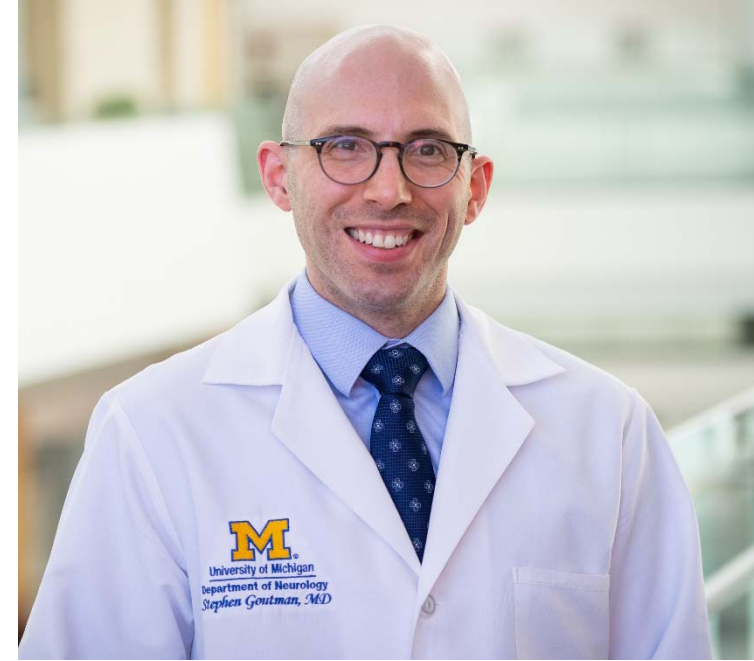




Stephen Goutman MD, MS
Associate Professor of Neurology

ALS Environmental Risk Factors

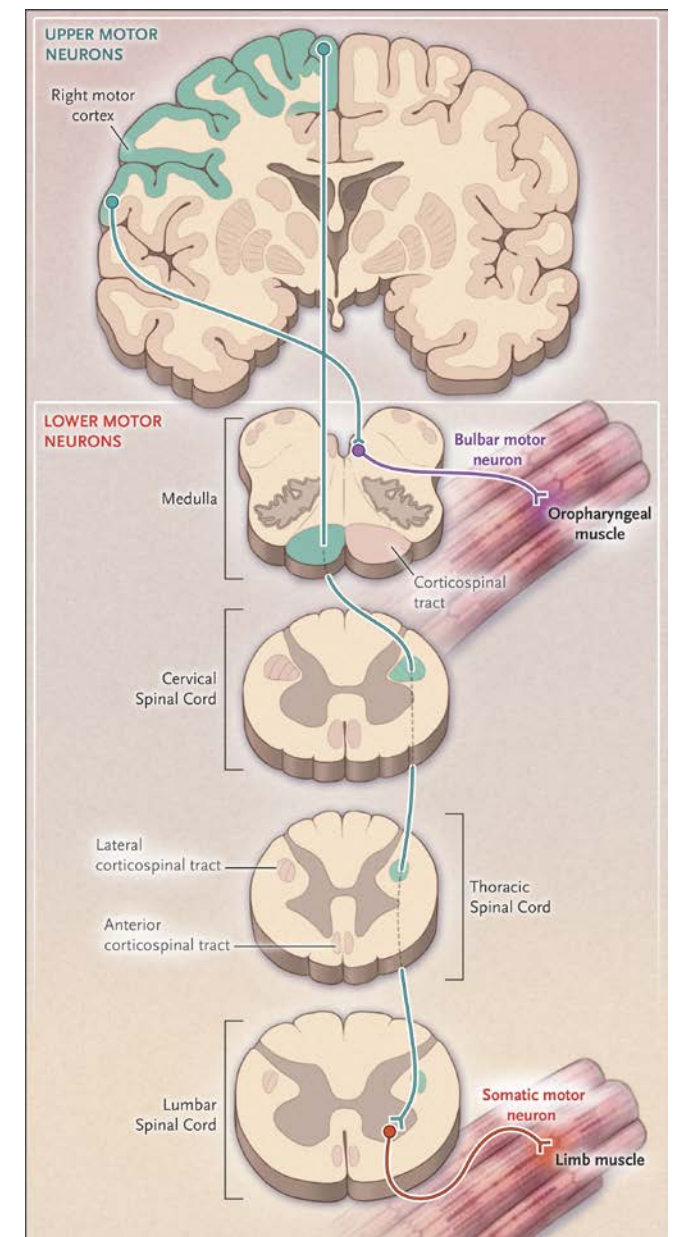
Eva L. Feldman, MD, PhD
Russell N. DeJong Professor of Neurology
Director, ALS Center of Excellence
No Disclosures

ALS Clinical/Research Teams



Amyotrophic Lateral Sclerosis (ALS)

- Progressive, degenerative disease of the motor neurons in the brain, brainstem, and spinal cord
- Non-curable
 - 2 FDA approved drugs that can slow disease
 - Riluzole
 - Edaravone
- Death results typically within 2-4/3-5 years of symptom onset
- Cause of death is typically respiratory related (respiratory failure w/wo pneumonia)



Brown, *NEJM*, 2017

ALS Global Incidence & Prevalence and Heritability

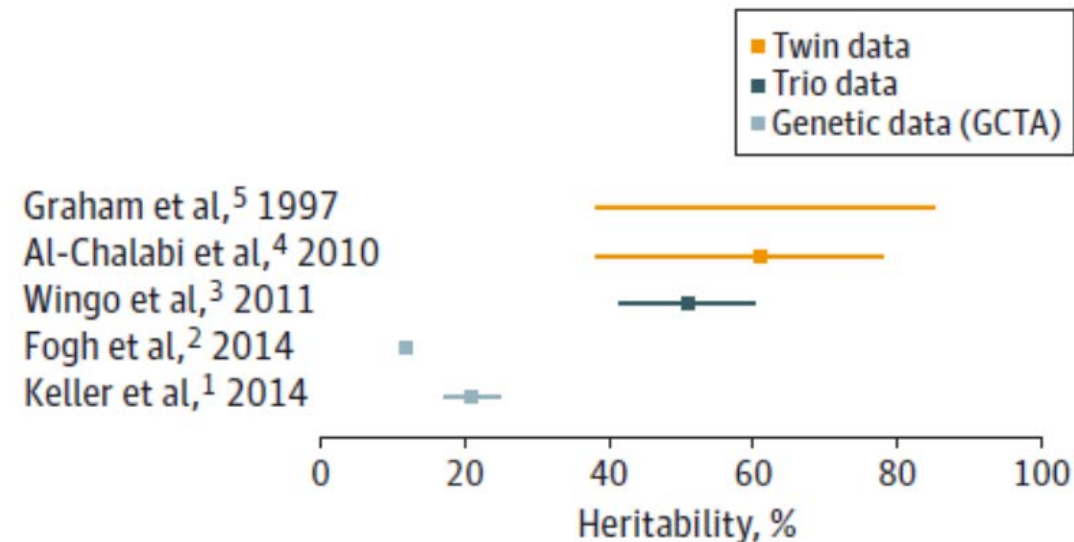
Incidence / 100,000

Region	Median	IQR
Europe	2.08	1.47-2.43
N. Amer	1.80	1.75-2.02
Asia	0.46	0.38-0.53

Prevalence / 100,000

Region	Median	IQR
Europe	5.40	4.06-7.89
N. Amer	3.40	3.15-3.65
Asia	2.01	1.48-2.54

