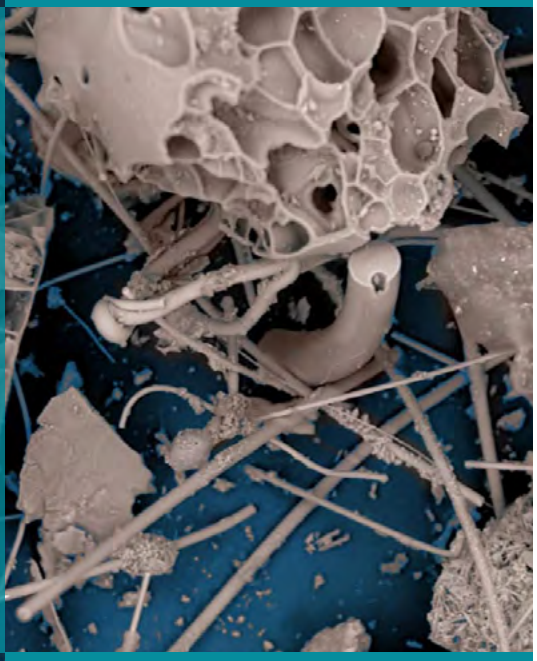

June 12, 2024

Research Meeting

Murphy Auditorium
550 1st Ave., New York, NY 10016

Visit **www.cdc.gov/wtc/research** or scan the QR code for digital meeting resources

9.11 World Trade Center Health Program | Research

Disclaimer: Funding for this meeting was made possible (in part) by the Centers for Disease Control and Prevention. The views expressed in written meeting materials or publications and by speakers and moderators do not necessarily re¬flect the official policies of the Department of Health and Human Services, nor does the mention of trade names, commercial practices, or organizations imply endorsement by the U.S. Government.

Some data presented may be preliminary and subject to change following peer-and journal review prior to publication.

Agenda

9 a.m. – 9:15 a.m. **Welcome**
Master of Ceremonies: Max Lum

9:15 – 10 a.m. **A life course exposomic approach to understanding World Trade Center health effects in youth**
35 min presentation, followed by a 10-minute Q&A
9:15 a.m. *Dr. Trasande and Dr. Herbstman*

10 a.m. – 10:10 a.m. **Break (10 Minutes)**

10:10 a.m. – NOON **Session 1: World Trade Center exposures and changes to cognition**
25 min presentations of key findings, impact, research gaps followed by 10-minute Q/A

10:15 a.m. **Dr. Clouston** - *Amyloidogenesis and neurodegeneration in WTC exposure-related cognitive dysfunction: A study of WTC responders*
10:50 a.m. **Dr. Mann** - *Prevalence of cognitive impairment in World Trade Center exposed Fire Department of the City of New York and general emergency responders*
11:25 a.m. **Dr. Kritikos** - *Neuroimaging of inflammation in WTC-exposed responders*

NOON – 1 p.m. **Lunch**

1 p.m. - 1:10 p.m. **Welcome back from lunch**

1:10 p.m. – 3 p.m. **Session 2: Research in molecular imaging and the importance of PTSD**
25 min presentations of key findings, impact, research gaps followed by 10-minute Q/A

1:15 p.m. **Dr. Vaska** - *Direct assessment of brain beta-amyloid plaques in WTC first responders*
1:50 p.m. **Dr. Sampson** - *Post-traumatic stress disorder and physical function over time among World Trade Center responders*
2:25 p.m. **Dr. Waszczuk** - *Polygenic prediction in 9/11 responders: What have we learned and where are we going?*

3 p.m. – 3:10 p.m. **Break (10 minutes)**

3:10 p.m. – 3:45 p.m. **Panel Discussion for Sessions 1 and 2**
Moderated by Dr. Luft

3:45 p.m. – 4 p.m. **Final Comments**

Table of Contents

Leonardo Trasande, MD MPP

Early life exposure to the WTC disaster: Revisiting research priorities and new directions

Leonardo Trasande, MD, MPP is an internationally renowned leader in children's environmental health. His research focuses on identifying the role of environmental exposures in childhood obesity and cardiovascular risks, and documenting the economic costs for policy makers of failing to prevent diseases of environmental origin in children proactively. He also holds appointments in the Wagner School of Public Service and NYU's College of Global Public Health. He is perhaps best known for a series of studies published in Lancet Diabetes and Endocrinology and the Journal of Clinical Endocrinology and Metabolism that document disease costs due to endocrine disrupting chemicals in the US and Europe of $340 billion and €163 billion annually, respectively. Dr. Trasande leads one of 35 centers across the country as part of the National Institute of Health's Environmental Influences on Child Health Outcomes program. He is leveraging the NYU Children's Health and Environment Study as well as another birth cohort to examine phthalates, bisphenols, organophosphate pesticides and polycyclic aromatic hydrocarbons and their effects on fetal as well as postnatal growth and early cardiovascular and renal risks. These two cohorts are part of a larger initiative nationally to identify preventable and environmental factors that influence child health and disease. He is Principal Investigator on numerous other NIH-funded projects. These include a study on prenatal and childhood phthalate and bisphenol exposures in Generation R (a Dutch birth cohort) to examine obesity and cardiovascular risks, as well as another project studying the effect of these dietary contaminants in children with chronic kidney disease, with the hypothesis that these exposures create oxidant stress and accelerate disease progression. He is also Principal Investigator for a research project comparing neurodevelopment, cardiometabolic and respiratory profiles of children exposed in utero to the World Trade Center disaster to a comparison group. He has served as a member of numerous scientific committees and expert panels, including: the American Academy of Pediatrics' Executive Committee of the Council for Environmental Health; the Science and Technical Advisory Committee for the World Trade Center Health

Leonardo Trasande, MD MPP

Program; the National Children's Study Methodological Review Panel of the National Academy of Sciences; the United Nations Environment Programme Steering Committee on a Global Outlook for Chemicals; and the Board of Scientific Counselors for the National Center for Environmental Health at the Centers for Disease Control and Prevention (CDC). After receiving his bachelor, medical and public policy degrees from Harvard, he completed the Boston Combined Residency in Pediatrics and a legislative fellowship in the Office of Senator Hillary Rodham Clinton. Prior to coming to NYU, he completed fellowship training in environmental pediatrics. For five years he also was a Lead Investigator in one of the original (Vanguard) locations of the National Children's Study, and Deputy Director for the largest (eight location) Study Center spanning a region from upstate New York to central New Jersey.

Early Life Exposure to the WTC Disaster: Revisiting Research Priorities and New Directions

Leonardo Trasande, MD, MPP
Director, NYU Grossman Center for the Investigation of Environmental Hazards
Jim G. Hendrick, MD Professor of Pediatrics and Vice Chair for Research in Pediatrics
Director, Division of Environmental Pediatrics
Professor of Population Health
NYU Grossman School of Medicine

Disclosures

Funding: NIH, CDC/NIOSH and EPA relating to effects of environmental chemicals on human health

Travel support: Endocrine Society, WHO, UNEP, Japan Environment and Health Ministries, American Academy of Pediatrics

Book Honoraria: Houghton Mifflin Harcourt, Audible, Paidos, Kobunsha (*Sicker Fatter Poorer: The Urgent Threat of Hormone-Disrupting Chemicals to Our Health and Future . . . and What We Can Do About It*)

Scientific Advisory Roles: Beautycounter, IS-Global, Footprint, Food Packaging Forum, Ahimsa

HASSENFELD CHILDREN'S HOSPITAL OF NEW YORK AT NYU LANGONE

WTC dust

Predominantly (95%) coarse particles and contained:

- pulverized cement,
- glass fibers,
- asbestos,
- lead,
- mercury,
- other heavy metals,
- polycyclic aromatic hydrocarbons (PAHs),
- polychlorinated biphenyls (PCBs),

Selected biomarker studies of WTC populations

- 368 firefighters had blood and urine collected October 1-5, 2001
- 110 chemicals (PAH, VOC, PCBs, cyanide, lead, mercury, 13 metals in urine; no PFAS/PBDE)
- 78 detected in >60%
- Higher levels of one dioxin (>95%ile NHANES), PAH, antimony (flame retardant in plastic) higher in relationship to exposure

Edelman et al EHP 2003

- Also higher odds of detecting one furan, cadmium, trichloroethylene and ethylbenzene

Selected biomarker studies of WTC populations

Responders have also been identified to have higher PFC biomarkers than nationally representative samples, as well as higher levels of PFCs in relationship to WTC dust/smoke exposure.

Tao et al ES&T 2008;42(9):3472-3478.

Selected biomarker studies of WTC populations

Mercury and polybrominated diphenyl ethers (PBDEs) not significantly different among women living/working near the site

- Women in their second half of pregnancy on September 11, 2001 did have children with higher cord blood PBDE levels

Herbstman et al EHP 2010

Selected biomarker studies of WTC populations

Dioxins in adolescents exposed 12 years after disaster markedly higher than matched comparisons and often above 95th percentile for contemporaneous NHANES adolescents

Lower 2,3,7,8-TCDD (10 ppt) than other environmental disasters Yusho and Seveso (192 ppt), but higher lipid adjusted total PCDD than Chapaevsk, Russia cohort (Volga chemical plant contamination of water)

Table A.4
Distributions and TEQs of serum PCDD/Fs in WTCHR vs. Russian Children's Study participants.

	WTCHR (n = 60)		Russian Children's Study (n = 482)	
	Median (25th, 75th percentile)	Median TEQ*	Median (25th, 75th percentile)	Median TEQ*
Serum polychlorinated dibenzo-*p*-dioxins (PCDDs) (pg/g lipid)				
2,3,7,8-TCDD	1.71 (0.74, 20.2)	1.71	2.75 (1.34, 3.90)	2.75
1,2,3,7,8-PenCDD	14.1 (0.65, 34.4)	14.1	4.10 (1.41, 7.00)	4.10
1,2,3,4,7,8-HexCDD	0.01 (0.01, 12.5)	0.001	2.00 (0.71, 3.90)	0.20
1,2,3,6,7,8-HexCDD	0.02 (0.02, 0.04)	0.002	8.70 (5.40, 16.6)	0.87
1,2,3,7,8,9-HexCDD	14.4 (10.3, 27.0)	1.44	2.61 (0.85, 4.60)	0.26
1,2,3,4,6,7,8-HepCDD	23.5 (14.0, 47.2)	0.23	12.2 (8.20, 19.5)	0.12
OCDD	135 (64.8, 394)	0.04	96.1 (69.0, 134)	0.03
Σ PCDD	197 (128, 580)	17.5	136 (93, 189)	8.2
Serum polychlorinated dibenzofurans (PCDFs) (pg/g lipid)				
2,3,7,8-TCDF	29.1 (15.5, 48.9)	2.91	0.50 (0.42, 1.63)	0.05
1,2,3,7,8-PenCDF	13.2 (0.01, 28.9)	0.40	0.57 (0.42, 1.91)	0.02
2,3,4,7,8-PenCDF	12.1 (0.24, 22.3)	3.64	9.0 (6.20, 14.6)	2.70
1,2,3,4,7,8-HexCDF	0.03 (0.02, 13.4)	0.0003	6.65 (4.10, 12.5)	0.67
1,2,3,6,7,8-HexCDF	0.02 (0.02, 0.05)	0.0002	4.20 (2.90, 6.70)	0.42
2,3,4,6,7,8-HexCDF	0.01 (0.01, 0.01)	0.0001	0.57 (0.42, 1.41)	0.06
1,2,3,7,8,9-HexCDF	6.29 (0.02, 33.2)	0.06	0.57 (0.42, 1.84)	0.06
1,2,3,4,6,7,8-HepCDF	77.5 (41.4, 161)	0.77	7.50 (5.47, 11.3)	0.08
1,2,3,4,7,8,9-HepCDF	0.01 (0.01, 0.01)	0.0001	0.64 (0.50, 2.26)	0.01
OCDF	26.4 (0.01, 110)	0.01	2.90 (1.80, 5.00)	0.001

Kahn et al; Env Int 2018

Selected biomarker studies of WTC populations

Though PFAS exposures were higher among WTCHR adolescents than comparisons, median WTCHR PFAS levels were below median NHANES adolescents.

Serum PFASs, ng/mL Median (IQR)			
PFHxS (n < LOD= 0%)	0.53 (0.47)	0.67 (0.69)	**<0.0001**
PFOS (n < LOD= 0%)	2.78 (2.18)	3.72 (2.82)	**<0.0001**
PFOA (n < LOD= 0%)	1.39 (0.75)	1.81 (0.90)	**<0.0001**
PFNA (n < LOD= 0.3%)	0.49 (0.33)	0.61 (0.36)	**<0.0001**
PFDA (n < LOD= 25%)	0.11 (0.15)	0.14 (0.12)	**<0.0001**
PFUnDA (n < LOD= 47%)	0.04 (0.16)	0.12 (0.21)	**0.007**
Calories,** Median (IQR)	1537.39 (1014.41)	1708.75 (1317.49)	**0.008**

Trasande et al Env Res 2017

PFOA levels in cord blood collected after delivery between 12/2001-6/2002 13% higher among those living or working within 2 mi of WTC site in 4 weeks following the event

- Median PFOS (6 ng/mL) lower than median NHANES 2003-4 (20 ng/mL among >20 year old women)
- Association was stronger when comparing just those who lived, regardless of work location.

Spratlen et al Env Poll in review

Selected biomarker studies of WTC populations

Exposure Index (EI) developed for 187 pregnant women at/near WTC site on/soon after September 11

- Most located within 8 blocks of site, much lower over next 4 weeks
- No association with PAH-DNA adducts
- Lead and cobalt in urine were nonsignificantlly associated with EI
- Median sum of PCB 118, 138, 153, and 180 = 84 ng/g lipid, nonsignificant positive association with EI
- Median 1,2,3,4,6,7,8-Heptachlorodibenzodioxin levels (30 pg/g lipid) similar to levels reported in WTC-exposed firefighters, not associated with EI.

Wolff et al EHP 2005

Selected biomarker studies of WTC populations

PAH-DNA adducts in cord and maternal blood highest among newborns and mothers who resided <1 mi of the WTC site during month after September 11

Perera et al Environ Health Perspect. 2005

Doubling among ETS-exposed subjects only: 276-g (8%) reduction in birth weight (p = 0.03) and a 1.3-cm (3%) reduction in head circumference (p = 0.04).

Perera et al Cancer Epidemiol Biomarkers Prev. 2005

WTC mothers: 57.5% detectable PAH-DNA adducts, compared to Northern Manhattan (36.8%), Krakow (72.9%), Tongliang (73.4%)

WTC newborns: 60.6% compared to Northern Manhattan (42.4%), Krakow (71.1%), Tongliang (79.5%).

Perera et al Environ Health Perspect. 2007

Significant interaction between cord blood adducts and in utero exposure to ETS on mental development index score at 3 years of age (p = 0.02, n = 98) whereas neither adducts nor ETS alone was a significant predictor of (BSID-II) cognitive development.

Summarizing knowledge (and lack of knowledge) regarding WTC chemical exposure

Exposure	Responders	Pregnant Women	Community children	Community adults
Lead	NS	NS (0/1)	?	?
Mercury	NS	NS (0/1)	?	?
Other heavy metals	Antimony, cadmium	?	?	?
PBDE	?	NS (0/2)	?	?
PFAS	NS	+	+	?
Dioxins/furans	+	+	+	?
PCBs	NS	?	?	?
PAHs/adducts	+	+ (1/2), NS (1/2)	?	?

Summarizing knowledge (and gaps of knowledge) regarding WTC chemical exposure

Strongest evidence for dioxins > PFAS, PAH > PBDE, PCB >> Pb, Hg

Limited evidence for antimony, cadmium

PFAS studies limited in part by lag to collection in one study

PBDE studies limited in part by power, exposure imprecision

Inconsistency in one pregnancy study for PAH could be byproduct of power (n=100; 44 collected February-March 2002)

Highest exposed group studies limited by immediate measurement

- Fires continued for months afterwards, producing accumulation of exposures

What did we know about the potential health effects of WTC chemicals in 2001?

- Neurodevelopmental effects of *in utero* exposure
- Cancer risk for all exposed populations
- Respiratory irritation and asthma (irritant > immune disruption)

What do we know now about the health effects of WTC chemicals?

- Neurodevelopmental effects of *in utero* exposure
- Cancer risk for all exposed populations
- Respiratory irritation and asthma (irritant > immune disruption)
- *Endocrine disruption*

Endocrine-Disrupting Chemicals: An Endocrine Society Scientific Statement

Evanthia Diamanti-Kandarakis, Jean-Pierre Bourguignon, Linda C. Giudice, Russ Hauser, Gail S. Prins, Ana M. Soto, R. Thomas Zoeller, and Andrea C. Gore

There is growing interest in the possible health threat posed by endocrine-disrupting chemicals (EDCs), which are substances in our environment, food, and consumer products that interfere with hormone biosynthesis, metabolism, or action resulting in a deviation from normal homeostatic control or reproduction. In this first Scientific Statement of The Endocrine Society, we present the evidence that endocrine disruptors have effects on male and female reproduction, breast development and cancer, prostate cancer, neuroendocrinology, thyroid, metabolism and obesity, and cardiovascular endocrinology. Results from animal models, human clinical observations, and epidemiological studies converge to implicate EDCs as a significant concern to public health. The mechanisms of EDCs involve divergent pathways including (but not limited to) estrogenic, antiandrogenic, thyroid, peroxisome proliferator-activated receptor γ, retinoid, and actions through other nuclear receptors; steroidogenic enzymes; neurotransmitter receptors and systems; and many other pathways that are highly conserved in wildlife and humans, and which can be modeled in laboratory in vitro and in vivo models. Furthermore, EDCs represent a broad class of molecules such as organochlorinated pesticides and industrial chemicals, plastics and plasticizers, fuels, and many other chemicals that are present in the environment or are in widespread use. We make a number of recommendations to increase understanding of effects of EDCs, including enhancing increased basic and clinical research, invoking the precautionary principle, and advocating involvement of individual and scientific society stakeholders in communicating and implementing changes in public policy and awareness. (Endocrine Reviews 30: 293–342, 2009)

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ETIOLOGY AND PATHOPHYSIOLOGY

OBESITY REVIEWS WILEY

Endocrine-disrupting chemicals and obesity risk: A review of recommendations for obesity prevention policies

Tim Lobstein[1,2] | Kelly D. Brownell[3]

[1]World Obesity Federation, London, UK
[2]Boden Collaboration, University of Sydney, Camperdown, New South Wales, Australia
[3]Duke World Food Policy Center, Sanford School of Public Policy, Durham, North Carolina, USA

Correspondence
Tim Lobstein, World Obesity Federation, Suite 406, 107-111 Fleet Street, London EC4A 2AB, UK.
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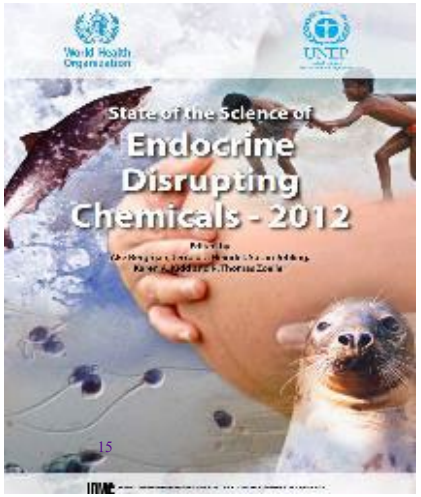
Summary
Emerging evidence indicates that industrially produced endocrine-disrupting chemicals (EDCs) may be as obesogenic as poor dietary patterns and should be considered in obesity prevention policies. The authors conducted two reviews: (a) a systematic search of four electronic databases for papers published since January 2010 to identify the policy recommendations contained in scientific reviews of EDC exposure and obesity risk and (b) a narrative review of obesity policy documents published since January 2012 to identify the recommendations of national and international agencies. A search of four electronic databases found 63 scientific reviews with policy recommendations, of which 26 suggested individual responsibility to avoid exposure, 11 suggested medical interventions to counter the effects of exposure, and 42 suggested regulatory control of hazardous chemicals. Of sixty policy documents examined, six mentioned pollutants as a possible risk factor for obesity, and only one made explicit reference to strategies for reducing exposure to EDCs. The UN Sustainable Development Goals include targets to prevent ill health from hazardous chemicals (Targets 3.9 and 12.4) a
environment (Targets 6.3, 11.6, 12.
explicitly linked to World Health A

POLICY STATEMENT Organizational Principles to Guide and Define the Child Health Care System and/or Improve the Health of all Children

American Academy of Pediatrics
DEDICATED TO THE HEALTH OF ALL CHILDREN™

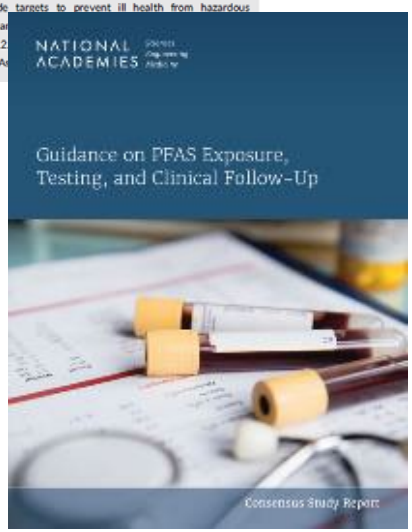
Food Additives and Child Health

Leonardo Trasande, MD, MPP, FAAP,[a] Rachel M. Shaffer, MPH,[b] Sheela Sathyanarayana, MD, MPH,[b,c]
COUNCIL ON ENVIRONMENTAL HEALTH



EDC-2: The Endocrine Society's Second Scientific Statement on Endocrine-Disrupting Chemicals

A. C. Gore, V. A. Chappell, S. E. Fenton, J. A. Flaws, A. Nadal, G. S. Prins, J. Toppari, and R. T. Zoeller



Life course perspective

Outcomes for a cohort

TABLE 1. Disorders of the human reproductive system possibly involving EDCs in their pathogenesis: A sexually dimorphic life cycle perspective

	Fetal/neonatal	Prepubertal	Pubertal	Adult
Processes	Intrauterine growth Sexual differentiation	Adrenarche	Gonadarche	Spermatogenesis Ovulation Hormonal control of prostate, breast, uterus, and lactation
Male disorders	IUGR (15) Cryptorchidism (14, 20)[a] Hypospadias (14, 20)[a]	Premature pubarche	Small testes and high FSH (18) Early puberty (25) Delayed puberty (25)	Oligospermia (14, 20)[a] Testicular cancer (14, 20)[a] Prostate hyperplasia (24)
Female disorders	IUGR	Premature thelarche (25) Peripheral precocious puberty (17) Premature pubarche (18)	Secondary central precocious puberty (17, 27) PCOS (18, 25) Delayed ovulatory cycles (17, 18)	Vaginal adenocarcinoma (19, 28) Disorders of ovulation (29) Benign breast disease (29, 31) Breast cancer (30, 31) Uterine fibroids (29) Disturbed lactation (29)

[a] Cryptorchidism, hypospadias, oligospermia and testicular cancer are four components of the "testicular dysgenesis syndrome" as a common entity.

Endocrine Reviews, June 2009, 30(4):293–342

World Trade Center exposures

WTC chemicals with human data suggesting role in obesity, diabetes and cardiovascular disease

Dioxins

Warner et al 2013

Perfluoroalkyl chemicals

Halldorsson et al 2012

Polycyclic aromatic hydrocarbons

Rundle et al Am J Epidem 2012

Polybrominated diphenyl ethers

Lim et al Diabetes Care 2008

Endocrine disruption and fertility

Fertility is a condition of a couple, where reproductive health of both sexes plays a role

Louis et al 2013

Fetal exposure to phthalates with reduced infant anogenital distance (AGD)

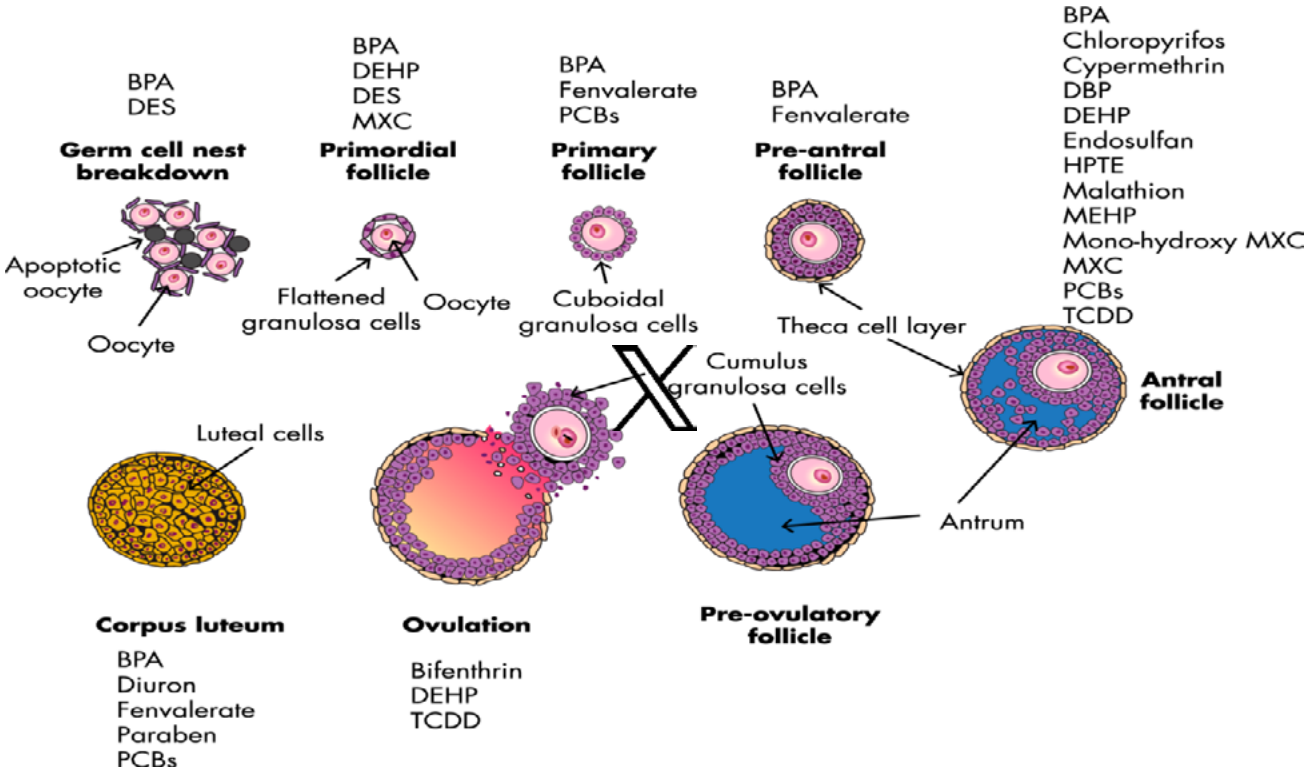
Swan et al EHP 2005, Bornehag et al EHP 2014

Shortened adult AGD is associated with reduced semen quality and testosterone level

Multiple studies have identified reduced male fertility and poor semen quality with multiple EDCs, including phthalates, bisphenol A, and polyfluorinated chemicals

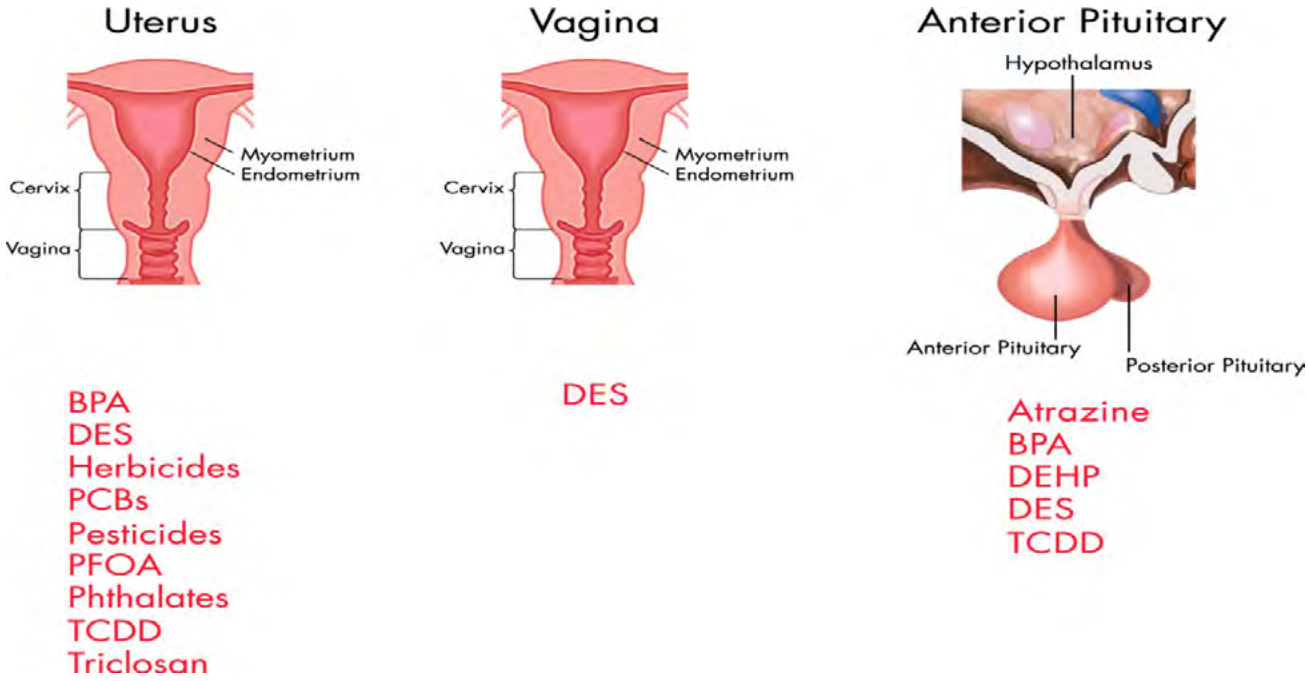
Juul et al Nat Rev Endo 2014

The effects of EDCs on the ovary



From: EDC-2: The Endocrine Society's Second Scientific Statement on Endocrine-Disrupting Chemicals
Endocr Rev. 2015;36(6):E1-E150. doi:10.1210/er.2015-1010

EDC-2: The Endocrine Society's Second Scientific Statement on Endocrine-Disrupting Chemicals



From: EDC-2: The Endocrine Society's Second Scientific Statement on Endocrine-Disrupting Chemicals
Endocr Rev. 2015;36(6):E1-E150. doi:10.1210/er.2015-1010

WTC-related EDCs and puberty

In addition to other studies abroad, in a WV-based study near a contaminated site, higher serum concentrations of PFOA or PFOS were associated with later age of sexual maturation in 2931 girls aged 9–18 years (130-d delay for PFOA and 138-d delay for PFOS exposure)

Lopez-Espinosa et al ES&T 2011

In Chapaevsk cohort, higher dioxin TEQs were associated with later pubertal onset by testicular volume (hazard ratio = 0.68, 95% confidence interval, 0.49–0.95 for the highest compared with the lowest quartile).

