Veterans & Parkinson's

Parkinson's Foundation

Environmental Exposures

The program will begin shortly.
A few notes before we start:

- All attendees will be muted and off camera.
- Share a comment by using the **chat** box.
- Submit a question by using the **Q&A** feature.

- **More resources for Veterans:**
  - www.Parkinson.org/Veterans

Better Lives. Together.

Parkinson's Foundation

Environmental Exposures in Veterans with Parkinson's

Better Lives. Together.

Our Mission

The Parkinson's Foundation makes life better for people with Parkinson's disease by improving care and advancing research toward a cure. In everything we do, we build on the energy, experience and passion of our global Parkinson's community.

We have everything you need to live better with Parkinson's.

Our Goals

To help our global community live better with Parkinson's, we pursue **three goals:**

- **Improve care for everyone with Parkinson's**
- **Advance research toward a cure**
- **Empower and educate our global community**

PD Health @ Home

Weekly programming that includes:

- Mindfulness Mondays
- Wellness Wednesdays
- Fitness Fridays
- Expert Briefings
- EP Salud en Casa

www.Parkinson.org/Veterans

Thank you

Parkinson's Foundation

DON and LORRAINE FREEBERG FOUNDATION

Parkinson's Foundation

Environmental Exposures in Veterans with Parkinson's

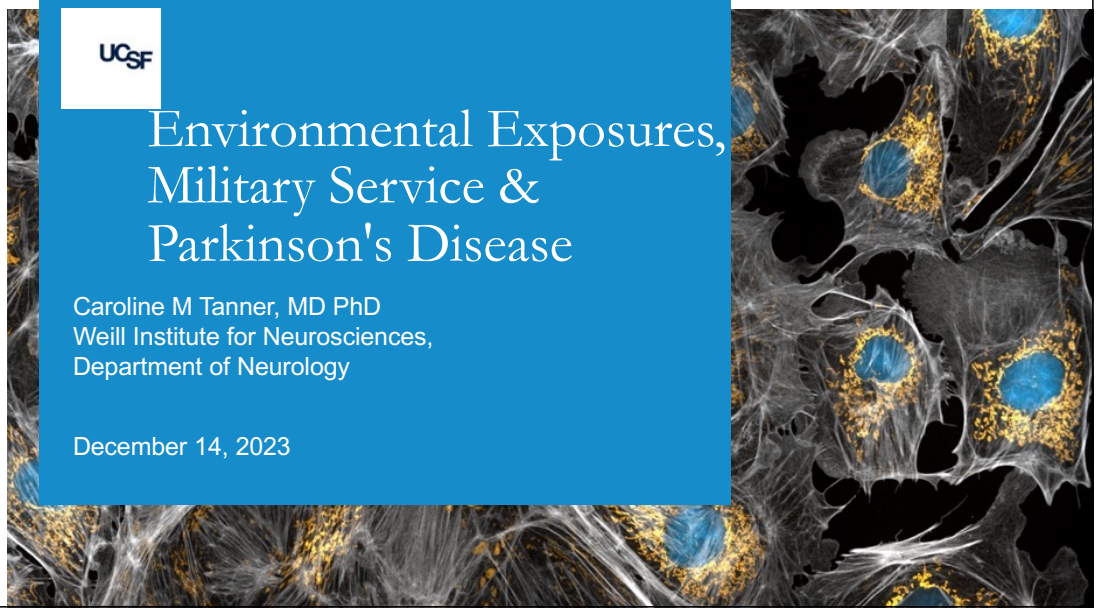
Better Lives. Together.

Caroline M. Tanner, MD, PhD, FAAN

- Professor of Neurology
- Vice Chair for Clinical Research
- Dept of Neurology at the Weill Institute of Neurosciences
- University of California
- San Francisco, CA

Patrick W. Welch, PhD

- Retired U.S. Marine Corps
- Infantry Squad Leader in Vietnam
- Founder of The Center for Veterans and Veteran Family Services at Daemen College
- Parkinson's Foundation Ambassador



Environmental Exposures, Military Service & Parkinson's Disease

Caroline M Tanner, MD PhD
Weill Institute for Neurosciences,
Department of Neurology

December 14, 2023

What Causes Parkinson's Disease?

Twins: Mother Nature's Controlled Study

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

- MZ twins share ~100% of genes
- DZ twins share ~50% of genes

Hypothesis: If Parkinson's disease is primarily a genetic disorder, then concordance in MZ twins should be > than in DZ twins.