Figure. Heritability Estimates in Amyotrophic Lateral Sclerosis



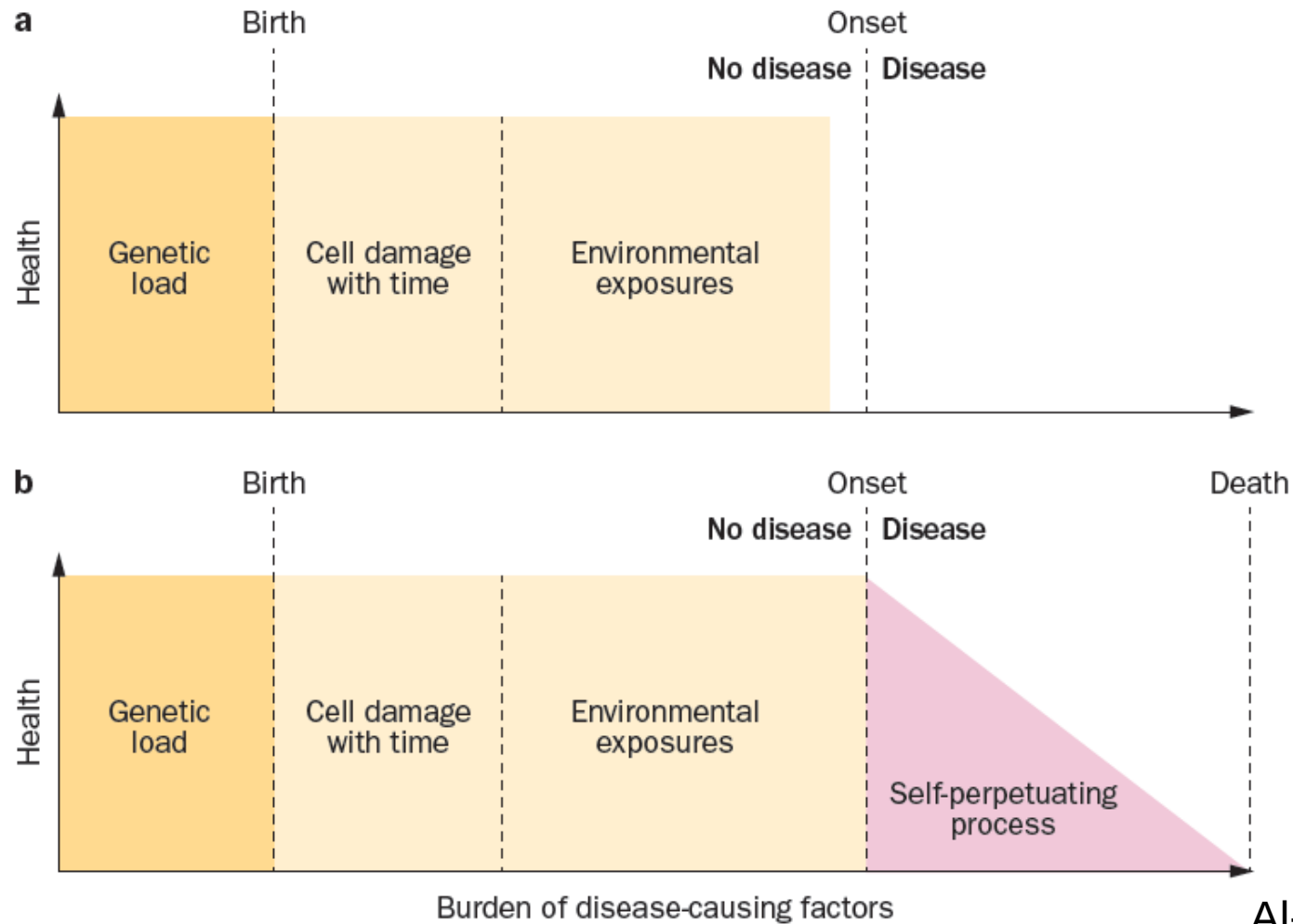
Point estimates, when provided by the study, are denoted by squares; horizontal bars indicate the error of the study (usually 95% CI). GCTA indicates genome-wide complex trait analysis.

Published ALS Environmental Risk Factors (Meta-analysis)

Risk Factor	Odds Ratio	95%CI	Case/Control (n/n)
Lead	1.72	1.33-2.23	1107/1433
Heavy Metals	1.69	1.13-2.52	352/454
Pesticides	1.48	1.18-1.86	2001/99,405
Agricultural Chemicals	3.08	1.43-6.63	143/207
Solvent Exposure	1.43	1.10-1.86	701/1286

Wang, Neurotoxicology, 2017

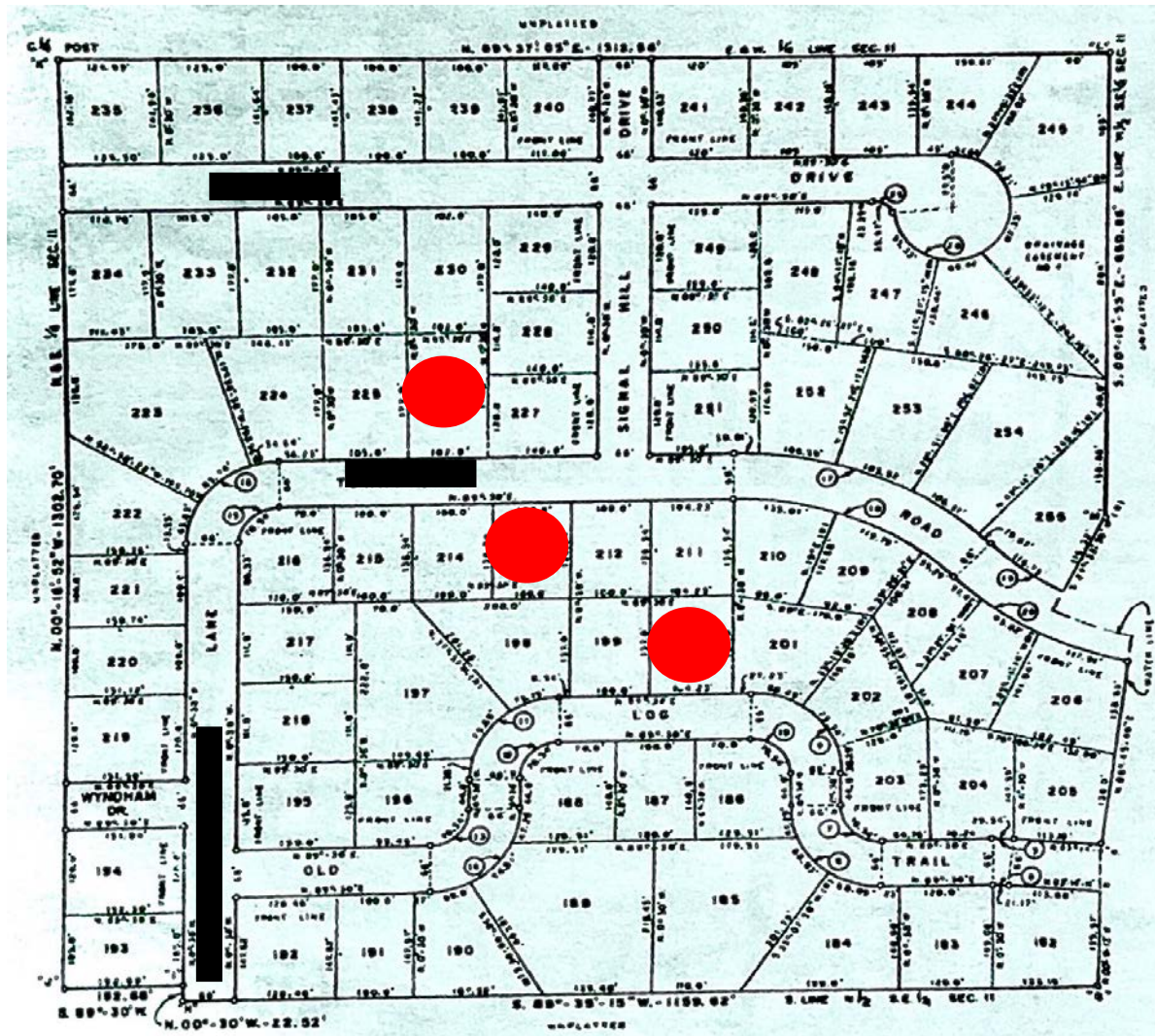
Gene-Time-Environment Hypothesis



Al-Chalabi (2013)