Korrick et al EHP 2011

WTC-related EDCs and endocrine cancers

TCDD (OR 2.1) associated in Seveso Women's Health Study with incident breast cancer

(Warner et al EHP 2002)

Greenlandic Inuit women: positive association between serum concentrations of perfluorinated compounds and increased breast cancer risk

(Bonefeld-Jorgensen et al Environ Health 2011)

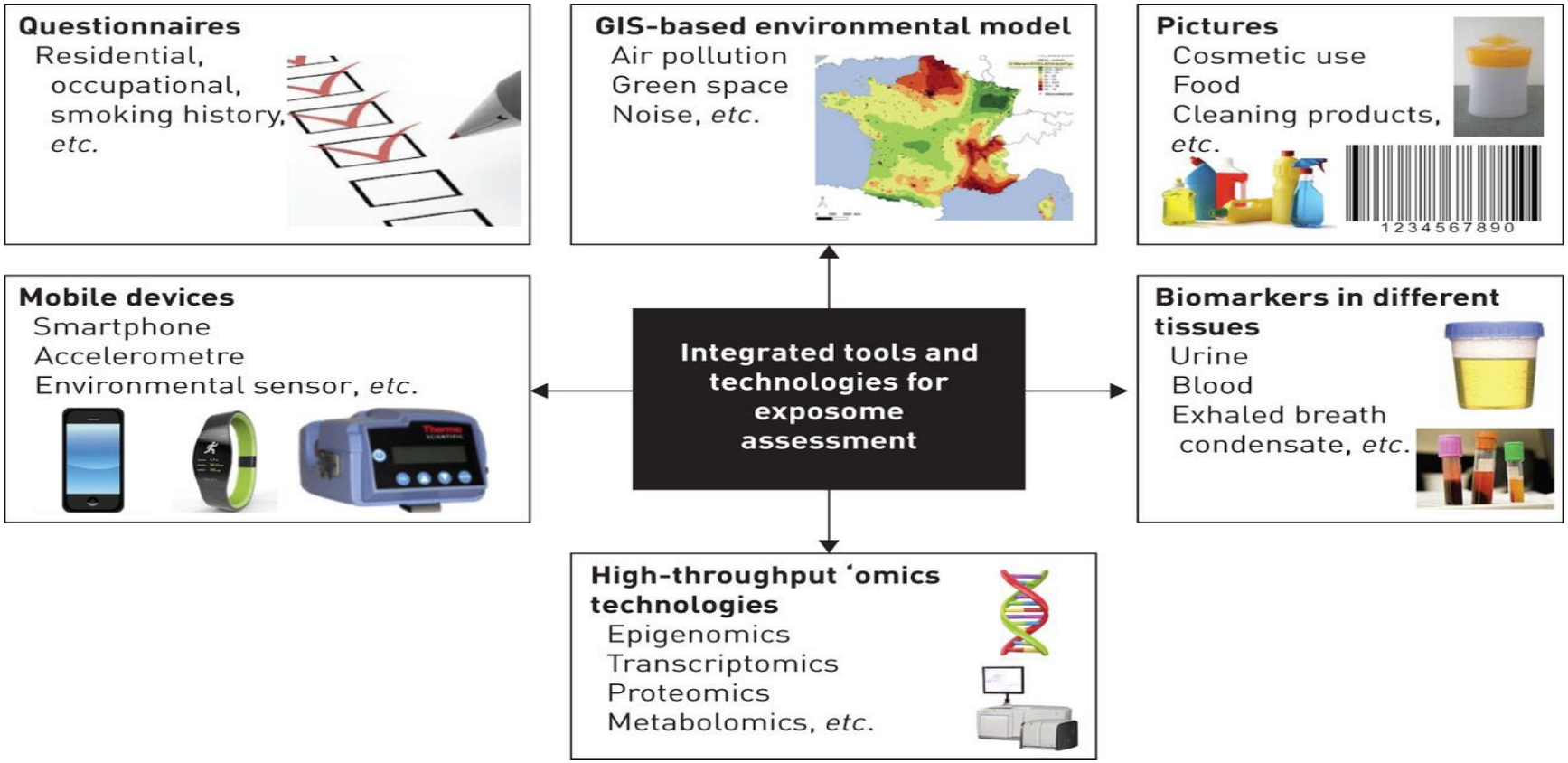
Increased prostate cancer rates in Agent Orange-exposed veterans (RR 2.3–6.0 in the highest exposure group)

(IOM 2012)

Does the exposome represent a way forward?

Coined by IARC director Christopher Wild in 2005

- Broad notion inclusive of all types of environmental exposures (chemical, social, physical, etc.)
- Molecular techniques (epigenomics, metabolomics, biomarkers of exposure and effect, etc.) can be used to measure these factors
- Embedded in the notion of the life course, especially that early exposures influence child and adult outcomes



Valérie Siroux et al. Eur Respir Rev 2016;25:124-129

How to leverage exposome to fill gaps?

Many chemicals (save dioxins) are not detectable > 18 years later

- Stored samples not available in WTCHR
- Responder/worker cohorts?

Epigenomic, metabolomic, proteomic methods may be useful as markers of WTC-chemical exposures and signal later disease risks

Skating where the puck is headed

Responder, worker and community adults

- Need to move beyond respiratory and mental health
- Shift to endocrine-related conditions

WTC populations as vulnerable to later EDC exposures

Need to consider subsequent exposures as they add to or have synergy with WTC exposures

Opportunities for intervention

Changes in research program allocation?

Passive, survey longitudinal follow up insufficient

Reallocate component of WTCHR funding to biorepository?

Stress/PTSD effects likely confounded

Future applications should require control for WTC-related chemical exposures

Exposome methods nested in extant/new populations

Thank you

HASSENFELD
CHILDREN'S
HOSPITAL
OF NEW YORK
AT NYU LANGONE

Julie B. Herbstman, PhD ScM

High-resolution mass spectrometric characterization of in utero exposure to World Trade Center (WTC) dust and associated chemicals

Trained as an epidemiologist, Julie Herbstman's research focuses on the impact of prenatal exposures to environmental pollutants, including polybrominated diphenyl ethers (PBDEs) and polycyclic aromatic hydrocarbons (PAHs) on child growth and development. She has also been involved in research exploring the long-term environmental health impact of exposure to pollutants from the collapse of the World Trade Center on 9/11. She is the director of the Columbia Center for Children's Environmental Health, where she oversees longitudinal birth cohort studies in New York City. Her work also involves the integration of epigenetic biomarkers to explore the mechanistic pathway between prenatal exposures and disease risk.

There are no background readings for this presentation

HIGH-RESOLUTION MASS SPECTROMETRIC CHARACTERIZATION OF *IN UTERO* EXPOSURE TO WORLD TRADE CENTER (WTC) DUST AND ASSOCIATED CHEMICALS

Julie Herbstman, PhD ScM

June 2024

Vrinda Kalia, PhD
Associate Research Scientist
Columbia University,
New York, USA

The collapse of the WTC towers released several toxic chemicals

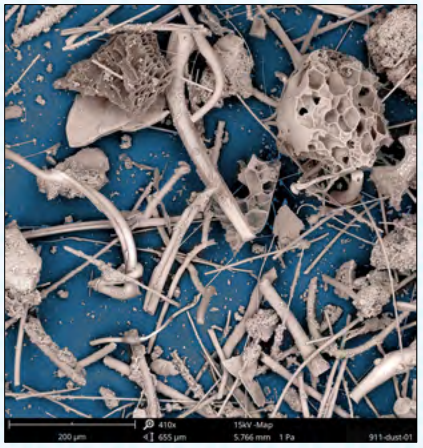
Persistent organic pollutants

- Perfluoroalkyl substances (PFAS)
- Dioxins
- Polybrominated diphenyl ethers (PBDE)
- Polychlorinated biphenyls (PCB)

WTC dust

- The dust was highly alkaline, comprising largely of concrete, gypsum, and synthetic fibers
- Asbestos fibers
- Heavy metals

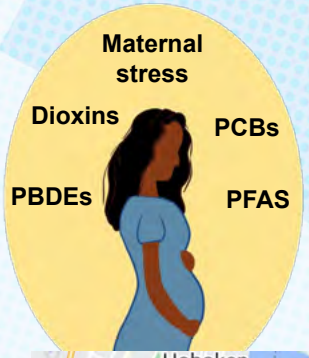
Lippmann, Morton, Mitchell D. Cohen, and Lung-Chi Chen. Critical reviews in toxicology 45.6 (2015): 492-530.



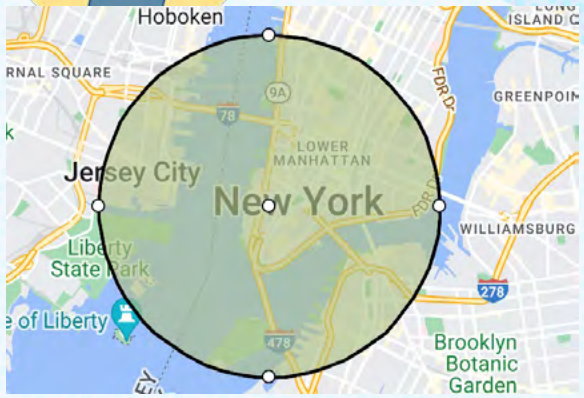
Scanning electron micrograph of WTC dust
NIOSH's Health Effects Laboratory Division (HELD) and WTC Health Program

WTC exposures have been associated with birth outcomes, neurodevelopment, & cord blood lipid metabolites

- Our group has been studying the effect of WTC exposures on pregnant women and child development.
- Found higher levels of PFAS in cord blood of women living/working within 2 miles of WTC site
- Found associations between exposure to WTC associated chemicals and:
  - Birth weight
  - Neurodevelopment
  - Lipid metabolism



COLUMBIA CENTER FOR CHILDREN'S ENVIRONMENTAL HEALTH
MAILMAN SCHOOL OF PUBLIC HEALTH
COLUMBIA UNIVERSITY



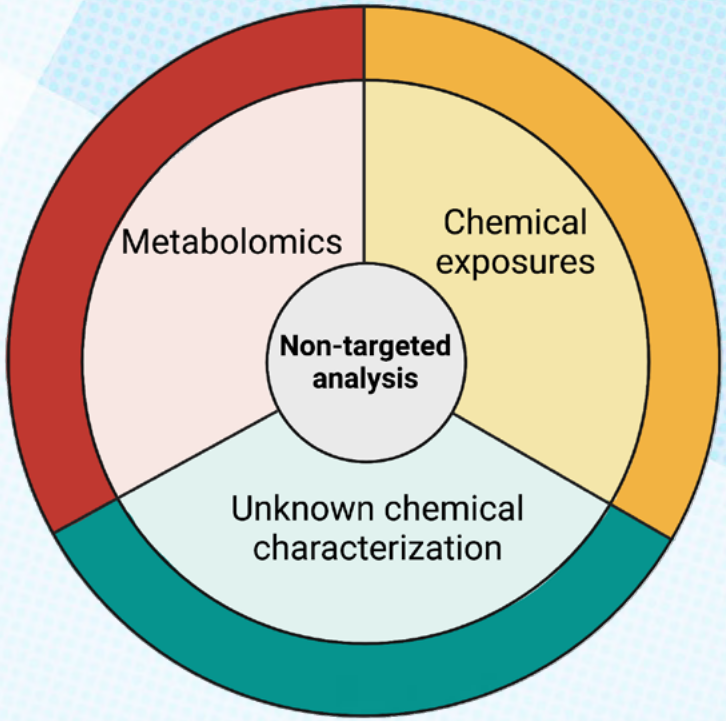
The chemical characteristics of WTC dust relevant to *in utero* exposure and the associated health effects are poorly understood.

Non-targeted analysis can reveal previously unknown health effects and exposures

Non-targeted liquid chromatography based mass spectrometry provides a wealth of data:

- Biochemical characterization
- Exposure levels of environmental toxicants
- Characterization of previously unknown chemical exposures and biomarkers

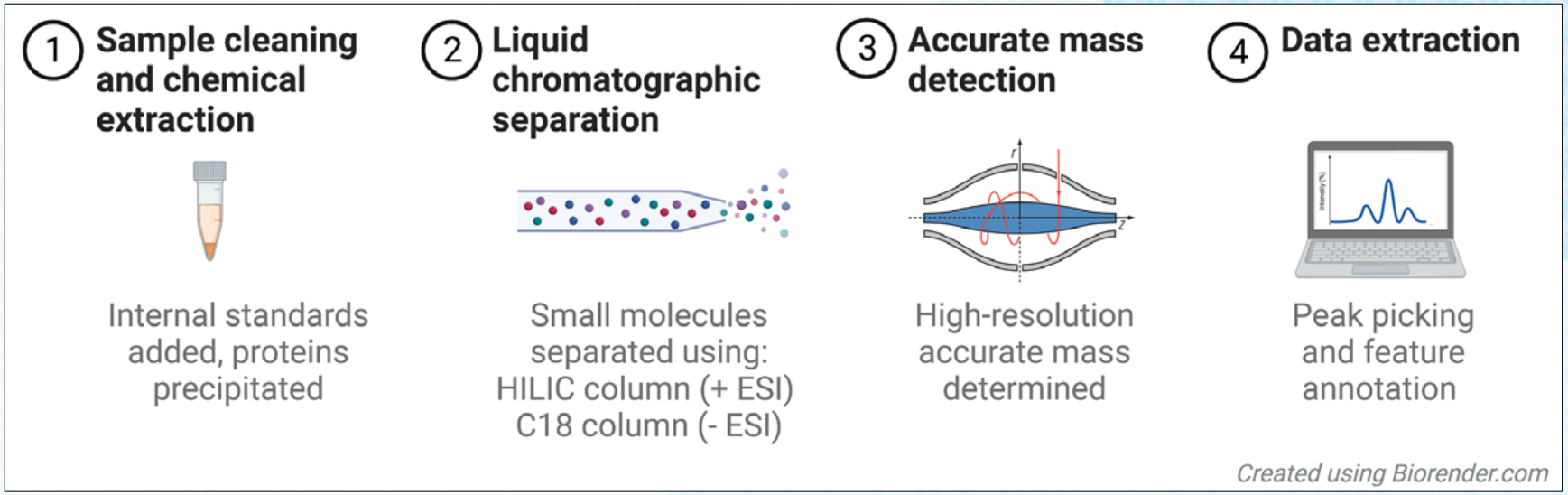
Application of non-targeted analysis (NTA) in cord blood samples can allow us to discover as yet unknown health effects and exposures



- What cord blood non-targeted chemical features are associated with exposure to dust from the WTC?
- What cord blood metabolomic features are associated with exposure to perfluorinated chemicals?

Non-targeted analysis using 100 µL of cord blood plasma

Conducted at the Columbia Exposomics core



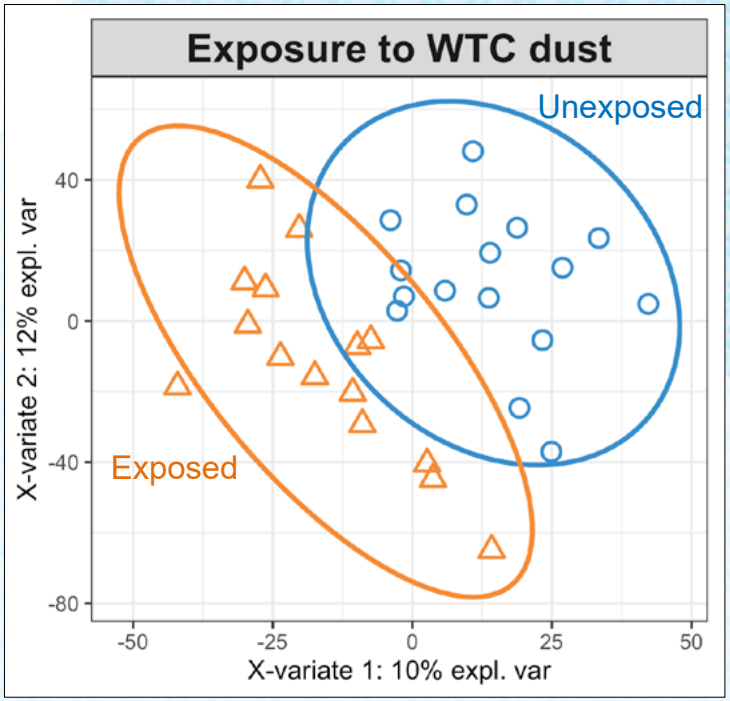
Women who reported physical exposure to dust were compared to matched controls

- Columbia University birth cohort designed to investigate the effects of WTC exposures on pregnancy outcomes and child development
- Women with singleton pregnancies enrolled between Dec 13, 2001, and June 26, 2002 at one of 3 hospitals near the WTC site
- Restricted analysis to 16 women who reported that dust from the WTC fell on them on 9/11, and matched 16 women who reported that dust did not fall on them

	No contact with dust on 9/11 (N=16)	Dust fell on them on 9/11 (N=16)
Maternal age (years)		
Mean (SD)	28.6 (5.87)	31.8 (5.06)
Median [Min, Max]	28.3 [18.1, 35.8]	32.7 [21.7, 39.7]
Gestational age (days)		
Mean (SD)	277 (9.38)	275 (10.7)
Median [Min, Max]	277 [263, 294]	278 [247, 294]
Body mass index (kg/m2)		
Mean (SD)	26.0 (6.45)	25.0 (5.72)
Median [Min, Max]	24.2 [19.0, 43.7]	22.0 [19.5, 37.0]
Missing	0 (0%)	1 (6.3%)
Education		
< High School	5 (31.3%)	1 (6.3%)
High School	2 (12.5%)	2 (12.5%)
> High School	9 (56.3%)	13 (81.3%)

Dimensionality reduction to discover features associated with exposure

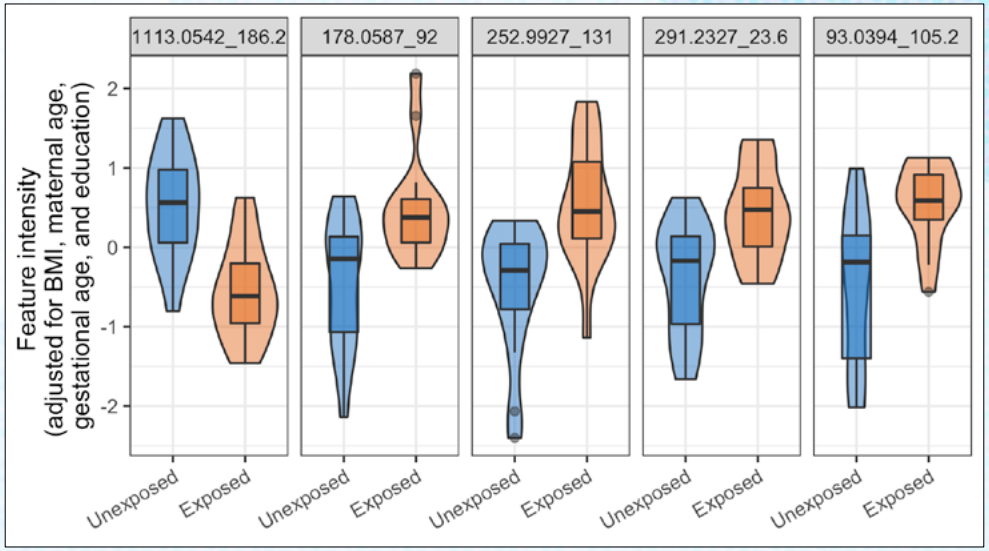
- Used supervised dimensionality reduction to study the relationship between the chemical features and self-reported exposure to WTC dust
- Partial least squares discriminant analysis (PLS-DA) can determine the features important in discriminating membership in the exposed group
- Analysis was adjusted for maternal age, gestational age, maternal BMI, and maternal education



Non-targeted features can discriminate between those exposed and unexposed

- Three of the top 5 features of importance for component 1 may be of exogenous origin, including a feature putatively annotated as a fluorinated molecule
- One of the top five did not have a match in the human metabolome database

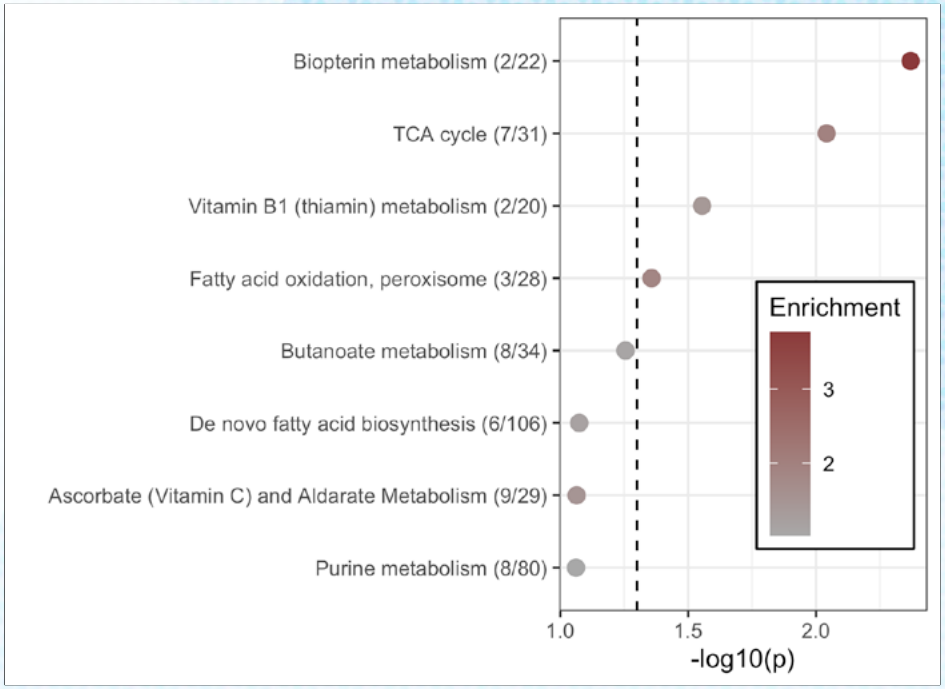
m/z	Retention time (s)	Putative annotation	VIP score	ESI
1113.0542	186.2	*Unknown*	3.58	+
178.0587	92	3-Hydrazinyl-4-(trifluoromethyl)pyridine	2.99	+
252.9927	131	Isofenchlorfos	3.09	+
291.2327	23.6	A steroid metabolite	2.97	+
93.0394	105.2	2-(Methylthio)ethanol	3.04	+



Exposure to dust associated with lipid, amino acid & xenobiotic metabolism

Features with a high variable importance score on component **1 enriched pathways related to:**

- Energy generation
- Fatty acid metabolism
- Cofactors and vitamin metabolism



- **What cord blood non-targeted chemical features are associated with exposure to dust from the WTC?**
  - PLS-DA could discriminate exposure to dust along component 1
  - Chemical features of importance for component 1 maybe of exogenous source
  - Enriched pathways related to energy, lipid, cofactors, and vitamin metabolism
- **How are perfluorinated chemicals associated with cord blood metabolomic profiles?**

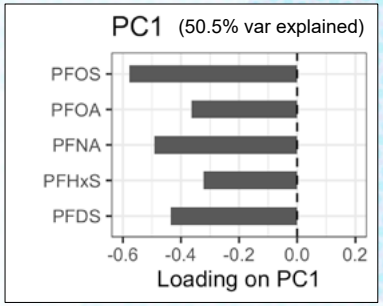
Small molecules associated with exposure to perfluoroalkyl substances (PFAS)

- In a previous study, our group determined levels of several PFAS in cord blood samples from the Columbia birth cohort
- We restricted the analysis to women with cord blood PFAS and non-targeted data available
- Five PFAS were detected in >50% of samples, including PFOS, PFOA, PFHxS, PFDS, PFNA
- We used principal component analysis to investigate any mixture effects from the PFAS
- Analyses were adjusted for maternal age, gestational age, maternal BMI, and maternal education

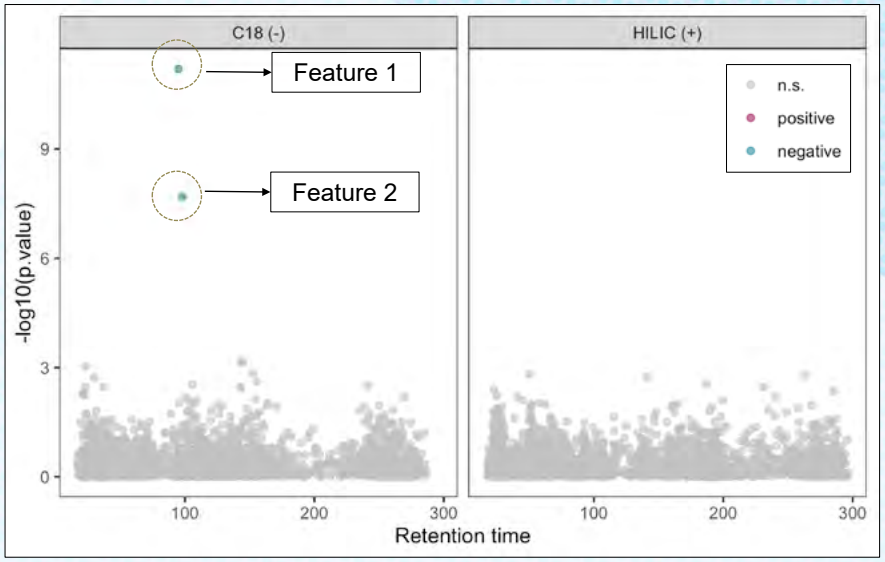
	Samples with PFAS and cord blood NTA data (N=62)
PFOA	
Mean (SD)	2.74 (1.33)
Median [Min, Max]	2.52 [0.865, 7.14]
PFOS	
Mean (SD)	6.50 (2.88)
Median [Min, Max]	6.00 [1.05, 15.5]
PFHxS	
Mean (SD)	0.771 (0.450)
Median [Min, Max]	0.658 [0.152, 2.38]
PFDS	
Mean (SD)	0.123 (0.0400)
Median [Min, Max]	0.112 [0.0804, 0.282]
<LOQ	3 (4.8%)
PFNA	
Mean (SD)	0.620 (0.474)
Median [Min, Max]	0.404 [0.203, 2.34]
<LOQ	7 (11.3%)

PC1 with loadings from all PFAS is associated with a fluorinated chemical

- PC1 captured 50% of the variance in the PFAS levels
- 2 features were significantly associated with PC1
- One of the features was annotated as PFOS while the other did not match any database entries

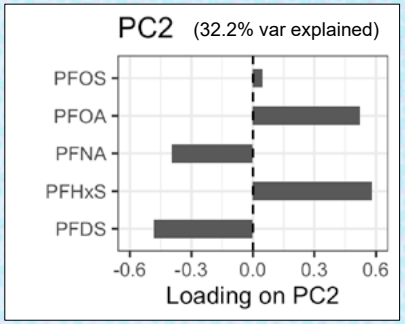


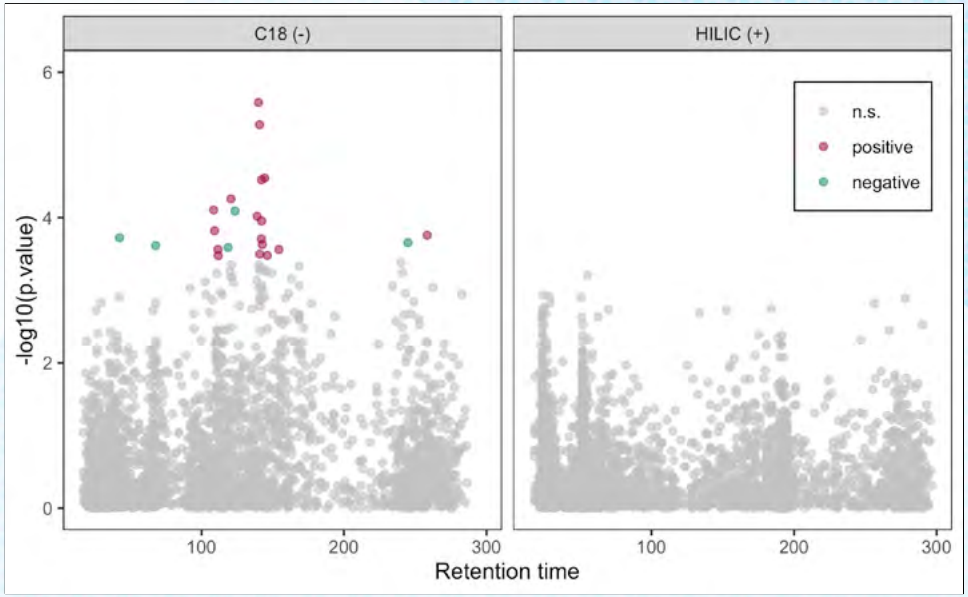
Attribute	Feature 1	Feature 2
m/z	499.9337	498.929
Retention time (s)	94.9	98
Putative annotation	*unknown*	PFOS
ρ PFOS	0.73	0.71
ρ PFOA	0.41	0.47



PC2, with largest loadings from PFHxS and PFOA, was associated with several small molecules

