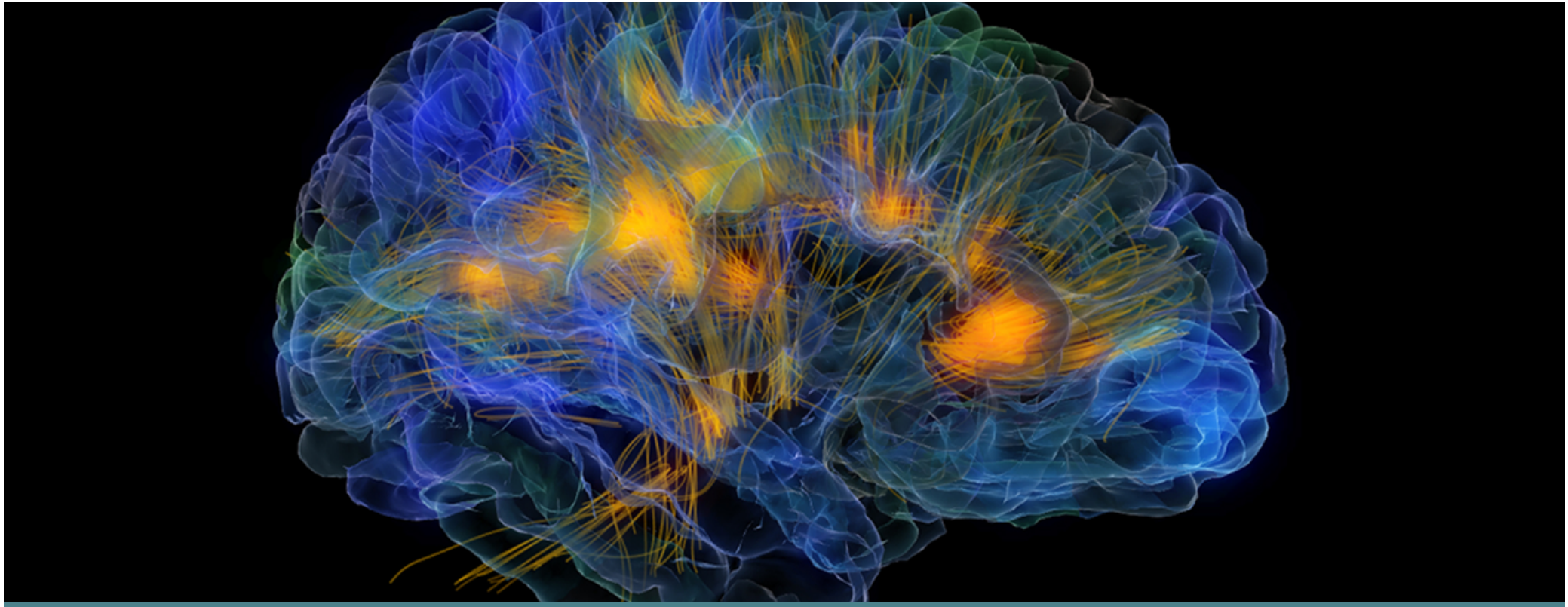


Cognitive decline, dementia, and Parkinson's disease: Environmental contributors and potential pathways to prevention

CHE Webinar, January 2020

Samuel M. Goldman, MD, MPH
Professor, UCSF Division of Occupational & Environmental Medicine
& Department of Neurology

PEHSU Pediatric Environmental Health Specialty Units

Environmental Risk for Neurodegenerative Disease

COGNITIVE DECLINE Sam's Story

Sam tells George what's been going on with him forgetting things and missing appointments. Sam says he doesn't know what could be causing these problems but that he knows he's kind of let himself go since his wife died. George says he understands how that can happen.

"George, did your doctor tell you what could have caused your disease?" asks Sam.

"He told me it could be any number of things, from exposure to environmental chemicals such as pesticides to head trauma to genetics, or even some combination of them," says George.

Sam shakes his head.

"I don't think I was exposed to pesticides but apparently they are used everywhere," says George. "A lot of my neighbors spray their lawns all the time."

"Yes, I see that too," says Sam." Well, George, I have to get going, says Sam. "Take care, I'll stop by again soon."

Environmental risk factors for Parkinson's disease

Ref: Goldman/Tanner chapter in Jankovic, 2014

Twins & Parkinson's: Nature's Experiment

Tanner, Goldman, et al, JAMA 1999

NAS/NRC WWII
VETERAN TWINS ROSTER
31,848 TWINS BORN 1917 - 1927

- Identical twins share 100% of genes
- Fraternal twins share ~ 50% of genes

Hypothesis:

If PD is primarily a genetic disorder, MZ concordance should be >> DZ concordance

Results:

Similar concordance in MZ & DZ twin pairs
Heritability ≤ age 50 ~100%
Heritability > age 50 only 7%

Conclusions:

- Environment is a major contributor to the cause of typical PD
- 13% concordance in DZ twins is 3x higher than other 1st-degree relatives: shared early environment!