ALS Self-Identified Clusters are Common in Michigan

NB: Midwest Has the Highest Prevalence of ALS in USA



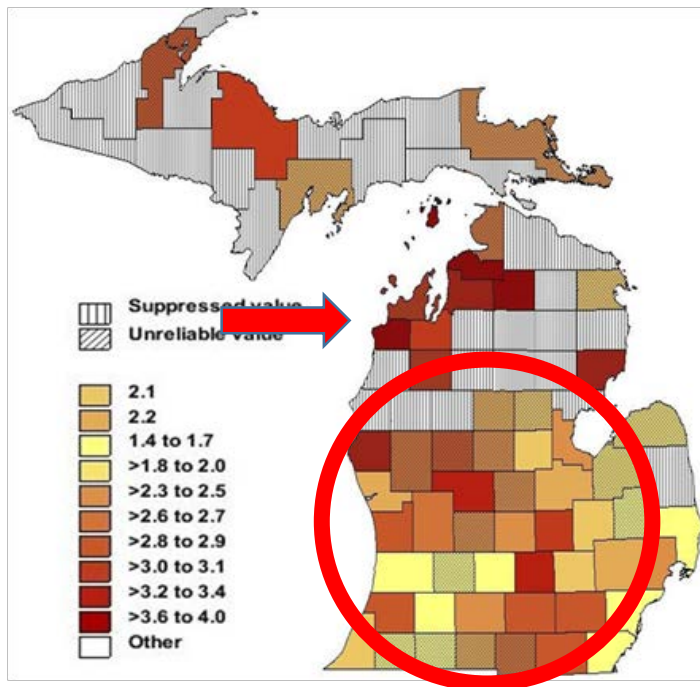
Red circles indicate childhood homes of 3 friends that later developed ALS around the same time and self identified and came to us in 2018 (Street names are redacted, although these individuals shared their story in the media)

<https://www.pbs.org/video/als-xmw7rw/> is a PBS broadcast on these women

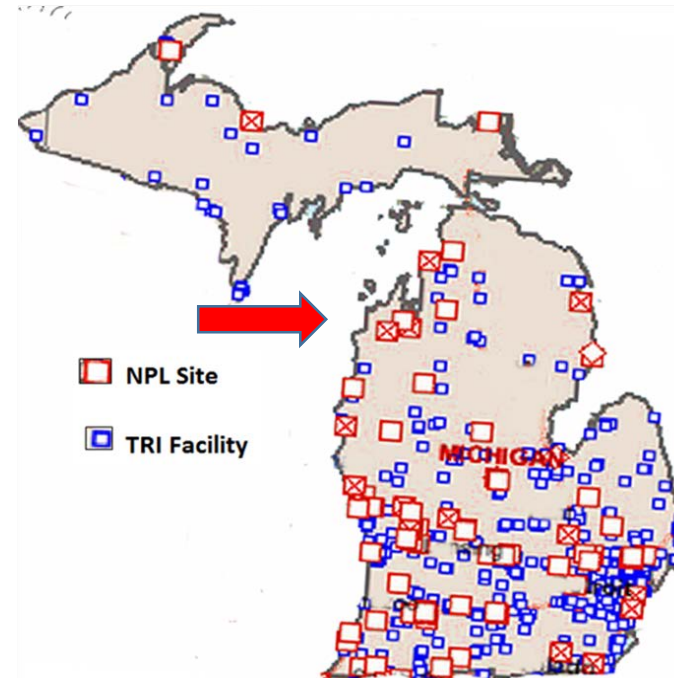
Please email me for link:
efeldman@umich.edu

Environmental Risk Factors and Amyotrophic Lateral Sclerosis (ALS): A Case-Control Study of ALS in Michigan. PLOS ONE 9(6): e101186, 2014

Identifying Environmental Risk Factors for ALS – Michigan



Age-adjusted death rates for motor neuron disease (ICD-10: G12.2) in Michigan from 1999 to 2010. Rates expressed per 100,000 population using 2000 US standard population



Location of major emissions of toxic substances in Michigan. Facilities from the Toxics Release Inventory (TRI) system for 2011 and locations of National Priority List (NPL) Superfund sites are shown

Project Goals

- Identify potential environmental risk factors associated with ALS, including environmental and occupational exposures to toxins
- Identify the source of exposures, both early and late in life
- Evaluate the metabolome that results from toxin exposure and the downstream effects on function
- Determine the polygenic risk (and epigenetic changes) that mediate/modulate an individual's response to toxins

Exposure Measurements

- Three groups of chemicals were measured in whole blood by GC/MS.
- Detection frequency > 30% required to be included in analysis

Chlorinated Pesticides

- e.g., pentachlorobenzene, trans-nonachlor, DDT
- Banned since the 1980s
- Highly persistent in the environment (decades to hundreds of years; bioaccumulation) and human (years to decades)
- Exposure primarily from diet
- Affect the nervous system, reproductive system, liver
- IARC Group 2B



Brominated Flame Retardants (BFRs)

- e.g., Polybromobisphenol, bromodiphenyl ether (**PBDE**)
- Added to plastics and foam products to make them difficult to burn
- Persistent in the environment (months to years) and human (months to years)
- Exposure primarily from diet or contaminated air
- Affect the thyroid, liver, immune system, cause neurobehavioral alterations
- IARC Group 3



Polychlorinated Biphenyls (PCBs)

- e.g., PCB 66 - PCB203
- Used widely as coolants and lubricants in electrical equipment
- Banned in 1979
- Persistent in the environment (months to years; bioaccumulation) and human (years to decades)
- Exposure primarily from diet or contaminated air
- Affect the endocrine glands, liver, immune system, nervous system
- IARC Group 1



IARC:
International
Agency for
Research on
Cancer

Research

Original Investigation

Association of Environmental Toxins With Amyotrophic Lateral Sclerosis

Feng-Chiao Su, PhD; Stephen A. Goutman, MD; Sergey Chernyak, PhD; Bhramar Mukherjee, PhD;
Brian C. Callaghan, MD; Stuart Batterman, PhD; Eva L. Feldman, MD, PhD

IMPORTANCE Persistent environmental pollutants may represent a modifiable risk factor involved in the gene-time-environment hypothesis in amyotrophic lateral sclerosis (ALS).

OBJECTIVE To evaluate the association of occupational exposures and environmental toxins on the odds of developing ALS in Michigan.

Pesticide Exposure May Increase Risk of A.L.S.

BY NICHOLAS BAKALAR MAY 12, 2016 1:39 PM 26

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Exposure to pesticides may increase the risk for amyotrophic lateral sclerosis, also known as Lou Gehrig's disease, a new study has found.

The [study, in JAMA Neurology](#), included 156 patients with A.L.S. and 128 controls. All participants completed questionnaires providing information on age, sex, ethnicity, education, marital status, residential history, occupational history,

Editorial

Supplement
jamaneu



Demographics

	Cases		Controls		
	n		n		P-value
Mean Age (years)	156	60.5 +/- 11.1	128	60.4 +/- 9.4	0.950
Females	60	38.5%	54	42.2%	0.524
Live >= 20 km from UM	111	71.2%	38	29.7%	<0.001
< bachelor's degree	81	63.3%	47	39.5%	<0.001
Nonsmoker	60	46.5%	53	44.2%	0.72