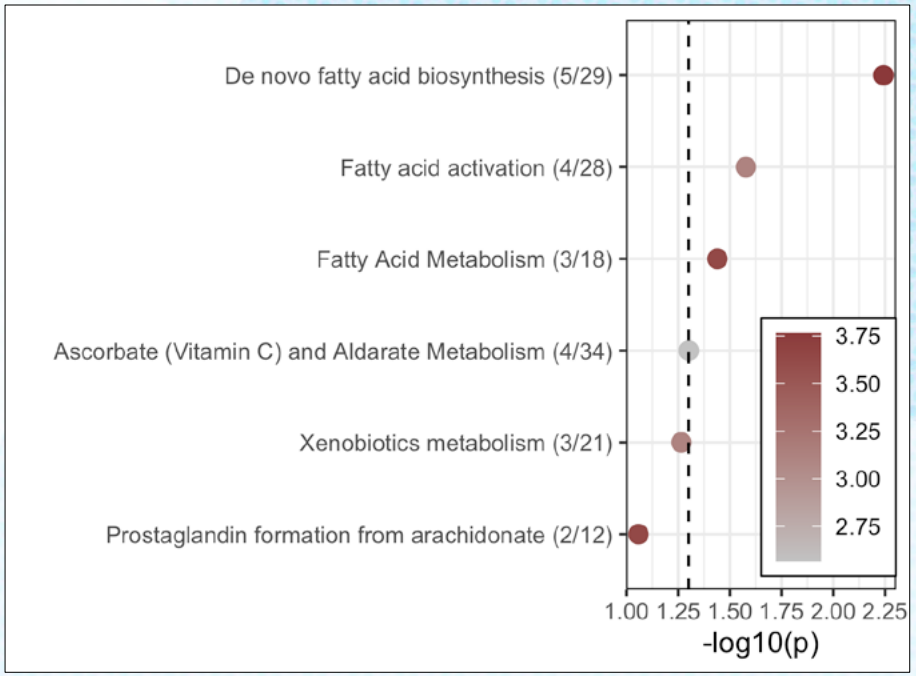
- PC2 captured ~32% of the variance in the PFAS levels
- PFHxS and PFOA had the largest positive loading on the PC
- 22 features were associated with PC2 after correcting for multiple comparisons





Lipid metabolic pathways are associated with PFAS

- The features associated with PC2 enriched several pathways associated with lipid metabolism
- Xenobiotic metabolism and vitamin C metabolism
- Some of the pathways associated with exposure to WTC dust are also associated with PFAS



- What cord blood non-targeted chemical features are associated with exposure to dust from the WTC?
- **What cord blood metabolomic features are associated with exposure to perfluorinated chemicals?**
  - Two features were associated with loadings from all PFAS, one was putatively annotated as PFOS
  - Several chemical features were associated with largest loadings from PFOA and PFHxS
  - Pathways related to lipid, xenobiotic, and vitamin metabolism were enriched by these chemical features

- Exposure to dust from the collapse of the WTC towers was associated with several cord blood small molecules and pathways related to energy, lipid, cofactor, and vitamin metabolism
- Exposure to perfluorinated compounds was related to altered cord blood lipid, vitamin, and xenobiotic metabolism
- Both WTC dust and PFAS exposure were associated with altered lipid and vitamin metabolism but exposure to dust was also associated with altered energy and cofactor metabolism

Next Steps

- Determine if metabolic features associated WTC dust and PFAS exposure with are associated with health outcomes
- Re-run blood samples using GC/MS

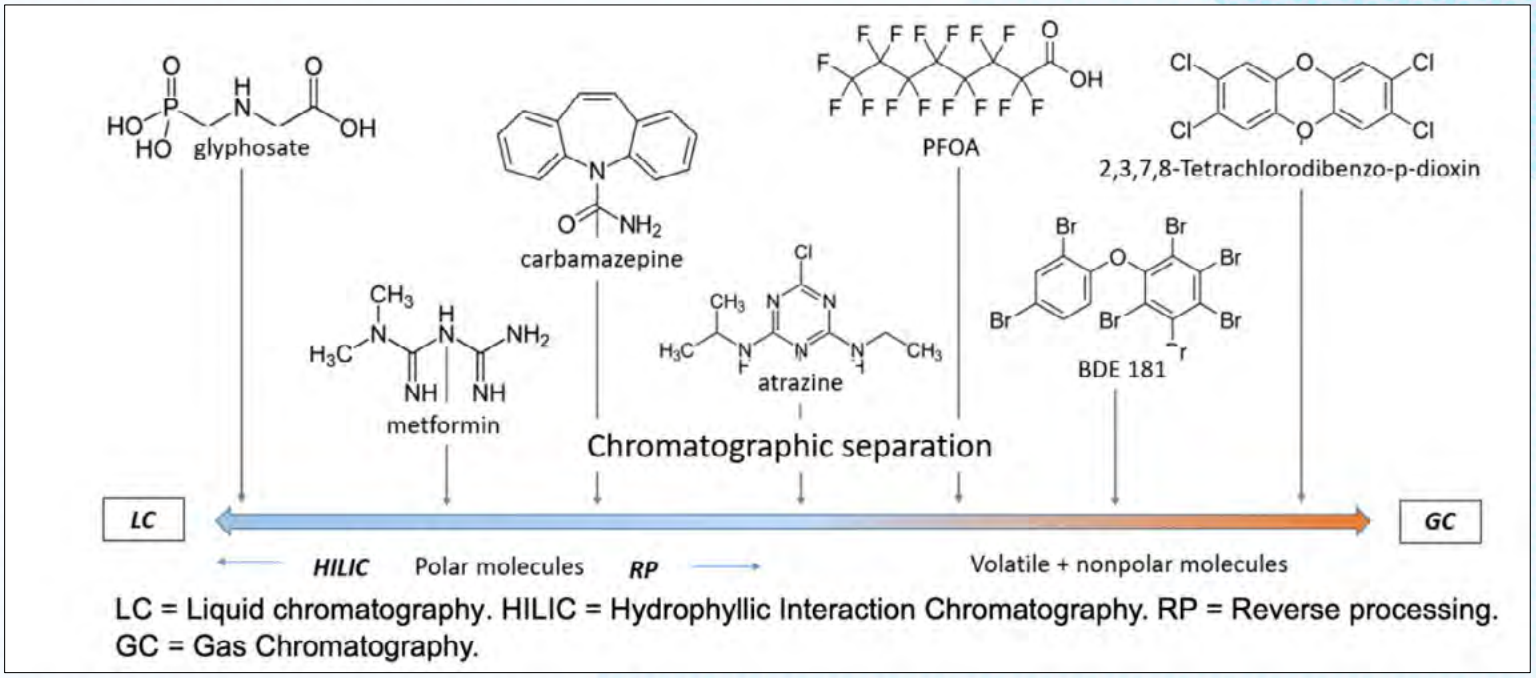


Figure courtesy of R. Singh

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NOTES

NOTES

Sean Clouston, PhD

Amyloidogenesis and neurodegeneration in WTC exposure-related cognitive dysfunction: A study of WTC responders

Dr. Clouston is Director of Public Health Research and Professor of Family, Population, and Preventive Medicine at the Renaissance School of Medicine at Stony Brook University. Dr. Clouston is a social neuroepidemiologist whose work takes a life-course approach to understanding social determinants of population aging. His work with WTC responders focuses on understanding the association between exposures at the WTC and more rapid cognitive aging. He integrates information from a range of diagnostic tools and objective measures including cognitive and physical functioning with proteomic and neuroimaging-based to help inform the etiology of observed and reported symptoms. He has awards examining using biomarkers including plasma-based measures of neuropathology and PET/MR data to help explain MCI burden in WTC responders.

Scan this code to access articles

Additional Reading

Reading 1: Kritikos, M., Diminich, E. D., Meliker, J., Mielke, M., Bennett, D. A., Finch, C. E., Gandy, S. E., Carr, M. A., Yang, X., Kotov, R., Kuan, P. F., Bromet, E. J., Clouston, S. A. P., & Luft, B. J. (2023). Plasma amyloid beta 40/42, phosphorylated tau 181, and neurofilament light are associated with cognitive impairment and neuropathological changes among World Trade Center responders: A prospective cohort study of exposures and cognitive aging at midlife. *Alzheimer's & Dementia: Diagnosis, Assessment & Disease Monitoring*, 15(1), e12409. https://doi.org/10.1002/dad2.12409

Reading 2: Natale, G., Kritikos, M., Kuan, P.-F., Carr, M. A., Yang, X., Yang, Y., Kotov, R., Bromet, E. J., Clouston, S. A. P., & Luft, B. J. (2023). Glial suppression and post-traumatic stress disorder: A cross-sectional study of 1,520 world trade center responders. *Brain, Behavior, & Immunity - Health*, 30, 100631. https://doi.org/https://doi.org/10.1016/j.bbih.2023.100631

NOTES

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Amyloidogenesis and neurodegeneration in WTC exposure-related cognitive dysfunction: A study of WTC responders

Sean Clouston, Ph.D., Stony Brook University

FAR BEYOND

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Goals

1) Understand results from ongoing studies of neurological and neurodegenerative biomarkers in the blood of WTC responders

2) Determine the extent to which WTC exposures are associated with changes in serological markers of neurodegeneration

3) See whether changes fit an existing profile

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Exposures after 9/11

Exposures at 9/11 were severe and happened over the course of ~10 months:

- Physical
- Emotional

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- This study of children shows evidence of fine metal particles from air pollution that is similar to studies of elderly people with AD

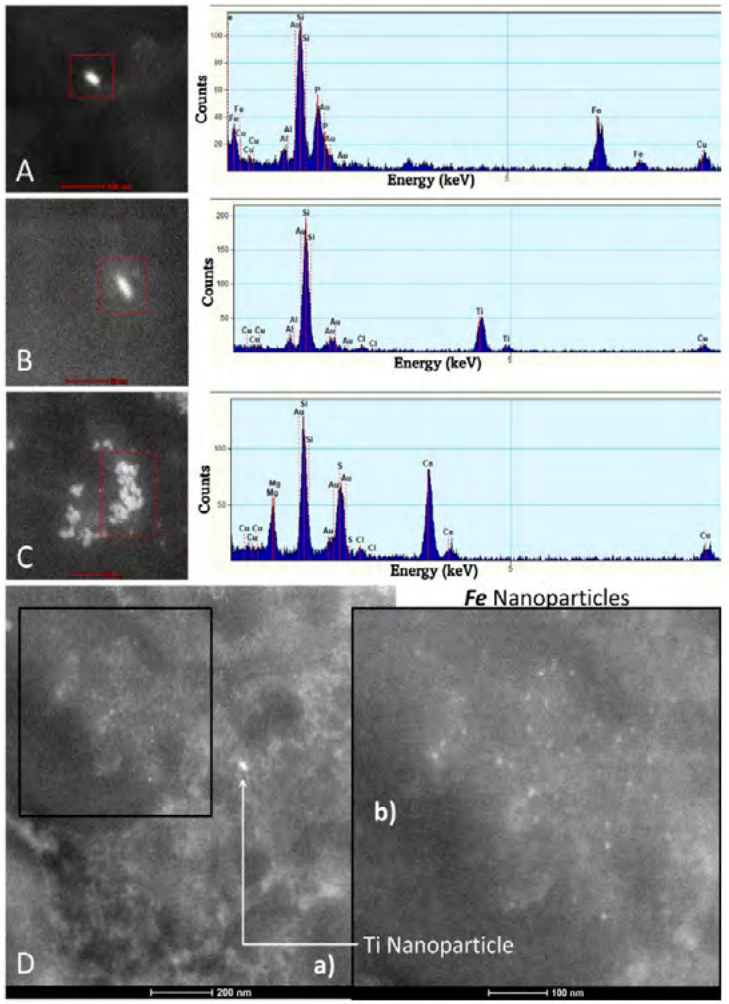

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FIGURE 10
TEM Z-Contrast technique, NPs are documented in the caudate head from a 21-year-old male through EDX that shows the element's peak. In **(A–C)**, it is confirmed that the presence of NPs composed of Fe, Ti, and Ca is common, while the other elements appearing in the spectra are part of the matrix embedding the tissue. Fe (10 nm) and Ti (25 nm) NPs are shown in **(D)**. The presence of Au and Cu is due to the materials from the Au grids.

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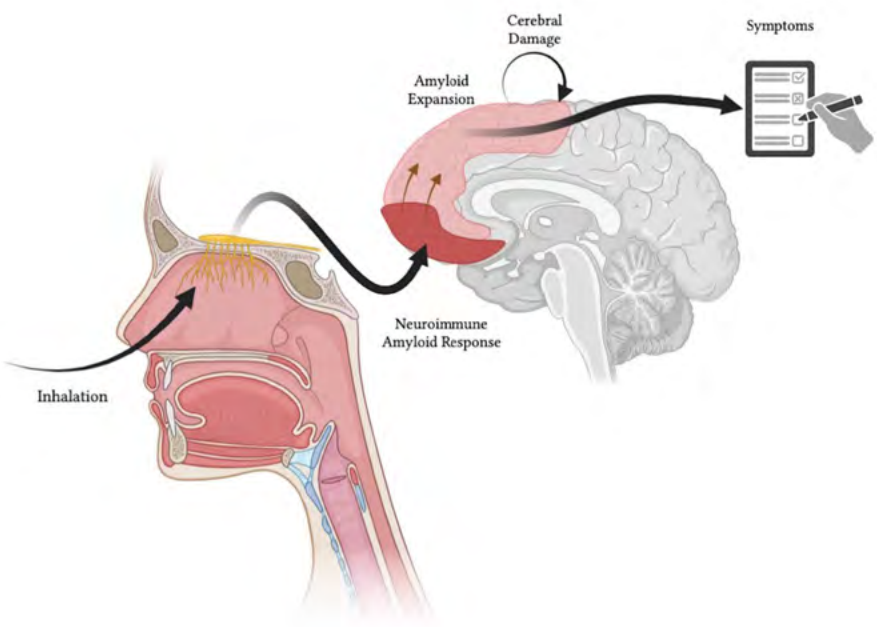
- This study of children shows evidence of fine metal particles from air pollution that is similar to studies of elderly people with AD



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Result from AI Model

- Incidence of WTC dysfunction was 10.0 [8.67-11.58] per 100 person-years
- Incidence of WTC dementia was 1.3 [0.96-1.89] per 100 person-years

Characteristics	Multivariable-adjusted model		
	aHR	95% CI	*P*
Probable post-traumatic stress disorder	2.072	1.408–3.050	<0.001
Pulmonary exposure severity	0.958	0.929–0.987	0.005
Injured at the WTC site	1.087	0.746–1.584	0.664
>5 weeks on-site	2.815	1.781–4.449	<0.001

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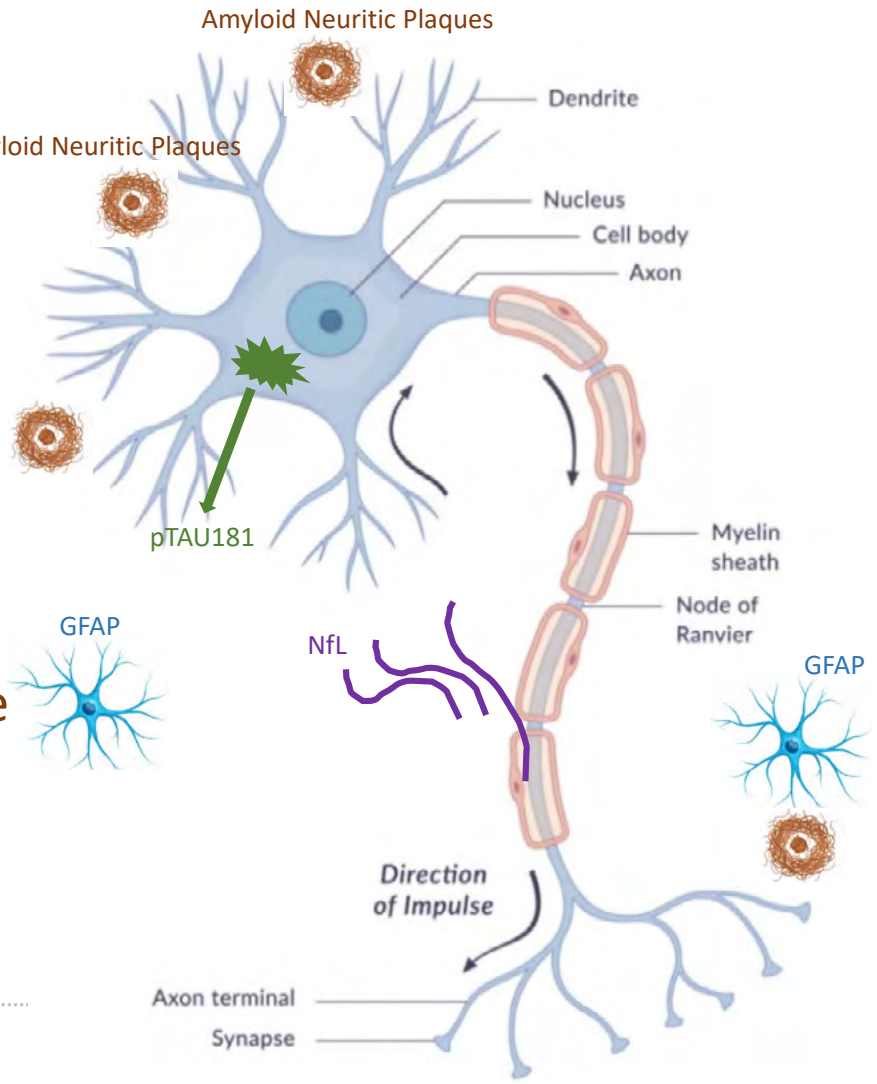
Neurons

- Tau Phosphorylation (pTAU181)
- Axonal Degeneration (NfL)
- Amyloid Response (AB40 & 42)
- Glial Response (GFAP)



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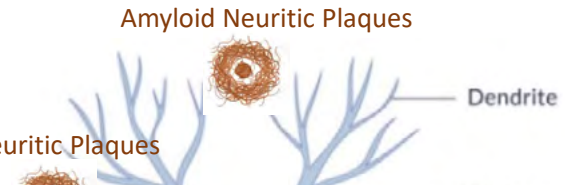
Neurons



- Tau Phosphorylation (pTAU181)
- Axonal Degeneration (NfL)
- Amyloid Response (AB40 & 42)
- Glial Response (GFAP)

Putative Biomarkers	Expectations in Neurodegenerative Disease
Amyloid 40	No Change
Amyloid 42	Decrease
Amyloid 42/40	Decrease
Amyloid 40/42	Increase
pTAU-181	Increase
NfL	Increase
GFAP	Increase
Cortical Thickness	Decrease
Hippocampal Volume	Decrease

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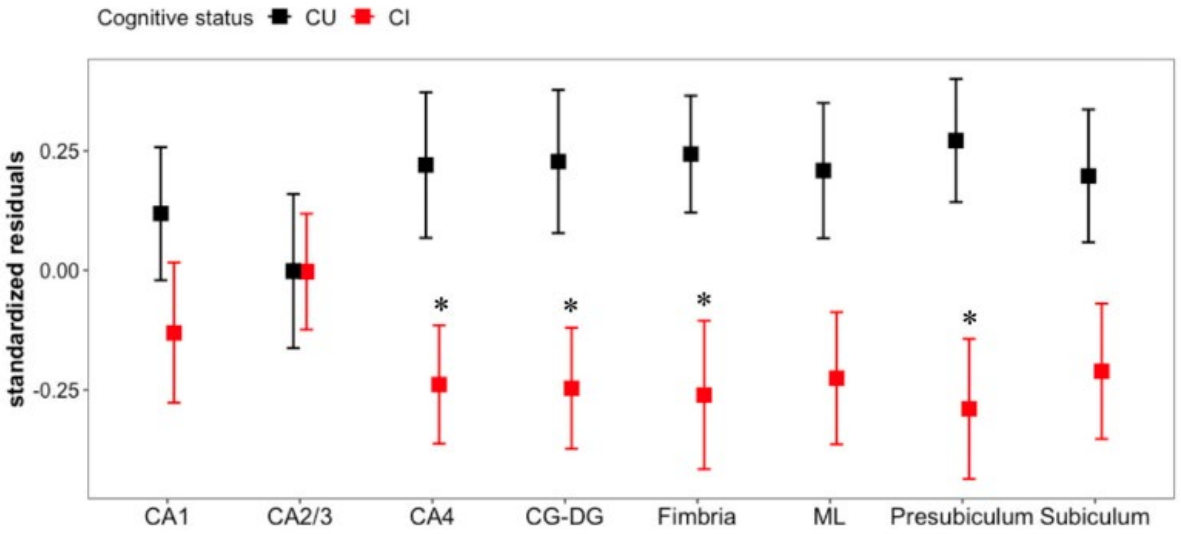
Hippocampal volume reduction



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Hippocampal volume reduction

TABLE 3 Association between both cognitive status and length of time worked on the WTC site and hippocampal subfield volumes

	Panel A: Standardized regression coefficients showing size of cognitive impairment association			Panel B: Standardized regression coefficients showing size of association with total months on site		
Subregion name	β	SE	P	β	SE	P
CA1	−0.10	0.086	0.245	−0.16	0.087	0.148
CA2/3	−0.11	0.087	0.218	0.09	0.088	0.333
CA4	−0.22	0.084	0.031*	−0.07	0.085	0.394
CG-DG	−0.21	0.083	0.031*	−0.1	0.084	0.333
ML	−0.18	0.083	0.056	−0.2	0.084	0.045*
Subiculum	−0.18	0.086	0.056	−0.24	0.087	0.031*
Presubiculum	−0.28	0.085	0.013*	−0.29	0.086	0.0095**
Fimbria	−0.19	0.097	0.074	−0.11	0.098	0.333

Notes: Regression models included both cognitive impairment and total time worked at the WTC site (months) simultaneously as predictors were used to test associations with hippocampal subfield volumes adjusted for TIV. Resulted standardized beta coefficients (β) represent the change in standard deviation units of subregion volume associated with CI (Panel A) and length of time worked on the WTC site (Panel B). *P*-values (P) were corrected for false discovery rate. *$P < 0.05$ and **$P < 0.01$.

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Samples

- Sampling done in 2019, prior to the COVID-19 pandemic
- Cross-section of WTC responders
- Responders are relatively young for this kind of study
- Many responders have mild cognitive impairment or dementia

FAR BEYOND

TABLE 1 World Trade Center responder sample characteristics.

Participant characteristic	*N* (%) or Mean (SD)
Demographics	
Age, years	57.48 (7.76)
Female sex	86 (7.29)
Educational attainment	
High school or less	312 (26.46)
Some college	545 (46.23)
University degree	322 (27.31)
Biomarkers	
Amyloid beta 40/42 ratio, pg/mL	15.87 (3.99)
Phosphorylated tau 181, pg/mL	1.70 (1.09)
Neurofilament light chain, pg/mL	10.94 (6.93)
Cognitive status	
Unimpaired	913 (79.39)
Mild cognitive impairment	188 (16.35)
Possible dementia	49 (4.26)
WTC exposure	
Untrained responder	337 (28.58)
Supervisor	163 (13.83)
Probable post-traumatic stress disorder at enrollment	129 (11.22)
≥ 15 weeks on site	253 (21.46)
Dust cloud exposure	552 (47.42)
Medical comorbidities	
Hypertension	325 (27.85)
Diabetes	65 (5.58)
Obstructive airway disease	55 (4.66)
Cancer	179 (15.18)

Note: Data are *N* (%), mean (SD) for the enrolled study cohort. Non-supervisors included volunteers, construction workers, police, and security officers; Probable post-traumatic stress disorder based on cut-off score of 44 on PCL-C.
Abbreviations: PCL-C, PTSD Checklist; pg/mL, picogram per millimeter; SD, standard deviation; WTC, World Trade Center.

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Aβ 40/42, pTau181, and NfL
(Kritikos et al. 2023)

- Results from bloodwork

TABLE 3 Prevalence of amyloid beta 40/42 ratio, phosphorylated tau 181, and neurofilament light chain in sample.

Amyloid status	Tau status		Neurofilament status	
			N+	N−
A+	T+	%	**3.45%**	**1.87%**
			(2.6–4.7)	**(1.29–2.85)**
		O/E, *P*	**4.32, *P* <0.001**	**0.58, *P* = 0.013**
	T−	%	**3.35%**	11.67%
			(2.68–4.8)	(10–13.67)
		O/E, *P*	1.11, *P* = 0.518	0.91, *P* = 0.269
A	T+	%	**5.32%**	**9.52%**
			(4.22–6.8)	**(8.02–11.38)**
		O/E, *P*	**1.66, *P* < 0.001**	**0.74, *P* = 0.001**
	T−	%	**7.66%**	56.96%
			(6.32–9.36)	(54.15–59.81)
		O/E, *P*	**0.60, *P* < 0.001**	1.11, *P* = 0.998

Notes: Bold typeface shows statistically significant results. *P*-values were derived from tests of proportions examining the hypothesis that the cell proportion was different from expected depending on random chance.
Abbreviations: A+, amyloid beta 40/42 ratios in the top sex-specific quintile; N+, neurofilament light chain results in the top sex-specific quintile; T+, phosphorylated tau 181 results in the top sex-specific quintiles. A-, T-, and N- indicate results that are not in the positive category.

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Exposure correlates

- Multvariable-adjusted results

TABLE 4 Multivariable-adjusted risk ratios showing degree of association between World Trade Center related PTSD and exposures with plasma AT(N), Aβ40/42 ratio (A), phosphorylated tau 181 (T), and neurofilament-light (N) status.

	Model 1 Amyloid beta 40/42 (A+), ratio			Model 2 Phosphorylated tau 181 positive (T+), pg/mL			Model 3 Neurofilament light positive (N+), pg/mL		
Characteristics	aRR	95% CI	*P*	aRR	95% CI	*P*	aRR	95% CI	*P*
Age, years	**1.044**	**1.03–1.06**	<0.001	**1.059**	**1.04–1.08**	**<0.001**	**1.114**	**1.1–1.13**	<0.001
≥15 weeks on-site	1.000	0.97–1.03	0.982	**1.031**	**1.01–1.05**	**0.009**	1.001	0.98–1.03	0.936
PTSD	**1.028**	**1.00–1.06**	0.089	1.012	0.98–1.05	0.504	1.018	0.98–1.05	0.323
Non-supervisorial role	1.049	0.73–1.51	0.795	**1.733**	**1.09–2.75**	**0.020**	1.027	0.73–1.44	0.878
Dust cloud	1.226	0.94–1.59	0.127	0.815	0.61–1.08	0.157	1.010	0.77–1.32	0.944

Note: Bold typeface shows statistically significant results.

Abbreviations: 95% CI, 95% confidence interval; A+, those with elevated Aβ40/42 ratio; Aβ, amyloid beta; aRR, adjusted risk ratio, models adjusted for demographics including age, race/ethnicity, sex, and education; N+, those with elevated neurofilament light chain; PTSD, post-traumatic stress disorder; Occupation role, responders self-reported classification as supervisor/non-supervisor while on site at the World Trade Center; T+, those with elevated phosphorylated tau 181.

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Clouston - WTC Cancer

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PTSD and GFAP (Natale et al. 2023)

Table 3

Multivariable-adjusted finite mixture model showing predictors of the distribution volume of glial fibrillary acidic protein in responders determined to have normal glial fibrillary acidic protein levels.