Pesticides & Parkinson's Disease

A Story of Health

COGNITIVE DECLINE Sam's Story

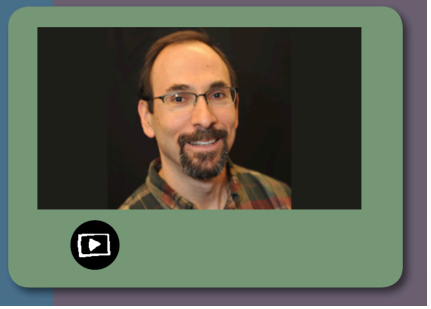
Pesticides and Parkinson's Disease

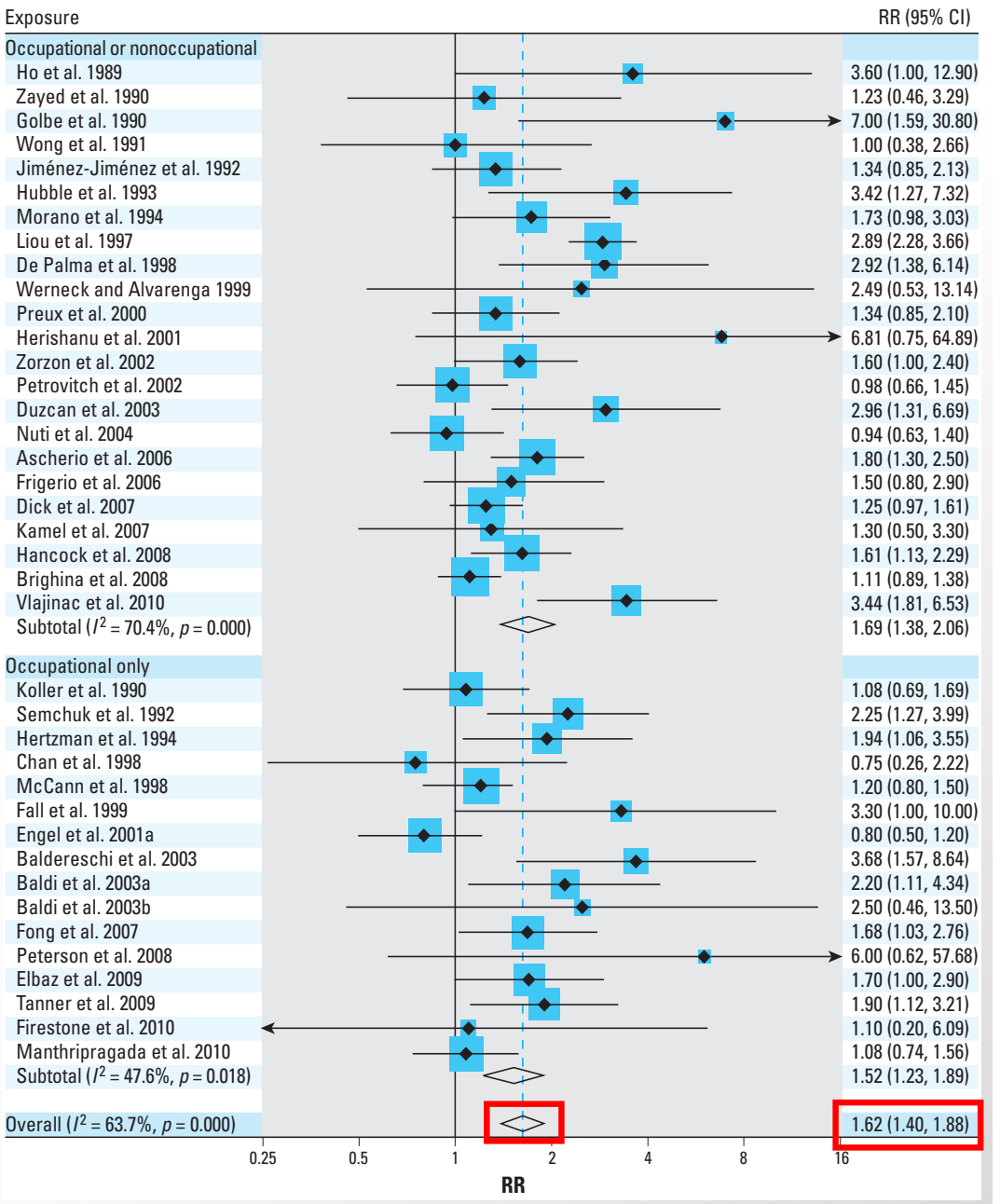
- Many epidemiologic studies find that pesticide use/exposure is associated with an increased risk of Parkinson's disease, although exposure levels are usually difficult to assess. Meta-analyses of data from ~50 studies found 60-70% increased risk, although risk varied considerably among the individual studies (van der Mark, 2012; Pezzoli, 2013).
- Because many people don't know which specific pesticides they may have been exposed to, individual agents have been infrequently studied. Nonetheless, a more than doubling of Parkinson's disease risk has been associated with the insecticide rotenone (Tanner, 2011), the herbicide paraquat (Tanner, 2011; Gatto, 2009), and with several organochlorine insecticides (Elbaz, 2009; Fitzmaurice, 2014), among others (Goldman, 2014).
- These findings are biologically plausible since studies in tissue models and in laboratory animals (predominantly rodents) show that many pesticides damage dopaminergic neurons in the striatal region of the brain, a primary area involved in the pathology of Parkinson's disease (Uversky, 2004; Baltazar, 2014). In fact, several of these compounds (e.g., rotenone, paraquat) are used to produce animal models of Parkinson's disease, because they so closely reproduce the pathological and clinical features of the disease (McCormack, 2002; Cannon, 2009).
- Studies in rodents also show that prenatal or early life exposures may be particularly important, and may increase sensitivity to these same chemicals later during adult life (Barlow, 2004; Nasuti, 2017).

For more info:
USDA Agricultural Chemical Use Program

Watch: Pesticides and Parkinson's disease

Samuel M. Goldman MD, MPH, University of California, San Francisco, Division of Occupational and Environmental Medicine and Department of Neurology, Co-Director PEHSU Region 9





Van der Mark et al, EHP, 2012

Parkinson's in the Agricultural Health Study

Tanner, Kamel Goldman, et al, EHP, 2011

- Professional pesticide applicators (mostly farmers) & spouses
- Asked about use of 31 specific pesticides
- Very good historians!
- Only 2 pesticides were significantly associated with PD

Pesticide	PD Risk	P-value
Rotenone	2.8	0.005
Paraquat	2.5	0.004

	Paraquat	Rotenone
Mitochondrial poison	+	+
Oxidative stress	+	+
Generates an animal model	+	+
Nigrostriatal injury	+	+

Pesticides & Dementia

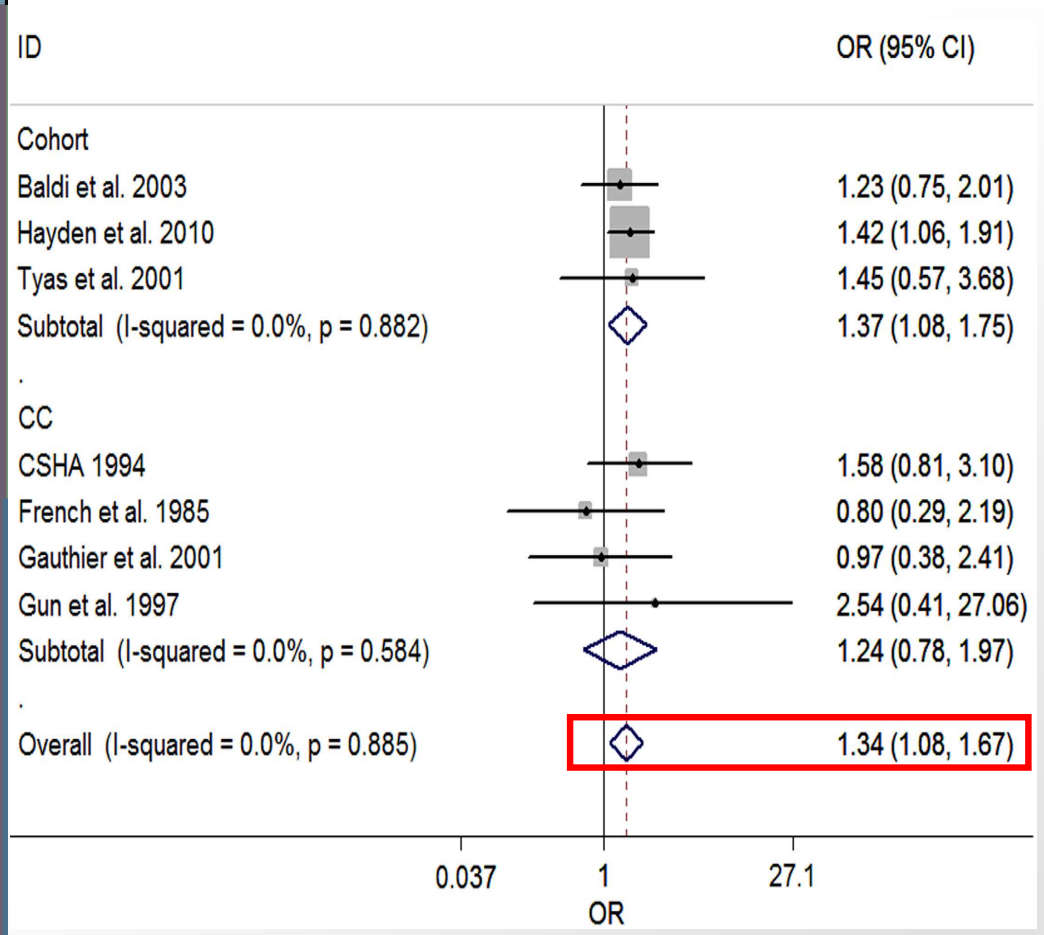
A Story of Health

COGNITIVE DECLINE Sam's Story

Pesticides and cognitive decline/ dementia

- Despite challenges in quantitative exposure assessments, a growing number of studies link pesticide exposure to cognitive dysfunction and dementia, including Alzheimer's disease.
- A review of 14 studies (6 prospective cohort, 7 case-control, 1 ecologic) evaluated the association of pesticide exposure with cognitive and neurobehavioral performance, cognitive dysfunction, Alzheimer's disease, frontotemporal lobe dementia, vascular dementia and Parkinson's disease dementia (Zaganas, 2013). Three studies of cognitive function each reported poorer performance associated with a history of pesticide exposures. Five of seven studies of Alzheimer's disease reported a significantly increased risk with a history of pesticide use (OR or RR 1.42-4.35). Three studies also showed an increased risk of vascular dementia (OR 2.05; 2.6) or PD-dementia.
- In a more recent study of 430 older Mexican Americans from the Sacramento Area Latino Study on Aging, those who were exposed to higher levels of organophosphate pesticides beginning five years prior to assessment, as determined by residential proximity to agricultural fields where pesticides were applied, experienced faster cognitive decline and higher mortality over a follow-up period of nine years (Paul, 2018).

