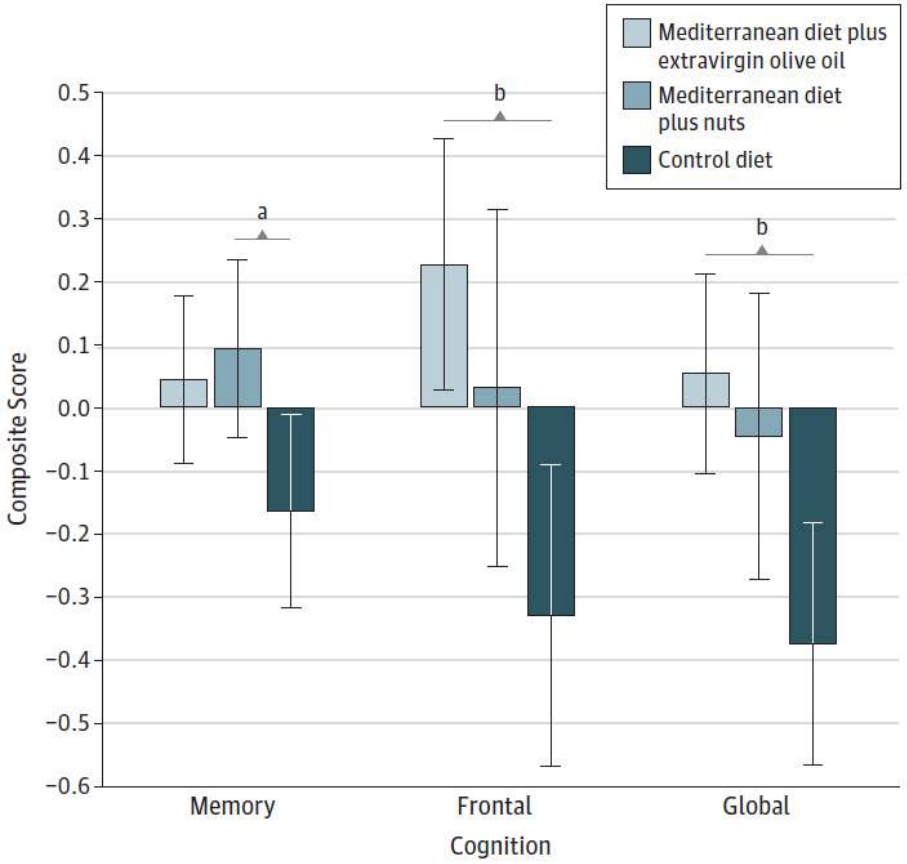
Heterogeneity: Tau² = 0.00; Chi² = 0.43, df = 1 (P = 0.51); I² = 0%
Test for overall effect: Z = 2.69 (P = 0.007)



Singh B, Parsaik AK, Mielke MM, et al. Association of Mediterranean diet with mild cognitive impairment and Alzheimer's disease: a systematic review and meta-analysis. J Alzheimers Dis. 2014;39(2):271-82 PMID: 24164735