A Single model

Compound

PBDE 154

PBDE 85

PBDE 99

PBDE 100

PBDE 66

PBDE 47

PBDE 28

TBBPA

PCB 198

PCB 170/190

PCB 180

PCB 202

PCB 174

PCB 175

PCB 138/163

PCB 132/153

PCB 118

PCB 135/144

PCB 151

PCB 110

p,p'-DDE

trans-Nonachlor

cis-Chlordane

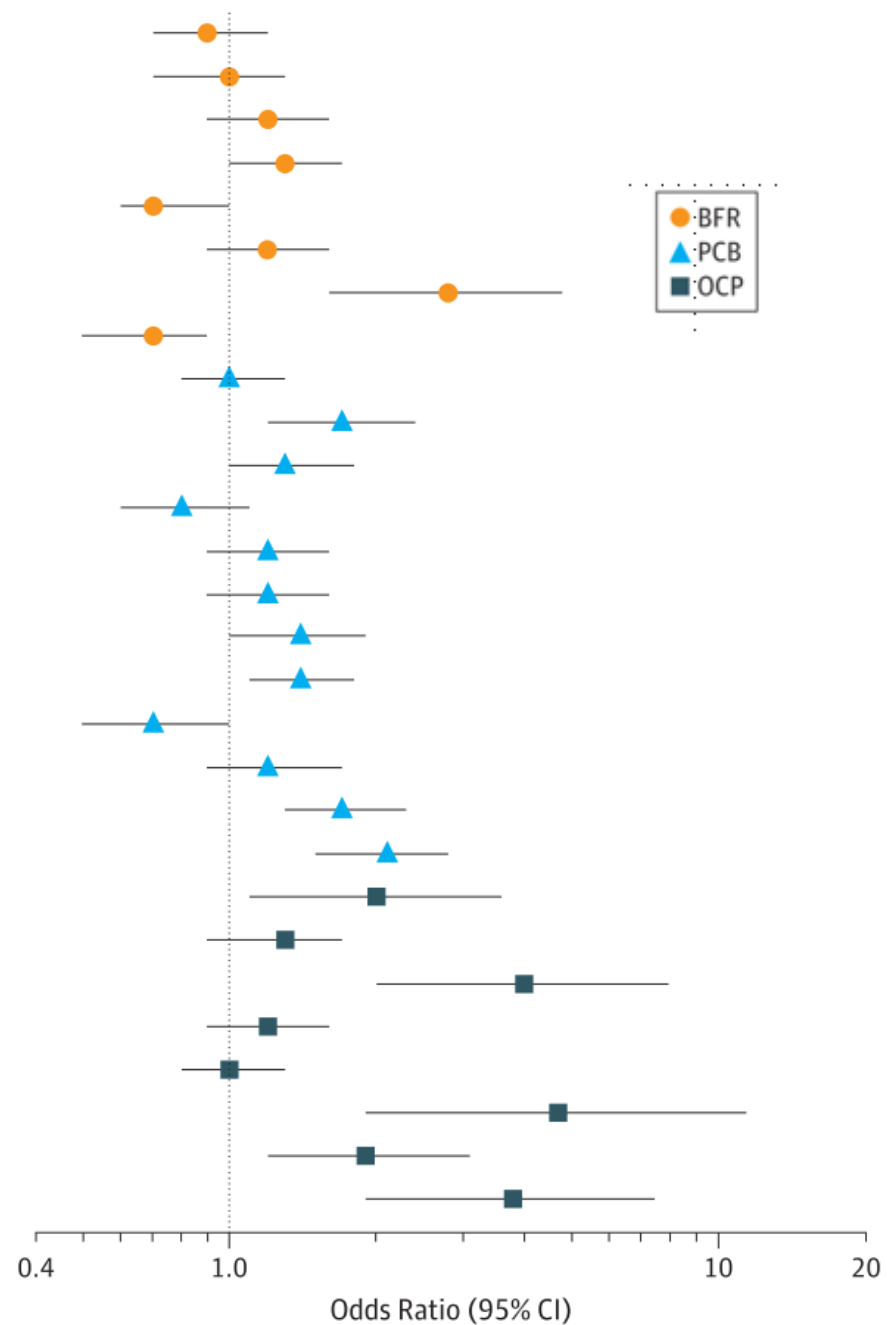
trans-Chlordane

Dacthal

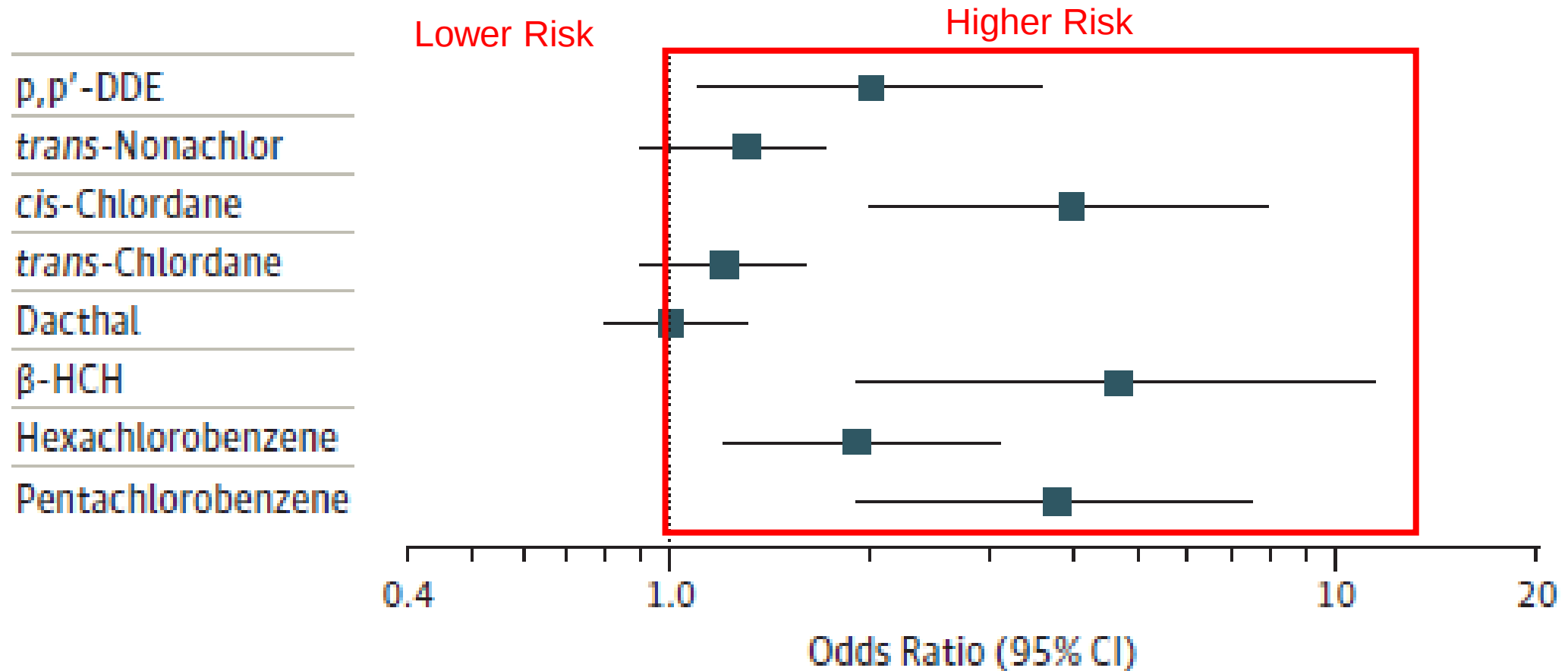
β-HCH

Hexachlorobenzene

Pentachlorobenzene



Pesticides Increase ALS Risk



Exposure Assessment via Surveys

Exposure ever happened in the entire occupational history

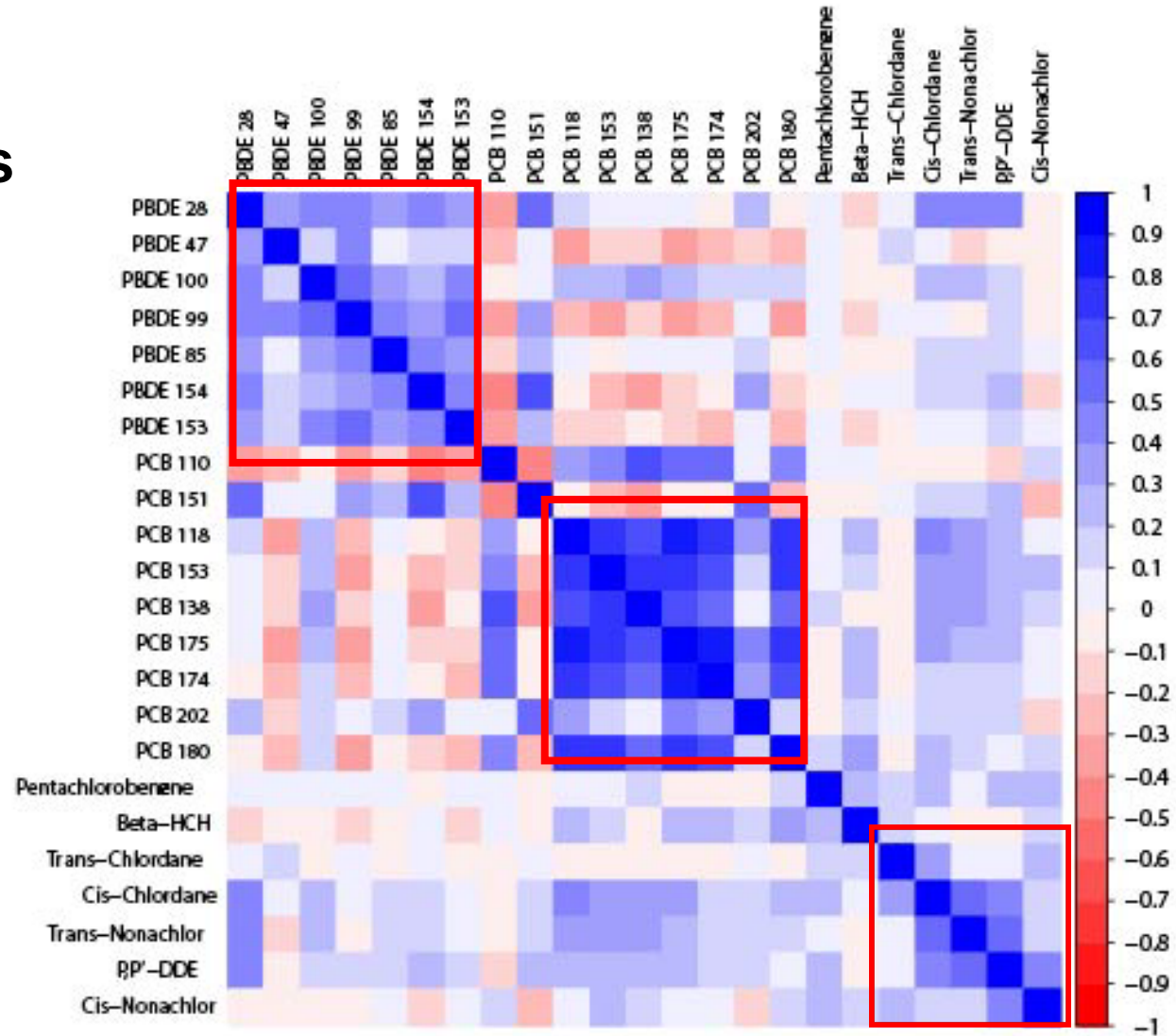
Variable		OR	95% CI	
Age	Year	1.00	0.97	1.03
Gender	Male	0.76	0.37	1.56
Educational level	>= College	0.30	0.17	0.54
Smoker	Current(Former)	1.06(0.79)	0.33(0.35)	3.43(1.78)
Ever work in US armed forces	Yes	2.31	1.02	5.25
Occupational exposure to lead	Yes	0.38	0.15	0.94
Occupational exposure to pesticides	Yes	5.09	1.85	14.0
Industry: health care/social assistance	Yes	0.35	0.17	0.74
Industry: accommodation, food services	Yes	0.23	0.07	0.77
Industry: public administration	Yes	0.38	0.14	1.04

Case / Control Risk Model

Covariate	Cases (167)	Controls (99)	P-Value
Age (years)*	61.6 (53.3-68.8)	61.6 (54.7-68.1)	0.824
BMI at consent (kg/m ²)**	25.7 (22.3-28.4)	27.1 (24.5-30.3)	0.012
BMI Slope**	-0.2 (-0.6-0.1)	0.0 (-0.3-0.2)	0.008
Education			<0.001
HS/GED or Less	54 (32.3)	5 (5.1)	
Some College / Associate's	44 (26.3)	30 (30.3)	
Bachelor's	42 (25.1)	25 (25.3)	
Master's / Professional	26 (15.6)	30 (30.3)	
Military Service			0.856
No	133 (79.6)	75 (75.8)	
Yes	26 (15.6)	13 (13.1)	
Sex			1.000
Female	68 (40.7)	40 (40.4)	
Male	99 (59.3)	59 (59.6)	
Smoking			0.713
Non-Smoker	92 (55.1)	50 (50.5)	
Former Smoker	52 (31.1)	35 (35.4)	
Current Smoker	18 (10.8)	12 (12.1)	