Watch: Pesticides and Alzheimer's disease
Samuel M. Goldman MD, MPH, University of California, San Francisco, Division of Occupational and Environmental Medicine and Department of Neurology, Co-Director PEHSU Region 9

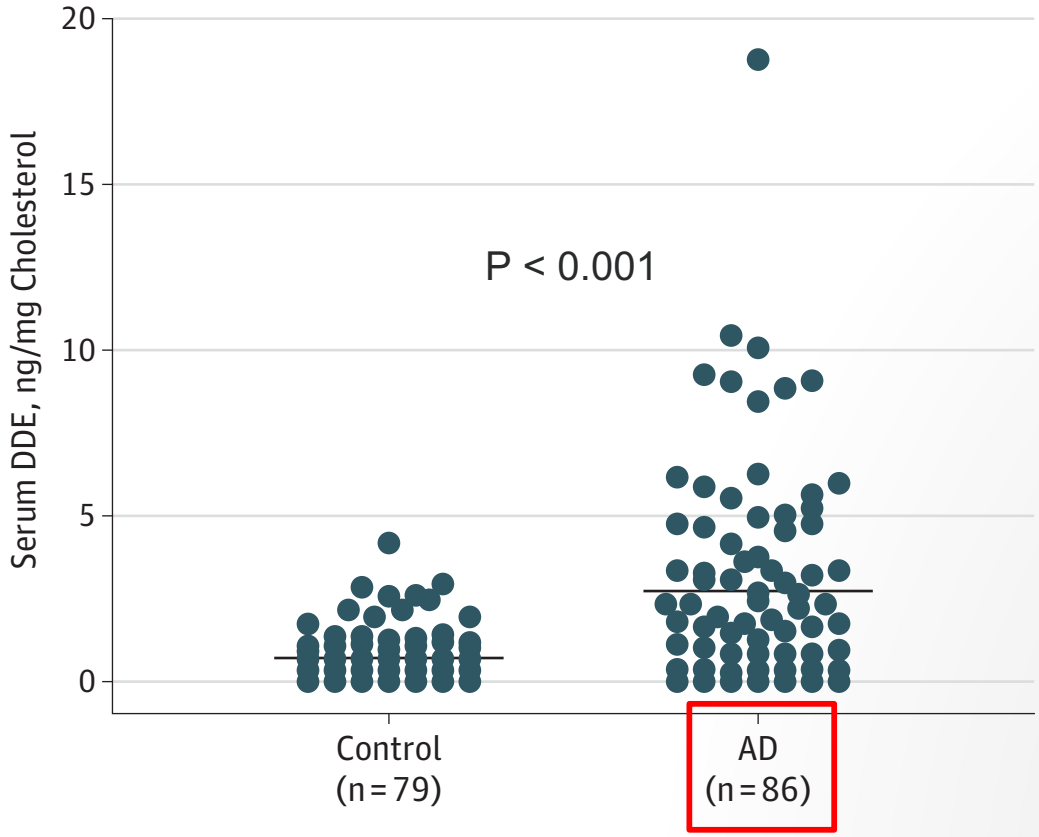


Yan et al, Scientific Reports, 2016

Pesticides & Alzheimer's Disease

- Richardson et al, JAMA Neurol, 2014
- DDT's primary metabolite DDE is highly persistent ($t_{1/2}$ ~10 years)

Figure 1. Serum Levels of Dichlorodiphenyldichloroethylene (DDE)



Those in the highest third of DDE levels had a 4-fold increased risk of Alzheimer's

Early Life Pesticide Exposures & Cognition

- CHAMACOS study (Gunier et al, EHP, 2017)
  - Salinas Valley, California
  - Pesticide application data mapped to mother's residence during pregnancy
  - Lower IQ at age 7

	Full-Scale IQ ($n = 255$)		Verbal Comprehension ($n = 283$)	
Neurotoxic pesticides	β	(95% CI)	β	(95% CI)
OPs	–2.1	(–3.8, –0.3)	–2.5	(–4.1, –1.0)**
Acephate	–2.3	(–3.9, –0.6)**	–2.7	(–4.3, –1.2)**
Chlorpyrifos	–1.4	(–3.0, 0.2)	–2.2	(–3.7, –0.7)**
Diazinon	–1.7	(–3.4, 0.1)	–1.6	(–3.2, –0.1)*
Malathion	–0.8	(–2.5, 0.8)	–1.3	(–2.8, 0.2)
Oxydemeton–methyl	–2.3	(–4.0, –0.7)**	–2.8	(–4.3, –1.3)**
OPs toxicity weighted	–2.2	(–3.9, –0.5)**	–2.9	(–4.4, –1.3)**

Gene * Environment Interaction

COGNITIVE DECLINE Sam's Story

Finally, Dr. Todd tells Sam and Lisa that everything she has seen so far is consistent with mild cognitive impairment, perhaps related to Sam's depression.

She tells Sam she wants to see what the additional tests show and see him again in two months.

She also says she is happy to refer him to the environmental health clinic as he might be eligible for benefits because of his exposures during his time in the military.