Results:
Twins aged 72-82:
MZ & DZ concordance similar;
Except **in young onset MZ > DZ**

Twenty year followup:
11 living, 97% valid NDI matches

Tanner, et al, JAMA, 1999;
Goldman et al, Ann Neurol, 2019

Concordance for Parkinson's Disease in Twins: a 20-year Update

- U.S. National Death Index (NDI) through 12/31/2015
- ICD codes – underlying & all causes of death

→ Looking across the lifespan:
Identical twins (MZ, monozygotic):
20% PD in both twins

Fraternal twins (DZ, dizygotic):
14% PD in both twins

PD dx age in twin-1	Zygosity	Concordance
Overall	MZ	**0.20**
	DZ	**0.14**
≤ 50	MZ	**0.75**
	DZ	**0.20**
>50	MZ	**0.16**
	DZ	**0.11**

Conclusion: Environment is an important contributor to the cause of PD

Tanner, et al, JAMA, 1999; Goldman et al, Ann Neurol, 2019

What Causes Parkinson's Disease?

Genes

Risk

- Mendelian < 20 - 30 % PD
- Penetrance reduced: Other genes & environmental factors

- **Autosomal Dominant. ~ 5% PD**
  PARK-*SNCA*, PARK-*LRRK2*, PARK-*VPS35*
- **Autosomal Recessive < 5% PD**
  PARK-*Parkin*, PARK-*PINK1*, PARK-*DJ1,* PARK-*DNAJC6*
- **Complex phenotypes < 1% PD**
- **Glucocerebrosidase 5 – 8 % PD**

GWAS: Many variants → small contributions to risk

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Poewe et al,2017; Obeso et al, 2017; Nalls et al, 2019

PD GENEration: Mapping the Future of Parkinson's Disease

CALL OUR HELPLINE: 1-800-4PD-INFO (473-4636)

Parkinson's Foundation

Parkinson.org

Why Participate

- Improve management of your disease in the future
- Learn about your family's risk for Parkinson's
- Help scientists understand Parkinson's disease
- Improve Parkinson's care and research
- Accelerate enrollment in clinical trials
- Aid in development of improved treatments and personalized medicine for you and future generations

8,506

genetic tests completed, as of June 2023

12.7%

of PD GENEration participants have a genetic link to PD, as of June 2023.

What Causes Parkinson's Disease?

Genes

Risk

- Mendelian < 20 - 30 % PD
- Penetrance reduced:
  Other genes & environmental factors

GWAS: Many variants → small contributions to risk

- **Autosomal Dominant. ~ 5% PD**
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Environment

Risk

- **Pesticides**

Paraquat, rotenone, 2,4-D, organochlorines, organophosphates

- **Solvents**

PERC, TCE, CCl_4

- **Head Injury (Traumatic Brain Injury/TBI)**
- **Air Pollution**
- **Others**

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Poewe et al,2017; Obeso et al, 2017; Nalls et al, 2019

Pesticides

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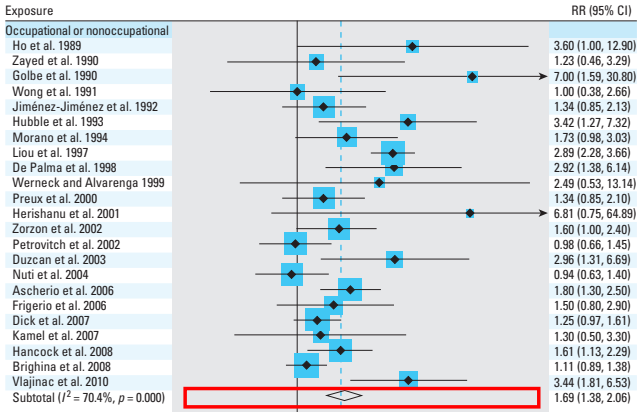
Pesticides & PD

Van der Mark et al, EHP, 2012



- Pesticide use associated with PD in >50 studies worldwide

- **BUT: Specific compounds rarely studied**

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PD in the Agricultural Health Study

Tanner, Kamel et al, EHP, 2011

Pesticide	Functional Class	PD Risk (OR)	95%CI	p-value
Rotenone	Insecticide, piscicide	2.8	1.4-5.8	0.005
Paraquat	Herbicide	2.5	1.3-4.7	0.004

<u>Biological plausibility</u>:

BOTH pesticides produce a selective animal model of parkinsonism

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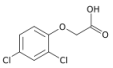
SEARCH Study:
Case Control Study of Occupational Risk Factors

Tanner et al, Arch Neurol, 2009

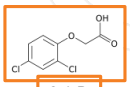
- 519 PD cases, 511 controls in 8 MD centers
- Lifelong, job-task-based occupational histories; other risk factors

Pesticide	Functional Class	PD Risk (OR)	95%CI
Paraquat	Herbicide	2.8	0.8-9.7
2,4-D	Herbicide	2.6	1.03-6.5