	Model 1			Model 2		
	B	SE	P	B	SE	P
Post-Traumatic Stress Disorder, Symptoms	−0.753	0.192	<0.001	−0.558	0.187	0.003
Age, years	1.070	0.115	<0.001	1.134	0.113	<0.001
Female	2.033	4.552	0.655	−1.118	4.032	0.782
Height, cm				−0.158	0.091	0.084
Body Mass, kg/m^2				−1.050	0.120	<0.001
Exposure Duration, Ln-Weeks				−0.869	1.281	0.498
Dust Cloud				−2.330	1.571	0.138
No Supervisory Work				−2.253	1.902	0.236

FAR BEYOND

Clouston - WTC Cancer

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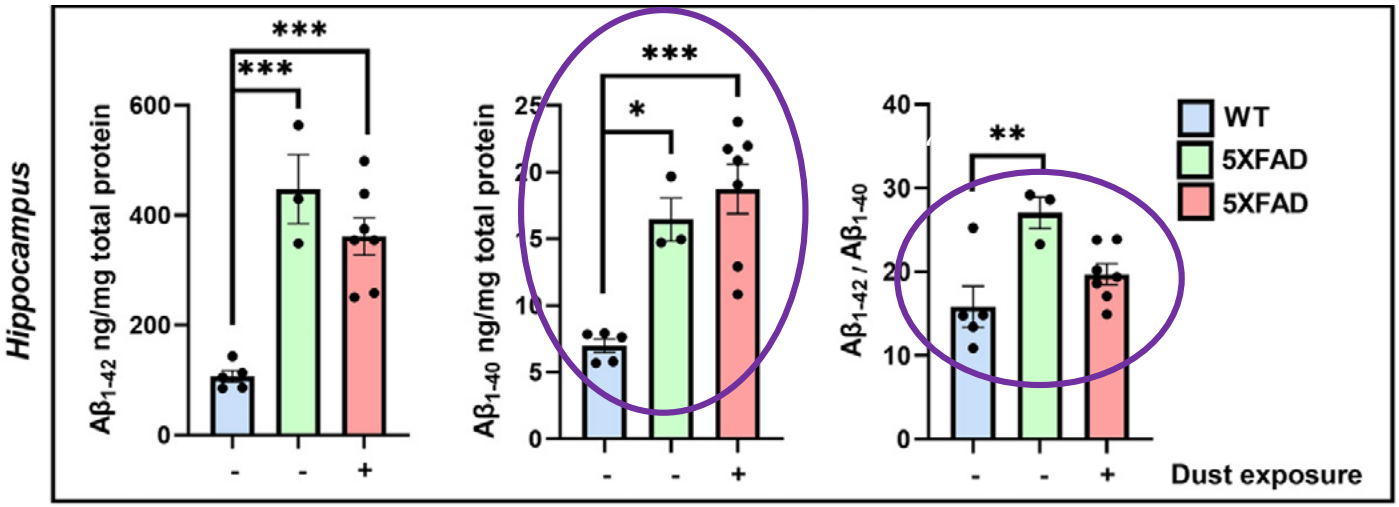
WTC Exposures in Mice

- Mouse model results on WTC-exposed mice



- Hernandez et al. 2022, Iban-Arias et al. 2023

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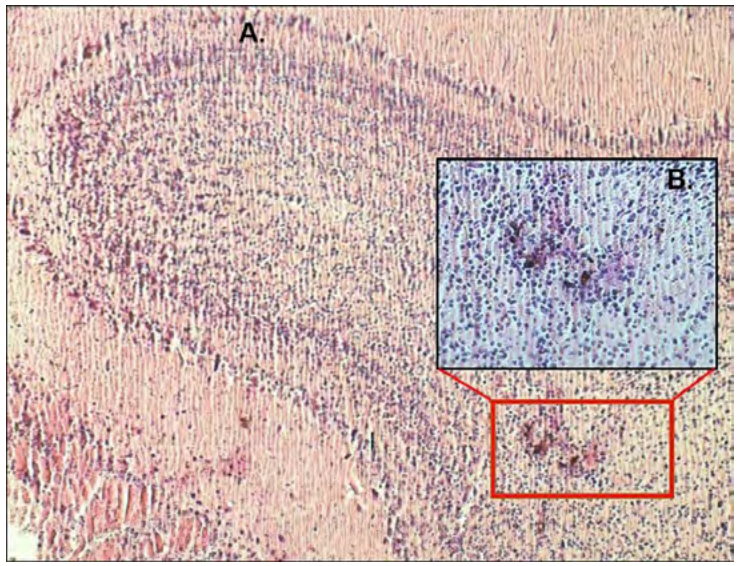
WTC Exposures in Mice

- Mouse model results on WTC-exposed mice



- Hernandez et al. 2022, Iban-Arias et al. 2023

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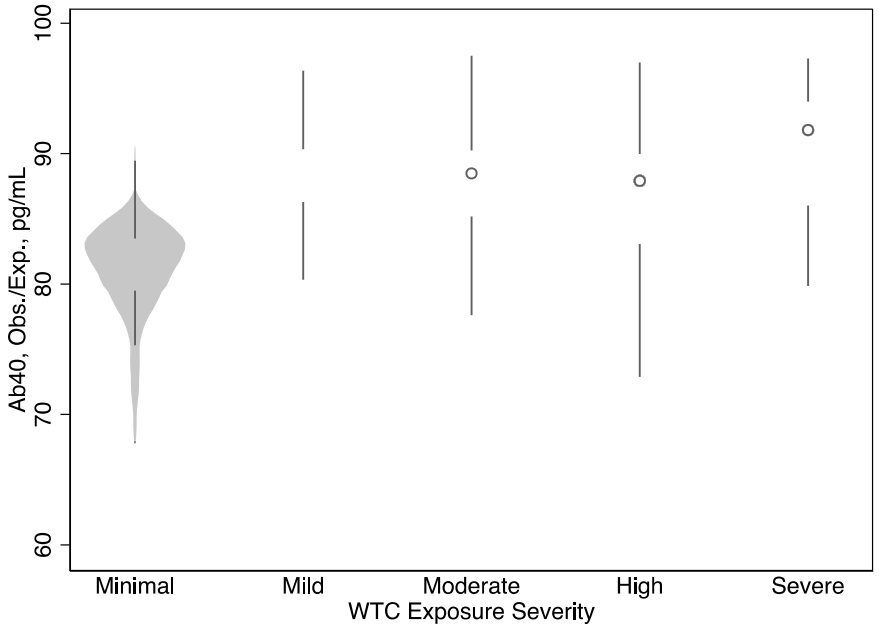
Amyloidogenesis?

- Exposure Severity Ranking
- All groups are significantly higher than minimally exposed (no dust, always PPE) responders



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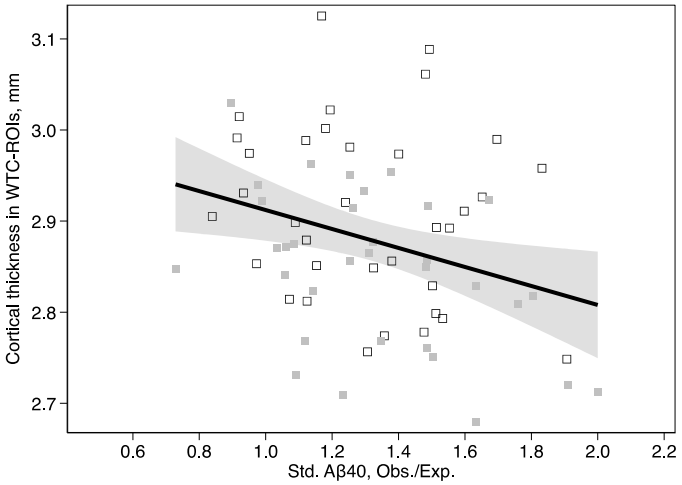
Amyloidogenesis Outcomes

- Serological and Imaging-based Correlates of Aβ40 Elevation

	Standardized β-Amyloid 1-40	
Plasma Levels	Rho	P
Phosphorylated Tau 181	0.16	<0.001
β-Amyloid1-42	0.54	<0.001
Neurofilament Light	0.16	<0.001
Glial Fibrillary Acidic Protein	0.14	<0.001
Ratios		
Amyloid Ratio	0.31	<0.001
Amyloid Tauopathy	-0.28	<0.001
Neurodegenerative Tau	0.18	<0.001
Neuroinflammation	-0.02	0.593
Early Tauopathy	-0.02	0.628



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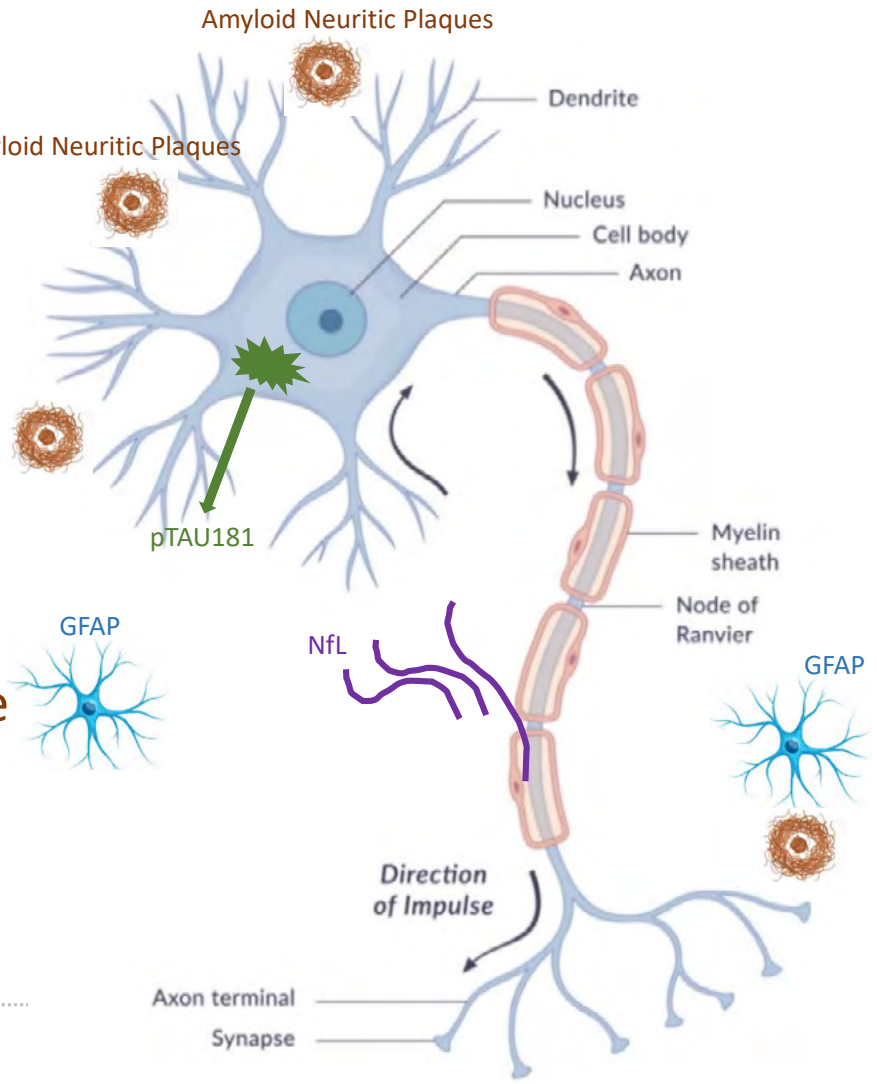
Neurons

- Tau Phosphorylation (pTAU181)
- Axonal Degeneration (NfL)
- Amyloid Response (AB40 & 42)
- Glial Response (GFAP)



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Neurons

- Tau Phosphorylation (pTAU181)
- Axonal Degeneration (NfL)
- Amyloid Response (AB40 & 42)
- Glial Response (GFAP)

Expectations in Neurodegenerative Disease

Putative Biomarkers	Disease
Amyloid 40	No Change
Amyloid 42	Decrease
Amyloid 42/40	Decrease
Amyloid 40/42	Increase
pTAU-181	Increase
NfL	Increase
GFAP	Increase
Cortical Thickness	Decrease
Hippocampal Volume	Decrease

FAR BEYOND

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Future Research Needs

- We do not know how to correctly diagnose WTC Exposure-related Dementia and PTSD-related Dementia in comparison to normal Alzheimer's Disease or other well-known phenotypes
- We also do not know whether there are ways to see if a person who is alive is exposed or not
- We do not know whether amyloidogenesis in the blood reflects amyloidosis in the brain or is earlier and reflects glial activation
- *Future work at Stony Brook is focusing on these main questions with hopes of being able to answer them*

FAR BEYOND

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Acknowledgements

Funding -

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- NIH/NIA R21 AG074706
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- CDC/NIOSH U01 OH012258
- CDC/NIOSH U01 OH012257

Collaborators –

SBU: Luft BJ, Bromet EJ, Kotov R, Meliker J, Mann F, Sampson L, Kritikos M, Deri Y,

ISMMS: Lucchini R (@FIU), Sano M, Gandy S, Horton M,

FDNY: Hall C, Zeig-Owens R, Prezant D

FAR BEYOND

NOTES

Frank D. Mann, PhD

Prevalence of cognitive impairment in World Trade Center exposed Fire Department of the City of New York and general emergency responders

In 2006, Dr. Mann began his undergraduate studies at the State University of New York at Brockport, where he dual majored in psychology and philosophy. After obtaining his B.S. in 2010, he began work as a research assistant at the Mt. Hope Family Center, University of Rochester, on a study investigating the impact of parental conflict and at-risk environments on preschool children's coping and adjustment. In 2013 he began a Ph.D. at the University of Texas at Austin co-advised by Drs. Elliot Tucker-Drob and K. Paige Harden. During his doctoral training, Dr. Mann developed expertise in quantitative genetics and applied statistics, including structural equation modeling and item response theory, and became a core member of the Texas Twin Project. After obtaining his Ph.D. in only 4 years, he began a post-doctoral appointment at the University of Minnesota, working with Dr. Robert Krueger and Dr. Colin DeYoung. During this time, he also worked as a statistical consultant for the Center for Practice Transformation and taught research methods and statistics at Augsburg University. In the fall 2020, he began working at Stony Brook University in the Department of Family, Population, and Preventative Medicine. To date, Dr. Mann has 15 years of experience working on NIH-funded studies facilitating the collection, analysis, and presentation of data. He is a former LRP awardee from the NIH and principal investigator of an R21 from the NIA. In 2021, he received the Early Career Award from the International Society for the Study of Individual Differences. He is author of over 50 peer-reviewed scientific articles, which have accrued over 1,700 citations. He has presented dozens of papers and posters at academic conferences and completed over 180 reviews for scientific journals. Today, he will be presenting study findings from collaborative efforts of investigators at the SBU WTC Health Clinic and the FDNY. The title of his presentation is "Prevalence of Mild Cognitive Impairment and Dementia in World Trade Center Exposed New York City Fire Department (FDNY) Responders."

Frank D. Mann, PhD

Prevalence of Cognitive Impairment in World Trade Center Exposed Fire Department of the City of New York and General Emergency Responders

Additional Reading

Reading 1: Clouston, S. A. P., Hall, C. B., Kritikos, M., Bennett, D. A., DeKosky, S., Edwards, J., Finch, C., Kreisl, W. C., Mielke, M., Peskind, E. R., Raskind, M., Richards, M., Sloan, R. P., Spiro, A., 3rd, Vasdev, N., Brackbill, R., Farfel, M., Horton, M., Lowe, S., . . . Luft, B. J. (2022). Cognitive impairment and World Trade Centre-related exposures. *Nat Rev Neurol*, 18(2), 103-116. https://doi.org/10.1038/s41582-021-00576-8

Reading 2: Singh, A., Zeig-Owens, R., Hall, C. B., Liu, Y., Rabin, L., Schwartz, T., Webber, M. P., Appel, D., & Prezant, D. J. (2020). World Trade Center exposure, post-traumatic stress disorder, and subjective cognitive concerns in a cohort of rescue/recovery workers. *Acta Psychiatr Scand*, 141(3), 275-284. https://doi.org/10.1111/acps.13127

Reading 3: Singh, A., Zeig-Owens, R., Rabin, L., Schwartz, T., Webber, M. P., Appel, D., Prezant, D. J., & Hall, C. B. (2020). PTSD and Depressive Symptoms as Potential Mediators of the Association between World Trade Center Exposure and Subjective Cognitive Concerns in Rescue/Recovery Workers. *Int J Environ Res Public Health*, 17(16). https://doi.org/10.3390/ijerph17165683

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Prevalence of Cognitive Impairment in World Trade Center Exposed Fire Department of the City of New York and General Emergency Responders

A Preliminary Report of Initial Findings

Presented by Frank D. Mann

Quick Summary of What We Know

Our team's past and recent work highlights:

- A high incidence of mild cognitive impairment (MCI) and early onset dementia (EOD) in the General Responder Cohort (GRC), which includes World Trade Center (WTC) responders who were not members of the FDNY on 9/11/2001, consisting mostly of law enforcement, construction workers, and civilian volunteers (henceforth called GRC responders).

- The central role of long-term exposures to fine particulate matter in GRC responders, and while these responders were exposed to a number of known pollutants, they may have been exposed to different types of particulate matter and for different lengths of time as compared to FDNY responders.

Motivation

- This is a critical time to examine prevalence of MCI and possible dementia in FDNY responders since it is well documented that less severely, but often more chronically exposed responders from the GRC are developing MCI and early onset dementia, making examination and characterization in FDNY responders timely at this juncture.

- Screen for MCI and possible dementia in a large sample (n ~ 300) of WTC-exposed FDNY responders

- Enable a test of out-of-sample replication for the high levels of cognitive impairment observed in the GRC

Critical Next Steps

Goals of the Present Study:

1. Determine whether FDNY and GRC cohorts differ in the prevalence of MCI, as well as more severe cognitive impairments indicative of possible dementia.

2. Assess whether the operational definition of MCI (MoCA, Jak/Bondi criteria, Petersen criteria, and NIA-AA criteria) impacts prevalence estimates.

3. Help determine clinical significance by comparing prevalence estimates in the FDNY and GRC to meta-analytic estimates of MCI and EOD from different global, community, and clinical populations.

4. Thoroughly characterize the domain-specific deficits of cognitively impaired FDNY responders by analyzing scores from a large battery of objective neurocognitive tests.

Criteria for Enrollment

Inclusion criteria: **1)** Age 45-69 years old; **2)** capacity to provide informed consent or assent combined with consent from a legally authorized representative (LAR); **3)** willingness to travel to SBU and do PET/MRI imaging.

Exclusion criteria: Because we are interested in the high burden of un-explained MCI in this cohort, but also due to concerns with measurement, ethical considerations, and MRI safety, we propose to exclude individuals with: a **1)** history of stroke; **2)** history of serious head trauma or other neurological disorders such as epilepsy; **3)** benign brain tumors; **4)** brain cancer; **5)** indication of unmanaged diabetes; **6)** chronic autoimmune disease such as MS; **7)** Heart failure or MI in the past year; **8)** embedded ferromagnetic implants, history of claustrophobia or conditions that would preclude PET or MRI (e.g., pacemaker, fear of needles, shrapnel, surgical implants that are not MRI safe); **9)** current pregnancy, engagement in breastfeeding, or of child-bearing potential without using adequate contraception.

Sample Characteristics

Table 1. Sample Characteristics

	WTC-Exposed FDNY Responders (n = 343)		WTC-Exposed GRC Responders (n = 7102)	
	M/*f*	*SD*/%	*M*/*f*	*SD*/%
Age	59.58	6.25	57.39	6.31
Sex				
Male	338	98.54	6443	90.72
Female	5	1.46	659	9.28
Race/Ethnicity				
White	322	93.88	5879	82.78
Black	7	2.03	812	11.43
Latino	7	2.03	314	4.42
Asian	0	0.00	43	0.61
Other	7	2.03	54	0.76
Education				
No High School Diploma	0	0.00	1185	16.69
High School Diploma	37	10.79	1006	14.17
Some College/Tech. School	177	51.60	2993	42.14
Bachelor's Degree	102	29.74	1522	21.43
Graduate School or Higher	27	7.87	396	5.58
Occupation				
Civilian Public Sector	0	0.00	341	4.80
Construction Worker	0	0.00	583	8.21
Emergency Medical Services (EMS)	27	7.87	0	0.00
EMS – Supervisor	1	0.29	0	0.00
Firefighter	308	89.80	0	0.00
Firefighter – Supervisor	7	2.03	0	0.00
Law Enforcement	0	0.00	3713	52.28
Unemployed	0	0.00	10	0.14
Other	0	0.00	2331	32.82
Missing	0	0.00	124	1.75
County of Residence				
Suffolk	182	53.06	3416	44.26
Nassau	155	45.19	3331	42.47
Other	6	1.74	943	13.28

Notes. n = sample size. f = frequency. M = mean. SD = standard deviation. % = percent

Descriptive Statistics

Table 2. Descriptive Statistics for Neurocognitive, Psychiatric, and Physical Functional Measures for FDNY Responders

(*n* = 343)	*f*	*M*	*SD*	*Min.*	*Max.*
Experimenter Adminstered					
MoCA	343	23.83	2.49	13.00	29.00
Lower Extremity Function (SPPB)	342	10.63	1.47	3.00	12.00
Maximal Handgrip Strength	339	65.54	16.33	12.88	113.03
Verbal Episodic Memory (HVLT)	342	21.80	4.65	10.00	35.00
Verbal Recall (HVLT)	342	7.38	2.62	0.00	12.00
Verbal Retention (HVLT)	342	80.57	22.79	0.00	175.00
Verbal Recognition (HVLT)	342	9.52	1.79	2.00	12.00
Animal Recognition (BNT)	343	29.49	0.95	19.00	30.00
General Cognition (WRAT)	343	62.46	4.44	41.00	70.00
Psychomotor Speed (TMT-A)	343	30.61	10.03	13.57	103.75
Choice Reaction Speed (TMT-B)	342	74.25	29.86	28.61	254.06
Working Memory (SDMT)	342	43.94	7.99	19.00	73.00
Verbal Fluency (COWA)	342	39.56	11.20	10.00	72.00
Computerized Assessments					
Episodic Memory	323	0.70	0.19	0.40	1.38
Visual Working Memory	323	0.98	0.09	0.59	1.21
Reaction Speed	323	0.08	0.01	0.05	0.09
Processing Speed	323	0.06	0.00	0.05	0.07
Cognitive Throughput	323	0.05	0.01	0.03	0.07
Visuospatial Function	324	0.02	0.01	0.00	0.04
Working Memory	321	0.16	0.14	0.03	1.00
Self-Report Measures					
Depressive Symptoms (PHQ-9)	339	3.50	4.36	0.00	33.00
Subjective Cognitive Concern (CFI)	339	2.58	2.59	0.00	12.00

Notes. *f* = number of observations. *M* = mean. *SD* = standard deviation. *Min.* = minimum observed value. *Max.* = maximum observed value.

Specific Aims

Goals of the Present Study:

1. Determine whether FDNY and GRC differ in the prevalence of MCI, as well as more severe cognitive impairments indicative of possible dementia.

2. Assess whether the operational definition of MCI (MoCA, Jak/Bondi criteria, Petersen criteria, and NIA-AA criteria) impacts prevalence estimates.

3. Help determine clinical significance by comparing prevalence estimates in FDNY and GRC to meta-analytic estimates of MCI and EOD (typically defined as all-cause dementia before the age of 65 years) from different global, community, and clinical populations.

4. Thoroughly characterize the domain-specific deficits of cognitively impaired FDNY responders by analyzing scores from a large battery of objective neurocognitive tests.

Results of Generalized Linear Models Testing Cohort Differences in Cognitive Impairment

	Mild Cognitive Impairment (MCI)						Possible Dementia					
	Unadjusted			Adjusted			Unadjusted			Adjusted		
Poisson Regression	*RR*[1]	*95% CI*[3]	*p*	*RR*[2]	*95% CI*	*p*	*RR*[1]	*95% CI*	*p*	*RR*[2]	*95% CI*	*p*
Cohort												
General Responder	—	—		—	—		—	—		—	—	
FDNY Responder	1.42	1.16, 1.74	.001	1.63	1.31, 2.02	<.001	0.77	0.46 1.30	.324	0.89	0.51, 1.55	.686
Logistic Regression	*OR*[4]	*95% CI*[3]	*p*	*OR*	*95% CI*[3]	*p*	*OR*	*95% CI*[3]	*p*	*OR*	*95% CI*[3]	*p*
Cohort												
General Responder	—	—		—	—		—	—		—	—	
FDNY Responder	1.54	1.19, 2.00	.001	1.83	1.38, 2.43	<.001	0.76	0.44, 1.31	.321	0.88	0.49 1.59	.683

[1]RR = Risk ratio unadjusted for demographic differences. [2]RR = Risk ratio adjusted for age, sex, race/ethnicity, level of education, and county of residence. [3]CI = Confidence Intervals calculated using robust standard errors computed using a sandwich estimator. [4]OR *p* = probability of the estimated coefficient having been observed if the null hypothesis is true unadjusted for multiple testing. MCI = 23>MoCA total score >19; Possible Dementia = MoCA total score ≤19.

Critical Next Steps

Goals of the Present Study:

1. Determine whether FDNY and GRC responders differ in the prevalence of MCI, as well as more severe cognitive impairments indicative of possible dementia.

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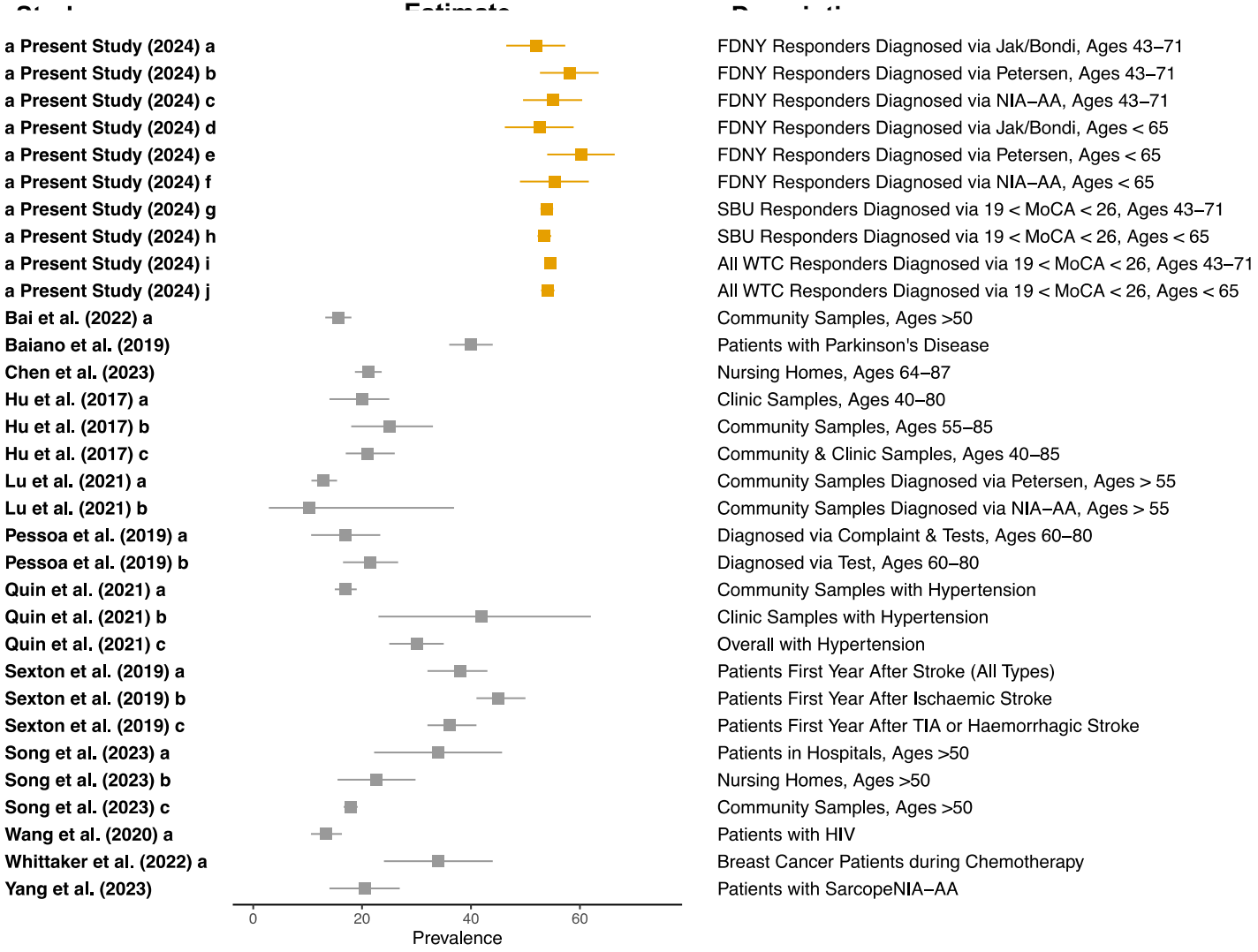
4. Thoroughly characterize the domain-specific deficits of cognitively impaired FDNY responders by analyzing scores from a large battery of objective neurocognitive tests.