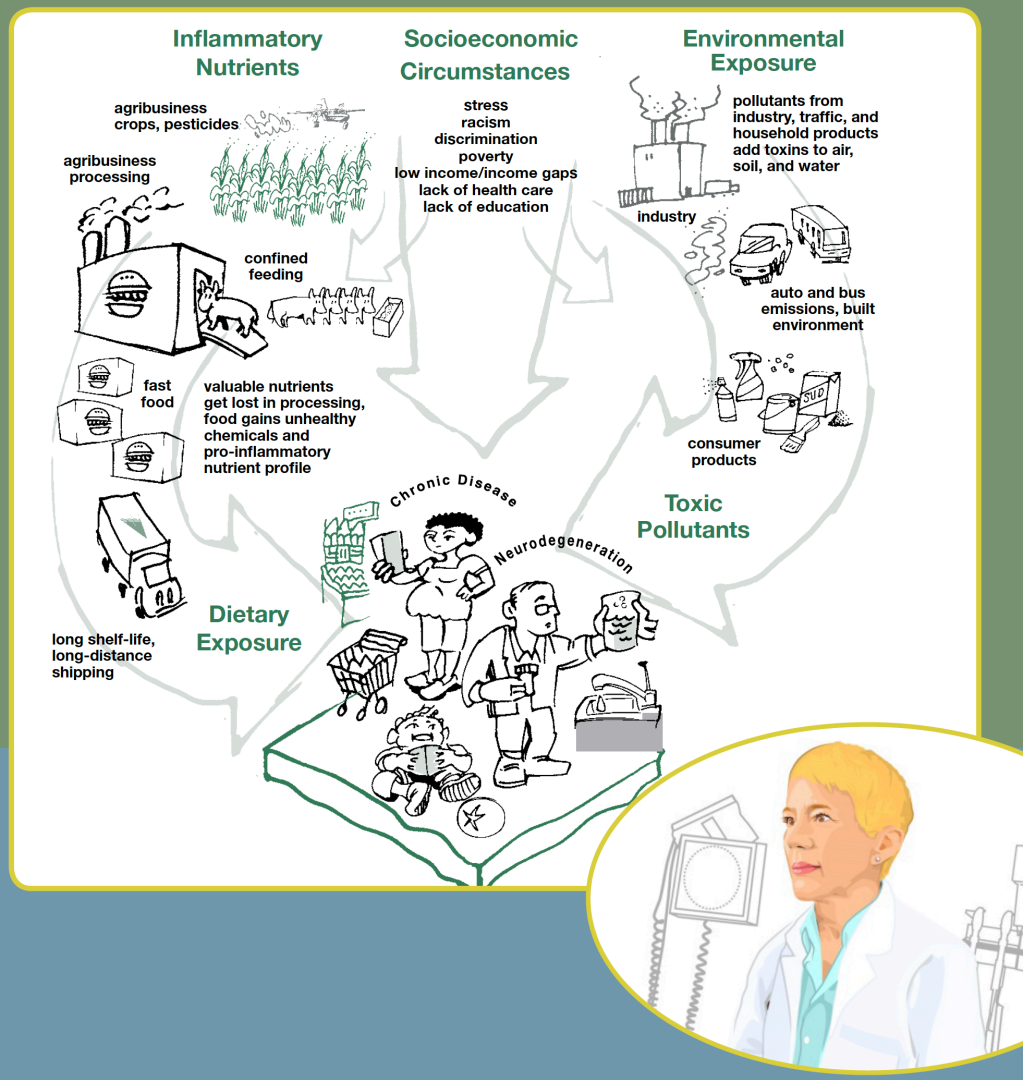
Sam says he'll think about that.

Sam asks Dr. Todd what causes cognitive decline or diseases like Alzheimer's. Dr. Todd says it's different for every individual but it is usually a complex interaction of environmental and genetic factors.

Key Concept: Gene-environment interactions

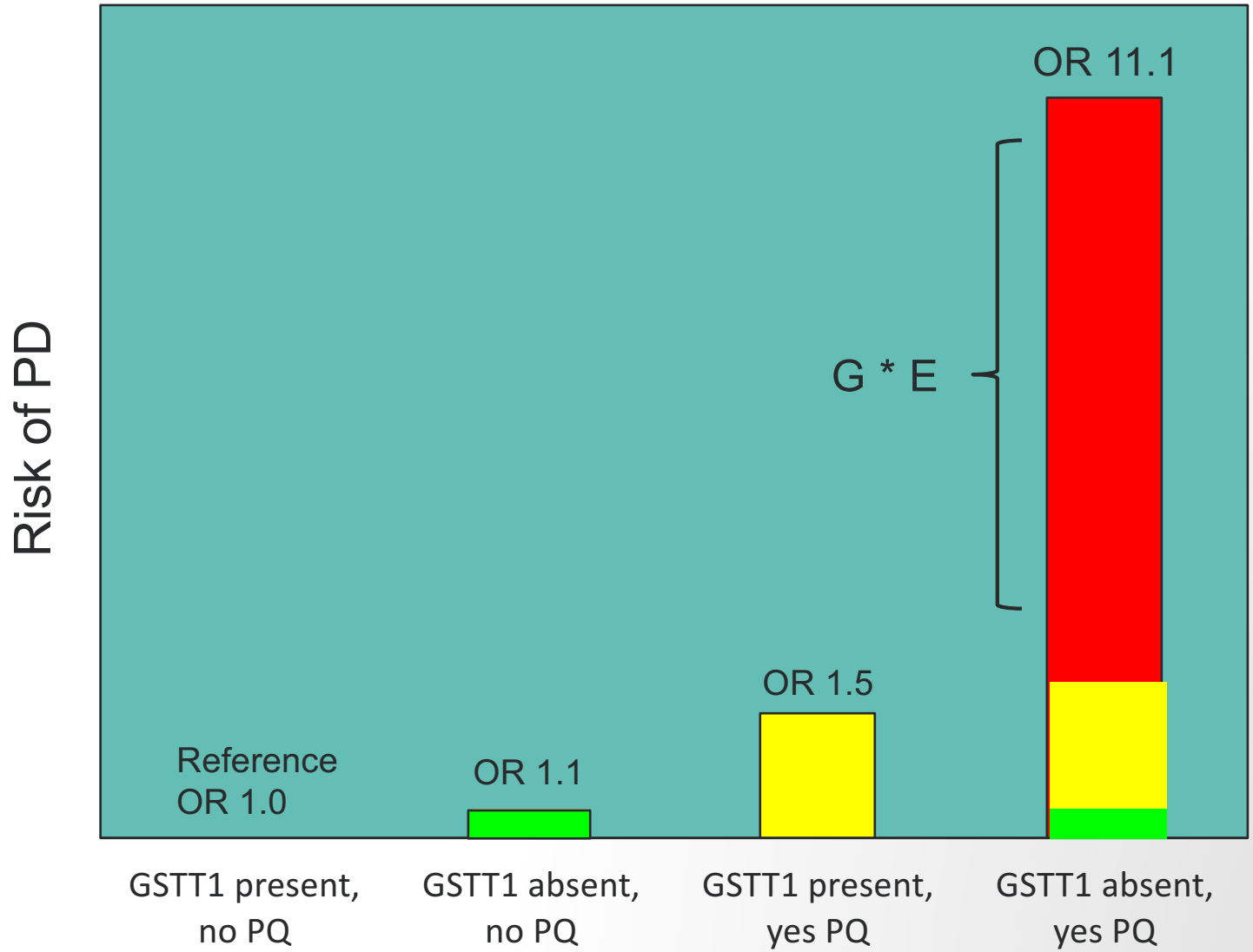
Enlarge graphic

A complex interaction of environmental and genetic factors



Gene * Environment interaction:

Risk of PD from paraquat exposure in pesticide applicators with a common genetic variant



Solvent Exposures & Parkinson's Disease

Acute solvent intoxications can cause cognitive impairment and parkinson*ism:*

- methanol
- n-hexane (Pezzoli et al, 1989)
- hydrocarbon and solvent mixtures

BUT, associations with idiopathic **PD**

are *not* consistent

TCE (trichloroethylene)

Gash et al, Ann Neurol, 2008

- industrial plant metal degreasing
- PD in 3 co-workers ≥ 25 years exposure
- mild parkinsonian signs/symptoms in others