Persistent Organic Pollutant Correlations

ALS Cases



Multiple Pollutant Exposure Models



Statistical strategies for constructing health risk models with multiple pollutants and their interactions: possible choices and comparisons

Zhichao Sun^{1*}, Yebin Tao¹, Shi Li¹, Kelly K Ferguson², John D Meeker², Sung Kyun Park², Stuart A Batterman² and Bhramar Mukherjee¹

- Summary score to characterize disease risk from exposures to mixtures of pollutants
- $[ERS]_i = (\beta_1) \hat{E}(1, i) + (\beta_2) \hat{E}(2, i) + \dots + (\beta_p) \hat{E}(p, i)$
- $[ERS]_i$ is the environmental risk score for each case (i)
- $(\beta_1) \dots (\beta_p)$ are the regression coefficients for the given environmental pollutant (1 to p)
- $E(1, i) \dots E(p, i)$ are the standardized concentrations of the given environmental pollutant for each case

Logistic Regression Model

	N = 266 (167 cases, 99 controls)		
ERS / Covariate	OR	95% CI	P-Value
ERS	7.37	(3.97, 13.69)	<0.001
BMI at Survey Consent (kg/m2)	0.94	(0.89, 1.01)	0.102
Rate of Change in BMI	0.50	(0.26, 0.95)	0.035
Age at Blood Draw (years)	0.98	(0.95, 1.01)	0.183
Military Service	1.29	(0.47, 3.53)	0.617
Sex	0.87	(0.43, 1.77)	0.698
Former Smoker	0.77	(0.38, 1.57)	0.470
Current Smoker	1.02	(0.33, 3.19)	0.967
> HS/GED	0.08	(0.03, 0.25)	<0.001

Does Exposure to Persistent
Organic Pollutants Influence
Survival?

High plasma concentrations of organic pollutants negatively impact survival in amyotrophic lateral sclerosis

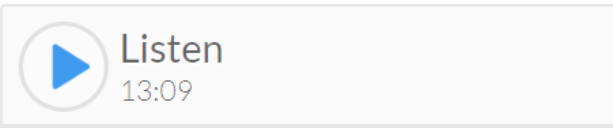
Stephen A Goutman^{1, 2}, Jonathan Boss³, Adam Patterson^{1, 2}, Bhramar Mukherjee³, Stuart Batterman⁴, Eva L Feldman^{1, 2}

Detroit Free Press

New study: Michigan's manufacturing legacy may be affecting our health, environment