Mediterranean Diet Improved with Nuts

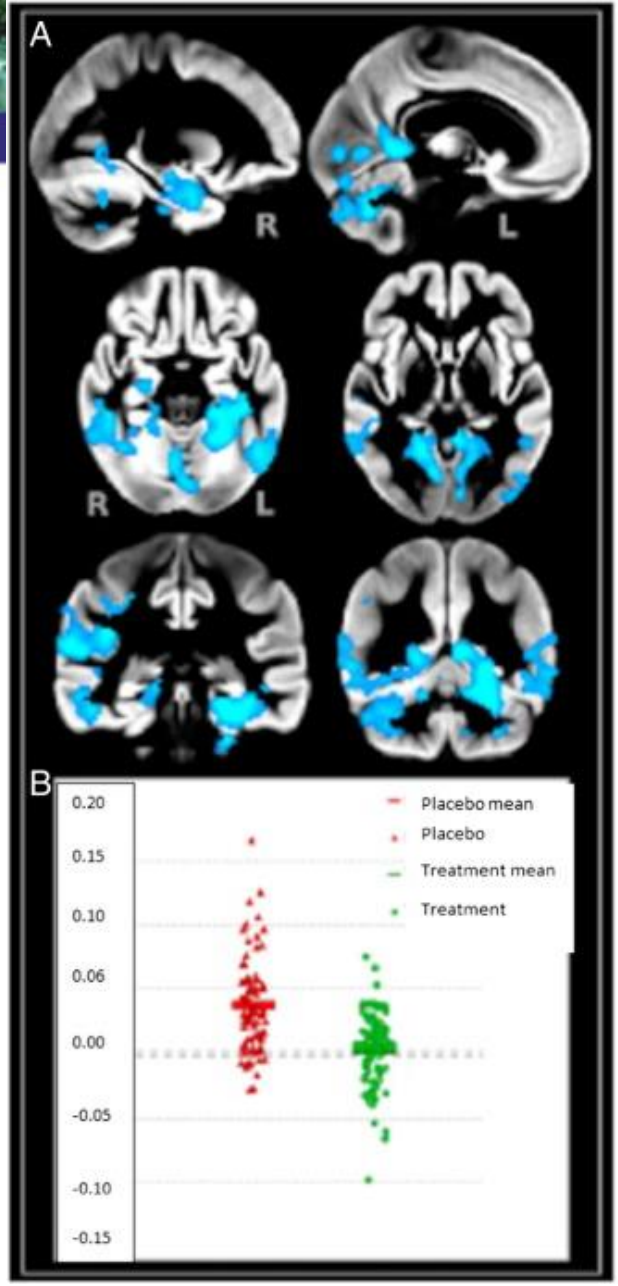
- 4-year intervention
- 447 initially cognitive normal
- Average age 66.9
- Olive oil (1L/week)
- Walnuts (15g), hazelnuts 7.5 g), almonds (7.5g)/day