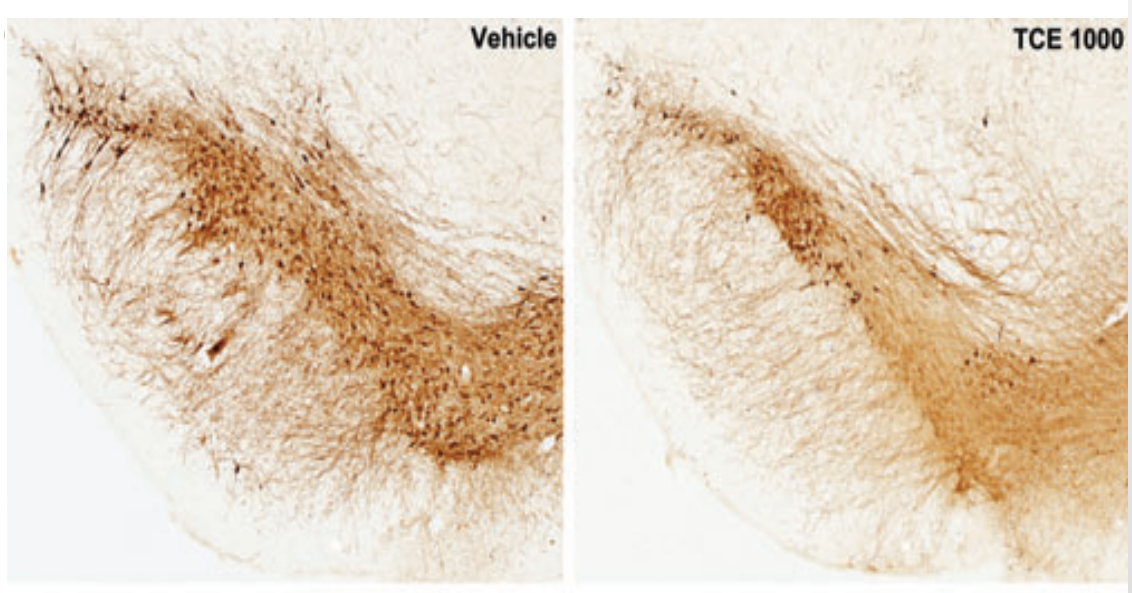
- **Common exposures since the 1920s**
  - Degreasing metal parts (85%), computer circuits
  - Dry-cleaning
  - Surgical anesthetic (until 1977)
  - Decaffeinated coffee (until 1977)
  - Typewriter correction fluids, adhesives, paints, carpet cleaners, spot removers…..
  - **Most frequently reported organic contaminant in groundwater (e.g. Camp Lejeune)**

Occupational Solvent Exposures in PD-discordant twins *Goldman et al, Ann Neurol, 2012*

Of all the solvents we studied, 2 were associated with PD risk

Compound	Odds ratio	p-value
TCE	**6.1**	**0.034**
PERC	**10.5**	**0.053**

In a rat model, oral TCE causes selective degeneration of dopaminergic neurons in substantia nigra



Liu, et al, J Neurochem 2010

Air Pollution & Dementia

Proximity to roads in Canada

Chen et al, 2017, Lancet

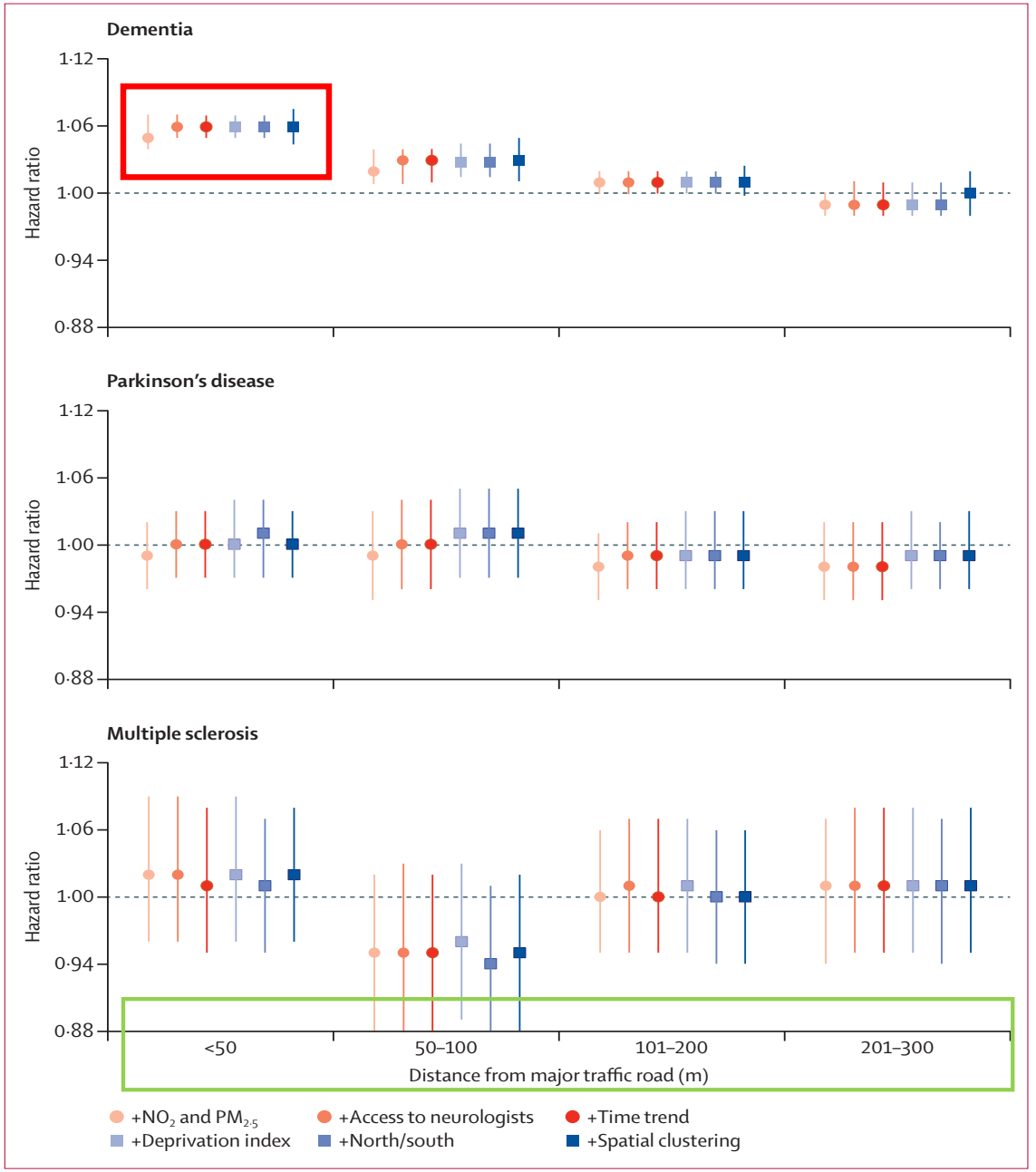
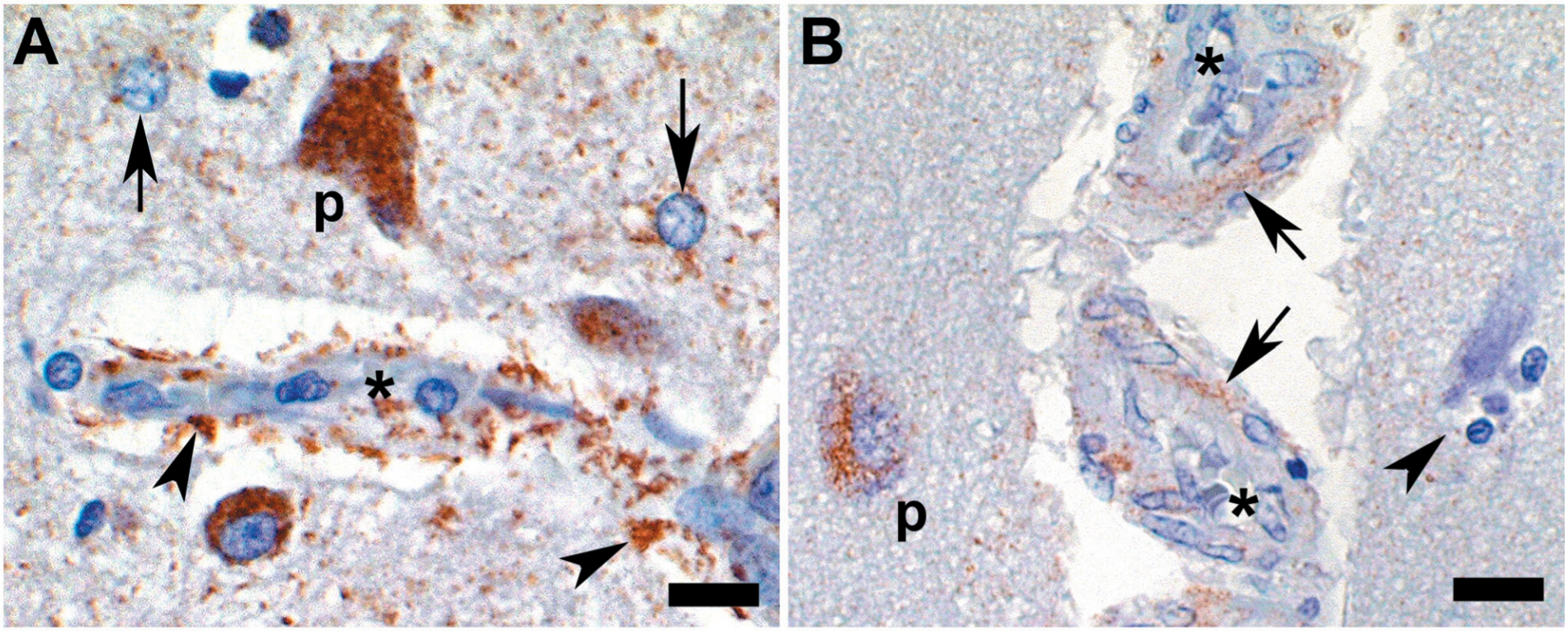