Kristen Jordan Shamus, Detroit Free Press Published 6:01

Study finds link between pesticide exposure and ALS in Michigan patients

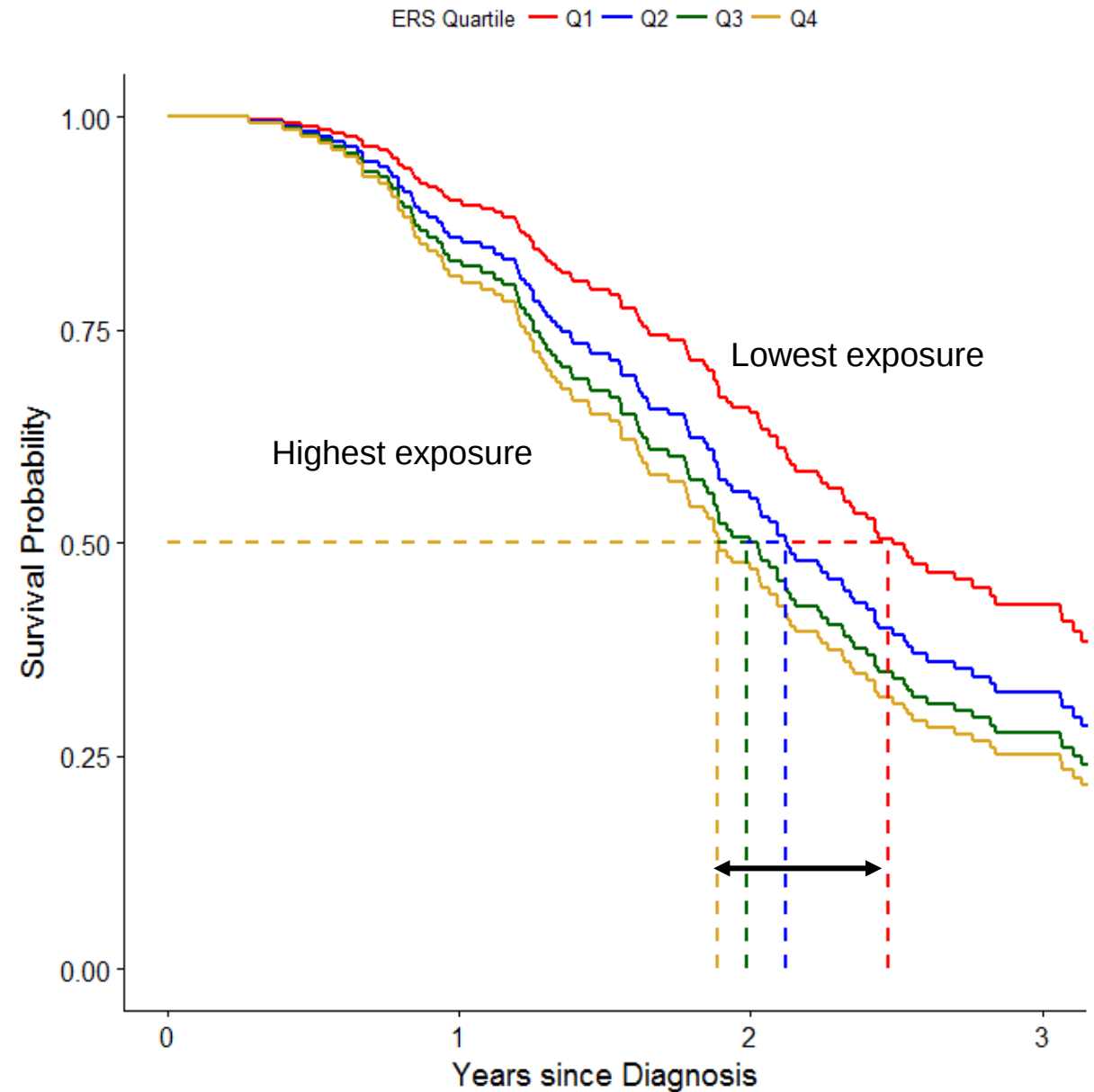


Stateside's conversation with Dr. Stephen Goutman



Two-fold Greater Mortality Rate with Highest ERS Exposure after Covariate Adjustments

ERS / Covariate	HR	95% CI	P-Value
ERS Quartile 2	1.50	(0.82, 2.76)	0.189
ERS Quartile 3	1.84	(0.96, 3.52)	0.065
ERS Quartile 4	2.07	(1.13, 3.80)	0.018
NIV User	0.85	(0.54, 1.34)	0.488
BMI at study entry (kg/m ²)	1.00	(0.95, 1.06)	0.994
Rate of change in BMI	0.82	(0.55, 1.23)	0.343
Age at Diagnosis (years)	1.02	(0.99, 1.04)	0.159
Time between symptom onset and diagnosis (years)*	0.59	(0.43, 0.81)	0.001
Time between diagnosis and blood draw (years)*	0.42	(0.30, 0.58)	<0.001
Family History of ALS	1.21	(0.62, 2.36)	0.578
Military Service	0.94	(0.44, 2.03)	0.877
Sex (Reference = Male)	1.03	(0.60, 1.75)	0.924
Former Smoker	1.05	(0.62, 1.76)	0.864
Current Smoker	1.25	(0.56, 2.77)	0.581
> HS/GED	1.27	(0.80, 2.02)	0.312
Bulbar Onset	1.35	(0.76, 2.41)	0.309
Lumbar Onset	0.87	(0.51, 1.47)	0.595
El Escorial – Probable	1.64	(0.78, 3.47)	0.194
El Escorial – Probable, LS	2.30	(1.11, 4.77)	0.025
El Escorial – Definite	3.20	(1.52, 6.78)	0.002



Summary

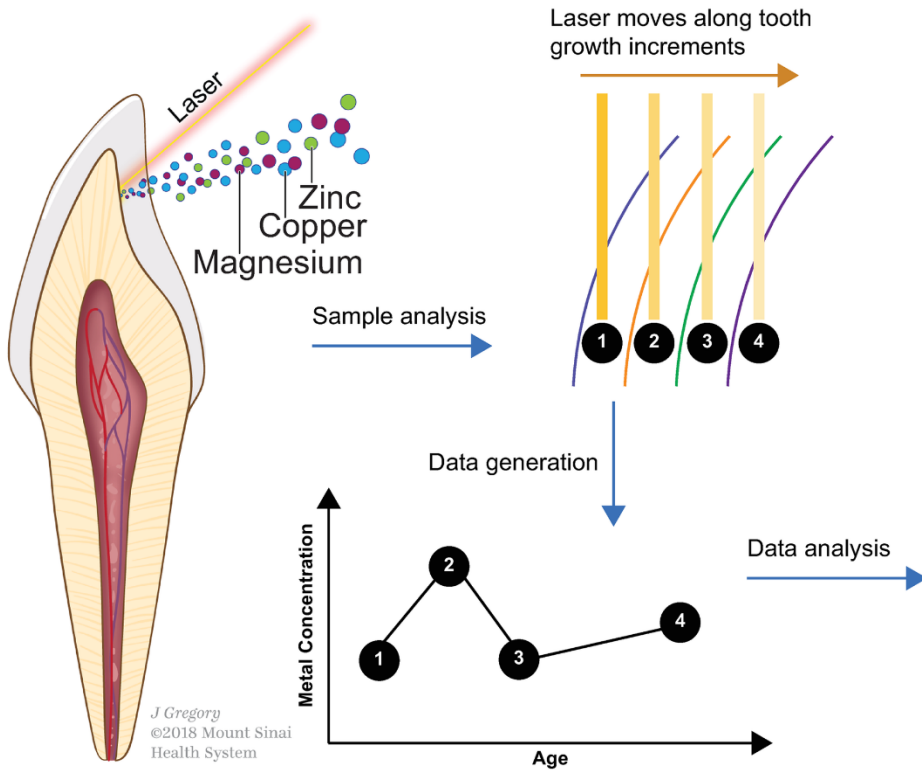
- Higher concentrations of persistent organic pollutants, particularly pesticides, measured from plasma are associated with an increased odds of having ALS.
- Survey based responses can yield insight into past exposures.
- ERS summates cumulative exposures to multiple pollutants.
- Higher ERS associates with increased ALS mortality.
- Lower concentrations of persistent organic pollutants measured from plasma in ALS subjects are associated with a longer survival.

Project Goals

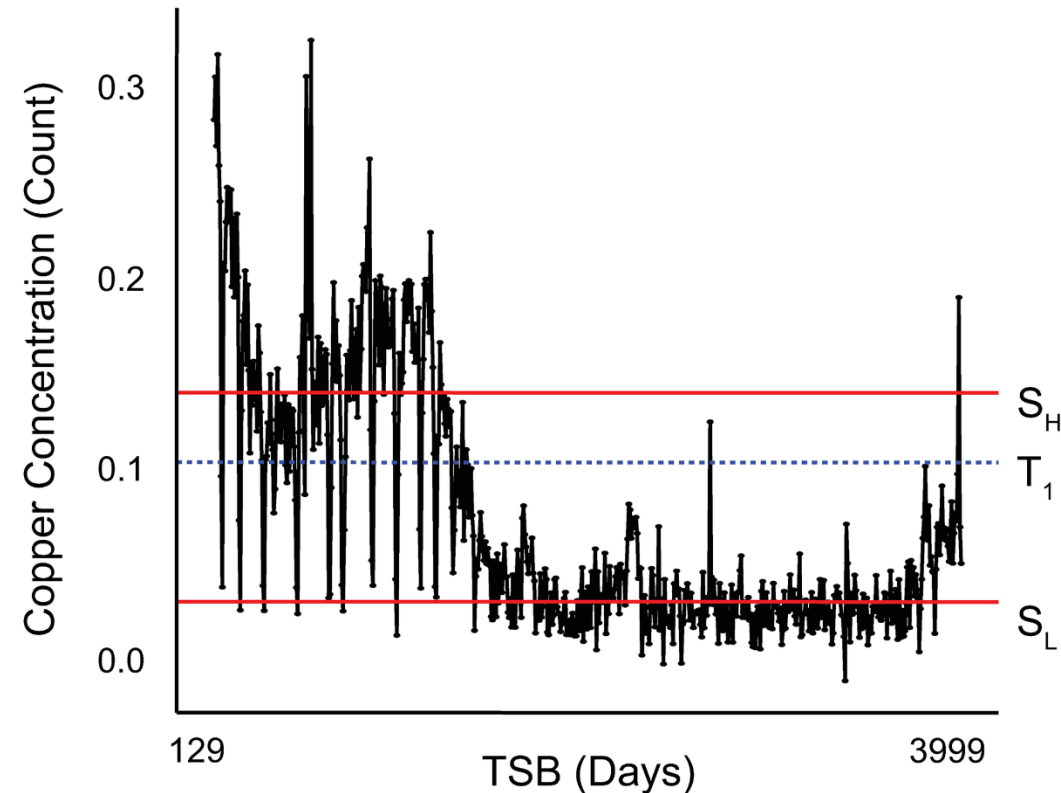
- Identify potential environmental risk factors associated with ALS, including environmental and occupational exposures to toxins
- Identify the source of exposures, both early and late in life
- Evaluate the metabolome that results from toxin exposure and the downstream effects on function
- Determine the polygenic risk (and epigenetic changes) that mediate/modulate an individual's response to toxins

Early Childhood Exposures

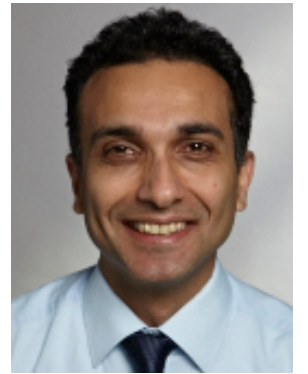
A.