Prevalence Rates of Mild Cognitive Impairment and Possible Dementia in WTC Responders

Cohort & Diagnosis	Criteria	*n*	Cases	Crude Period Prevalence	Lower 95%	Upper 95%
FDNY Responders						
Mild Cognitive Impairment	Jak/Bondi	341	177	51.91	46.46	57.32
	Petersen	339	198	58.11	52.66	63.42
	NIA-AA	338	186	55.03	49.55	60.42
	19 < MoCA < 26	343	235	68.51	63.31	73.40
	19 < MoCA < 23	343	78	22.74	18.41	27.55
Possible Dementia	MoCA ≤ 19	343	14	4.08	2.25	6.75
FDNY Responders (under 65 years old)						
Mild Cognitive Impairment	Jak/Bondi	253	133	52.57	46.22	58.86
	Petersen	252	152	60.32	53.99	66.40
	NIA-AA	251	139	55.38	49.00	61.63
	19 < MoCA< 26	255	176	69.02	62.95	74.64
	19 < MoCA< 23	255	59	23.14	18.10	28.81
Possible Dementia	MoCA ≤ 19	255	8	3.14	1.36	6.09
General Responders						
Mild Cognitive Impairment	19 < MoCA< 26	7102	3829	53.91	52.75	55.08
	19 < MoCA< 23	7102	1139	16.04	15.19	16.91
Possible Dementia	MoCA ≤ 19	7102	377	5.31	4.80	5.86
General Responders (under 65 years old)						
Mild Cognitive Impairment	19 < MoCA< 26	6185	3308	53.48	52.23	54.73
	19 < MoCA< 23	6185	948	15.33	14.44	16.25
Possible Dementia	MoCA ≤ 19	6185	294	4.75	4.24	5.31

Notes. *n* = sample size. Lower and Upper 95% = lower and upper bounds of 95% confidence interval. Prevalence rate is the number of cases per 100 individuals at risk.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Chen et al. (2023)
Hu et al. (2017) a
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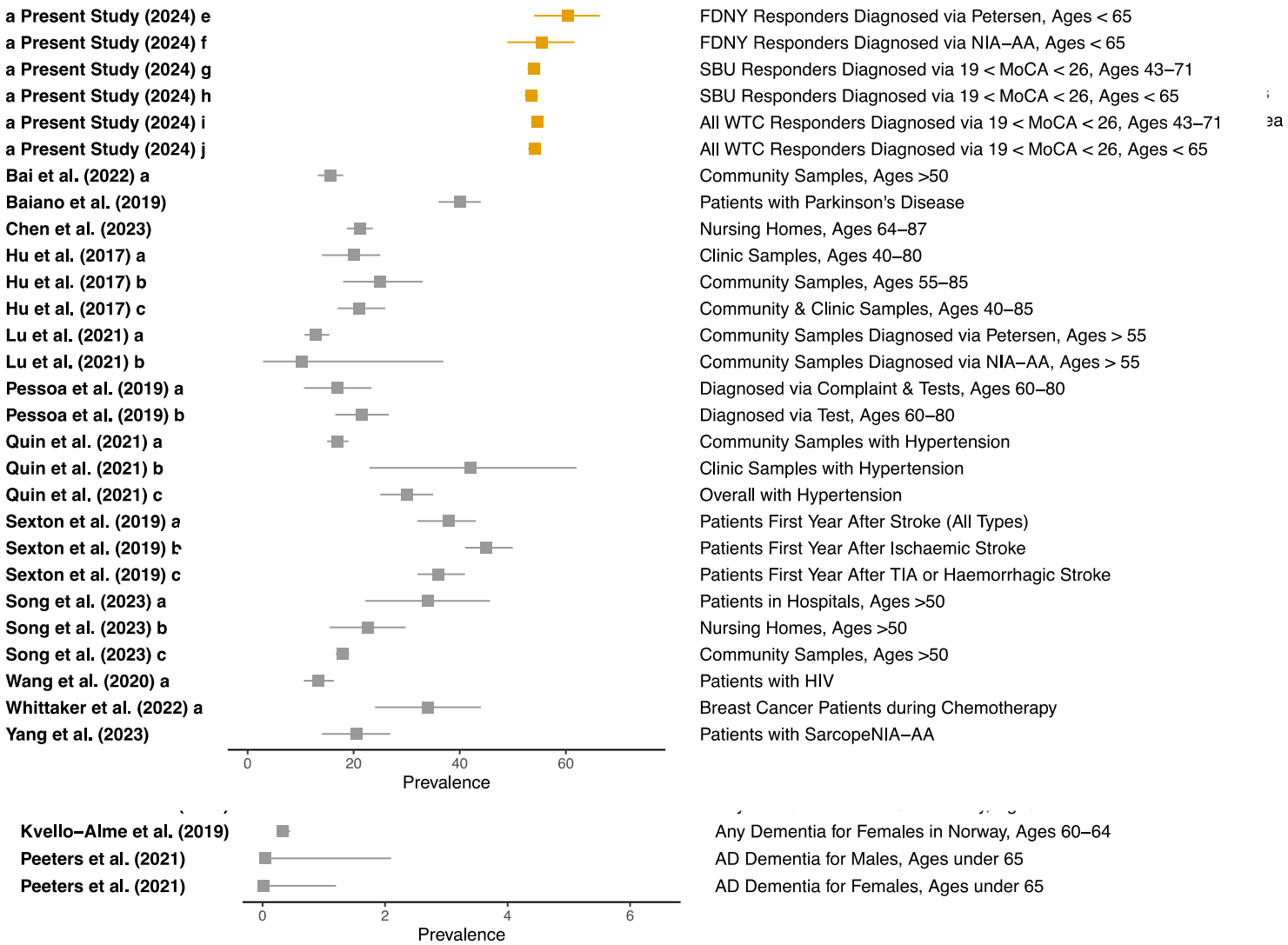
Song et al. (2023) a
Song et al. (2023) b
Song et al. (2023) c
Wang et al. (2020) a
Whittaker et al. (2022) a
Yang et al. (2023)
0
20
40
60
Prevalence
FDNY Responders Diagnosed via Jak/Bondi, Ages 43–71
FDNY Responders Diagnosed via Petersen, Ages 43–71
FDNY Responders Diagnosed via NIA–AA, Ages 43–71
FDNY Responders Diagnosed via Jak/Bondi, Ages < 65
FDNY Responders Diagnosed via Petersen, Ages < 65
FDNY Responders Diagnosed via NIA–AA, Ages < 65
SBU Responders Diagnosed via 19 < MoCA < 26, Ages 43–71
SBU Responders Diagnosed via 19 < MoCA < 26, Ages < 65
All WTC Responders Diagnosed via 19 < MoCA < 26, Ages 43–71
All WTC Responders Diagnosed via 19 < MoCA < 26, Ages < 65
Community Samples, Ages >50
Patients with Parkinson's Disease
Nursing Homes, Ages 64–87
Clinic Samples, Ages 40–80
Community Samples, Ages 55–85
Community & Clinic Samples, Ages 40–85
Community Samples Diagnosed via Petersen, Ages > 55
Community Samples Diagnosed via NIA–AA, Ages > 55
Diagnosed via Complaint & Tests, Ages 60–80
Diagnosed via Test, Ages 60–80
Community Samples with Hypertension
Clinic Samples with Hypertension
Overall with Hypertension
Patients First Year After Stroke (All Types)
Patients First Year After Ischaemic Stroke
Patients First Year After TIA or Haemorrhagic Stroke
Patients in Hospitals, Ages >50
Nursing Homes, Ages >50
Community Samples, Ages >50
Patients with HIV
Breast Cancer Patients during Chemotherapy
Patients with SarcopeNIA–AA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Song et al. (2023) c
Wang et al. (2020) a
Whittaker et al. (2022) a
Yang et al. (2023)
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20
40
60
Prevalence
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FDNY Responders Diagnosed via NIA–AA, Ages < 65
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Patients with HIV
Breast Cancer Patients during Chemotherapy
Patients with SarcopeNIA–AA
Kvello–Alme et al. (2019)
Peeters et al. (2021)
Peeters et al. (2021)
0
2
4
6
Prevalence
Any Dementia for Females in Norway, Ages 60–64
AD Dementia for Males, Ages under 65
AD Dementia for Females, Ages under 65

Critical Next Steps

Goals of the Present Study:

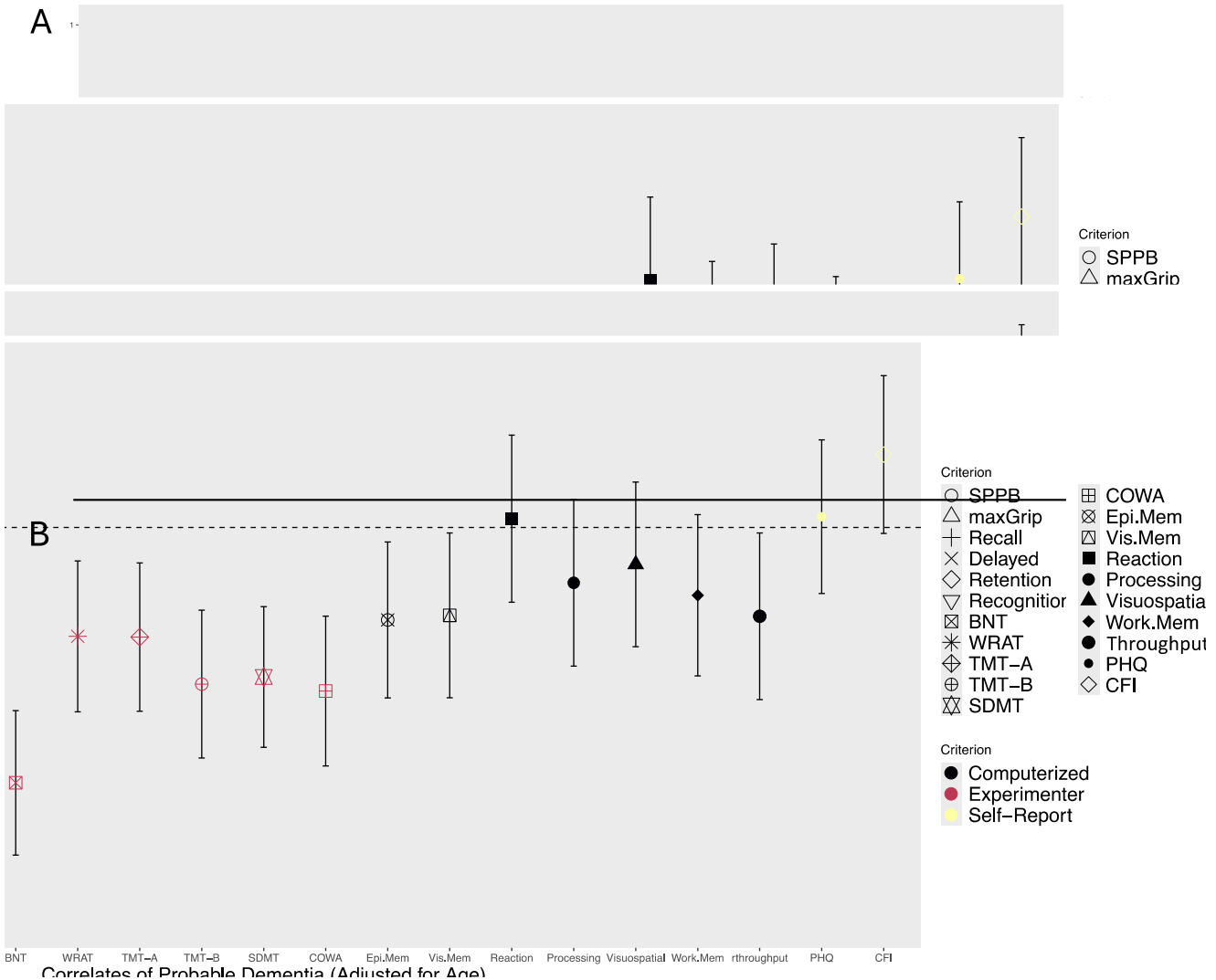
1. Determine whether FDNY and GRC responders differ in the prevalence of MCI, as well as more severe cognitive impairments indicative of possible dementia.

2. Assess whether the operational definition of MCI (MoCA, Jak/Bondi criteria, Petersen criteria, and NIA-AA criteria) impacts prevalence estimates.

3. Help determine clinical significance by comparing prevalence estimates in FDNY and GRC responders to meta-analytic estimates of MCI and EOD (typically defined as all-cause dementia before the age of 65 years) from different global, community, and clinical populations.

4. Thoroughly characterize the domain-specific deficits of cognitively impaired FDNY responders by analyzing scores from a large battery of objective neurocognitive tests.

Domain-Specific Neurocognitive, Psychiatric and Physical Functional Correlates of Cognitive Impairment and Possible Dementia Diagnosed Using Montreal Cognitive Assessment.



Summary of Preliminary Findings

1. The prevalence of MCI is significantly higher among FDNY responders, compared to GRC responders, but FDNY and GRC responders did *not* significantly differ in prevalence of possible dementia.

2. The operational definition of MCI (Jak/Bondi criteria, Petersen criteria, and NIA-AA criteria) had little impact on prevalence estimates; Using a conservative MoCA cut-off to define MCI resulted in significantly lower prevalence estimates compared to alternative definitions.

3. Prevalence of MCI in FDNY and GRC is noticeably higher than meta-analytic estimates of MCI from different community and clinical populations; Prevalence of possible dementia before the age of 65 years was higher than meta-analytic estimates of EOD prevalence from different global populations.

4. Cognitive impairments of FDNY responders were characterized primarily by deficits in verbal learning, verbal memory, episodic memory, and executive function.

Acknowledgements

National Institute for Occupational Safety and Health

Centers for Disease Control and Prevention

National Institutes of Health and National Institute on Aging

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  - CDC 2011-200-39361 awarded to Benjamin Luft
- Analyses were partially funded by
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Special thanks all WTC responders and to our many team members and collaborators at SBU and FDNY:
Charles B. Hall, Sean A. P. Clouston, Alexandra K. Mueller, Rachel Zeig-Owens, Jaeun Choi, David J. Prezant, Benjamin J. Luft, Melissa M. Carr, Alicia M. Fels, Christina Hennington, and many others!

Minos Kritikos, PhD

Neuroimaging of inflammation in WTC-exposed Responders

Dr. Kritikos is a Life Scientist with diverse expertise in the Neurosciences, ranging from the molecular world, to studying cell physiology under microscopes, to population level neuroimaging. He is currently investigating the intricate factors and mechanisms underlying dementia and PTSD, where each can lead to functional dysregulation in daily life. This talk will dive into World Trade Center 9/11 exposed responders, now at midlife, who endured acute and chronic physical and psychiatric injuries, ranging from noxious dust inhalations to intense emotional trauma. Now, more than two decades later, they have stratified into distinct subgroups presenting with either cognitive and psychological resilience to their exposures, or cognitive impairment (CI), or PTSD, or both CI with PTSD. We will review recent and ongoing efforts attempting to disentangle the neural correlates for these distinct outcomes, and what they can teach us about past, present, and possibly future populations at similar risks.

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Additional Reading

Reading 1: Huang, C., Kritikos, M., Sosa, M. S., Hagan, T., Domkan, A., Meliker, J., Pellecchia, A. C., Santiago-Michels, S., Carr, M. A., Kotov, R., Horton, M., Gandy, S., Sano, M., Bromet, E. J., Lucchini, R. G., Clouston, S. A. P., & Luft, B. J. (2023). World Trade Center Site Exposure Duration Is Associated with Hippocampal and Cerebral White Matter Neuroinflammation. *Mol Neurobiol*, 60(1), 160-170. https://doi.org/10.1007/s12035-022-03059-z

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Neuroimaging of Inflammation in WTC-Exposed Responders

Minos Kritikos, Ph.D.

Program in Public Health

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Siemens Biograph 3T PET/MRI

Background

- Responders to the World Trade Center (WTC) attacks on 9/11/2001 inhaled toxic dust and experienced severe trauma for a prolonged period.
- Studies report that WTC site exposure duration (cite) is associated with peripheral inflammation and risk for developing early-onset dementia (EOD).
- Free Water Fraction (FWF) can serve as a biomarker for neuroinflammation by measuring in vivo movement of free water across neurons.

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Background(1)

> Brain Behav Immun Health. 2021 Jun 30:16:100287. doi: 10.1016/j.bbih.2021.100287. eCollection 2021 Oct.

Neuroinflammation in World Trade Center responders at midlife: A pilot study using [^{18}F]-FEPPA PET imaging

Yael Deri [1], Sean A P Clouston [2], Christine DeLorenzo [3 4], John D Gardus 3rd [3], Elizabeth A Bartlett [5 6], Stephanie Santiago-Michels [7], Lev Bangiyev [8], William C Kreisl [9], Roman Kotov [3], Chuan Huang [3 4 8], Mark Slifstein [3], Ramin V Parsey [3 4], Benjamin J Luft [1 7]

Affiliations + expand

PMID: 34589784 PMCID: PMC8474562 DOI: 10.1016/j.bbih.2021.100287

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Background

> Brain Behav Immun Health. 2021 Jun 30:16:100287. doi: 10.1016/j.bbih.2021.100287. eCollection 2021 Oct.

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Greater **WTC exposure duration** was associated with higher *[18F]-FEPPA (TSPO) signal* in the **parietal** and **frontal** cortices.

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Table 2
Associations between [^{18}F]-FEPPA binding and WTC exposures.

Region Name	PTSD severity			Total months on WTC site		
	B ± SE	*d*	*P*	B ± SE	*d*	*P*
Frontal cortex	0.014 ± 0.004	0.71	*0.001***	0.030 ± 0.014	0.49	*0.029**
Parietal cortex	0.012 ± 0.005	0.60	*0.007***	0.032 ± 0.015	0.50	*0.027**
Temporal cortex	0.011 ± 0.007	0.53		*0.140*	0.035 ± 0.023	0.41 *0.136*
Occipital cortex	0.011 ± 0.005	0.33	*0.018**	0.027 ± 0.014	0.33	*0.065*#*
Cingulate cortex	0.011 ± 0.005	0.51	*0.025**	0.025 ± 0.015	0.37	*0.106*
Hippocampus	0.014 ± 0.004	0.75	*0.001***	0.017 ± 0.013	0.28	*0.208*
Whole brain	0.012 ± 0.005	0.58	*0.010**	0.026 ± 0.015	0.39	*0.080*#*

Note: Regression models showing the relationship between WTC exposures (i.e., PTSD symptom severity and total month working on the WTC sites) and [^{18}F]-FEPPA V_T in the frontal cortex, temporal cortex, parietal cortex, occipital pre-frontal cortex, hippocampus, and whole brain (not PVC) in WTC responders. GLM resulted beta coefficients (B), standard error for the beta coefficients (SE), Cohen's *d* (*d*) and nominal p-values (*P*) are reported. $^{\#}0.1 > P > 0.5$, $^{*}P < 0.05$ and $^{**}P < 0.01$.
Abbreviations: V_T = total distribution volume.

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Key Findings

> Mol Neurobiol. 2023 Jan;60(1):160-170. doi: 10.1007/s12035-022-03059-z. Epub 2022 Oct 15.

World Trade Center Site Exposure Duration Is Associated with Hippocampal and Cerebral White Matter Neuroinflammation

Chuan Huang [# 1 2 3], Minos Kritikos [# 4], Mario Serrano Sosa [3], Thomas Hagan [3], Alan Domkan [5], Jaymie Meliker [4], Alison C Pellecchia [6], Stephanie Santiago-Michels [6], Melissa A Carr [6], Roman Kotov [2], Megan Horton [7], Sam Gandy [8 9 10], Mary Sano [9 10], Evelyn J Bromet [2], Roberto G Lucchini [7], Sean A P Clouston [11], Benjamin J Luft [6 12]

Affiliations + expand

PMID: 36242735 PMCID: PMC9758101 DOI: 10.1007/s12035-022-03059-z

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Key Findings

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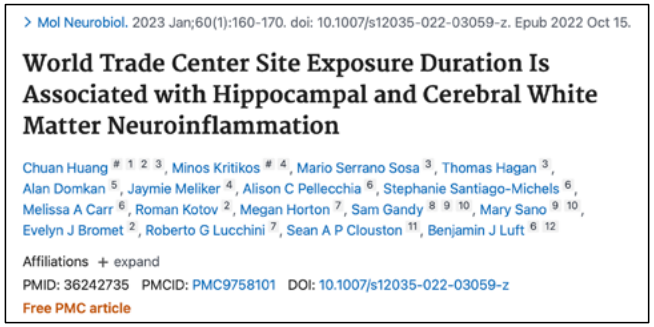
Characteristic	Overall	Cognitively unimpaired	Early-onset dementia	*t*-test/x^2
	***N* = 99**	***N* = 51**	***N* = 48**	***p***
Age	56.38 (0.52)	56.42 (0.63)	56.32 (0.86)	0.926
PTSD—DSM-IV (SCID-IV)				
No	52.50%	53.90%	51.10%	0.782
Yes	47.50%	46.20%	48.90%	
APOEε4 status (*n* = 91)				0.227
APOEε4 +	21.21%	21.57%	20.83%	
APOEε4-	67.68%	72.55%	62.50%	
Unknown	11.11%	5.88%	16.67%	
Sex				
Male	85.30%	80.80%	76.60%	0.612
Female	14.70%	19.20%	23.40%	
Minority status				
White	77.80%	86.50%	68.10%	0.087
Black	10.10%	5.80%	14.90%	
Hispanic	12.10%	7.70%	17.00%	
Occupation				
NYPD	56.60%	60.80%	52.10%	0.383
Other	43.40%	39.20%	47.90%	
Education				
High school or less	23.20%	17.70%	29.20%	0.359
Some college	47.50%	49.00%	45.80%	
University degree	29.30%	33.30%	25.00%	



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Affiliations + expand

PMID: 36242735 PMCID: PMC9758101 DOI: 10.1007/s12035-022-03059-z

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Table 1.

World Trade Center (WTC) responder sample characteristics

Values expressed as means (standard deviations) or percentages (%); *p*-values from Welch's *t*-tests or chi-squa red test comparisons examine the extent to which noted characteristics differ across groups; *PTSD*, post-traumatic stress disorder; *APOEε4*, the ε4 allele of the Apolipoprotein E (APOE) gene; *DSM-IV (SCID-IV),* Structured Clinical Interview using the Diagnostic and Statistical Manual IV; *NYPD*, New York Police Department

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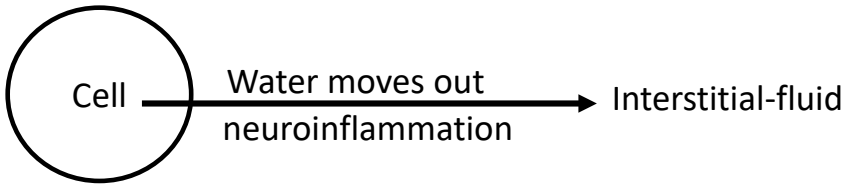
Key Findings

- Free water fraction (FWF) is an MRI diffusion tensor imaging (DTI) technique that has been previously shown to estimate underlying neuroinflammation in vivo and its association with CI

- A known byproduct of neuroinflammation is when the brain clears interstitial extra- neuronal spaces resulting in localized changes to diffusing free water, which is what FWF measures.



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Key Findings

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Correlations between World Trade Center site exposure duration (hours) and cerebral white matter free water fraction in 68 regions of interest (ROIs) from the Desikan-Killiany Atlas. Significant correlations are highlighted in **Bold; *=FDR**

Lobe	Regions of Interest	r	p	r#	P#
Frontal	Caudal Middle Frontal	0.10	0.302	0.09	0.430
	Frontal Pole	-0.03	0.746	-0.03	0.774
	Lateral Orbitofrontal	0.13	0.152	0.15	0.122
	Medial Orbitofrontal	0.16	0.109	0.13	0.177
	Pars Opercularis	**0.22**	**0.028**	0.17	0.082
	Pars Orbitalis	0.21	**0.040**	0.17	0.088
	Pars Triangularis	**0.27**	**0.008***	**0.23**	**0.021**
	Rostral Middle Frontal	**0.21**	**0.038**	0.19	0.057
	Superior Frontal	0.15	0.139	0.12	0.232
	Precentral	**0.23**	**0.026**	0.15	0.135
Limbic	Caudal Anterior Cingulate	0.18	0.059	0.19	0.053
	Rostral Anterior Cingulate	0.15	0.153	0.11	0.288
	Isthmus Cingulate	0.10	0.320	0.11	0.284
	Insula	0.18	0.078	0.16	0.099
	Parahippocampal	**0.28**	**0.005***	**0.32**	**<0.00**
	Posterior Cingulate	0.13	0.217	0.10	0.290
Temporal	Banks Superior Temporal Sulcus	0.16	0.116	0.14	0.156
	Entorhinal	**0.28**	**0.006***	**0.20**	**0.045**
	Inferior Temporal	0.17	0.060	0.12	0.209
	Middle Temporal	0.21	**0.043**	**0.18**	**0.063**
	Superior Temporal	0.15	0.071	0.18	0.062
	Temporal Pole	0.11	0.279	0.05	0.641
	Transverse Temporal	**0.27**	**0.007***	**0.24**	**0.014**
Parietal	Inferior Parietal	**0.24**	**0.020**	0.17	0.083
	Paracentral	0.14	0.181	0.09	0.343
	Postcentral	**0.20**	**0.045**	0.10	0.297
	Precuneus	0.15	0.079	0.13	0.198
	Superior Parietal	**0.22**	**0.032**	0.15	0.124
	Supramarginal	0.18	0.070	0.13	0.196
	Pericalcarine	0.06	0.533	0.02	0.826
	Fusiform	0.15	0.142	0.14	0.156
	Cuneus	0.13	0.161	0.08	0.430
	Lateral Occipital	0.08	0.435	0.04	0.725
	Lingual	0.13	0.223	0.11	0.284

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Key Findings

> Mol Neurobiol. 2023 Jan;60(1):160-170. doi: 10.1007/s12035-022-03059-z. Epub 2022 Oct 15.

World Trade Center Site Exposure Duration Is Associated with Hippocampal and Cerebral White Matter Neuroinflammation

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PMID: 36242735 PMCID: PMC9758101 DOI: 10.1007/s12035-022-03059-z

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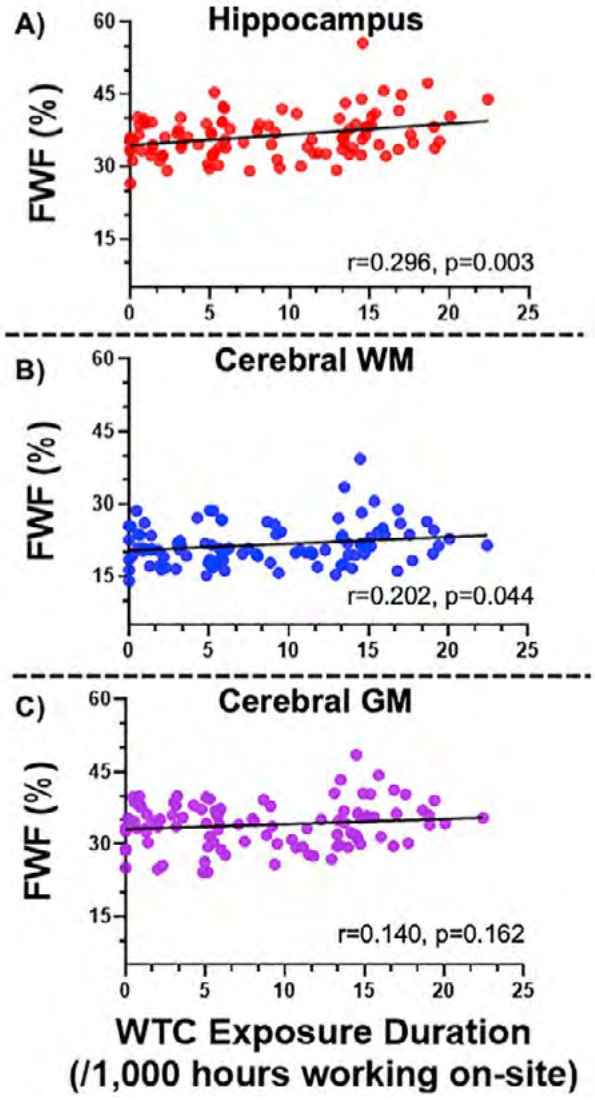
Hippocampal FWF was significantly associated with WTC site exposure duration (r = 0.30, p = 0.003), as was **cerebral white matter FWF** (r = 0.20, p = 0.044), and was highest when **APOEε4** was present (r = 0.48, p = 0.039)."



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Key Findings(5)

Mol Neurobiol. 2023 Jan;60(1):160-170. doi: 10.1007/s12035-022-03059-z. Epub 2022 Oct 15.

World Trade Center Site Exposure Duration Is Associated with Hippocampal and Cerebral White Matter Neuroinflammation

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PMID: 36242735 PMCID: PMC9758101 DOI: 10.1007/s12035-022-03059-z

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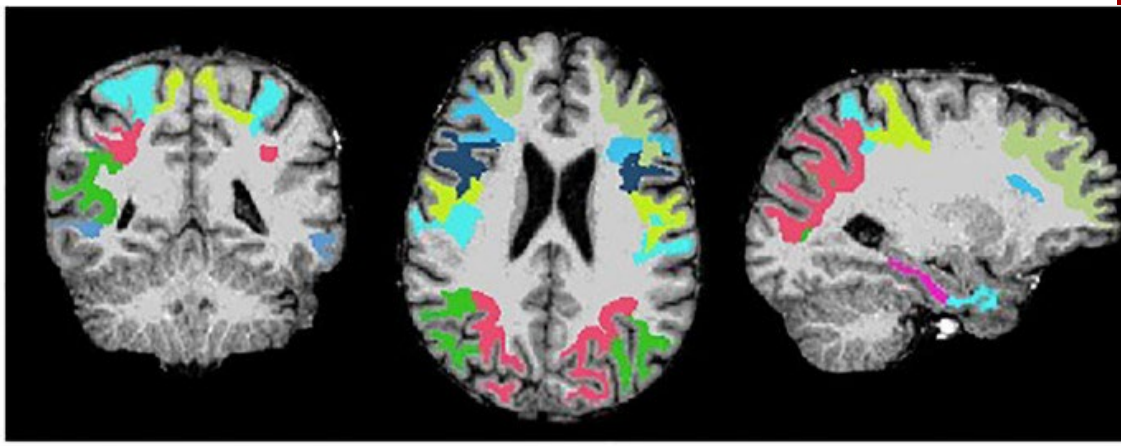
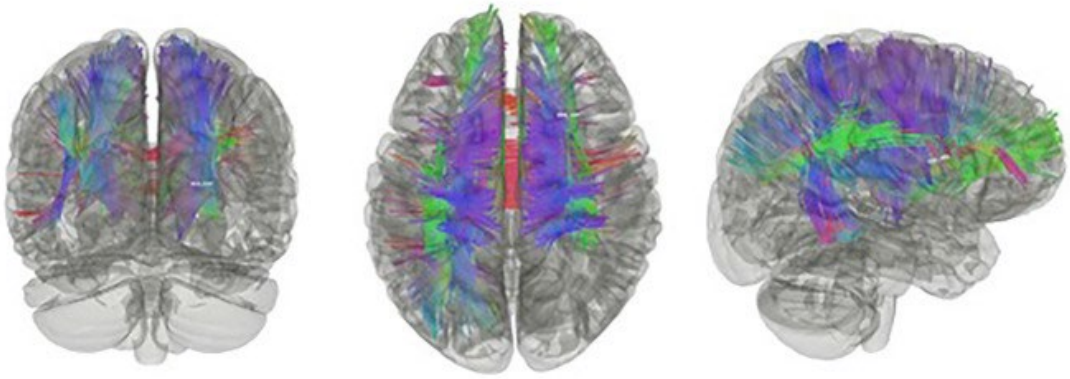
Correlational tractography. Free water fractions (FWF) within regions of interest (ROIs) (uncorrected) and ISO from correlational tractography analysis (bottom panel, t-threshold = 3, FDR = 0.011), were both **significantly correlated with WTC site exposure duration** in many overlapping ROIs, such as frontal and parietal regions

FWF Regions



ISO Correlation Regions



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Impact

- Our findings demonstrate that prolonged WTC site exposure in Responders is associated with increased:
  - hippocampal neuroinflammation
  - cerebral white matter neuroinflammation
  - possession of the APOEε4 allele exacerbates associations.
- Free Water Fraction (FWF) can serve as a biomarker for neuroinflammation by measuring in vivo movement of free water across neurons.