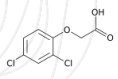
2,4-D

Agent Orange

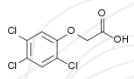


2,4-D

Operation Ranch Hand: 1962-1971
Other military service



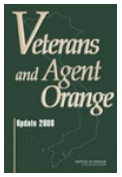
2,4,5-T

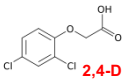


2,3,7,8 tetrachlorodibenzodioxin

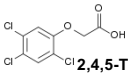
Agent Orange & Parkinson's Disease Risk

Operation Ranch Hand:
1962-1971
20 x 10^6 gallons Agent Orange

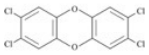




2,4-D



2,4,5-T



2,3,7,8 tetrachlorodibenzodioxin (DDT)

UNITED STATES
DEPARTMENT OF VETERANS AFFAIRS

- 2009: Agent Orange Linked to Parkinson's Disease established service-connection:
- Certain Vietnam Veterans may be eligible for: disability compensation and health care benefits.

Other Pesticide Exposures in Service Members

Examples:

Pesticides used in the Gulf War to prevent leshmania, malaria, etc.:

- **Uniform impregnation:**
  - Carbamates, organochlorines (e.g., Lindane)
  - Pyrethroids (permethrin)
- **Personal repellents**
  - DEET
- **Tents, camps**
  - Organophosphate pesticides (malathion, chlorpyrifos)

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Chlorinated Solvents

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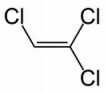
Trichloroethylene (TCE)



Study 1: Gash et al, 2008

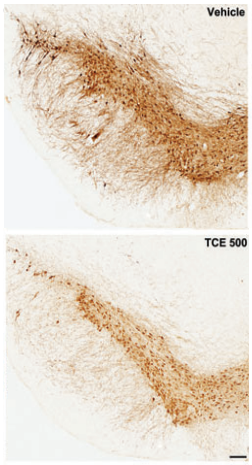
- Small Kentucky industrial plant with 30 employees
- PD in 3 co-workers
- Mild parkinsonian signs/symptoms in 14 others
- All exposed to open vapor-degreasing vat containing trichloroethylene (TCE)

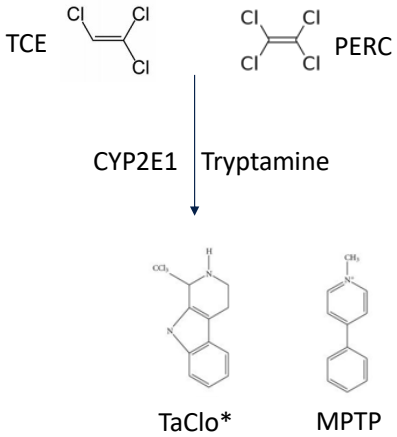
Study 2: Goldman et al, 2011

- 99 male twin pairs discordant for PD
- PD diagnosis validated by experts
- Lifelong job-task-specific occupational history
- Exposure assigned by industrial hygienist unaware of case status

Compound	Odds ratio	95% C.I.	p-value
TCE	**6.1**	**1.2-33**	**0.034**
PCE	**10.5**	**0.97-113**	**0.053**

Oral TCE causes selective dose-related degeneration of dopaminergic neurons in rat substantia nigra





Liu, et al, J Neurochem 2010

*1-trichloromethyl-1,2,3,4-tetrahydro-β-carboline

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Camp Lejeune Water Supplies

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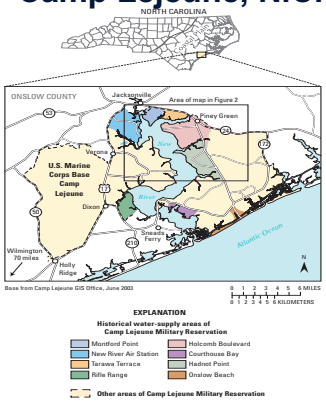
Camp Lejeune, N.C.



Agency for Toxic Substances and Disease Registry (ATSDR) 2014:
-Less than 6% of cohort had died
- **Excess mortality in Lejeune only servicemembers**

History

1953-1985 - Water contaminated with TCE & PCE (i.e., PERC)
1980 - Contaminants discovered;1987 - Wells closed

500,000 – 1,000,000 military & civilians exposed

Exposure levels:

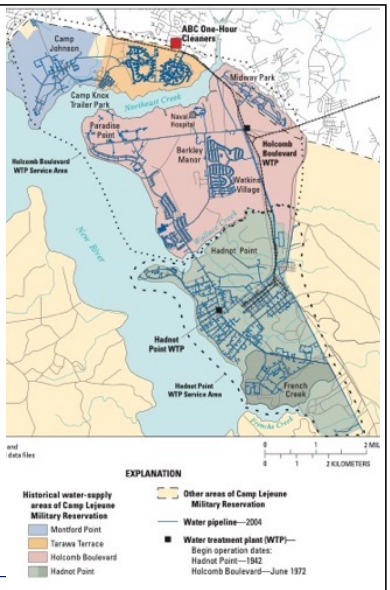
Est. monthly median (max. mean) ug/L: PCE: 85 (158); TCE: 366 (783)

→ TCE in water more than 70 times greater than US EPA maximum contaminant level: 5 ug/l

Goldman et al, 2023

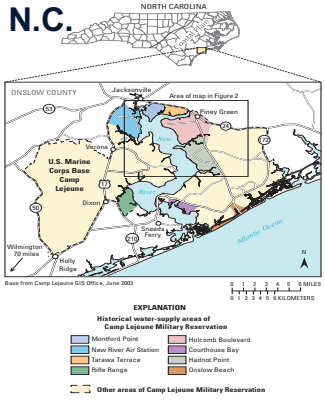
PD in Marine Base Camp Lejeune: Parkinson's Disease in ATSDR Exposure Cohort

- ATSDR cohort (n=400,000): Marines at Camp Lejeune 1975-1985 vs. Camp Pendleton
- Residential TCE and PCE exposures estimated for all Lejeune Marines (peak, cumulative)
- Linkage with:
  - VA CDW
  - CMS (Medicare)
  - NDI (cause of death)
- Manual chart review of 2,000 with a PD code



Historical water-supply areas and water-distribution systems serving Hadnot Point, Boulevard, and vicinity, U.S. Marine Corps Base Camp Lejeune, North Carolina.

Parkinson's Disease & Camp Lejeune, N.C.



Agency for Toxic Substances and Disease Registry (ATSDR) 2014:
-Less than 6% of cohort had died
- Excess mortality in Lejeune only servicemembers

Veterans Administration and Medicare databases
Followup through 2021

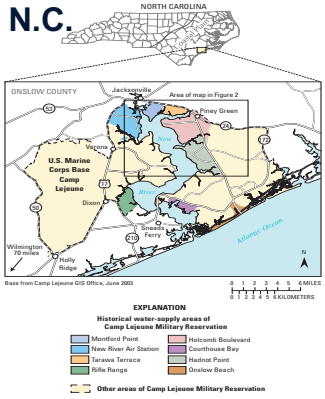
Results:

→ PD 70% more common in Lejeune vs Pendleton

Population: Lejeune 84,824 Pendleton 73,298
95% men
Mean Age: Lejeune 59.6 Pendleton 59.8
PD cases: Lejeune 279 Pendleton 171
Crude PD prevalence: 0.33% Lejeune 0.21% Pendleton.
Mean age at PD onset:
54.7 Lejeune. 53.2 Pendleton
OR for PD in Lejeune:
OR 1.70, 95%CI 1.39-2.07, p<0.0001

Goldman et al. 2023

Parkinson's Disease & Camp Lejeune, N.C.



Agency for Toxic Substances and Disease Registry (ATSDR) 2014:
-Less than 6% of cohort had died
- Excess mortality in Lejeune only servicemembers

Dept. of Veterans Affairs 2017

- 30 or more days of service 8/1/1953 to 12/31/1987
- Entitled to benefits

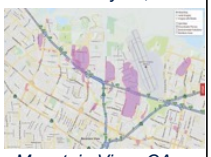
Goldman et al. 2023

Trichloroethylene (TCE) – Why Does It Matter?

- Used as a solvent in multiple industries since 1920's
- Millions of pounds used annually in US
- Multiple past uses including anesthesia, coffee decaffeination, dry cleaning
- **Environmentally persistent**
- **Present in ~ 33% of US water supplies**
- **Not monitored**
- **Volatile organic compound** – subsurface "plumes" evaporate & concentrate in homes, offices