B.



Claudia Figueroa-Romero, PhD



Manish Arora, PhD
Professor Environmental
Medicine & Public Health
Icahn School of Medicine at
Mt. Sinai

Laser ablation inductively-coupled plasma mass spectrometry (LA-ICP-MS) analysis measures metal concentrations in dentine growth increments of adult teeth

Ann Clin Transl Neurol. 2020 May 21. doi: 10.1002/acn3.51006. Online ahead of print.

ANNALS
of Clinical and Translational Neurology

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RESEARCH ARTICLE

Early life metal dysregulation in amyotrophic lateral sclerosis

Claudia Figueroa-Romero¹ , Kristen A. Mikhail¹, Chris Gennings², Paul Curtin², Ghalib A. Bello², Tatiana M. Botero³, Stephen A. Goutman¹, Eva L. Feldman¹, Manish Arora² & Christine Austin²

¹Department of Neurology, University of Michigan, Ann Arbor, MI, USA

²Department of Environmental Medicine and Public Health, and Senator Frank Lautenberg Laboratory for Environmental Health Sciences, Icahn School of Medicine at Mount Sinai, New York, NY, USA

³Department of Cariology, Restorative Sciences and Endodontics, School of Dentistry University of Michigan, Ann Arbor, MI, USA

RESEARCH ARTICLE

Dysregulated biodynamics in metabolic attractor systems precede the emergence of amyotrophic lateral sclerosis

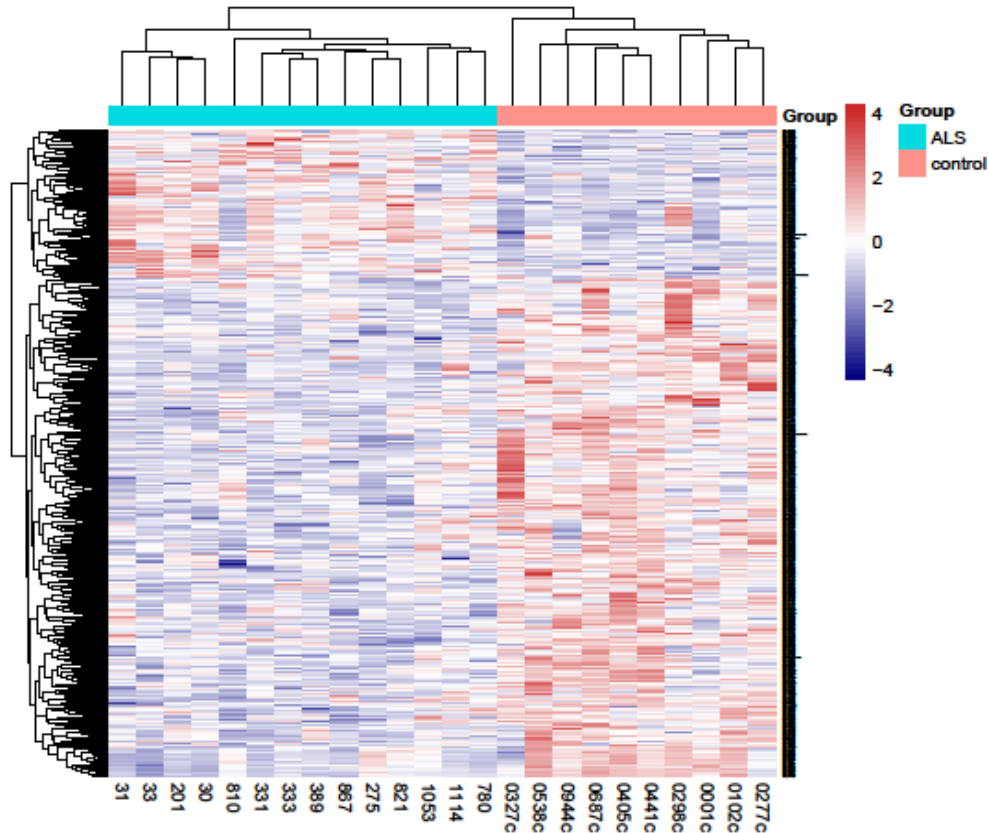
Paul Curtin¹ , Christine Austin¹ , Austen Curtin¹ , Chris Gennings¹ , Claudia Figueroa-Romero² , Kristen A. Mikhail², Tatiana M. Botero³, Stephen A. Goutman² , Eva L. Feldman² , Manish Arora¹ 

¹ Department of Environmental Medicine and Public Health, Icahn School of Medicine at Mount Sinai, New York, NY, United States of America, ² Department of Neurology, University of Michigan, Ann Arbor, MI, United States of America, ³ Department of Cariology, Restorative Sciences and Endodontics, School of Dentistry University of Michigan, Ann Arbor, MI, United States of America

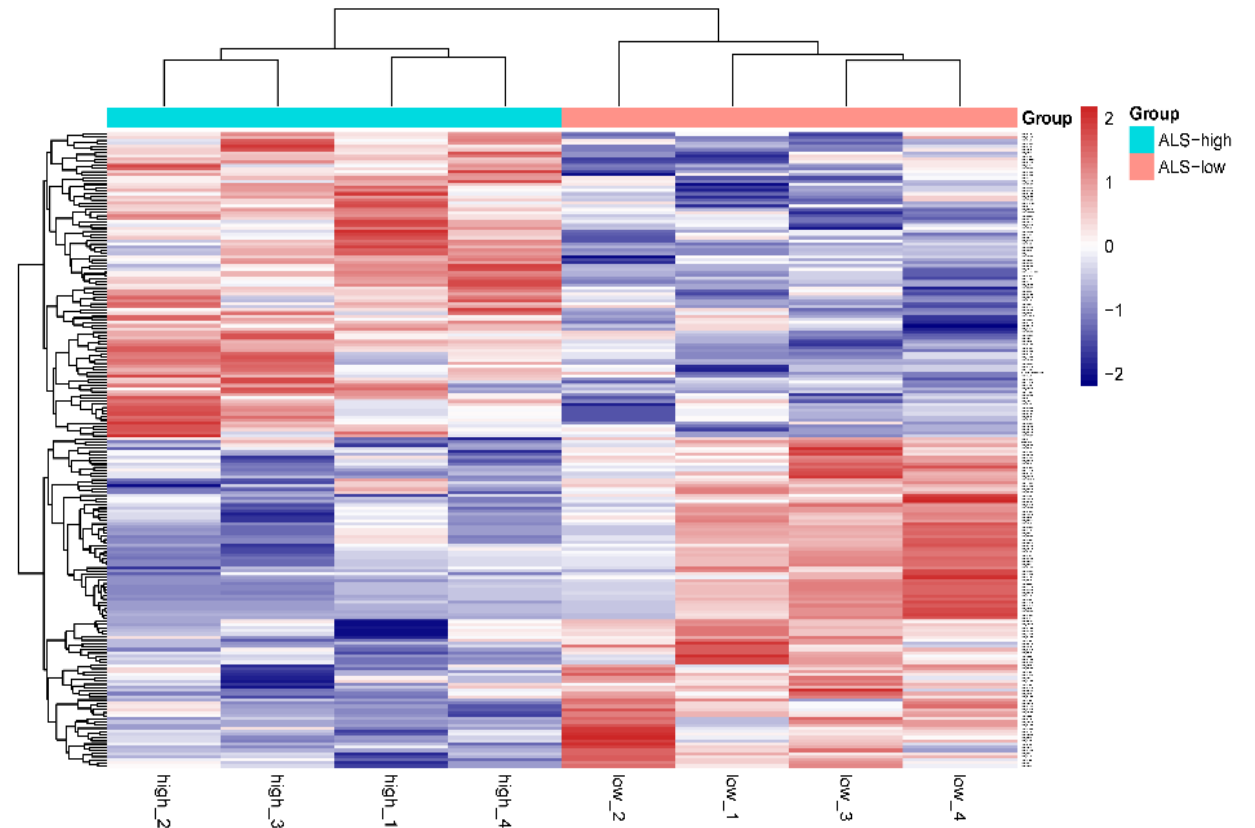
Exposures in childhood up to late teenage years of 11 metal toxicants present in teeth, including zinc, chromium and lead, associate with increase ALS risk.