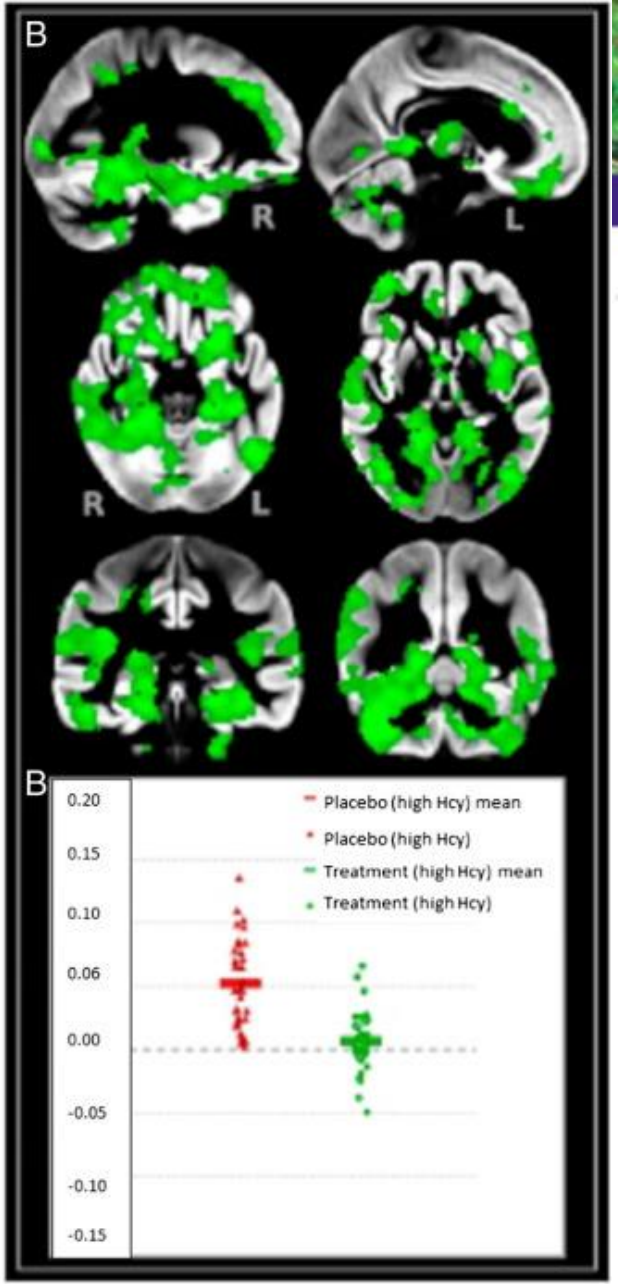


Valls-Pedret C, Sala-Vila A, Serra-Mir M, et al. Mediterranean Diet and Age-Related Cognitive Decline: A Randomized Clinical Trial. JAMA Intern Med. 2015 Jul;175(7):1094-1103 PMID: 25961184

B12 Critical!

- Measuring serum B12 alone is not sufficient
- Must measure functional markers of B12 adequacy such as methylmalonic acid & homocysteine
- 1,000 ug/d
- Methyl and adenosyl B12





Spence JD. Metabolic vitamin B12 deficiency: a missed opportunity to prevent dementia and stroke. Nutr Res. 2016 Feb;36(2):109-16 PMID: 26597770

Sauna Dose-Dependent Decrease in Neurological Disease

- Sauna substantially decrease dementia

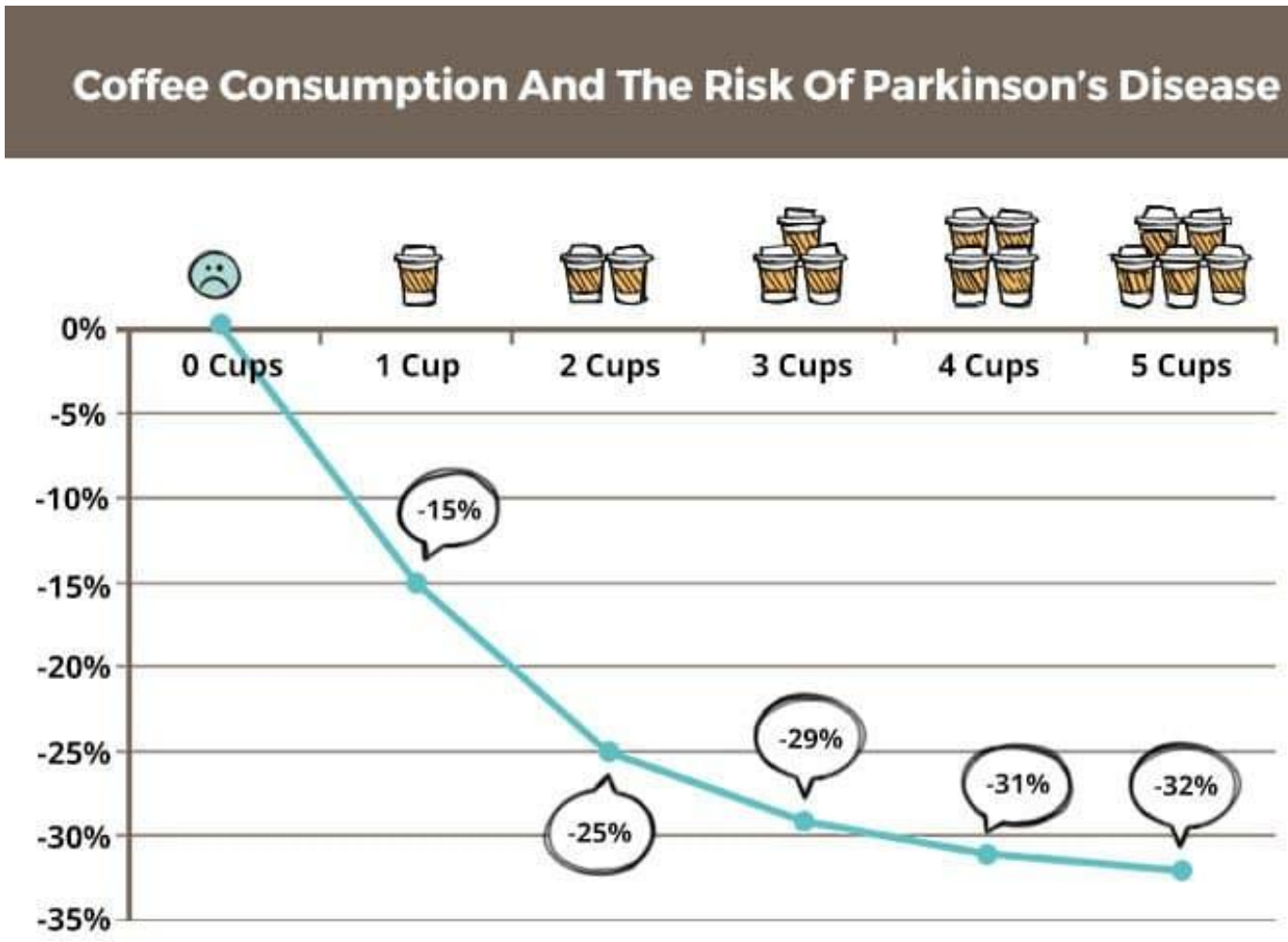
TABLE 61.2 Hazard Ratios of Finnish Males (Aged 42–60 Years of Age at Beginning of Study) for Dementia and Alzheimer's Disease Based on Their Sauna Frequency Over 20+ Years Follow-Up