Dayton, OH

Brooklyn, NY



Mountain View, CA

Minneapolis, MN

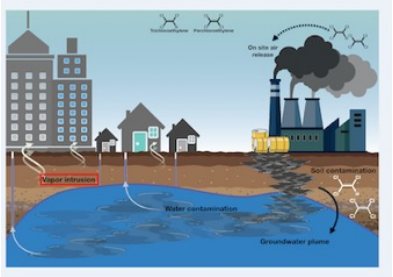
Tucson, AZ

Dry Cleaning Chemicals and Parkinson's Disease

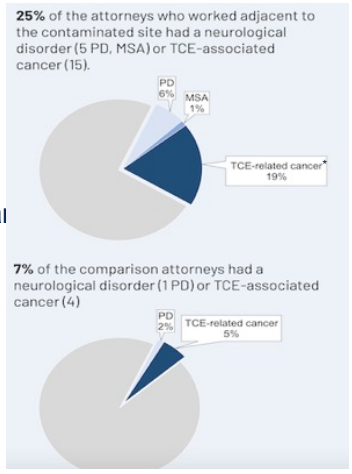
ME Pawlik [1], SE Lettenberger [1], M Zafar [1], M Coffey [1] P Auinger [1,2], CM Tanner [3], SM Goldman [4], B De Miranda [5], K Kieburtz [1,2], H Schwarz [2], M Braun [2], R Barbano [2], JL Adams [1,2], DR Kinel [1], ER Dorsey [1,2]

IPMDS 2023

Vapor Intrusion of TCE in a building adjacent to a dry clea



Evaluated :
- 79/82 attorneys in a law office in the building
- 75 comparison attorneys not working in this building



*Kidney, non-Hodgkins lymphoma, prostate, multiple myeloma

→ PD, MSA or TCE-associated cancers were found in 25% of attorneys working near to a contaminated site but 7% of comparison attorney group

Summary: TCE & Parkinson's Disease

- Occupational & residential exposure to TCE is associated with an **increased risk of Parkinson's disease**
- Residential exposure to TCE is also associated with an **increased risk of prodromal PD**
- People with PD and prior residential exposure to TCE experience **more rapid progression to disease milestones with poor prognosis** - falls, fractures & psychosis

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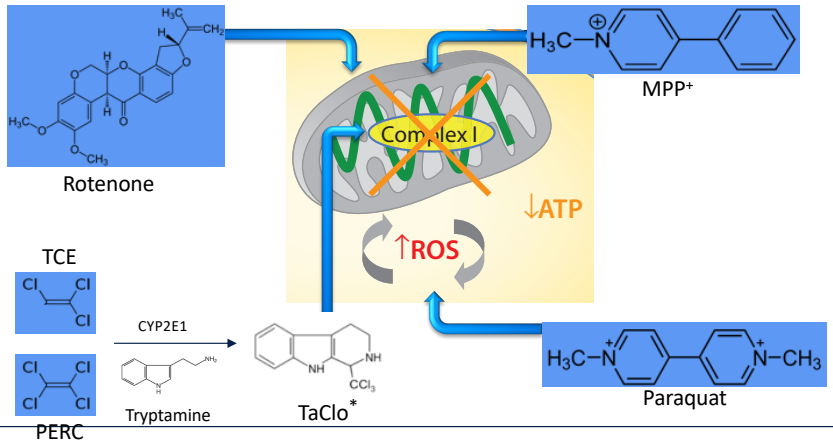
Toxicants Associated with PD Risk: Mechanistic & Structural Similarity



*1-trichloromethyl-1,2,3,4-tetrahydro-β-carboline

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Traumatic Brain Injury

UCSF

Head Injury and PD Risk in WWII Veteran Twins

Goldman, Tanner et al, Annals of Neurology 2006

Subjects: 93 discordant pairs with complete information →
26 pairs with at least one head injury

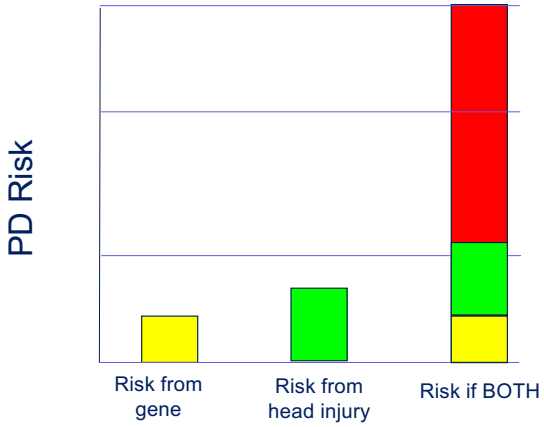
Results: 14.7% with head injury; 7.8% hospitalized

Head injury 37.4 yrs (mean) *before* PD onset

	OR	95% CI	p-value*
Overall	**3.0**	**1.14-9.2**	**0.023**
MZ	**3.3**	**0.86-19**	**0.092**
DZ	**2.7**	**0.64-16**	**0.23**

→ PD risk further increased with > 1 head injury:
1 injury: OR 2.6 (1.07,6.5; p = 0.035)
2 injuries: OR 5.1 (0.54, 48; p = 0.16)
Test for trend 0.042