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Future Research Needs

- Examine FWF associations with more recently developed exposure variables from **<u>WTC activities and exposures</u> involving higher potential neurotoxic dust exposures** *(Clouston et al., In Press),* for granular associations based on exposure classifications
- Interrogate auxiliary Glial activation biomarkers i.e., GFAP (suppressed in WTC-PTSD – *Natale et al., 2023*) and their associations with FWF and other morphometric measures of the brain beyond neuroinflammation.
- Analyses of associations between FWF and:
  - Aβ & Tau proteinopathies
  - Other structural and functional morphometric biomarkers

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Acknowledgements

Chuan Huang, Mario Serrano Sosa,Thomas Hagan, Alan Domkan, Jaymie Meliker, Alison C. Pellecchia, Stephanie Santiago-Michels, Melissa A. Carr, Roman Kotov, Megan Horton, Sam Gandy, Mary Sano, Evelyn J. Bromet, Roberto G. Lucchini, Sean A. P. Clouston, and Benjamin J. Luft

All 9/11 Responders and Survivors

EPIDEMIOLOGY: NIH R01 AG049953; CDC 200-2011-39361; U01 OH011314
IMAGING: NIH R01 AG067590; CDC U01 OH11478; NIH R21 AG074705;
ESI SUPPORT: NIH R21 AG074705; NIH R21 AG074705; NIH R21 AG074705;

Program in Public Health, Stony Brook University.
World Trade Center Health Program.
Social and Brain Aging Lab. ORCID

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NOTES

Paul Vaska, PhD

Direct assessment of brain beta-amyloid plaques in WTC first responders

Dr. Vaska earned his PhD in Experimental Nuclear Physics at Stony Brook University in 1997. He subsequently transitioned into medical imaging technology development, in industry (UGM Medical Systems which was absorbed by Philips Medical Systems) followed by the PET imaging group at Brookhaven National Laboratory. Since 2011, he has been Professor of Biomedical Engineering and Radiology at the Renaissance School of Medicine at Stony Brook University, with current research focus on PET imaging technology development and its many applications, mostly in the brain.

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Additional Reading

Reading 1: Kritikos, M., Franceschi, A. M., Vaska, P., Clouston, S. A. P., Huang, C., Salerno, M., Deri, Y., Tang, C., Pellecchia, A., Santiago-Michels, S., Sano, M., Bromet, E. J., Lucchini, R. G., Gandy, S., & Luft, B. J. (2022). Assessment of Alzheimer's Disease Imaging Biomarkers in World Trade Center Responders with Cognitive Impairment at Midlife. *World J Nucl Med*, 21(4), 267-275. https://doi.org/10.1055/s-0042-1750013

Reading 2: Clouston, S. A. P., Kritikos, M., Huang, C., Kuan, P. F., Vaska, P., Pellecchia, A. C., Santiago-Michels, S., Carr, M. A., Gandy, S., Sano, M., Bromet, E. J., Lucchini, R. G., & Luft, B. J. (2022). Reduced cerebellar cortical thickness in World Trade Center responders with cognitive impairment. *Transl Psychiatry*, 12(1), 107. https://doi.org/10.1038/s41398-022-01873-6

Direct assessment of brain beta-amyloid plaques in WTC first responders

Paul Vaska, Professor of Bioimedical Engineering and Radiology

Minos Kritikos, Juin-Wan Zhou, Chuan Huang, Sam Gandy, Alison C. Pellecchia, Stephanie Santiago-Michels, Melissa A. Carr, Shabab Islam, Megan K. Horton, Roberto G. Lucchini, Ana M. Franceschi, Lev Bangiyev, Paul Vaska, Sean A. P. Clouston, and Benjamin J. Luft

Renaissance School of Medicine at Stony Brook University

Icahn School of Medicine at Mt. Sinai

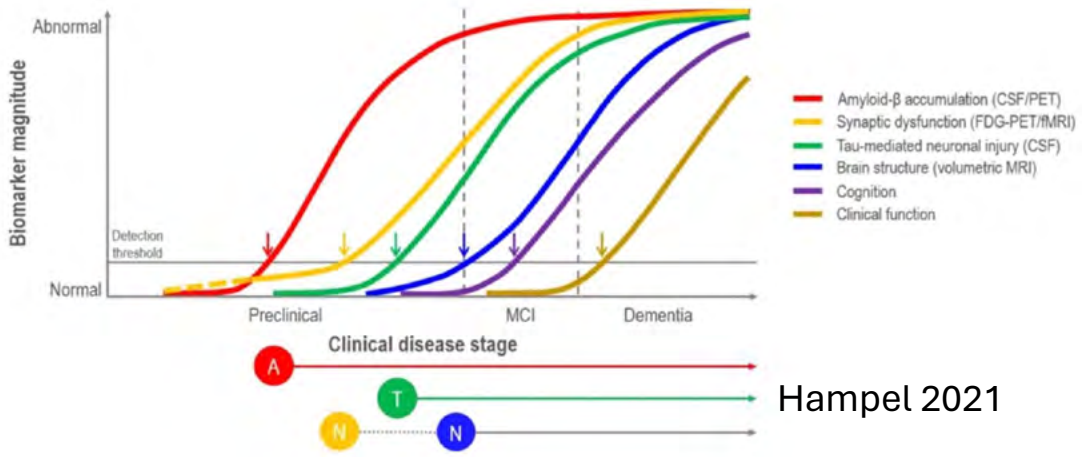
Emory University

Disclosures

- Dr. Gandy is a co-founder of Recuerdo Pharmaceuticals. He has served as a consultant in the past for J&J, Diagenic, and Pfizer, and he currently consults for Cognito Therapeutics, GLG Group, SVB Securities, Guidepoint, Third Bridge, MEDACORP, Altpep, Vigil Neurosciences, and Eisai. He has received research support in the past from Warner-Lambert, Pfizer, Baxter, and Avid. He currently receives research support from the NIH and the Cure Alzheimer's Fund.
- Dr. Franceschi has served as consultant for Biogen, Life Molecular Imaging, Roche/Genentech, and Eisai.
- No other authors have conflicts of interest to disclose.

Motivation

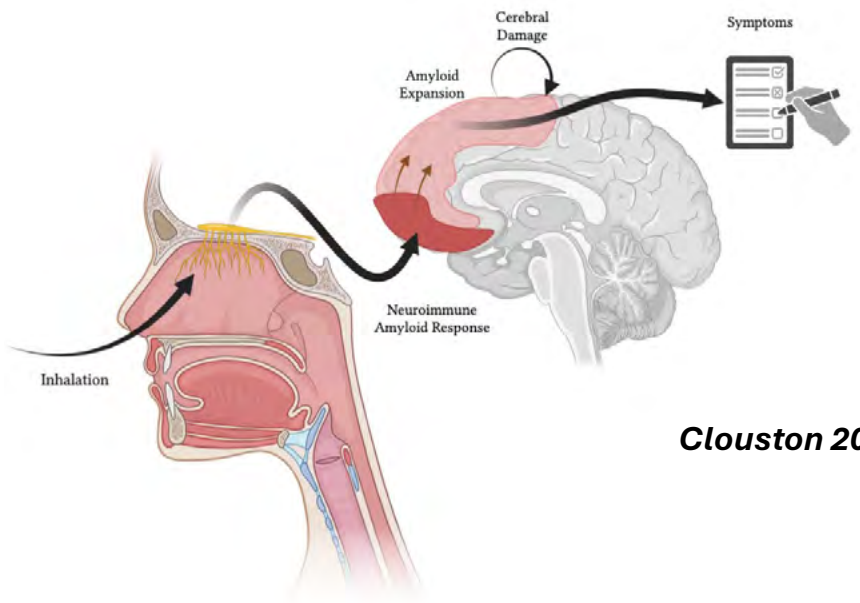
- WTC responders have greater cognitive impairment CI
- Is it related to Alzheimer's Disease (AD)?
- Beta amyloid is earliest biomarker
  - Known to be toxic, but not necessarily causative of AD
  - Risk factor



Hampel 2021

Motivation

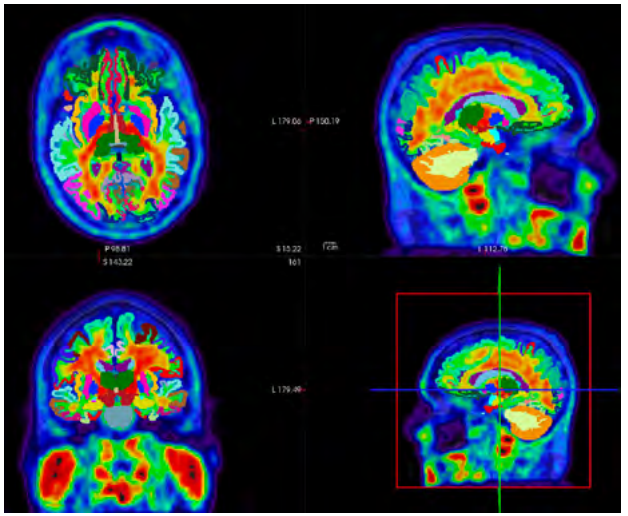
- Investigate potential olfactory involvement
- Investigate involvement of previously identified WTC regions



Clouston 2021

Methods

- WTC responders with and without cog impairment
  - CU: MoCA >= 26
  - CI: MoCA < 22
- Simultaneous PET and MRI brain scans
  - AD Centiloid scale (0-100)
  - Regional analysis
  - MRI cortical thickness and mean diffusivity
- Radiotracer
  - ^{18}F-florbetaben (FBB)
  - FDA approved

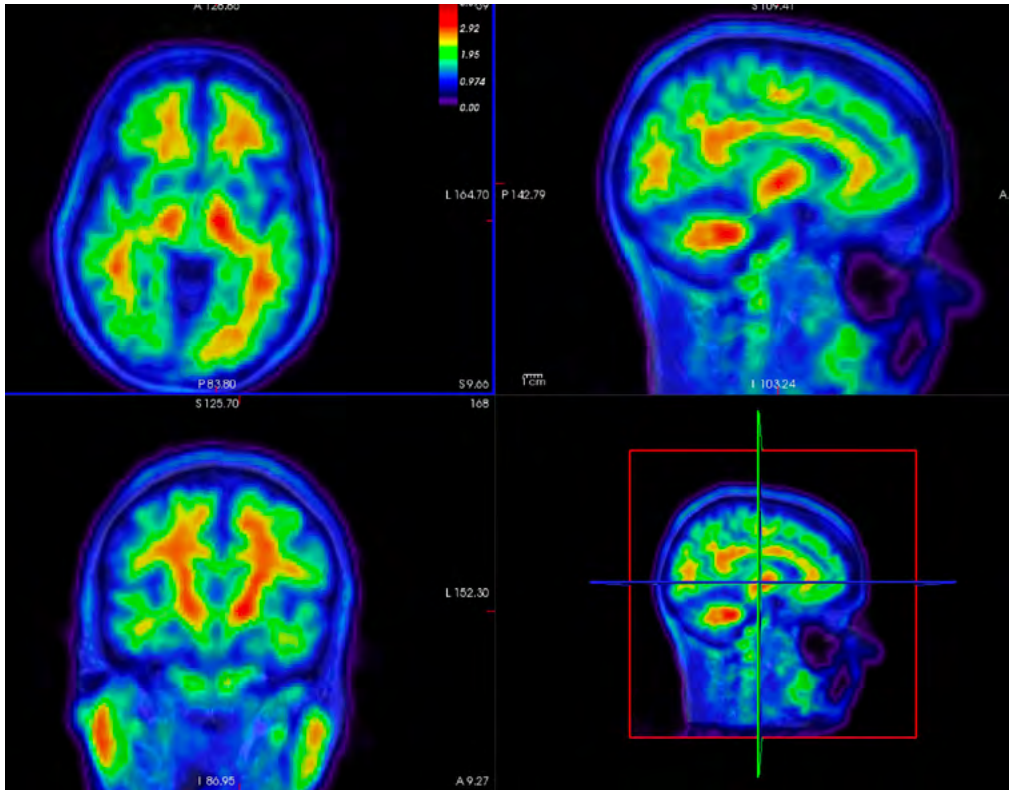


Results

Characteristic	Cognitively Impaired (n=18)	Cognitively Unimpaired (n=18)	P
Age	55.16 (4.73)	56.79 (5.53)	0.335
Body Mass Index, kg/m^2	28.26 (3.64)	30.43 (4.36)	0.105
Male	84.21%	68.42%	0.252
Race/Ethnicity			0.15
White	68.42%	84.21%	
Other	31.58%	15.79%	
Hispanic	21.05%	5.26%	
Education			0.71
Advanced Degree	36.84%	36.84%	
Associates / Some College	31.58%	42.11%	
Highschool or less	31.58%	21.05%	
Post-Traumatic Stress Disorder	42.11%	47.37%	0.744
Major Depressive Disorder	5.26%	10.53%	0.547
Exposure Duration, months	5.82 (3.04)	5.95 (3.01)	0.9
Early Arrival 9/11-9/12	88.24%	84.21%	0.727
Caught in the Dust Cloud	29.41%	21.05%	0.563
Law Enforcement (versus Other)	78.95%	73.68%	0.703
Cogstate:			
Episodic Memory	0.70 (0.15)	0.53 (0.19)	0.007
Visual Working Memory	1.02 (0.11)	0.86 (0.17)	0.003
Throughput, responses/cs	3.91 (0.96)	4.98 (0.69)	0.001
Response Speed, response/cs	6.66 (1.54)	7.91 (0.67)	0.006
Processing Speed, response/cs	6.08 (0.62)	6.63 (0.49)	0.011
Intra-individual variability, SD	1.35 (0.75)	0.86 (0.27)	0.027
Attention	1.42 (0.15)	1.20 (0.42)	0.053
Visuospatial Learning	1.96 (0.60)	1.23 (0.30)	<0.001
Visuospatial Memory	6.86 (2.39)	24.61 (3.09)	0.035

Results

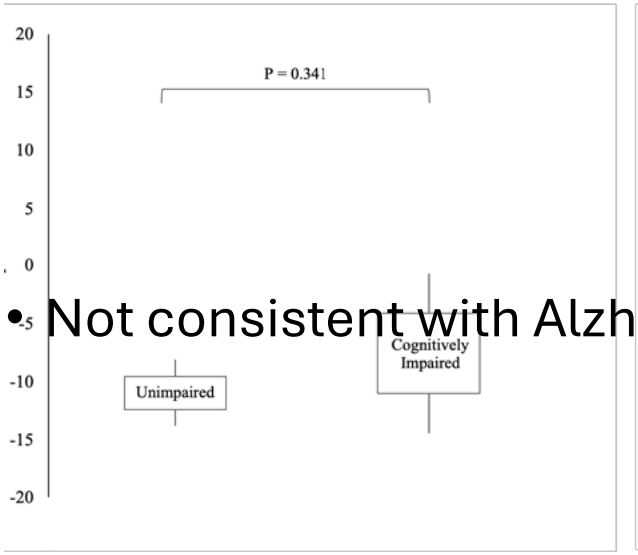
- Typical distribution



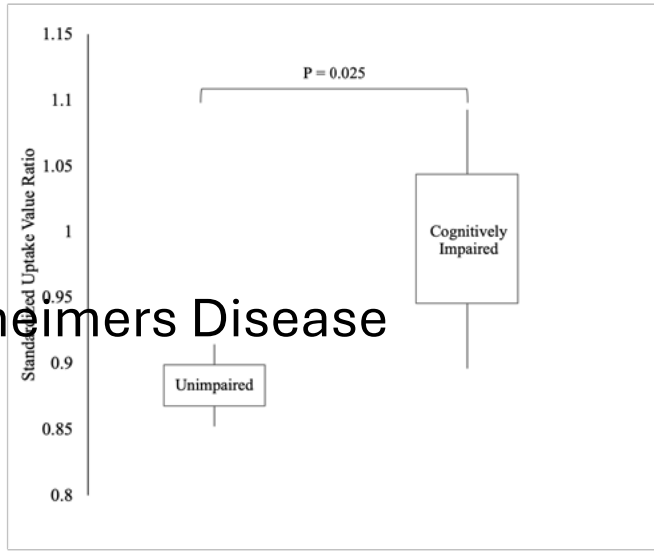
Results

- Centiloid values not consistent with AD
- FBB in WTC regions is different
- Not consistent with Alzheimers Disease

CENTILOID

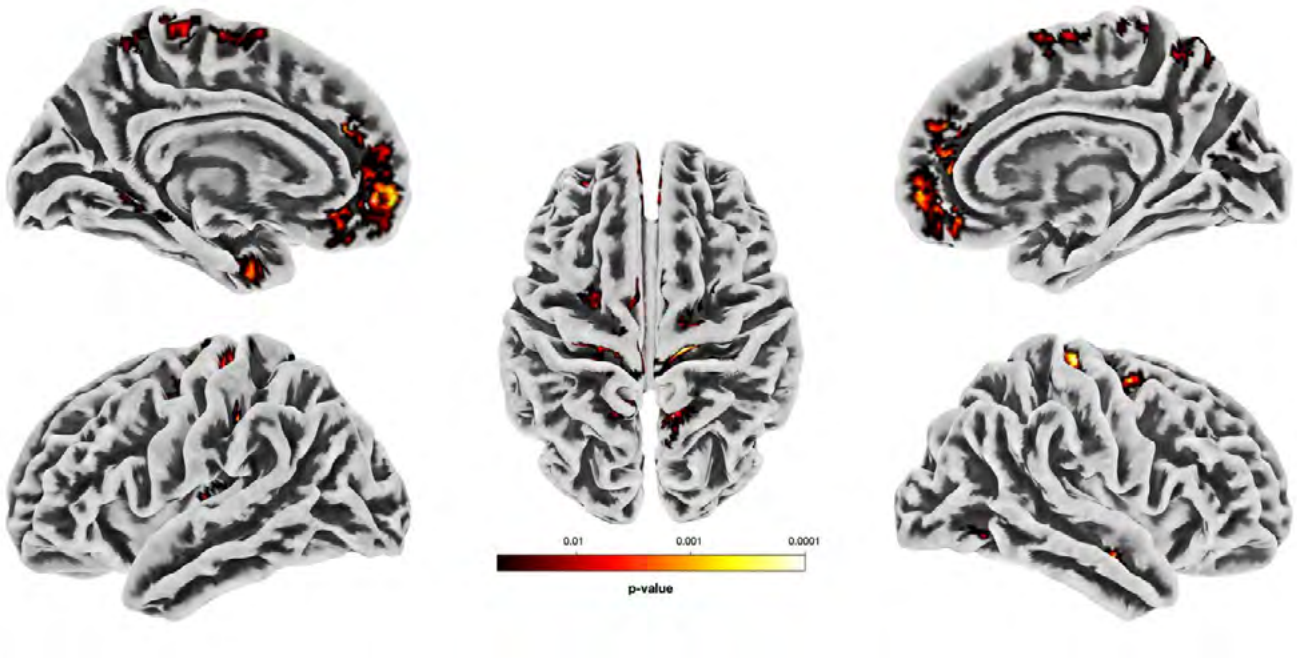


WTC meta-ROI

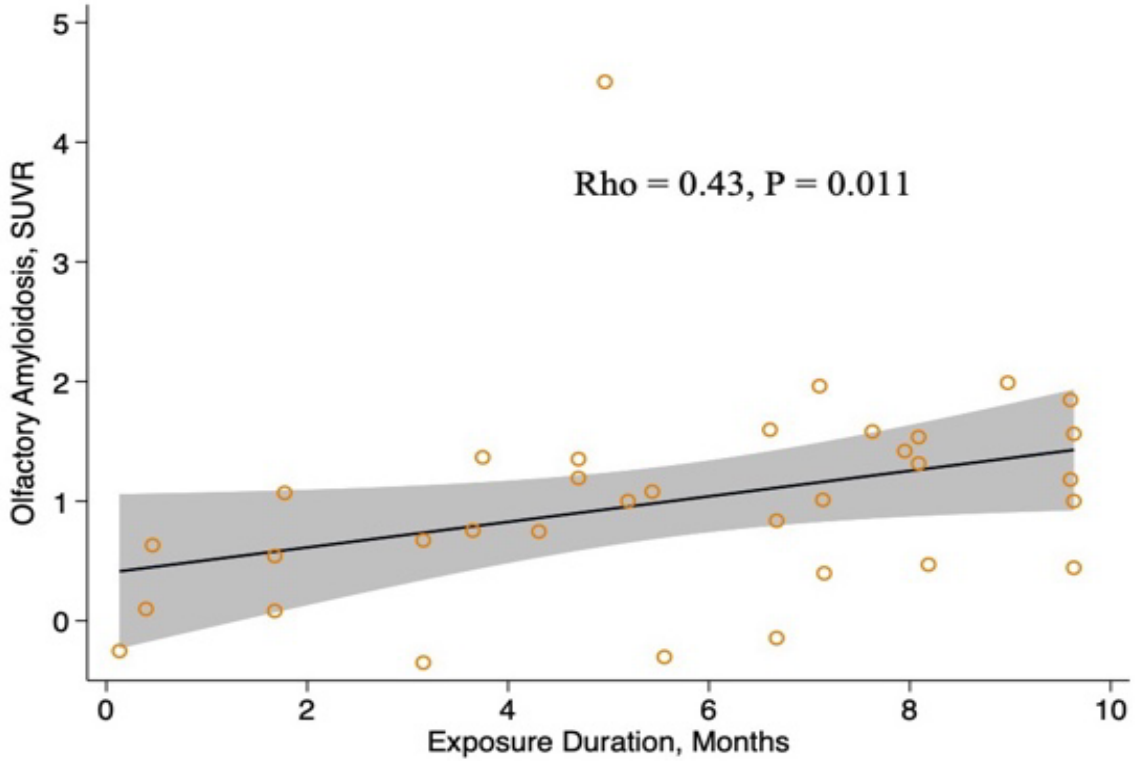


Results

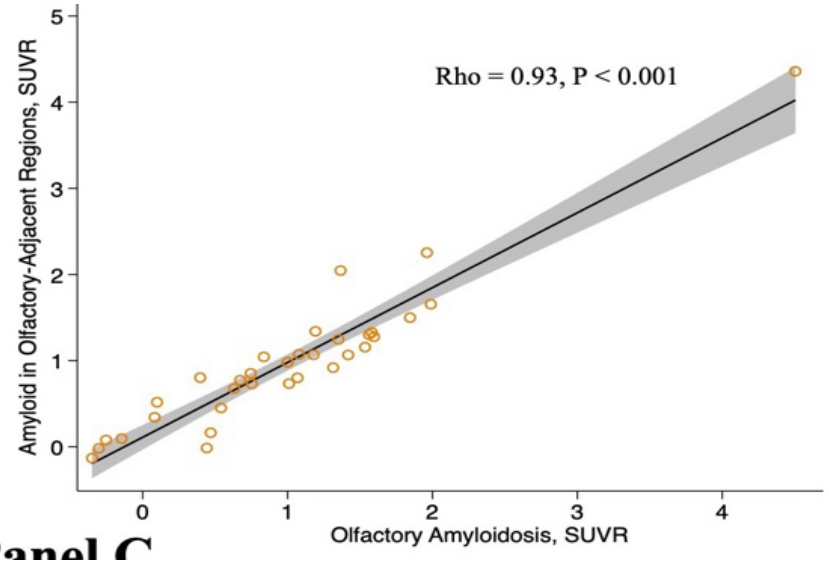
- Voxelwise differences between CI and CU
- After FDR, significant clusters in medial orbitofrontal, precentral, superior frontal



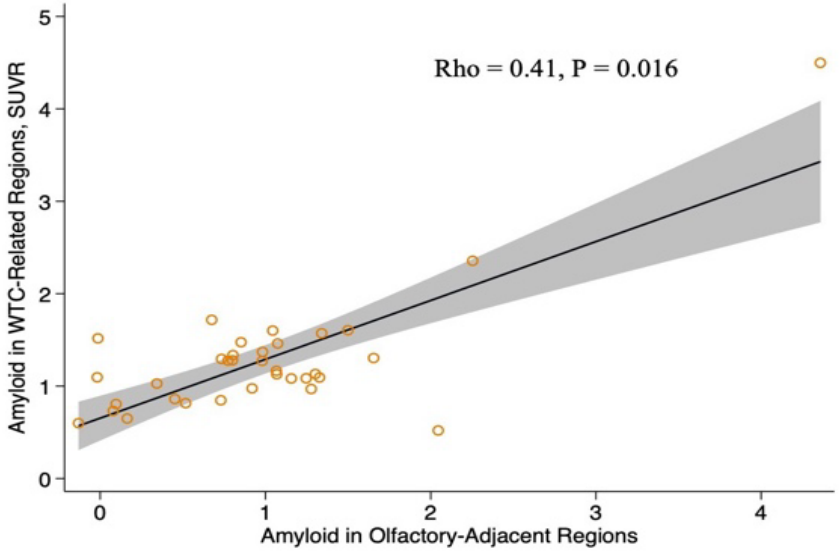
Results


Rho = 0.43, P = 0.011
Olfactory Amyloidosis, SUVR
Exposure Duration, Months
0
1
2
3
4
5
0
2
4
6
8
10

Results



Panel C



Results

- FBB correlates with MRI structural measures

Lobe	Region	Cortical Mean Diffusivity		Cortical Thickness, mm	
		Left	Right	Left	Right
Frontal	Superior Frontal	0.44	0.26	-0.28	-0.30
	Rostral Middle Frontal	0.09	***0.53***	-0.32	-0.36
	Caudal Middle Frontal	0.47	0.32	-0.13	-0.36
	Pars Opercularis	***0.55***	0.26	-0.28	-0.44
	Pars Orbitalis	-0.05	***0.55***	-0.04	-0.19
	Pars Triangularis	0.44	0.51	-0.44	-0.44
	Lateral Orbitofrontal	0.08	***0.70***	-0.20	-0.09
	Medial Orbitofrontal	0.02	***0.56***	-0.22	-0.34
	Paracentral	0.39	0.50	-0.10	-0.14
	Precentral	***0.58***	***0.61***	-0.17	-0.14
Parietal	Superior Parietal	***0.64***	***0.59***	-0.21	-0.25
	Inferior Parietal	***0.57***	***0.65***	-0.23	-0.32
	Supramarginal	***0.63***	***0.67***	-0.37	-0.40
	Postcentral	0.35	***0.54***	-0.09	-0.16
	Precuneus	0.52	***0.62***	-0.34	-0.35
	Insula	***0.67***	***0.70***	-0.37	-0.04
Temporal	Superior Temporal	0.12	0.46	-0.29	-0.15
	Middle Temporal	0.24	0.22	-0.38	-0.28
	Inferior Temporal	0.17	***0.58***	-0.10	-0.26
	Fusiform	***0.58***	0.10	-0.30	-0.23
	Transverse Temporal	***0.71***	0.46	-0.19	-0.09
Occipital	Lateral Occipital	***0.55***	***0.63***	-0.17	-0.26
	Lingual	***0.57***	0.06	-0.32	-0.14
	Cuneus	***0.60***	***0.53***	-0.36	-0.34
	Pericalcarine	0.50	0.28	-0.21	-0.17
Limbic	Para hippocampal Gyrus	0.40	0.50	0.07	-0.10
	Rostral Anterior Cingulate	0.19	***0.53***	-0.17	-0.33
	Anterior Cingulate	0.36	0.46	-0.16	0.02
	Isthmus Cingulate	***0.61***	0.26	-0.39	***-0.53***
	Posterior Cingulate	0.21	0.43	-0.29	-0.28

Future Research Needs

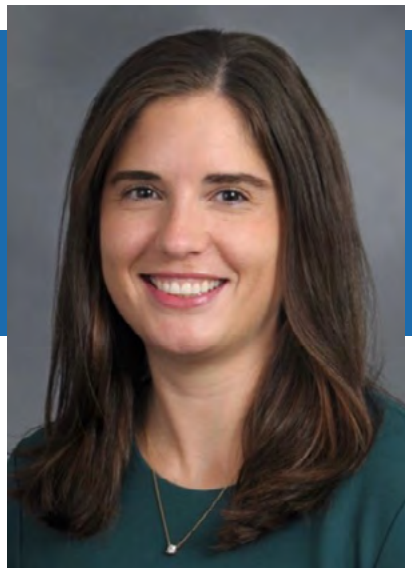
- Are amyloid plaques actually spreading?
  - Longitudinal PET studies
- Is amyloid part of immune response?
  - Measure neuroinflammation
  - PET can now target more specifically, eg COX enzymes
- Anti-amyloid treatments?
  - FDA approved and could be considered

Funding and Acknowledgements

- Centers for Disease Control and Prevention (CDC/NIOSH U01 OH011314; and CDC 200-2011-39361)
- National Institute on Aging (NIH/NIA R01 AG049953; NIH/NIA P30 AG066514).
- Thanks to the Stony Brook PET Imaging Core
- The study was reviewed by the institutional review board (CORIHS #1315306). All participants provided informed written consent.

NOTES

Laura Sampson, PhD



Post-traumatic stress disorder and physical function over time among World Trade Center responders

Laura Sampson, PhD is an Assistant Professor in the Program in Public Health and Department of Family, Population, and Preventive Medicine at Stony Brook University. She studies the mental and physical health effects of stress, trauma, depression, and posttraumatic stress disorder, especially as they relate to sleep, aging, and cardiovascular disease. She received her BA in Statistics from Harvard University and her PhD in Epidemiology from Boston University School of Public Health. She completed her post-doctoral training at the Harvard T.H. Chan School of Public Health.