***Figure 1*: Estimated associations between residential proximity to major roadways in 1996 and the risk of incident dementia, Parkinson's disease, multiple sclerosis in Ontario, 2001–12**
Measured by six sensitivity analyses to further control for potential confounding factors. Model further adjusted for exposure to NO_2 and $PM_{2.5}$ access to neurologists, time trend, deprivation, an indicator for North/South Ontario, and a frailty term to account for potential spatial clustering.

Alzheimer's & Air Pollution

Air pollution & Aβ42 accumulation in cognitively normal residents of Mexico city

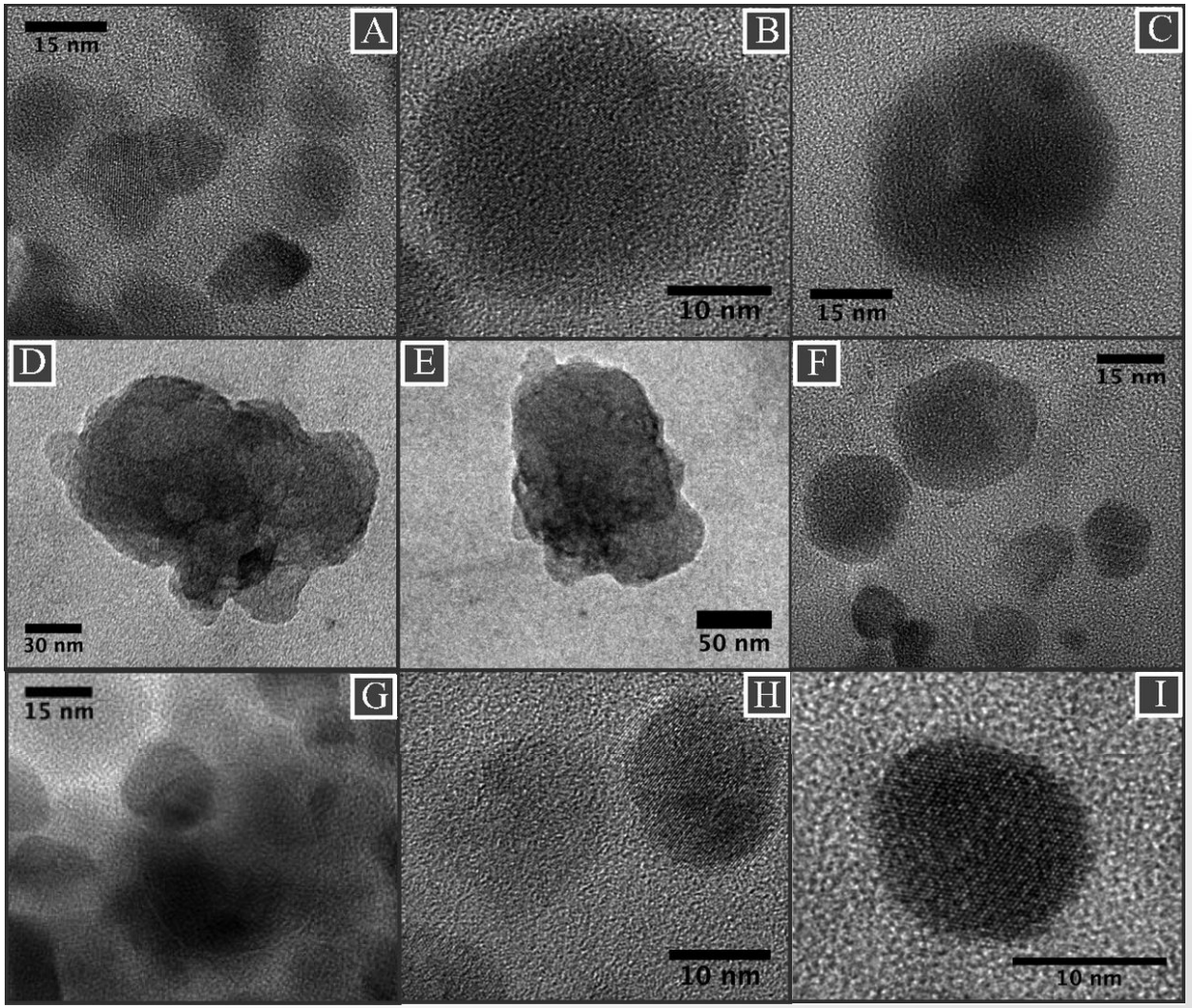


Calderon-Garcideunas 2004, Toxicol Pathol

Air Pollution: ultrafine “nano”particles (< 100nm)

Maher et al, PNAS, 2016

- Autopsy series in Manchester, England and Mexico City
- Magnetite nanoparticles likely from traffic-related combustion
- Direct cortical access via olfactory bulb
- Association with plaques & tangles



Scanning electron micrograph of magnetite particles extracted from frontal cortex