BOTH Head Injury & α-Synuclein Rep 1 Gene Variant



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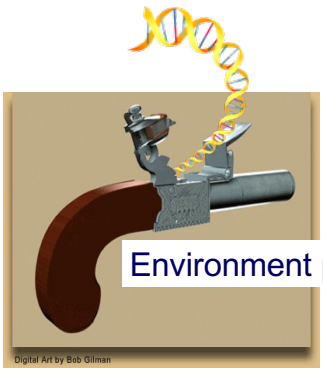
Parkinson's Disease : A Complex Disorder



Environment pulls the trigger

Traumatic Brain Injury (TBI) & Parkinsonism
2ary Service Connection

- December, 2013: 38 CFR 3.310(d) was amended to establish an association between TBI and certain illnesses:

In the absence of clear evidence to the contrary, Parkinsonism, including Parkinson's disease, following moderate or severe TBI is held to be a secondary result of TBI.

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Air Pollution
Other Exposures

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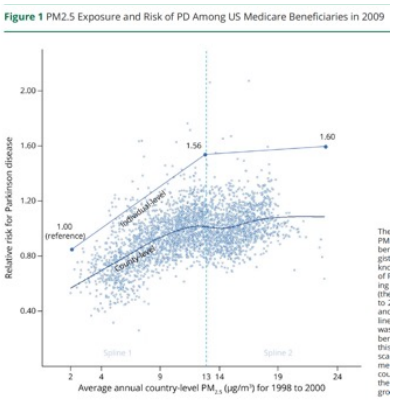
Fine Particulate Matter and Parkinson Disease Risk Among Medicare Beneficiaries

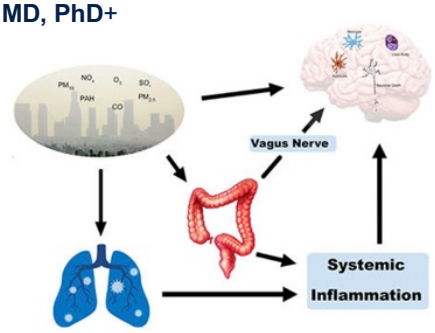
Brittany Krzyzanowski, PhD, Susan Searles Nielsen, PhD, Jay R. Turner, DSc, and Brad A. Racette, MD

Neurology® 2023;101:e2058-e2067. doi:10.1212/WNL.0000000000207871



Air Pollution and the Risk of Parkinson's Disease A Review

Hiromi Murata, PhD*, Lisa M. Barnhill, PhD*, Jeff M. Bronstein, MD, PhD+



ARTICLE OPEN

Check for updates

Incidence of Parkinson disease in North America

A. W. Willis[1✉], E. Roberts[2], J. C. Beck[3], B. Fiske[4], W. Ross[5], R. Savica[6], S. K. Van Den Eeden[7], C. M. Tanner[8], C. Marras[9] and on behalf of the Parkinson's Foundation P4 Group*

npj Parkinsons Disease 2022

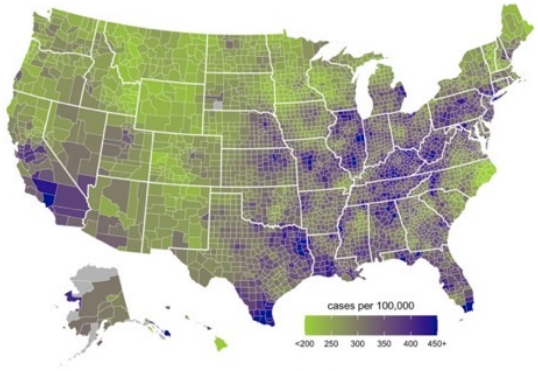


Fig. 2 Geographical variation in 2012 PD Incidence among 6,866,623 Medicare beneficiaries.

Incidence adjusted to 2010 US census

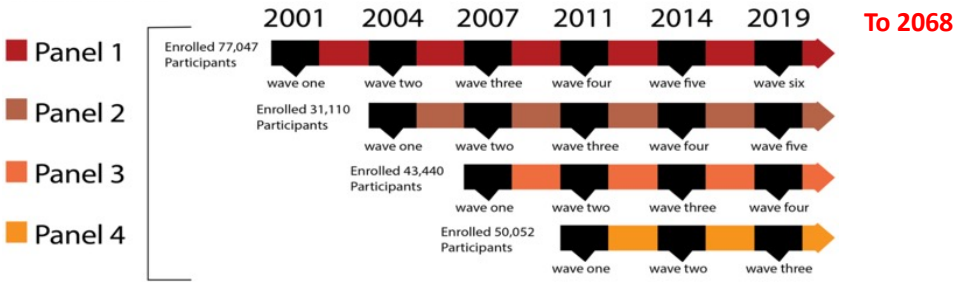
Is the geographical variation in PD incidence due to differences in environment ?