Metabolomics (in revision, J Neurol Neurosurg Psych)

Metabolomics differentiates cases and controls



Metabolomics differentiates cases based on pentachlorobenzene exposure classification



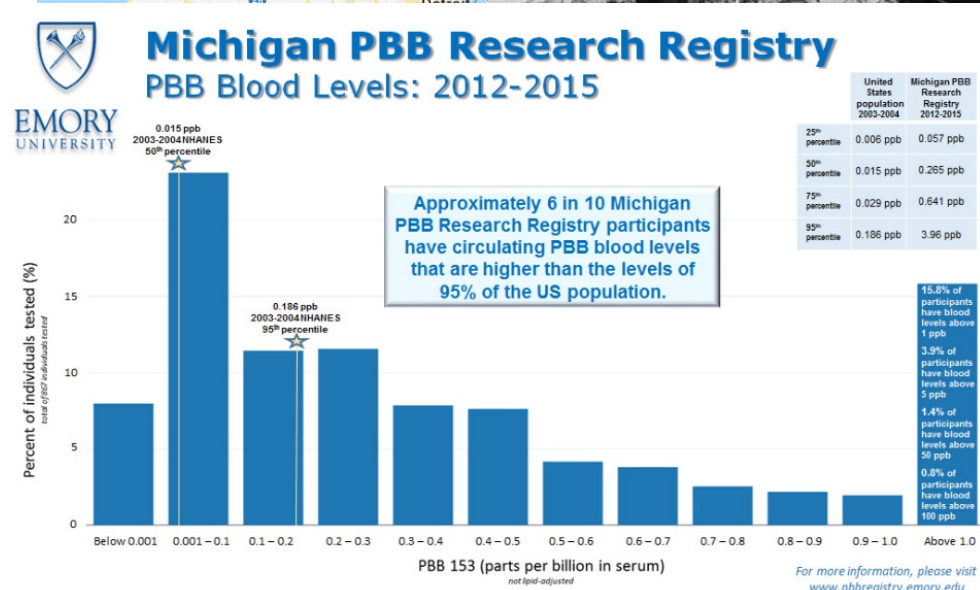
What We Must Do Now

- Healthy and diseased cohorts from broad geographic regions are necessary to advance these studies
- More funding to support environmental studies is needed, especially in regards to recruiting/maintaining cohorts (to later support hypothesis-based studies)
- Future research advances are expected, therefore, availability of samples in a biorepository for future use is important (especially when connected to phenotypic and other “–omics” data); we currently have over 600 ALS cases and equal number of controls
- We maintain there are sufficient data to demand efforts to ensure environmental clean-up

Michigan Chemical & St. Louis, MI

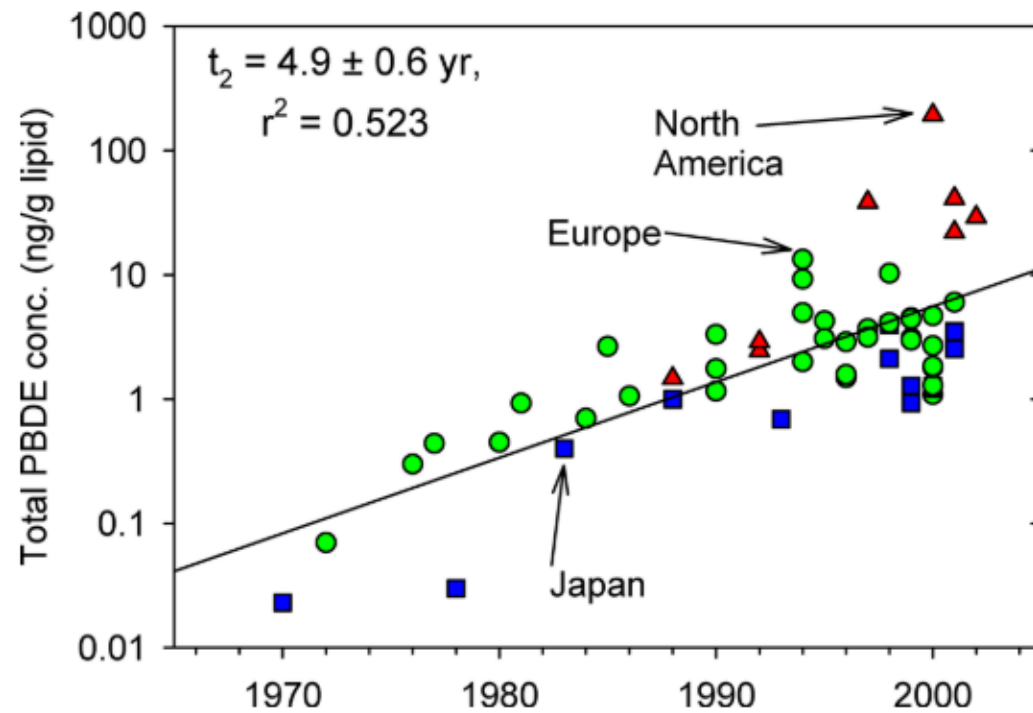


- Produced Polybrominated biphenyls (PBB): FireMaster
- Produced magnesium oxide for cattle feed: NutriMaster
- In 1973, bags were switched and PBB fed to cattle
- Affected 30,000 cattle, 1.5 million chickens, 1000s of pigs/rabbits; all destroyed
- PBBs remain in atmosphere (tree bark, ground, water samples)
- Clean up of Michigan Chemical site ~\$300 million and ongoing

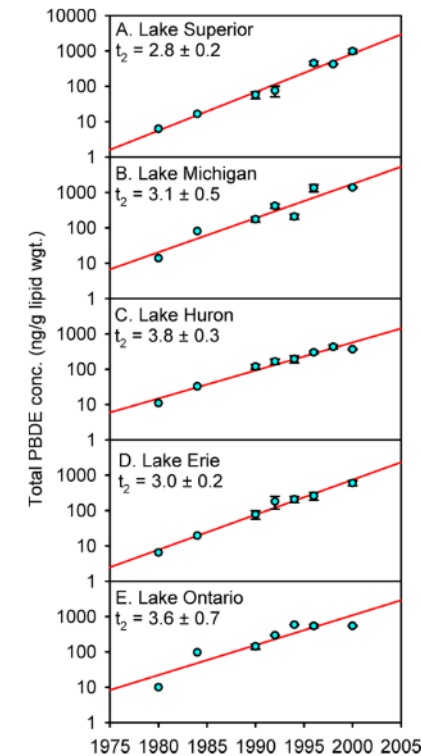


But, PBDEs Increasing in Humans/Fish

Humans



Fish



Venier, *Accounts of Chemical Research*, 2015

**This Issue**Views **2,121**Citations **0**Altmetric **18**Comments

Viewpoint

March 2, 2020

Voicing the Need for Amyotrophic Lateral Sclerosis Environmental Research

Stephen A. Goutman, MD, MS^{1,2}; Eva L. Feldman, MD, PhD^{1,2}

» [Author Affiliations](#)

JAMA Neurol. 2020;77(5):543-544. doi:10.1001/jamaneurol.2020.0051

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- ALS Association (2019-2022)
- NeuroNetwork for Emerging Therapies (Michigan Medicine) with a special thank you to Mr. Scott Pranger
- Centers for Disease Control (Contract #200-2013-56856) (2013-2017)



National Institute of
Environmental Health Sciences



Agency for Toxic Substances & Disease Registry