Traumatic Brain Injury & Neurodegenerative Disease

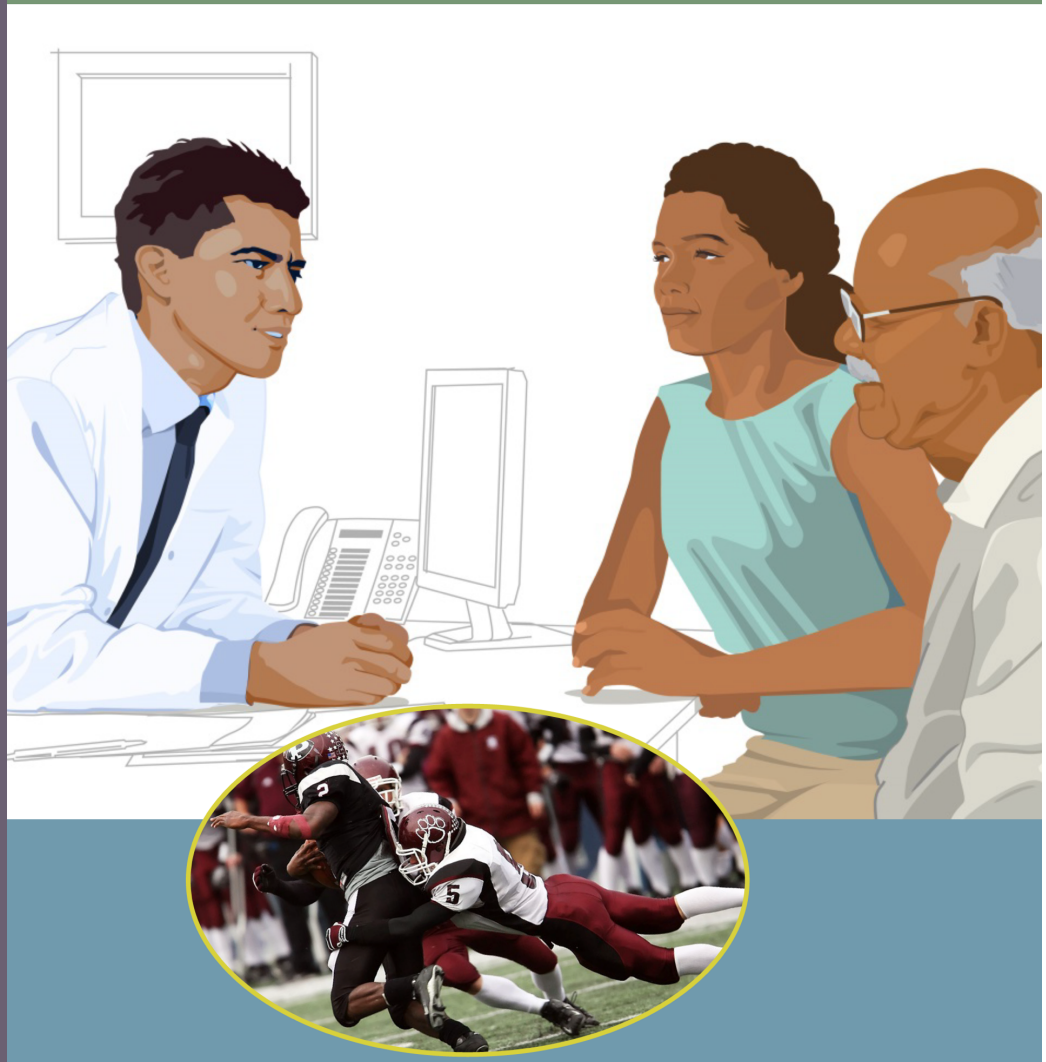
COGNITIVE DECLINE Sam's Story

Dr. Gomez then asks if Sam ever played football.

Sam says he played in high school but never had any unusual injuries.

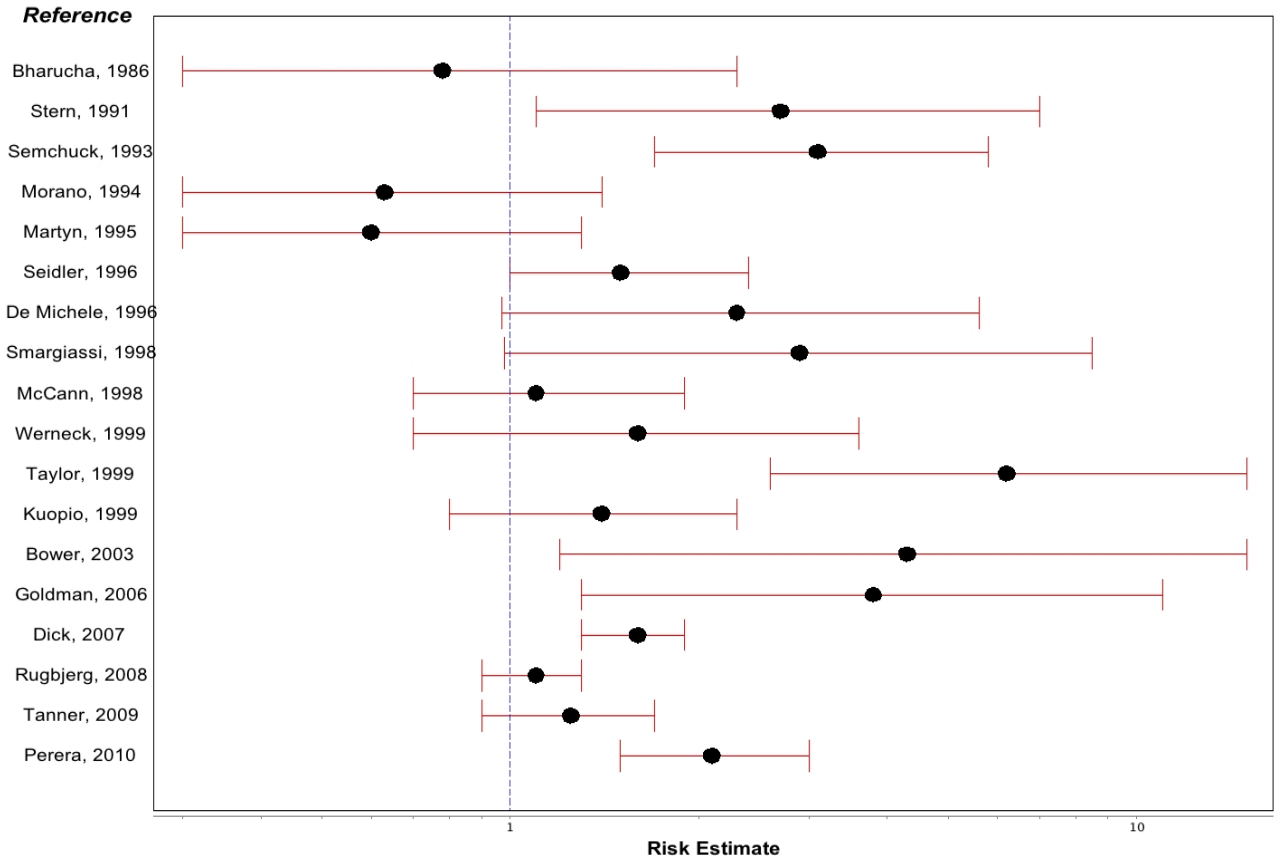
Lisa says she's read a lot about football head injuries because her son wants to play and she is concerned.