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Additional reading

Reading 1: Mukherjee, S., Clouston, S., Kotov, R., Bromet, E., & Luft, B. (2019). Handgrip Strength of World Trade Center (WTC) Responders: The Role of Re-Experiencing Post-traumatic Stress Disorder (PTSD) Symptoms [Article]. *Int J Environ Res Public Health*, 16(7). https://doi.org/10.3390/ijerph16071128

Reading 2: Pellecchia, A., Kritikos, M., Guralnik, J., Ahuvia, I., Santiago-Michels, S., Carr, M., Kotov, R., Bromet, E. J., Clouston, S. A. P., & Luft, B. J. (2022). Physical Functional Impairment and the Risk of Incident Mild Cognitive Impairment in an Observational Study of World Trade Center Responders. *Neurol Clin Pract*, 12(6), e162-e171. https://doi.org/10.1212/cpj.0000000000200089

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Post-traumatic stress disorder and physical function over time among WTC responders

Laura Sampson, PhD

June 12, 2024

Background and motivation

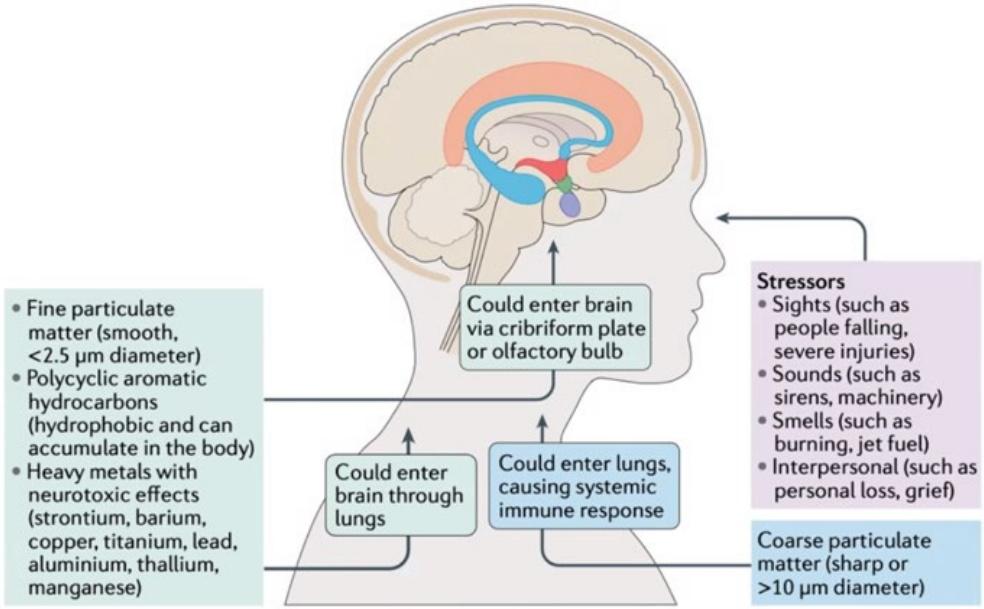
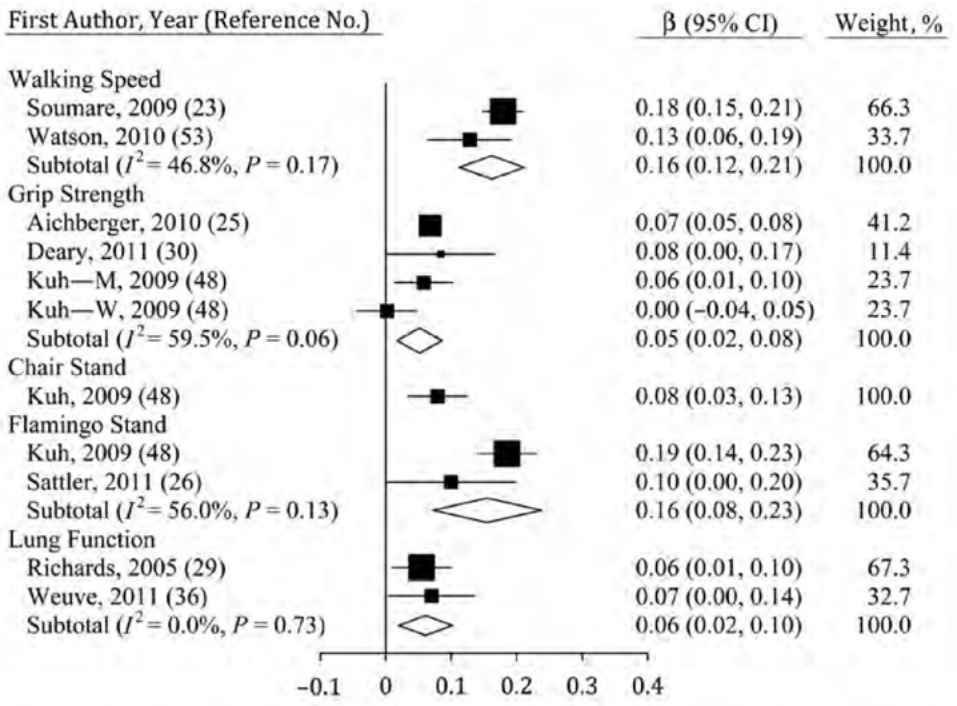


Fig. 1 | **WTC-related exposures and their potential routes to the brain.** Here we highlight the potential for WTC-related exposures to influence the risk of neurodegenerative disease in three different ways. First, by causing a severe and chronic stress response (purple box). Second, through inhalation or ingestion of coarse particulate matter, which induces a systemic immune response (blue box). Third, by entrance of neurotoxic materials directly into the brain, either through the olfactory centres or by passing from the lungs through the blood into the brain (green box).

Clouston SAP, Hall CB, Kritikos M, Bennett DA, DeKosky S, Edwards J, Finch C, Kreisl WC, Mielke M, Peskind ER, Raskind M, Richards M, Sloan RP, Spiro A 3rd, Vasdev N, Brackbill R, Farfel M, Horton M, Lowe S, Lucchini RG, Prezant D, Reibman J, Rosen R, Seil K, Zeig-Owens R, Deri Y, Diminich ED, Fausto BA, Gandy S, Sano M, Bromet EJ, Luft BJ. Cognitive impairment and World Trade Centre-related exposures. *Nat Rev Neurol*. 2022; 18(2): 103-116.

Findings from other cohorts

- Long-term exposure to air pollution → cognitive impairment
- PTSD → cognitive impairment
- Cognitive functioning is also associated with *physical functioning*, both cross-sectionally and longitudinally (figure)
- Physical function is associated with physical health outcomes, accelerated aging, and mortality



PTSD = post-traumatic stress disorder.

Chen H, et al. Living near major roads and the incidence of dementia, Parkinson's disease, and multiple sclerosis: a population-based cohort study. *Lancet* 2016.

Sumner JA, et al. Posttraumatic stress disorder symptoms and cognitive function in a large cohort of middle-aged women. *Depress Anxiety* 2017; 34:356–66.

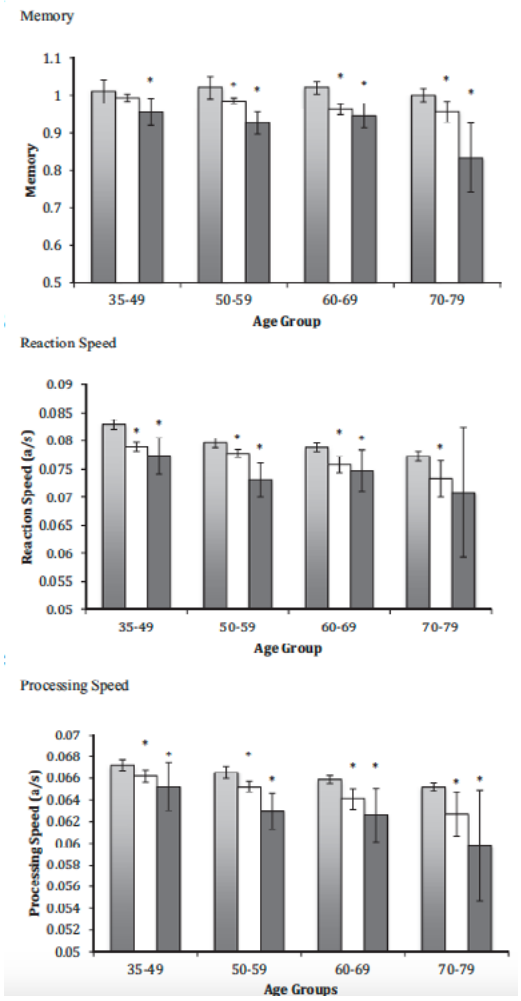
Clouston SAP, Brewster P, Kuh D, Richards M, Cooper R, Hardy R, Rubin MS, Hofer SM. The dynamic relationship between physical function and cognition in longitudinal aging cohorts. *Epidemiol Rev.* 2013; 35(1): 33-50.

Zammit AR, et al. A Coordinated Multi-study Analysis of the Longitudinal Association Between Handgrip Strength and Cognitive Function in Older Adults. *J Gerontol B Psychol Sci Soc Sci*. 2021; 76(2): 229-241.

Leong DP, et al. Prospective Urban Rural Epidemiology (PURE) Study investigators. Prognostic value of grip strength: findings from the Prospective Urban Rural Epidemiology (PURE) study. *Lancet*. 2015; 386(9990): 266-73.

Cognitive dysfunction in WTC

- 17.8% of responders were cognitively impaired at baseline, while an additional 14.2% developed MCI over 2.5 years
- Responders perform worse on cognitive/motor tasks compared to age-matched controls (figure)
- Possible causes: WTC exposure to neurotoxic particulate matter, and/or PTSD (~10%, decade after 9/11)
  - Both PTSD severity and longer time on-site associated with MCI



MCI = Mild cognitive impairment. PTSD = post-traumatic stress disorder.

Clouston SAP, et al. Cognitive impairment and World Trade Centre-related exposures. *Nat Rev Neurol*. 2022; 18(2): 103-116.

Clouston SAP, et al. Traumatic exposures, posttraumatic stress disorder, and cognitive functioning in World Trade Center responders. *Alzheimers Dement* (N Y). 2017; 3(4): 593-602.

Clouston SAP, et al. Incidence of mild cognitive impairment in World Trade Center responders: Long-term consequences of re-experiencing the events on 9/11/2001. *Alzheimers Dement (Amst).* 2019.

Bromet EJ, et al. DSM-IV post-traumatic stress disorder among World Trade Center responders 11-13 years after the disaster of 11 September 2001 (9/11). *Psychol Med*. 2016; 46(4): 771-83.

Physical functional impairment in WTC responders, associated with PTSD and with cognitive impairment

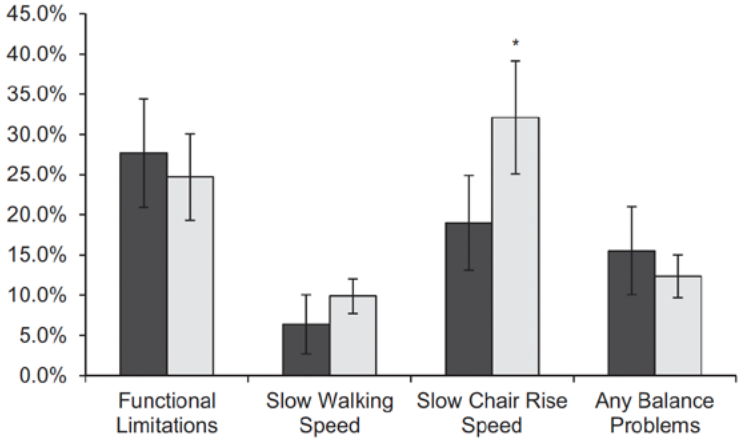
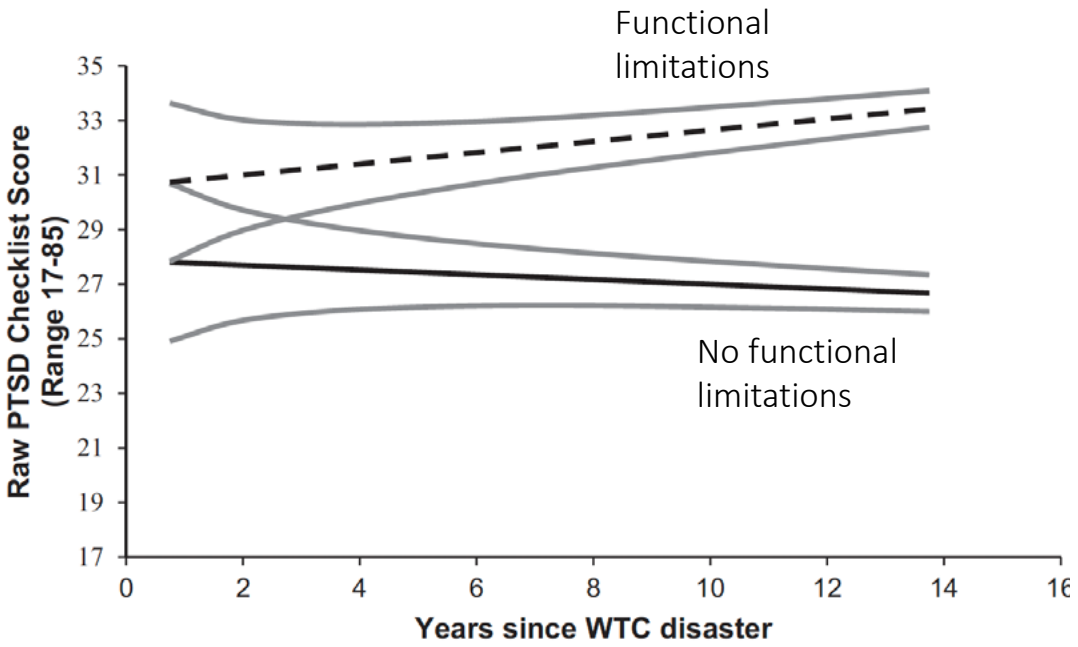


Figure 1. Comparing the risk of low physical functioning and functional limitations among responders to the September 11, 2001 World Trade Center (WTC) attacks and those of the National Health and Aging Trends Study (NHATS) respondents aged 65 to 69 years. Data were for 170 NHATS respondents (dark gray) and 81 WTC responders (light gray). 95% confidence intervals provided as error bars.
*$p = .003$.



Clouston SAP, Guralnik JM, Kotov R, Bromet EJ, Luft BJ. Functional Limitations Among Responders to the World Trade Center Attacks 14 Years After the Disaster: Implications of Chronic Posttraumatic Stress Disorder. *J Trauma Stress.* 2017; 30(5): 443-452.
Clouston SAP, Brewster P, Kuh D, Richards M, Cooper R, Hardy R, Rubin MS, Hofer SM. The dynamic relationship between physical function and cognition in longitudinal aging cohorts. *Epidemiol Rev.* 2013; 35(1): 33-50.

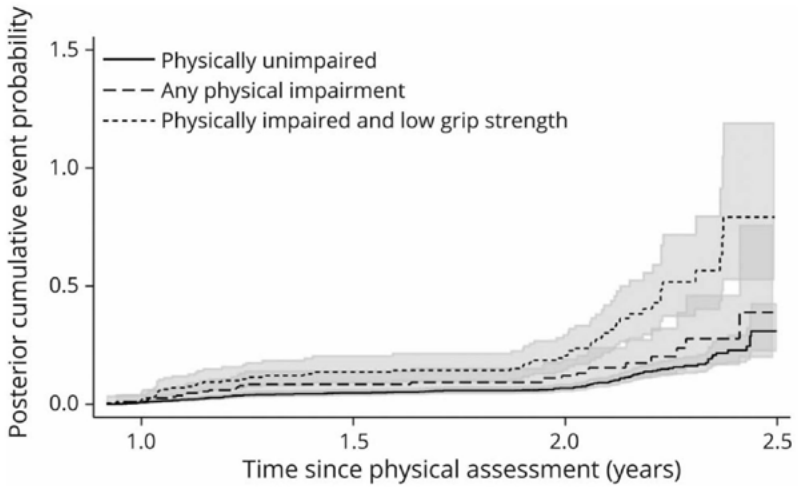
Weaker grip strength additionally associated with PTSD, cognitive impairment, and other health outcomes

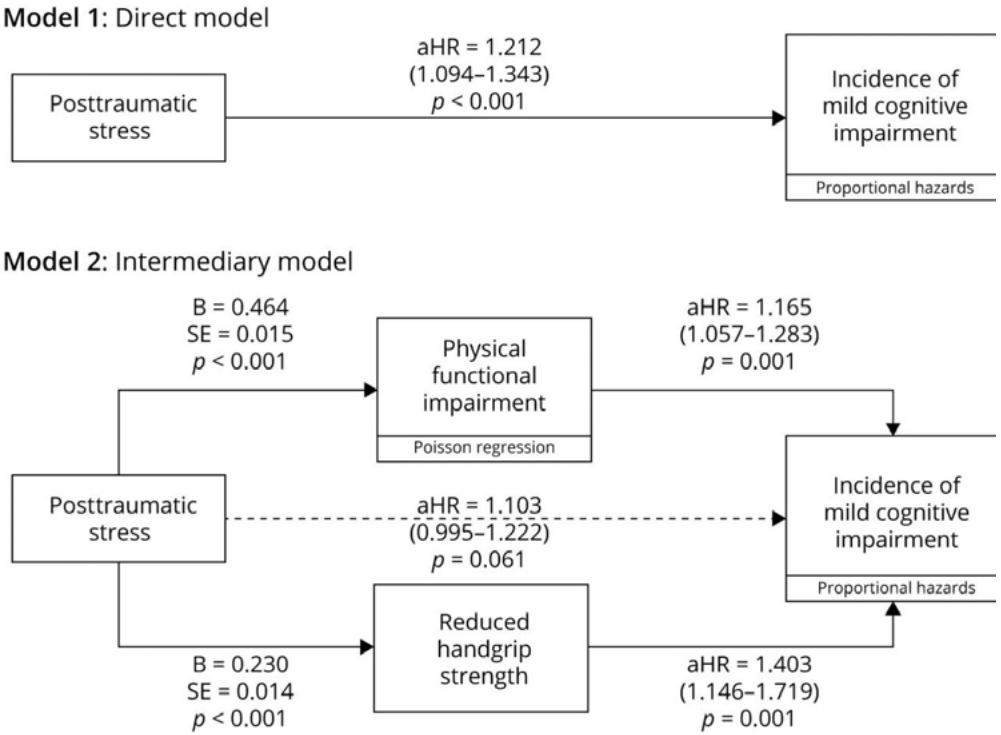
- Handgrip strength (HGS) = surrogate for aging
- Lower HGS associated with PTSD, re-experiencing symptoms specifically, and depression (Mukherjee et al., 2019)
- Diminich et al. (2021) further showed that PTSD was linked to over 3x the risk of comorbid cognitive and physical impairment, including HGS measure
- Reduction in HGS was the most likely to be comorbid with cognitive impairment, compared to other physical impairment conditions

Mukherjee S, et al. Handgrip Strength of World Trade Center (WTC) Responders: The Role of Re-Experiencing Posttraumatic Stress Disorder (PTSD) Symptoms. *Int J Environ Res Public Health* 2019; 16(7): 1128.
Diminich ED, et al. Chronic Posttraumatic Stress Disorder and Comorbid Cognitive and Physical Impairments in World Trade Center Responders. *J Trauma Stress* 2021; 34(3): 616-627.
Leong DP, et al. Prospective Urban Rural Epidemiology (PURE) Study investigators. Prognostic value of grip strength: findings from the Prospective Urban Rural Epidemiology (PURE) study. *Lancet* 2015; 386(9990): 266-73. Sayer AA, Kirkwood TB. Grip strength and mortality: a biomarker of ageing? *Lancet* 2015 ; 386(9990): 226-7.

Physical functional impairment may precede MCI, possibly as a marker for later MCI

Figure 3 Cumulative Hazards of Developing Mild Cognitive Impairment at a Follow-up Based on Baseline Physical Functional Impairment Status





MCI = Mild cognitive impairment.

Pellecchia A, Kritikos M, Guralnik J, Ahuvia I, Santiago-Michels S, Carr M, Kotov R, Bromet EJ, Clouston SAP, Luft BJ. Physical functional impairment and the risk of incident mild cognitive impairment in an observational study of World Trade Center responders. *Neurol Clin Pract.* 2022;12(6):e162-e171.

Oveisgharan S, et al. The time course of motor and cognitive decline in older adults and their associations with brain pathologies: a multicohort study. *The Lancet Healthy Longevity* 2024; 5(5): e336-e45.

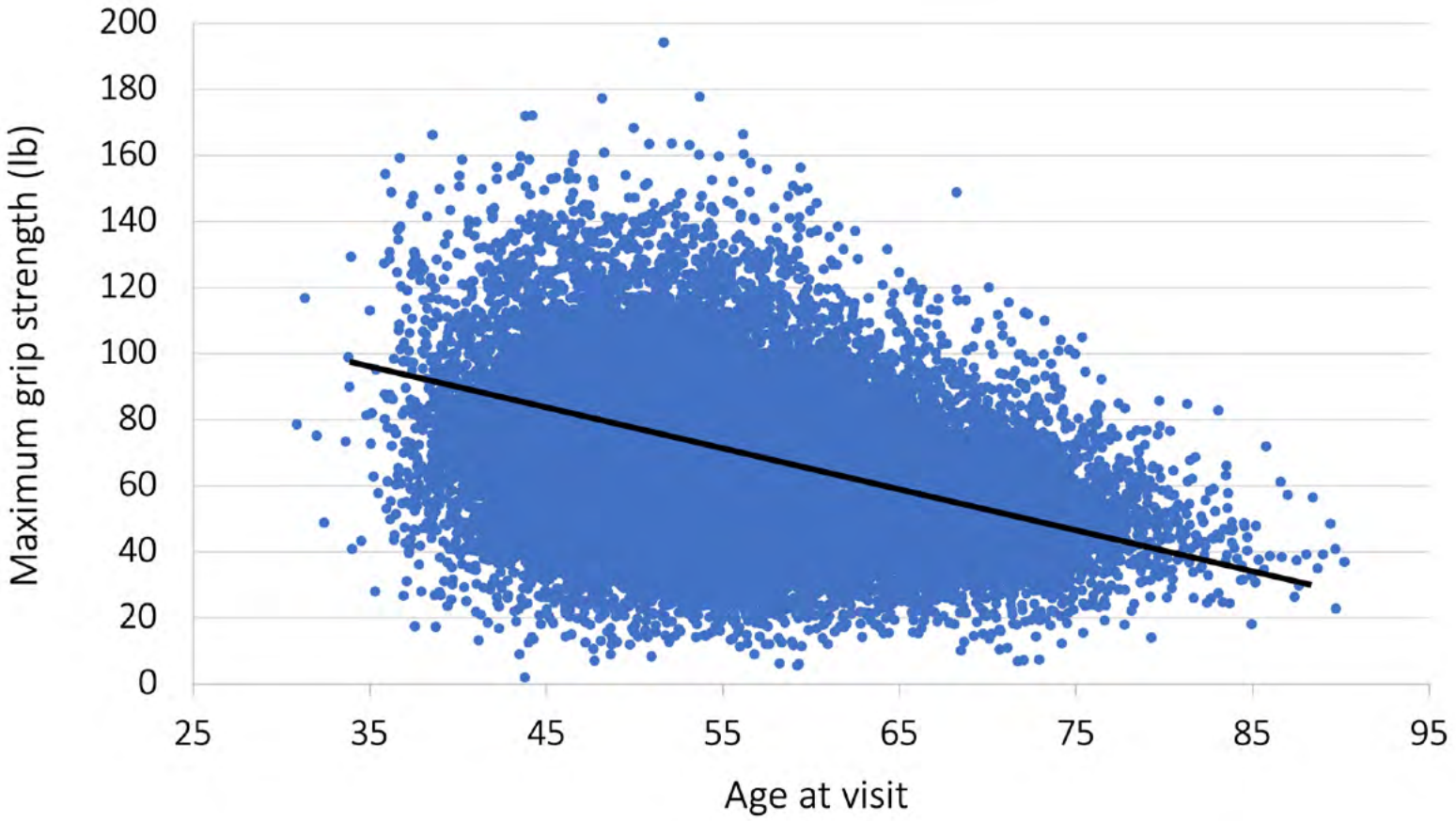
Methods for current study (updated data)

- General responder cohort based in Long Island
- 10,357 individuals (29,732 visits) with hand grip data, 2015-2023
- Maximum hand grip strength measured with dynamometer
- SPPB measures: chair speed, walking speed (smaller sample size, paused during pandemic)
- Probable PTSD at visit 1: PCL cut-off of 44 (DSM-IV)
- Generalized estimating equations
- Adjusted for demographics, medical conditions, and exposure variables

SPPB = Short Physical Performance Battery. PCL = PTSD CheckList for the DSM-IV.

Key findings from current study

Maximum handgrip strength by age



PTSD and physical function measures

Outcome	Crude beta estimate (95% CI)	Adjusted beta estimate (95% CI)
Maximum handgrip strength	-5.67 (-6.87, -4.46)	-4.26 (-5.46, -3.05)
Walking speed	-0.24 (-0.29, -0.20)	-0.19 (-0.24, -0.15)
Chair rise speed	-0.05 (-0.06, -0.04)	-0.04 (-0.06, -0.03)

Adjusted for: age, gender, race, marital status, education, exposure to dust cloud/time on site, 4-tier exposure composite variable, baseline BMI, baseline diabetes, baseline hypertension.

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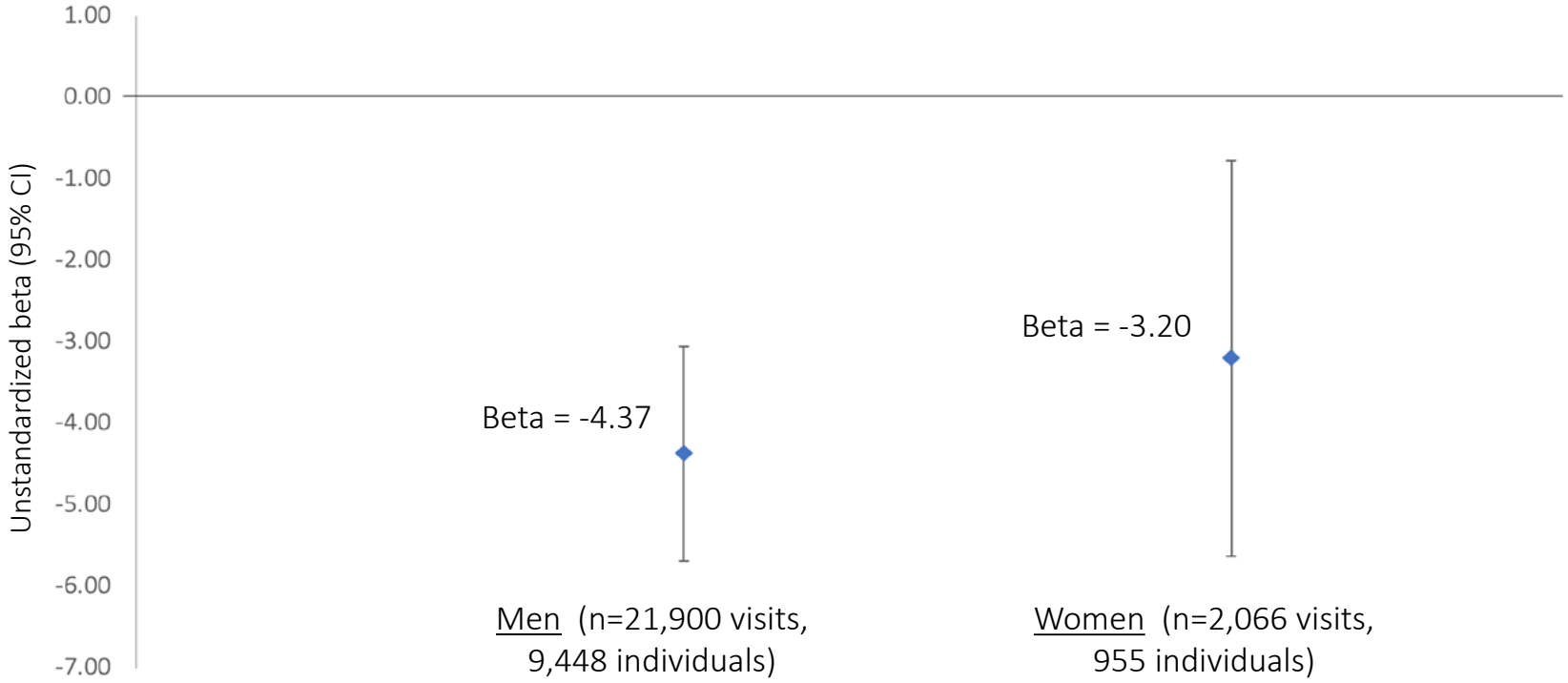
PTSD and maximum handgrip strength, stratified by gender



Adjusted for: age, race, marital status, education, exposure to dust cloud/time on site, 4-tier exposure composite variable, baseline BMI, baseline diabetes, baseline hypertension.

PTSD symptom clusters and max handgrip strength

	Crude beta estimate (95% CI)	Adjusted beta estimate (95% CI)
Re-experiencing	-3.74 (-4.24, -3.24)	-2.55 (-3.07, -2.02)
Avoidance	-2.23 (-2.59, -1.88)	-1.51 (-1.86, -1.16)
Hyperarousal	-2.87 (-3.28, -2.47)	-1.82 (-2.23, -1.42)
Emotional numbing	-3.59 (-4.07, -3.10)	-2.56 (-3.05, -2.06)

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Adjusted for: age, gender, race, marital status, education, exposure to dust cloud/time on site, 4-tier exposure composite variable, baseline BMI, baseline diabetes, baseline hypertension.

Conclusions, impact, and future research needs

- Consistent, longitudinal relationships between PTSD and objective physical functioning measures, even after adjusting for WTC exposures
  - Re-experiencing symptoms—and nightmares in particular—may be drive much of this relationship
  - Physical impairment may be an early marker for eventual cognitive decline
  - New post-traumatic neurocognitive disorder?

Next steps:

- PTSD symptom types/clusters for other SPPB outcomes
- Grip asymmetry, other outcomes
- Are there potential mediators? (e.g., lack of sleep/disrupted sleep, health factors)
- Understand change over time in *both* PTSD and outcomes (e.g., if PTSD improves over time, does physical function also improve, or does it still decline?)
- Do these relationships differ by race, age group, or level of WTC exposure?

Acknowledgements

- NIH: R01 AG049953
- Sean Clouston
- Benjamin Luft
- Frank Mann
- Roman Kotov
- Evelyn Bromet
- Erica Diminich
- Soumyadeep Mukherjee
- Alison Pellecchia

NOTES

NOTES

Monika Waszczuk, PhD

Polygenic prediction in 9/11 responders: What have we learned and where are we going?

Dr. Monika Waszczuk is an Associate Professor of Psychology at Rosalind Franklin University of Medicine and Science. She completed her undergraduate training at the Department of Experimental Psychology, University of Oxford, UK. Afterwards, Dr. Waszczuk received her MSc and PhD in Behavioral Genetics from the Social, Genetic and Developmental Psychiatry (SGDP) Centre at the Institute of Psychiatry, Psychology and Neuroscience (IoPPN), King's College London, UK. Following her graduate training, Dr. Waszczuk joined the Department of Psychiatry at Stony Brook University in New York, where she completed her postdoctoral training and conducted research as an Assistant Professor. Many of her projects at Stony Brook University have been in collaboration with the World Trade Center Health and Wellness Program.