Military Burn Pits & Particulate Matter Exposure

- ~ 3.5 million US military exposed to burn pits, sand storms during combat deployments in last 30 years
- Burn pits contain many types of waste, organic and chemical
- Particulate matter & volatile aromatic compounds result
- PACT Act of 2022 provides health benefits for some illnesses, not including Parkinson's disease
- VA has established burn pit registry

Research In Progress

The Millenium Cohort: DoD, NHRC



Questionnaires every 3-5 years:

- Exposures
- Experiences
- Lifestyle
- Health

201,619 enrolled

- Highly diverse
- All service branches
- 30% female
- 30% non-White

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MilCo Exposure Examples

Particulates, combustion products:

Substance/threat	Likely exposed group	Exposure route	Exposure duration
Burn pits	Deployed lower ranks	respiratory	daily in deployment
Oil well smoke	Vicinity burning oil fields	respiratory	months
Petroleum products	Fuel handlers, mechanics	respiratory, dermal	8h workday

Solvents, fuels:

Substance/threat	Likely exposed grp	Exposure route	Exposure duration
Solvents/TCE	Armorers	respiratory, dermal	8h workday
Jet fuel dust suppression	All deployed forces in tents	respiratory	daily in deployment

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MilCo Exposure Examples: Pesticides

Substance/threat	Likely exposed grp	Exposure route	Exposure duration
Permethrin	All troops >2005	dermal	chronic
Chlorpyrifos, malathion	All deployed forces in tents	respiratory	daily in deployment

- Unique exposure routes and combinations
- Chronic/repetitive dosing

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MilCo Exposure Examples: Unique, biologically plausible exposures

Substance/threat	Likely exposed grp	Exposure route	Exposure duration
Pyridostigmine bromide	All deployed forces	oral ingestion	daily in deployment
Low level sarin	Vicinity of Khamisiyah	respiratory	<1 day twice
Depleted uranium embedded fragments	friendly fire injuries	subdermal	chronic
Combat stress	All deployed forces	Combat stress	All deployed forces

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Parkinson's Disease – Presumptive Relationship to Qualifying Military Service

Presumptive diseases: Certain diseases assumed by VA to be related to a Veteran's qualifying military service.

Parkinson's disease:

Agent Orange (qualifying service in Vietnam, Korea, other) **+**
Parkinsonism 2021
Camp Lejeune residence 1953-1987 (Cl solvents in H_2O)
Traumatic brain injury (2ary)

Hope for the Future

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What Causes Parkinson's Disease?

Genes

Risk

- Mendelian < 20 - 30 % PD
- Penetrance reduced:
  Other genes & environmental factors

GWAS: Many variants → small contributions to risk

- **Autosomal Dominant. ~ 5% PD**
  PARK-*SNCA*, PARK-*LRRK2*, PARK-*VPS35*
- **Autosomal Recessive < 5% PD**
  PARK-*Parkin*, PARK-*PINK1*, PARK-*DJ1*, PARK-*DNAJC6*
- **Complex phenotypes < 1% PD**
- **Glucocerebrosidase 5 – 8 % PD**

Environment

Risk

- **Pesticides**
  Paraquat, rotenone, organochlorines, organophosphates
- **Solvents**
  PERC, TCE, CCl_4
- **Head Injury**
- **Air Pollution**
- **Others**

Risk

- **Physical Activity**
- **Healthy\Mediterranean Diet**
- Coffee & Tea Intake
- Tobacco Use
- Other

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Poewe et al,2017; Obeso et al, 2017; Nalls et al, 2019

Precision Medicine

-Personalized treatment – right person, right time

-Incorporates genetic, environmental, lifestyle characteristics

Requirements:

- Risk stratification
- Early detection of pathophysiologic processes
- Intervention that targets specific molecular pathophysiology *in an individual*