- Sports injuries/ concussions and cognitive impairment
- Mild Head Injury in Twin Pairs Discordant for Parkinson's Disease
- Head Injury and Parkinson's Disease: Odds Ratios, 95% CI
- Head Injury diagram

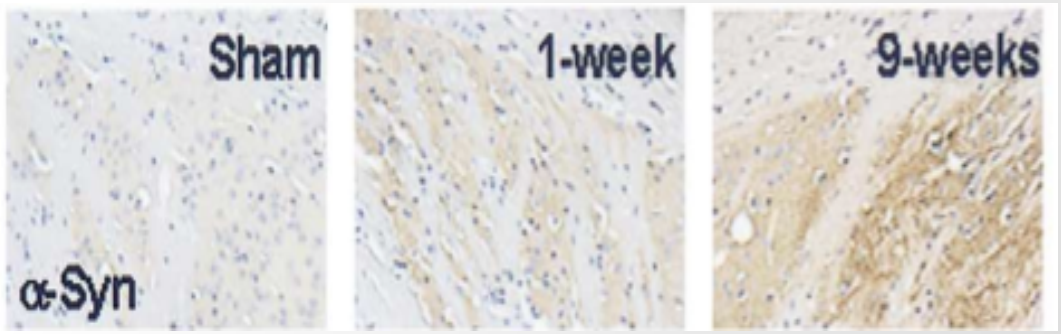


Head Injury & Parkinson's Disease

Human epidemiology is mostly consistent



Mouse model of TBI: increased α-synuclein in striatum



Uryu, et al, Experimental Neurol, 2003

Chronic Traumatic Encephalopathy

- “punch drunk” syndrome: Martland, 1928
- “*dementia pugilistica*”: Millspaugh, 1937
- “CTE”: Critchley, 1949
- Renewed interest after Omalu report of CTE in NFL player
- A progressive neurodegeneration associated with repetitive head trauma and associated cognitive and behavioral syndrome

CTE: Clinical Features & Risk Factors

Pathology

- Generalized cortical atrophy & **tauopathy**, differs from AD distribution

Epidemiology

- Incidence not well-established
- Case reports, small case series, highly selected autopsy series
- Often coexists with AD, FTD, PD
- Case definition continues to evolve

Taking An Occupational & Environmental History

COGNITIVE DECLINE Sam's Story

Dr. Gomez also asks about Sam's work history.

Sam says he worked as a house painter for many years and then started an auto body shop that is now managed by his son Jessie.

Sam explains that he used to go to the shop every day to help Jessie. Now he mainly goes in for coffee a few times a week and visits the shop much less.

Lisa tells Dr. Gomez that Sam was a pioneer in retrofitting his body shop to prevent community pollution as well as to prevent employee exposures to toxicants, in conjunction with a local neighborhood initiative.

Business interventions:
Reducing pollution from auto body shops, other industries in Boston area

Local organizing for healthy communities

npr

Listen:
NPR: California Nail Salons Start to Invest in Worker Safety

TURI
TOXICS USE REDUCTION INSTITUTE
UMASS LOWELL

For more info:
The MA Clean Auto Repair Guide

Watch: Safe Auto Shops Project
Tiffany Skogstrom, formerly with the Boston Public Health Commission

Local organizing resources:

- Dudley Street Neighborhood Initiative
- Alternatives for Community and Environment
- Urban Environmental Infrastructure in Boston: Case Study

Business interventions resources:

EPA:

- Clean Air Act Partnership programs
- Reducing pollution from auto body shops
- MA Toxics Use Reduction Institute
- California Healthy Nail Salon Collaborative

Taking an Exposure History

"When a doctor arrives to attend some patient of the working class. . . let him condescend to sit down. . . if not on a gilded chair. . . on a three-legged stool. . . . He should question the patient carefully. . . . So says Hippocrates in his work 'Affections.' I may venture to add one more question: What occupation does he follow?" *Bernardino Ramazzini*

Completeness of Information Gathered by Physician

Category	Percent of Records Containing Information
Gender history	99.9
Age history	99.1
Smoking history	76.0
Cancer history	42.9
Occupational history	27.8

Politi, et al, J Occup Env Med, 2004

Lifetime history

- All occupations
- Industry
- Specific job tasks, processes
- Products produced?
- Compounds, materials
- Protective equipment?
- Ever ill? Others ever ill?
- Military history: asbestos, lead, solvents, pesticides…
- Hobby history
- Household exposures: pesticides…

SOME FINAL THOUGHTS

COMMON THEMES

Although the fictional narratives in *A Story of Health* describe the lives of children and adults with different conditions and diseases – infertility, asthma, developmental disabilities, childhood leukemia and cognitive decline - common themes resonate. They include:

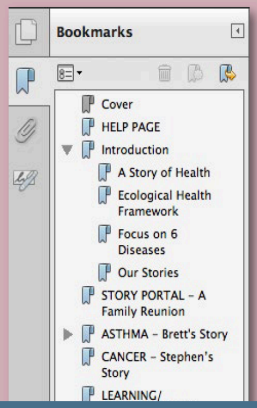
- Important environmental influences come from the natural, chemical, food, built, and social environments.
- Although there are exceptions, most diseases as well as good health are the result of complex interactions among multiple environmental influences and genetics.
- Early-life experiences, particularly during critical windows of development, can have profound beneficial or detrimental lifelong effects, even into elder years.
- Healthy people and healthy communities are interdependent. All people do not have equal access to nutritious food, clean air and water, safe workplaces, healthy housing, green spaces, peaceful neighborhoods or quality health care.
- Preventing disease and promoting health require actions and commitments from the individual, family, community and society. Health promoting public policies are necessary to make healthy living available to all people.

Watch: Samuel L. Goldman MD MPH's Summary: Opportunities for prevention

Samuel L. Goldman MD MPH, University of California, San Francisco, Division of Occupational and Environmental Medicine and Department of Neurology, Co-Director PEHSU Region 9

Resources

We have linked to many useful resources in each story relevant to a wide range of audiences, including clinicians. To quickly access resources on specific topics in each story, use the **Bookmarks** toolbar on the left (which you can open or close), or return to the **Help page** for more details on other eBook features.



Additional resources to help prevent disease and promote health:

Portal to Toxicant and Disease Database: A searchable database that summarizes links between chemical contaminants and approximately 180 human diseases or conditions.

Portal to Science Resources: Hundreds of additional resources on environmental health including organizations, publications, videos and more.

Pediatric Environmental Health Toolkit application for mobile devices

Approaches to Healthy Living: A 4-page guide on how to avoid toxicants, eat healthier, reduce stress.

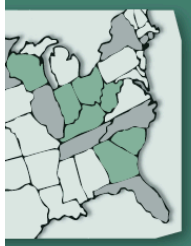
Healthy Aging: The Way Forward: An ecological approach to policy level interventions for healthy aging across the lifespan.

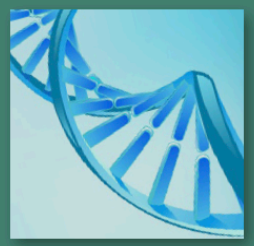
Continuing Education

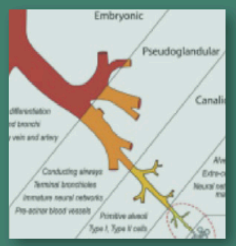
Register for Continuing Education (CE) for *A Story of Health* for a variety of health professions. Free credits are offered by the Centers for Disease Control and Prevention/Agency for Toxic Substances and Disease Registry at this link.

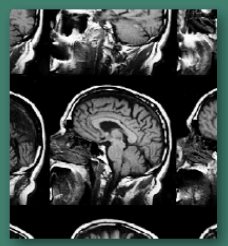
Another free CE course on environmental health offered by the CDC/ATSDR is the **Pediatric Environmental Health Toolkit** online course.

A Story of Health









A Story of Health

COGNITIVE DECLINE Sam's Story

Sam is a 72 year-old widower from the "Baby Boom" generation who grew up and still lives in the Boston area.

His wife of over 40 years passed away last year. Since her death he has not been as social and doesn't see friends and family as much as he used to.

Sam's family is concerned that he is forgetting things more than usual and missing appointments. They wonder if this is just normal for someone his age or if there is something else going on with his brain function.

They don't want to insult him and wonder how to approach the topic with him.

- Demographic shifts in global population
- Are all countries aging at the same pace?