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Additional Reading

Reading 1: Waszczuk, M. A., Kuan, P. F., Yang, X., Miao, J., Kotov, R., & Luft, B. J. (2023). Discovery and replication of blood-based proteomic signature of PTSD in 9/11 responders. *Transl Psychiatry*, 13(1), 8. https://doi.org/10.1038/s41398-022-02302-4

Reading 2: Waszczuk, M. A., Docherty, A. R., Shabalin, A. A., Miao, J., Yang, X., Kuan, P.-F., Bromet, E., Kotov, R., & Luft, B. J. (2020). Polygenic prediction of PTSD trajectories in 9/11 responders. *Psychol Med,* 1-9. https://doi.org/10.1017/S0033291720003839

Reading 3: Waszczuk, M. A., Morozova, O., Lhuillier, E., Docherty, A. R., Shabalin, A. A., Yang, X., Carr, M. A., Clouston, S. A. P., Kotov, R., & Luft, B. J. (2023). Polygenic risk scores for asthma and allergic disease associate with COVID-19 severity in 9/11 responders. *PLoS One,* 18(3), e0282271. https://doi.org/10.1371/journal.pone.0282271

NOTES

Polygenic prediction in 9/11 responders: What have we learned and where are we going?

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Associate Professor of Psychology
Rosalind Franklin University of Medicine and Science
she/her

@MAWaszczuk

CDC/NIOSH U01OH011864
MPI: Waszczuk and Kotov

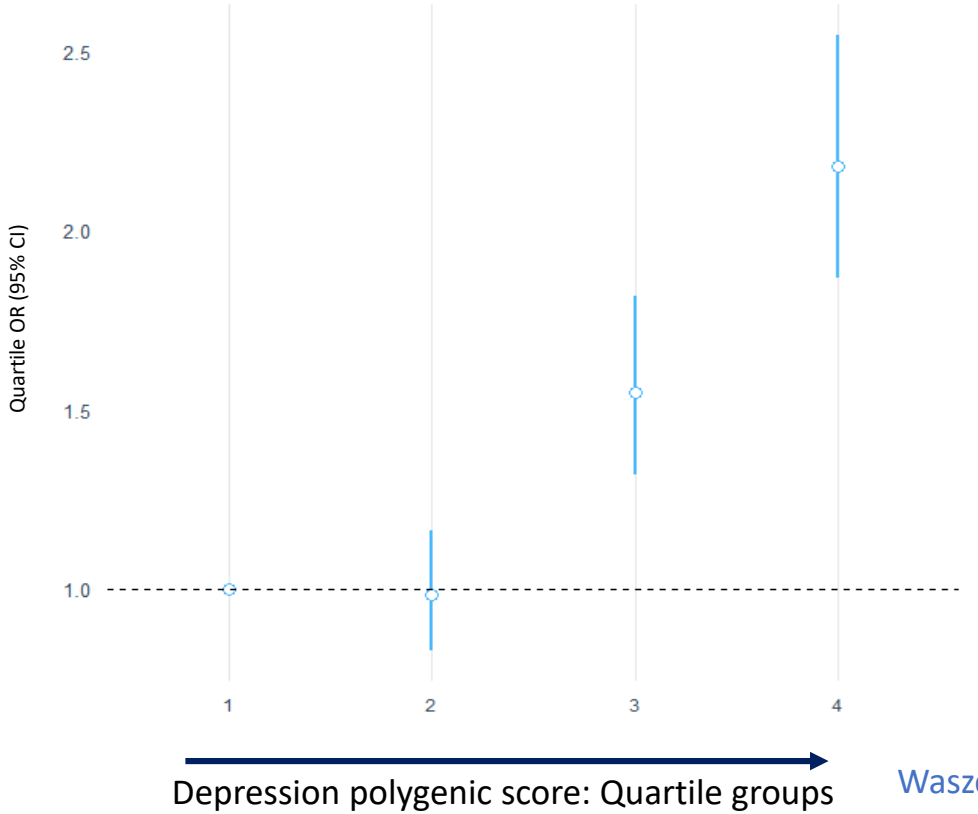
Why incorporate genetics into the WTC program?

- Help identify patient subpopulations with greatest intervention needs:
  - Chronic, treatment-resistant mental health conditions
  - Risk for future physical illness: cardiovascular, cancer, kidney disease
  - Risk of future cognitive decline
- Translation to other occupational cohorts:

Reduce burden of PTSD and other disorders by *identifying workers at risk prior to exposure* who would benefit from more resilience training, psychoeducation, and frequent screenings

Polygenic Risk Score (PRS) predicts PTSD diagnosis

Overall OR=1.37 for 1 SD increase on PRS

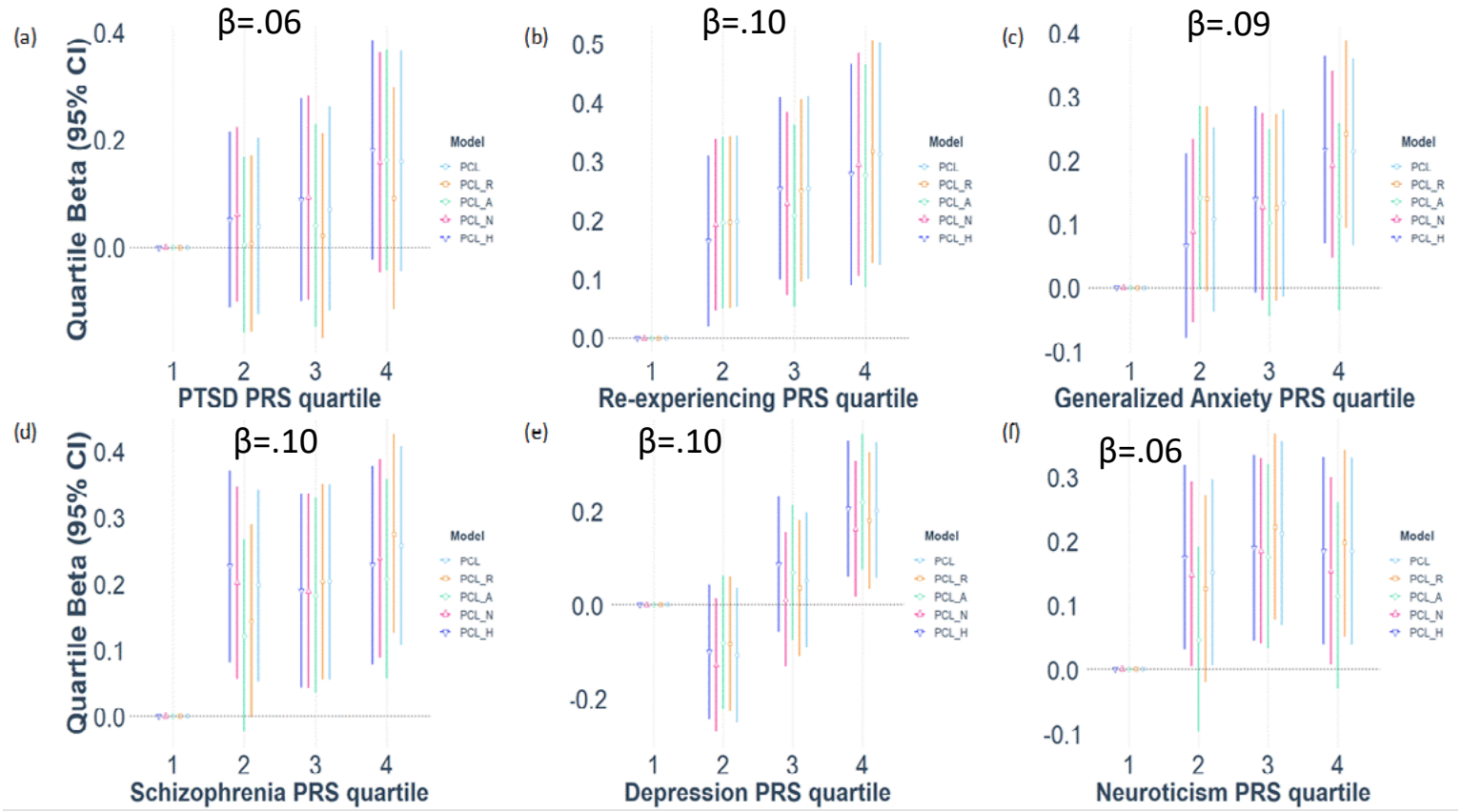


N=931

(222 PTSD cases and 709 trauma-exposed controls)

Waszczuk et al. (2022) *Psychological Medicine*

PRS predict PTSD symptom severity



N=1,490

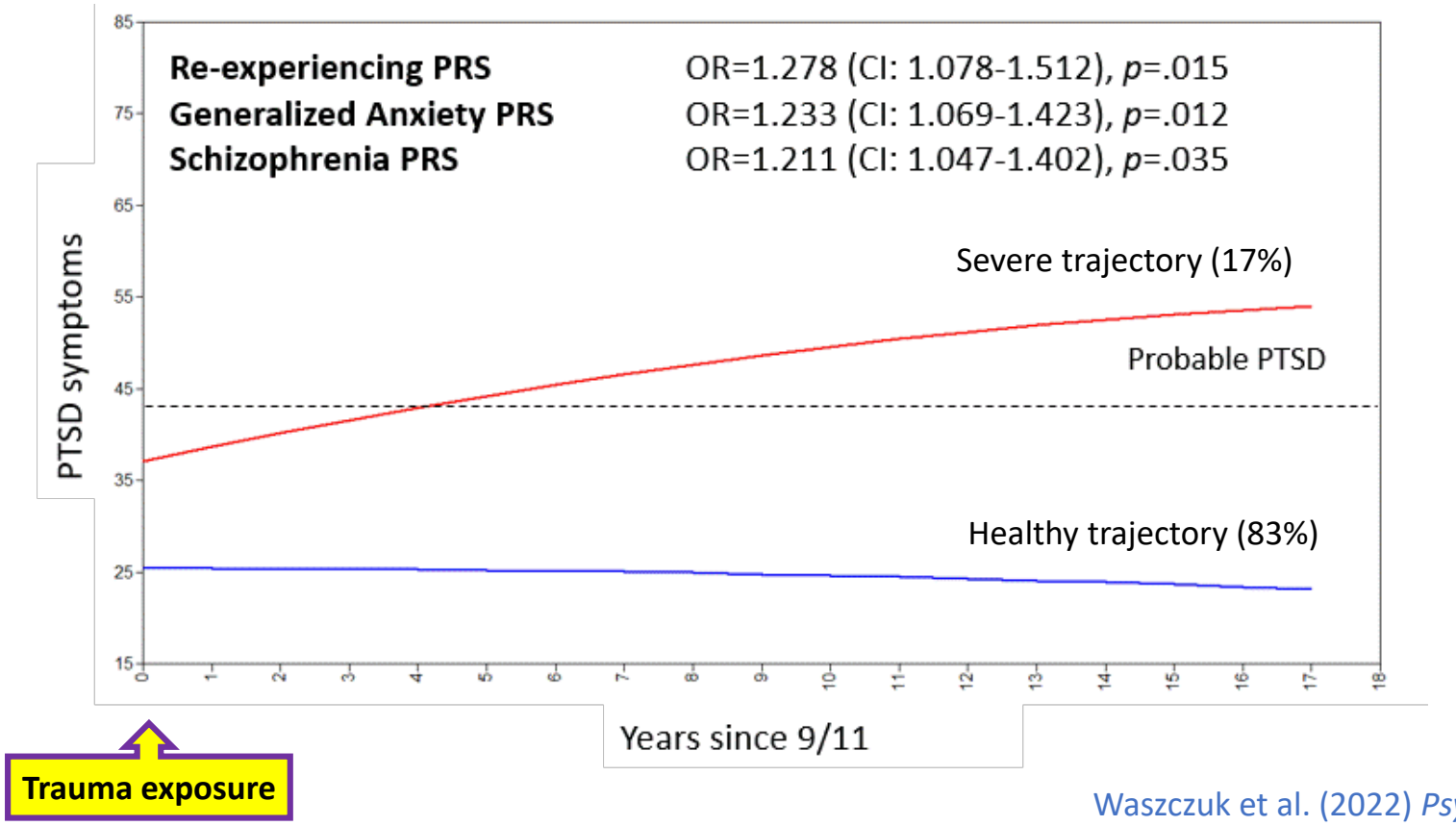
Replication in total genotyped sample

- Significant associations with PTSD, N=6,509

PRS:	PTSD	Re-experiencing	GAD	Schizophrenia	Depression	Neuroticism
OR	1.20 (1.06-1.35)	1.18 (1.05-1.33)	1.15 (1.06-1.24)	1.13 (1.04-1.23)	1.27 (1.17-1.37)	**1.16 (1.07-1.26)**
β	.10*	.13*	.09*	.06*	.08*	**.05***

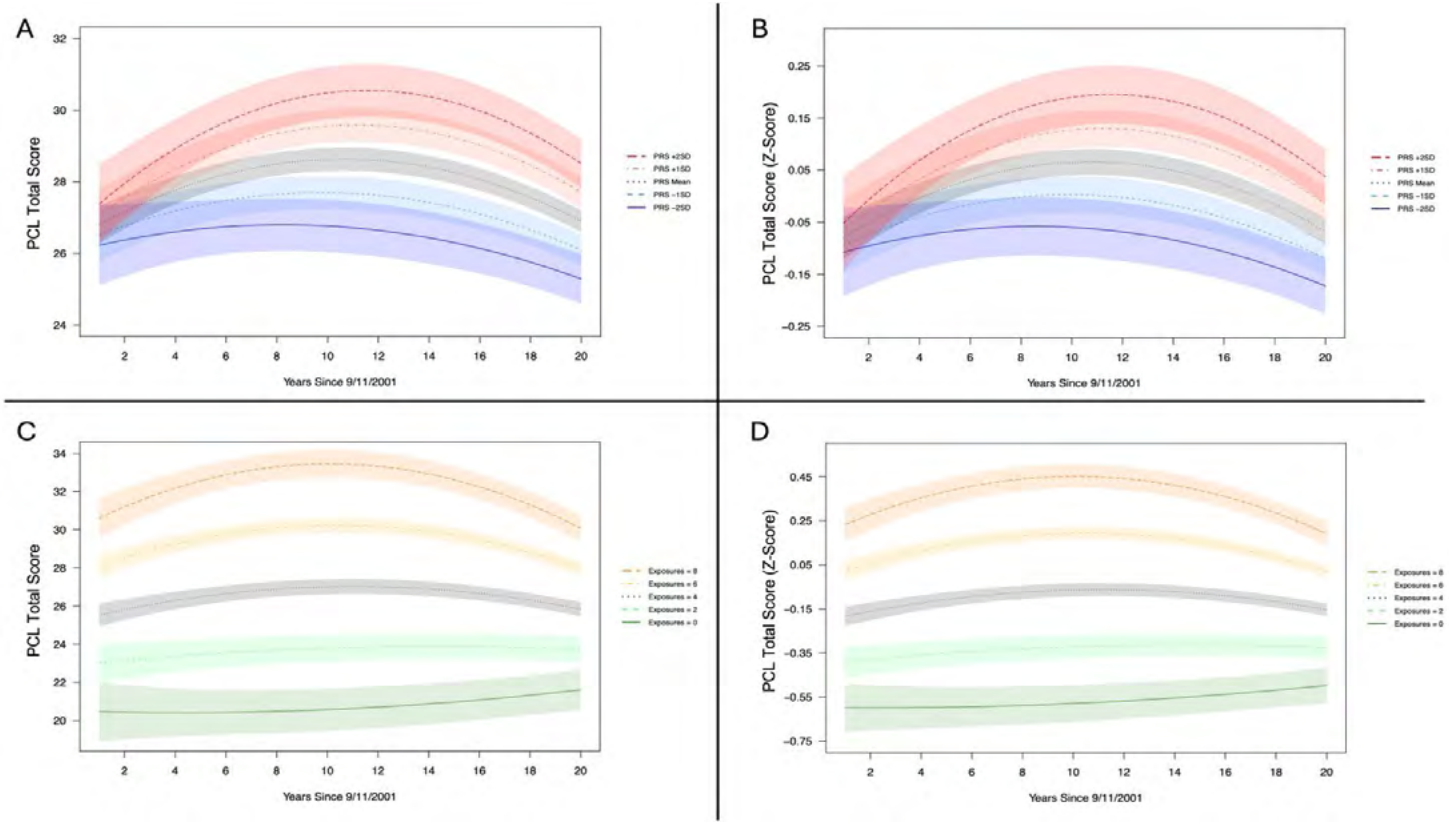
- Findings significant after adjustment for demographics and trauma exposure severity
- **Trauma exposure severity** independent from genetic influences on PTSD

Polygenic Risk Scores predict PTSD Trajectory



Waszczuk et al. (2022) *Psychological Medicine*

Polygenic Risk Scores predict PTSD Trajectory

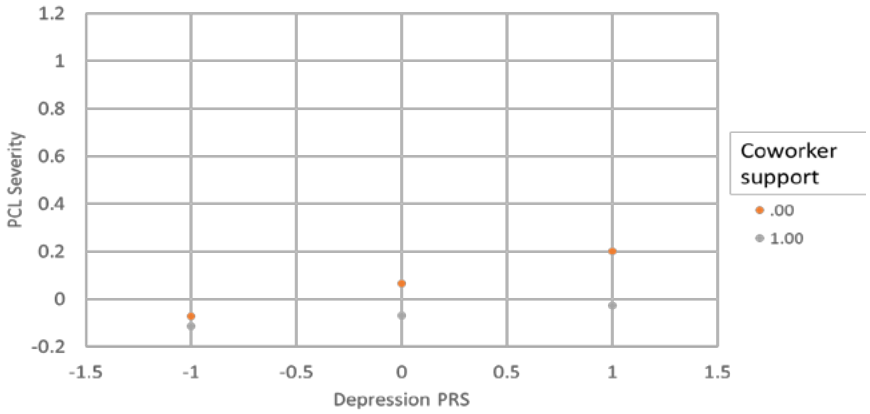


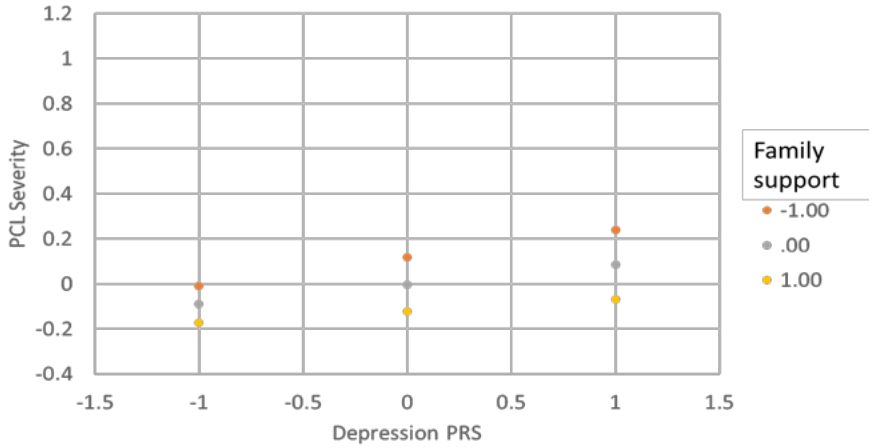
Mann et al. (under review) *Molecular Psychiatr*

Social support moderates genetic risk

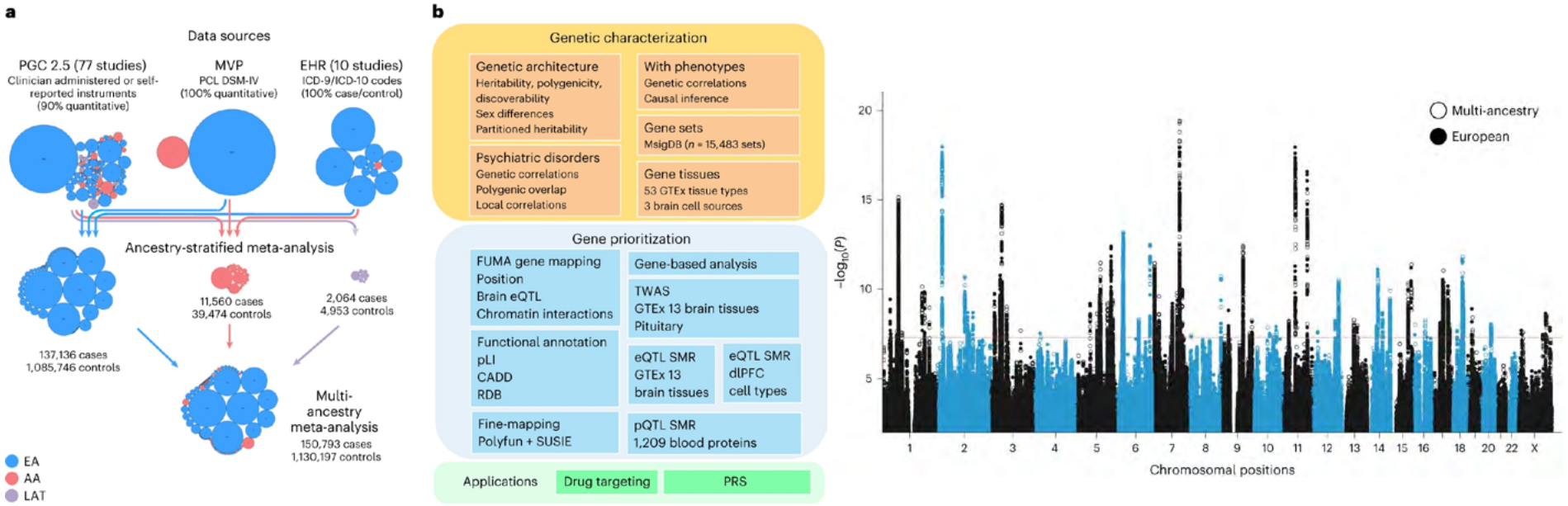
Palak Singh, Tampa VA

- Having **at least 1 supportive co-worker** during 9/11 buffered the association between MDD-PRS and PTSD severity (β=-.09*, *p*<.01)
- Family social support did not reach significance as a moderator (*p*=.08)



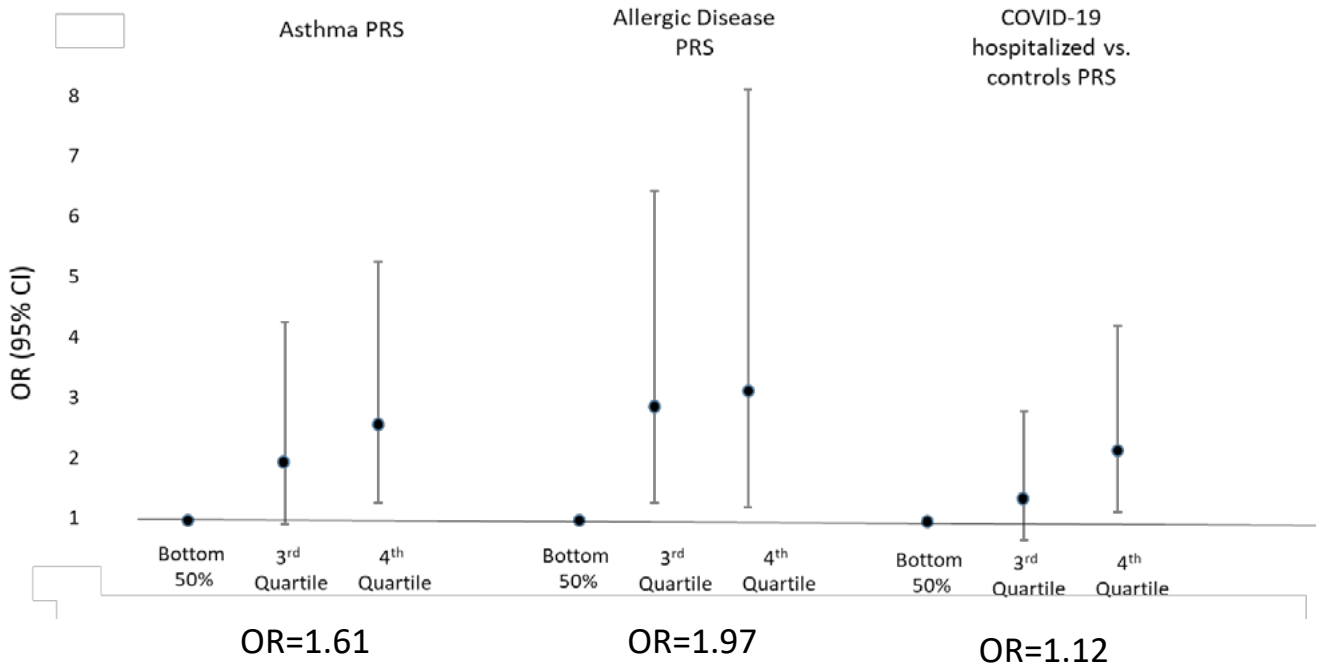


Psychiatric Genetics Consortium collaboration: 95 genome-wide significant loci (80 new)



Nievergelt et al. (2024) *Nature Genetics*

Polygenic Risk Scores predict COVID-19 Severity

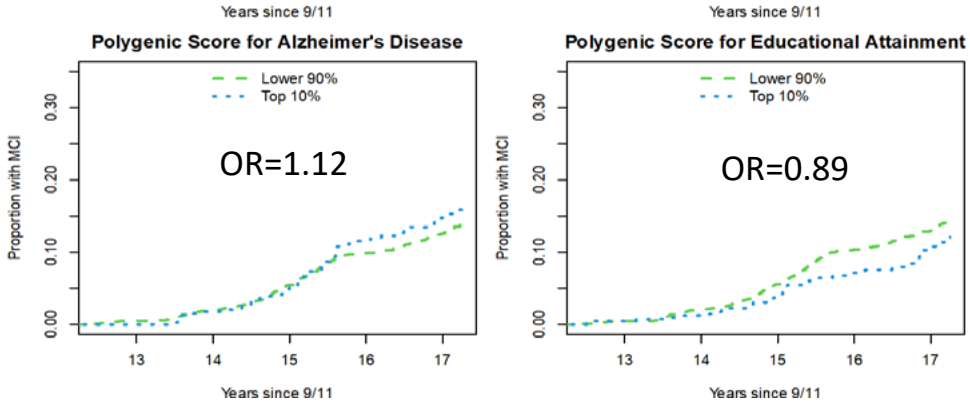


N=813 responders with confirmed infection

Covariates included age, sex, and lower + upper respiratory symptoms associated with 9/11 exposure

Waszczuk et al. (2022) *Plos One*

PRS and Cognitive impairment



Mann et al. (2023) *Journal of Alzheimer's Disease*

PRS and Chronic Kidney Disease

- Glomerular filtration rate PRS significantly associated with more advanced baseline CKD stage, both before and after adjusting for covariates (OR=1.18, CI: 1.06 to 1.32)

Koraishy et al. (2022) *BMC Nephrology*

Summary of empirical findings

- **Polygenic Risk Scores predict:**
  - Onset and long-term course of PTSD following trauma
  - Onset of MCI, but not Dementia
  - Decline in glomerular filtration rate (GFR) and kidney disease stage
  - Severity of COVID-19 symptoms, but not long COVID-19
- **Promising for prospective prediction, but can be combined with other risk and protective factors:**
  - Trauma severity and other environmental factors
  - Social support from work colleagues buffers genetic risk
  - Biomarkers, e.g. inflammation, proteomics, metabolic markers

Impact: Clinical Translation

- **PRSs not yet used clinically**
- **Opportunities for clinical translation and research**
  - At-risk and resilient patient subpopulations
  - Combining PRSs with other risk factors to develop algorithms/screeners in clinical populations
  - Prediction of long-term outcomes, over and above baseline information on PTSD severity, demographic characteristics, and trauma exposure severity

Future needs

- PRS use in our research studies would be expanded by:
  - **Larger N for other biological modalities**
  - Deep phenotyping of:
    - **Comorbid dx** (e.g. anxiety dx, substance use, pain, insomnia etc.)
    - **Behavioral determinants of health** (e.g. sleep, physical activity)
    - **Social determinants of health/environment/exposome** (e.g. social support, social networks, loneliness, acute and chronic stress)
    - **Ageing-relevant phenotypes** (e.g. functioning, retirement and economic vulnerability, healthcare utilization, caregiving/receiving car

Acknowledgements

- 9/11 Responders
- Stony Brook World Trade Center Health Program
- **Stony Brook University** team: Pei-Fen Kuan, Frank Mann, Farrukh Koraishy, Olga Morozova, Xiaohua Yang, Jiaju Miao, **Roman Kotov, Benjamin J. Luft**
- **University of Utah** team: Anna Docherty, Andrey Shabalin

Questions?

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MAWaszczuk

NOTES

Benjamin Luft, MD

Moderator for Panel Discussion

For over 25 years, Dr. Luft has been involved in the care of patients with occupation-related diseases. He has been the Director and PI of the World Trade Center Health Program (WTC-HP) since 2003. In this capacity, Dr. Luft has longitudinally followed a cohort of close to 11,700 subjects for medical, psychiatric and social issues, as well as developed a bio bank containing over 70,000 specimens (e.g. peripheral blood DNA, RNA, blood cells, serum and plasma) from his patient population. Prior to that, he was the Director of the Long Island Occupational and Environmental Health Center (LIOEHC) from 2002 to 2006. He is currently working on "Remembering 9/11: an Oral History of WTC Responders" project, to preserve the personal accounts of WTC responders which will be housed in the Library of Congress. Dr. Luft's research has been directed toward an epidemiologic and epigenetic understanding impact of the environment on medical and psychiatric disease. He will contribute intimate knowledge of the population participating in WTC Health Program, expertise in exposures and medical comorbidities, and clinical and laboratory resources that he can access within the program. Dr. Luft also has an active research program in the genetics, molecular biology and immune response to microbial pathogens that has been continuously federally funded for over 30 years. He has been funded by NIH and CDC for over 25 years and has served as a consultant to the FDA, NIH, CDC, IDSA, DOD, IOM and DTRA. He has served and led numerous national and international committees and directed more than six multi-centered national/international studies.

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