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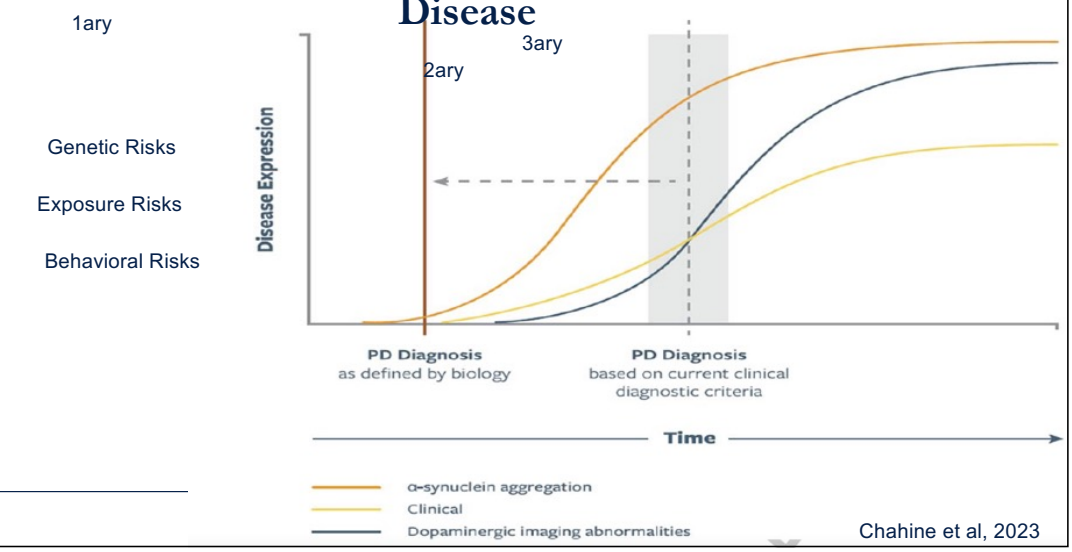
Biological vs Clinical Diagnosis of Parkinson's Disease



Chahine et al, 2023

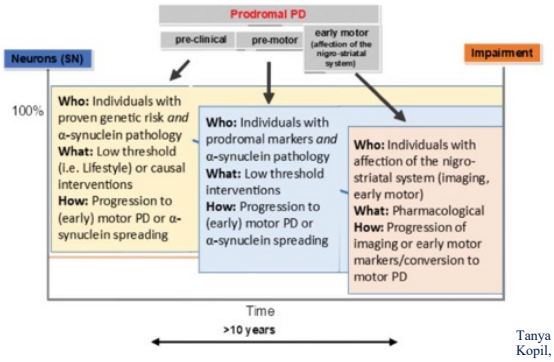
ARTICLE OPEN ACCESS

Path to Parkinson Disease Prevention

Conclusion and Outlook

Daniela Berg, MD, Grace F. Crotty, MD, Jessi L. Keavney, MBA, Michael A. Schwarzschild, MD, PhD, Tanya Simuni, MD, FAAN, and Caroline Tanner, MD, PhD

Neurology® 2022;99:S76-S83. doi:10.1212/WNL.0000000000200793



Next Steps

Parkinson's Progression Markers Initiative

P2P Clinical Trial:
-In planning stages
-PPMI Participants, Not PD
-Biologically-defined Risk
-Interventions to delay onset of motor or cognitive PD

Tanya Simuni, Christopher Coffey, Andrew Siderowf, Caroline Tanner, Sohini Chowdhury, Catherine Kopil, Todd Sherer, Michael Brumm, Karl Kieburtz, Kimberly Fabrizio, Ben Saville, Cora Allen-Savietta, Barbara Wendelberger, Amy Crawford and Ken Marek on behalf of the PPMI Investigators

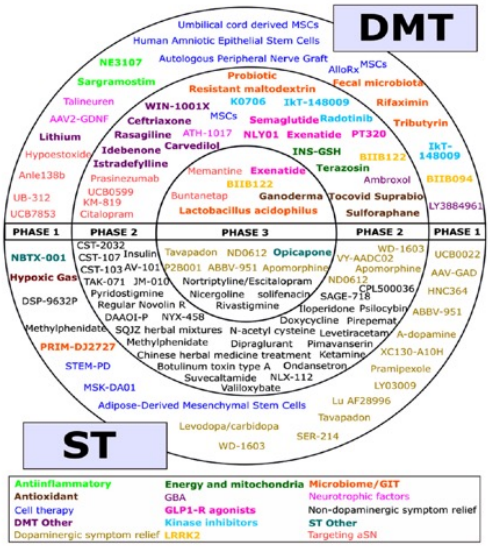
Hope for the Future - Agents in Active PD Drug Trials

63 Disease Modifying Therapy (DMT) Trials:

25 Phase I

32 Phase II

6 Phase III



DMT Therapy categories

- Antiinflammatory
- Antioxidants
- Cell therapy
- DMT Other
- Energy and mitochondria
- GBA
- GLP-1 agonists
- Kinase
- LRRK2
- Microbiome/GIT
- Neurotrophic factors
- Targeting alpha synuclein

McFarthing K, et al, *J Parkinsons Dis*

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THANK YOU!!

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Sponsors:

NIH Aging

National Institute of Neurological Disorders and Stroke

NIEHS

Neurotoxin Exposure Treatment Research Program

MMRP Military Operational Medicine Research Program

The Michael J. Fox Foundation for Parkinson's Research

James & Sharron Clark

Parkinson's Foundation

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