Disease	Sauna 1 × Weekly	Sauna 2–3 × Weekly	Sauna 4–7 × Weekly
Dementia	1	0.78	0.34
Alzheimer's	1	0.80	0.35

Data from Laukkanen, T., Kunutsor, S., Kauhanen, J., & Laukkanen, J. A. (2017). Sauna bathing is inversely associated with dementia and Alzheimer's disease in middle-aged Finnish men. *Age and Ageing, 46*(2), 245–249.

Coffee?

- Many studies have shown inverse correlation between coffee consumption and PD
- Phenols as important as caffeine



https://www.homegrounds.co/15-research-backed-health-benefits-of-coffee/ (accessed 2020-03-20

Marital Status and AD

- 3,675 non-demented individuals - married, divorced, widowed, never married (at outset of study)
- Followed up at 1, 3, and 5 years
- RR = 2.31 never married vs married

Helmer C, et al. Marital status and the risk of Alzheimer's disease. Neurology 1999;53:1953-8

Natural Therapies Effective in AD

- B-vitamins, esp B1, B12
- Zinc (most older adults <50% of RDI)
- Phosphatidylcholine & phosphatidylserine
- Acetyl-l-carnitine
- DHEA
- Melatonin

Nowicki J. Alzheimer's Disease. In Pizzorno J, Murray M. *Textbook of Natural Medicine*. Elsevier 2020

Parkinson's Disease

- Worst neurotoxins: MPTP, permethrin, paraquat, maneb, 4-dichlorophenoxyacetic acid, solvents, rotenone (?natural pesticide?)
- Main nutrient deficiencies: vitamin D
- Key interventions:
  - Food sources of L-dopa: fava beans (100g = 250 mg) (must rule out G6PD deficiency)
  - CoQ10: 250 mg/d
  - IV reduced NADH: 25-50 mg/d (IM not as effective)
  - Intranasal and IV glutathione: 25mg bid
  - *Mucuna puriens* (velvet bean): early animal research (L-dopa removed) shows substantia nigra regeneration

Summary

Control Causes

- Avoid neurotoxins
- Normalize sugar regulation
- Inflammation control
- Stress reduction
  - Spouse/significant other
  - Sleep
- Caloric restriction

Intervention

- Anti-inflammatories
- Ginkgo biloba
- Hyperhomocysteinemia
  - B6 (P5P)
  - Folate (BH4)
  - B12 (methyl & adenosyl)
- Cerebral glutathione
  - NAC
- Mitochondrial function
  - CoQ10
  - PQQ